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Thermal rearrangements of 1-methoxybicyclo [3.2.0]hepta-3,6-dien-2-one and exo-1-methoxybicyclo [3.2.0]hepta-3,6-dien-2-ol

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by

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Dean of Graduate College

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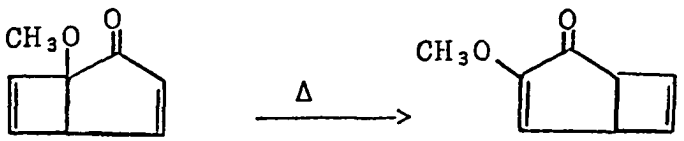
INTRODUCTION

With the development of the theory of conservation of orbital symmetry, first formulated by Woodward and Hoffman in 1965[1], the correlation of a wide range of known thermal and photochemical rearrangements has become possible. This formalism also predicts unique transformations which have been the subject of intense research activity. Several reviews of the selection rules, with representative examples, are available[2-5].

Numerous reports[6-9] and reviews[10,11] have appeared in the literature dealing with intramolecular photochemical rearrangements of simple and naturally occurring tropolone derivatives, and of the bicyclo[3.2.0]hepta-3,6-dien-2-ones which are formed as the primary photoproducts from them. These transformations are quite consistent with the Woodward-Hoffmann theory. However, the reports of thermal rearrangements within these series have generally been limited to pyrolysis of the bicyclic dienones to their troponoid precursors at temperatures above 300° as a means of structure elucidation.

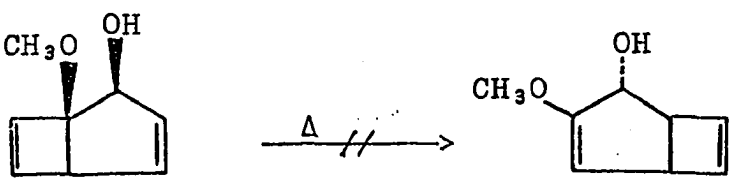
Only in the past three years, with the discovery of the thermal conversion of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) to its 3-methoxy isomer (2) has careful attention been given to rearrangements of the bicyclic dienones at more moderate temperatures.



1 2

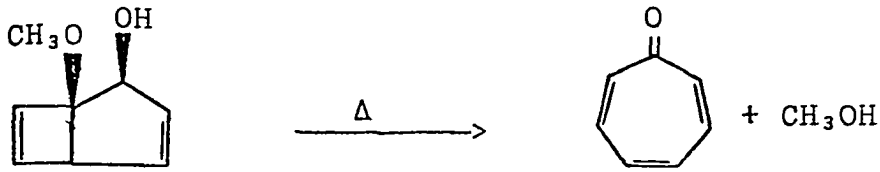
The work presented in the first part of this thesis deals with the determination of the mechanism of the above thermal rearrangement by substituent labeling of the 4, 5 and 6 positions of 1. A sidelight of this study was the elucidation of the photochemistry of 5-isopropyl-2-methoxytropone (26), which proves to be the only simple, alkyl substituted methoxytropone which rearranges significantly to a 3-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one product.

To test the generality of the proposed mechanism of the rearrangement of 1 to 2, a study of the thermal rearrangement of the dihydro derivative of 1, 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3), was carried out. The predicted bicyclic product, 4, would not only result in an apparent shift of the methoxyl group, but would have a change in the configuration of the hydroxyl group.



3 4

However, 3 was found to undergo an equally unique rearrangement to tropone (5), with elimination of methanol. The



3 5

mechanism of this rearrangement was probed by deuterium and oxygen-18 labeling and will be presented as the second part of this thesis.

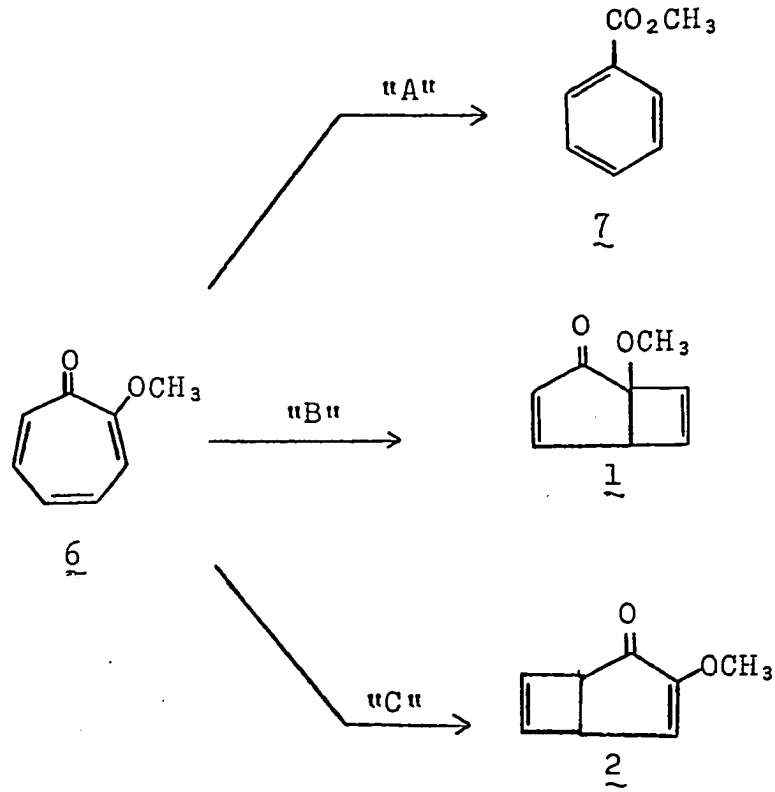
HISTORICAL

Photocyclization Reactions of 2-Methoxytropone (6) and Related Systems

Within the past fifteen years the photochemistry of 2-methoxytropone derivatives has been studied extensively by several research groups and has been shown to undergo a variety of interesting intramolecular rearrangements. These may be grouped under three general reaction types as summarized in Figure 1 (p 6). An example of type A rearrangement is the conversion of tetra-o-methylpurpurogallin to methyl-6,7,8-trimethoxynaphthoate.[9,12] Type B is common among the simple[13,14] and alkyl substituted[14] methoxytropones, with the exception of 3-methoxytropone (15), which gives complex dimers.[15] The troponoids colchicine[16-18] and isocolchicine[19,20] rearrange exclusively by pathway C. Both orbital symmetry theory[1-5] and considerations of changes in bond order in the excited state[21] fail to distinguish between paths B and C. Hence, the electrocyclic closure theoretically could occur by path B or C with equal probability.

The observed tendency of the simple α-tropolone methyl ethers to favor path B is attributed to the ability of the methoxyl group to stabilize the postulated dipolar transition state 8 with respect to 9.[22] The influence of the methoxyl group is further illustrated, firstly by the fact that irradiation of 4-methoxytropone (10) results in the formation of 12 with no evidence for the formation of its isomer, 14,[13]

Figure 1. Photochemical transformations of 2-methoxytropones


CO2CH3
"A"
7
O
OCH3
"B"
1
6
O
OCH3
"C"
2

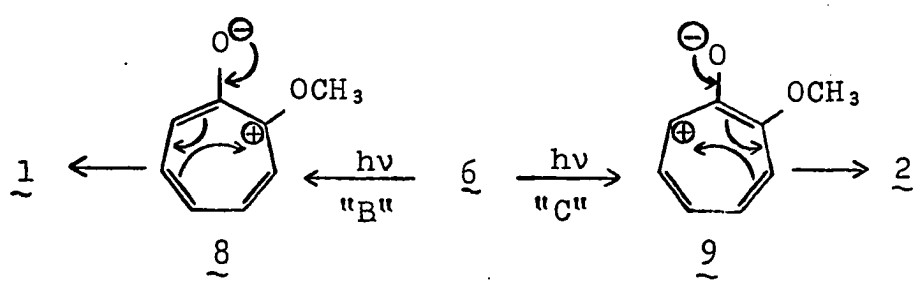
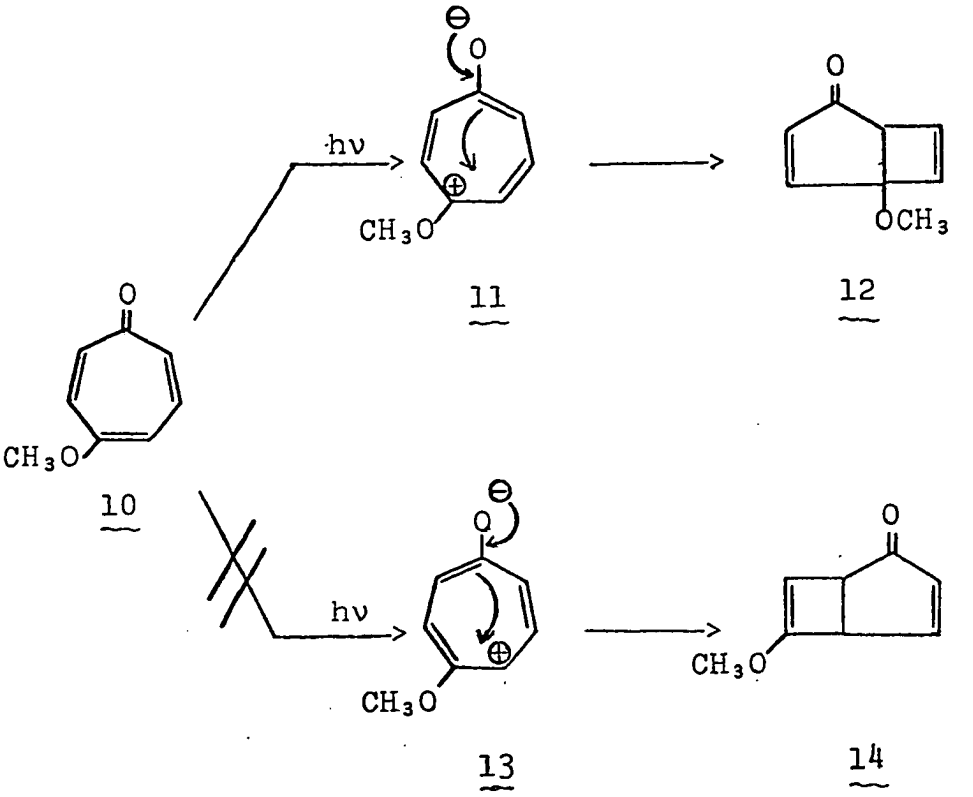
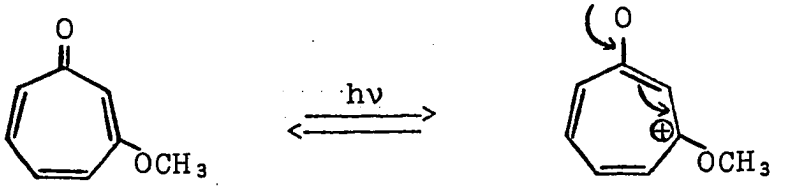

O
OCH3
1
hν
"B"
6
hν
"C"
O
OCH3
2
8
9

Figure 2. Directive effect of the methoxyl group in electrocyclic closure of methoxytropones



10 11 12 13 14



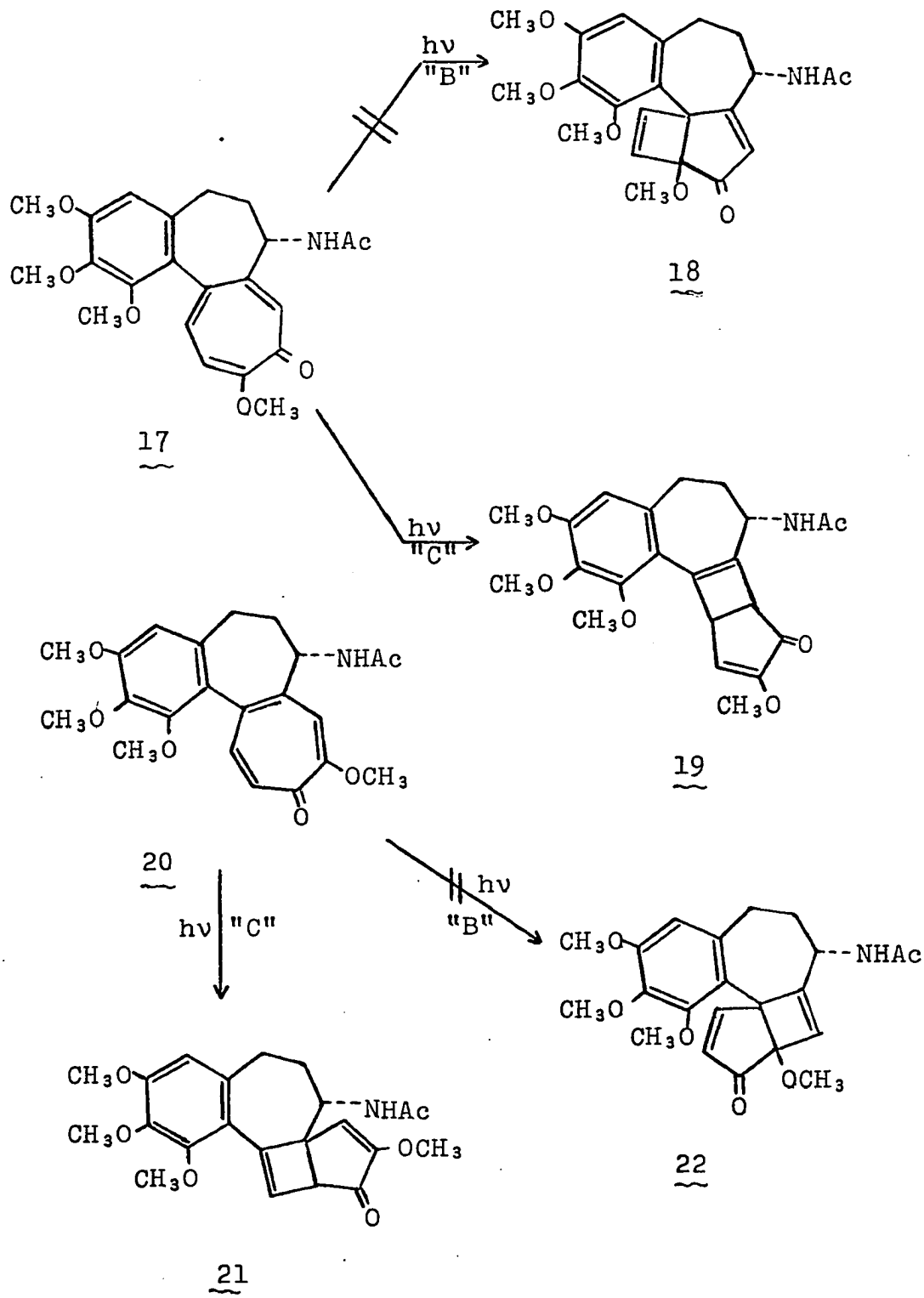
15 16

and secondly, by the absence of bicyclo[3.2.0]hepta-3,6-dien-2-one products in the irradiation of 3-methoxytropone (15).[15] The methoxyl substituent in 4-methoxytropone (10) stabilizes the intermediate, 11, more than 13, thus providing a facile pathway to the bicyclic product, 12. Collapse of the similarly stabilized excited state, 16, of 3-methoxytropone (15), however, regenerates the starting material rather than bicyclic products.[15]

In the more structurally complex troponoid, colchicine (17), the directive effect of the methoxyl group is more than overcome and type C closure operates exclusively. This deviation from the normal, type B closure has been attributed to the destabilizing steric interference in formation of the 1-methoxy bicyclic product, 18, or to the greater stability of the 3-methoxy isomer, 19, resulting from retention of the styrene chromophore through the transition state. Subsequent work with isocolchicine (20)[19,20] suggested that the styrene chromophore is more important, since this electrocyclization also proceeds exclusively by path C to give 21 rather than its isomer 22. Even though both possible products have comparable steric strain, only 21 retains the styryl conjugation.

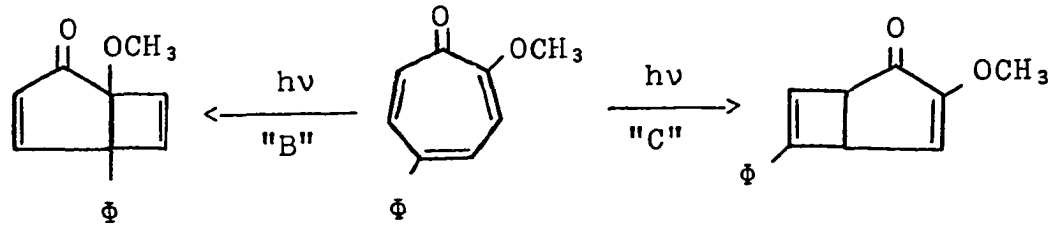
The degree to which the phenyl group dominates the control over the direction of cyclization in the absence of possible steric assistance is well illustrated by 5-phenyl-2-methoxytropone (23)[6]. Irradiation of a 1% methanolic solution of 23 for 70 hours gave a single isolable product, 24, in 30%

Figure 3. Photochemical isomerizations of colchicine (17) and isocolchicine (20)

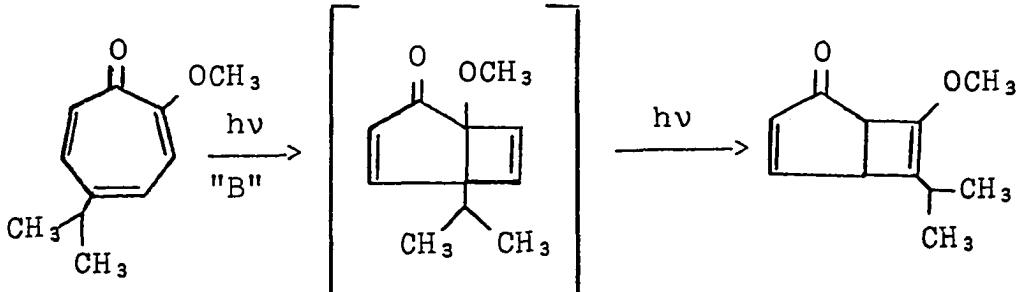


17 18 19 20 21 22

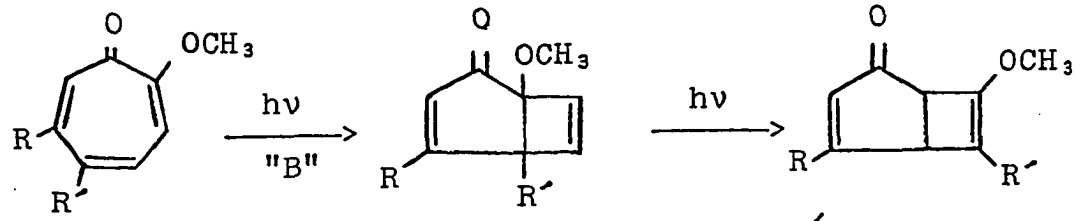
Figure 4. Photochemical isomerizations of 5- and 6-substituted 2-methoxytropones



25 23 24



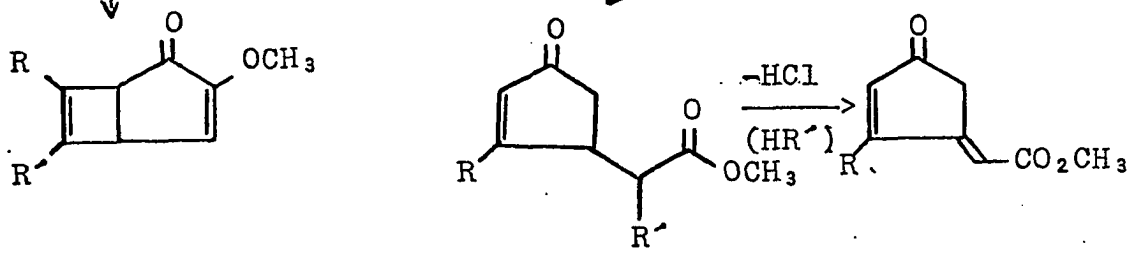
26 27 28



29a. R=Φ; R'=H
29b. R=H; R'=Cl

31a. 15%
31b. 0%

32a. 0%
32b. 10%



30a. 13%
30b. 30%

33a. 8%
33b. 0%

34b. 10%

yield together with 60% recovered starting material. Based on the report[14] that the major product, 28, isolated from the irradiation of 4-methoxytropone (26) was the result of an initial type B closure to 27, the steric interference between bulky substituents at the bridgehead positions was assumed not to be a serious hindrance to the formation of the 1-methoxy bicyclic product 25. Since neither 25 nor its photoproducts were detected, the effect of the phenyl group alone is apparently sufficient to override the methoxyl group's contribution and direct the rearrangement entirely through path C.

Movement of the phenyl substituent to the adjacent 6-position of 2-methoxytropone (29a)[8] would allow the styryl system to remain intact in either mode of cyclization. The influence of the methoxyl group is apparent, but it is not absolute in determining the cyclization pathway. The ratio of products from type B (31a and 33a) vs. type C (30a) is roughly 2:1; the isolated yields, in % of theoretical, are recorded in Figure 4 (p 13).

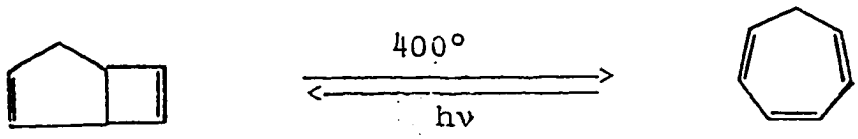
A second example of a simple, substituted 2-methoxytropone which undergoes both modes of cyclization is the 5-chloro derivative, 29b.[7] In this instance, the effect of the chlorine atom is to destabilize the path B transition state relative to path C more than the methoxyl group stabilizes it. However, the opposing effects are more nearly in balance than for the 5-phenyl derivative, 23, since products arising from type B (32b and 34b) and type C (30b) closures were isolated

in 10%, 10% and 30%, respectively. A troponoid system in which steric crowding significantly alters electronic control over the direction of photocyclic rearrangement has not been reported in the literature.

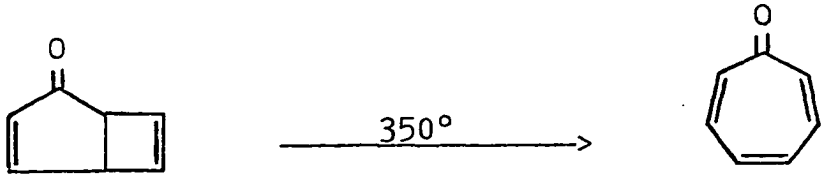
Thermal Rearrangements of Substituted Bicyclo[3.2.0]hepta-3,6-dienes

Relatively few thermal rearrangements of substituted bicyclo[3.2.0]heptadienes and bicyclo[3.2.0]heptadienones not related to systems already discussed have been reported. This is probably due to the difficulty in synthesizing the bicyclic diene from non-troponoid precursors. The parent diene, 35, was prepared simply, but in low yield, from tropilidene (36) by Dauben and Cargill.[23] Bicyclo[3.2.0]heptadiene (35) was known to be stable below 200°,[24] and was shown to revert to tropilidene (36) upon pyrolysis at 400°. Story and Fahrenholtz obtained the unsubstituted dienone, 37, in a six step synthesis from norbornadiene.[25-27] Bicyclo[3.2.0]hepta-3,6-dien-2-one (37) undergoes a nearly quantitative conversion to tropone (5), but requires a pyrolysis temperature of 350°.[27] Finally, simple, alkoxy substituted dienes, (38a,b) were shown by Chapman and coworkers to regenerate their photochemical precursors (39a,b, respectively) at temperatures in excess of 340° as a means of structure proof.[28] Pyrolyzing the bicyclic photoproduct to starting material to demonstrate whether or not skeletal rearrangement had occurred in the photochemical

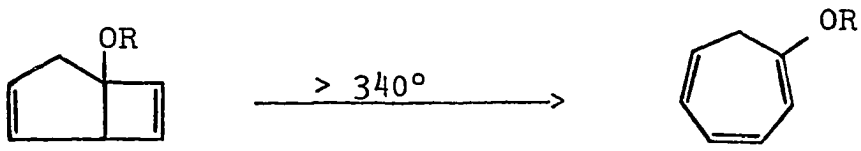
Figure 5. Thermal rearrangements of bicyclo[3.2.0]heptadienes of non-troponoid origin



35 36



37 5



38a. R=CH_3

38b. R=CH_2CH_3

39a. R=CH_3

39b. R=CH_2CH_3

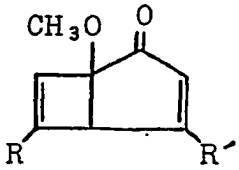
transformation is a general technique used extensively in papers discussed in the previous section. For completeness, these are summarized in Figure 6 (p 20).

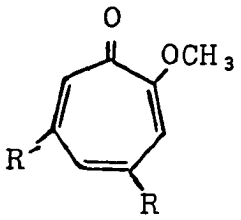
The final communication dealing with thermal rearrangements of bicyclo[3.2.0]hepta-3,6-dienones, by Mukai and coworkers[29], has a direct bearing upon the rearrangement of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1), the subject of the first part of this thesis. Aspects of this paper will be considered in detail in the following section.

Figure 6. Thermal rearrangements of bicyclo[3.2.0]hepta-3,6-dien-2-ones

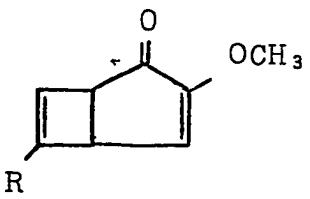
PYROLYSIS

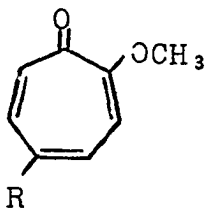
REFERENCE



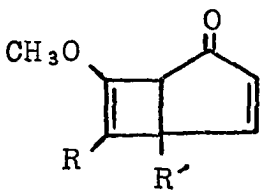


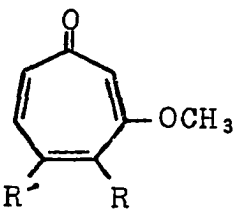
40a. R=R′=H	440°	41a. R=R′=H	14.
40b. R=CH_3; R′=H	360°	41b. R=CH_3; R′=H	14.
40c. R=H; R′=CH_3	395°	41c. R=H; R′=CH_3	14.





42a. R=Ø	450°	43a. R=Ø	6.
42b. R=Cl	430°	43b. R=Cl	7.





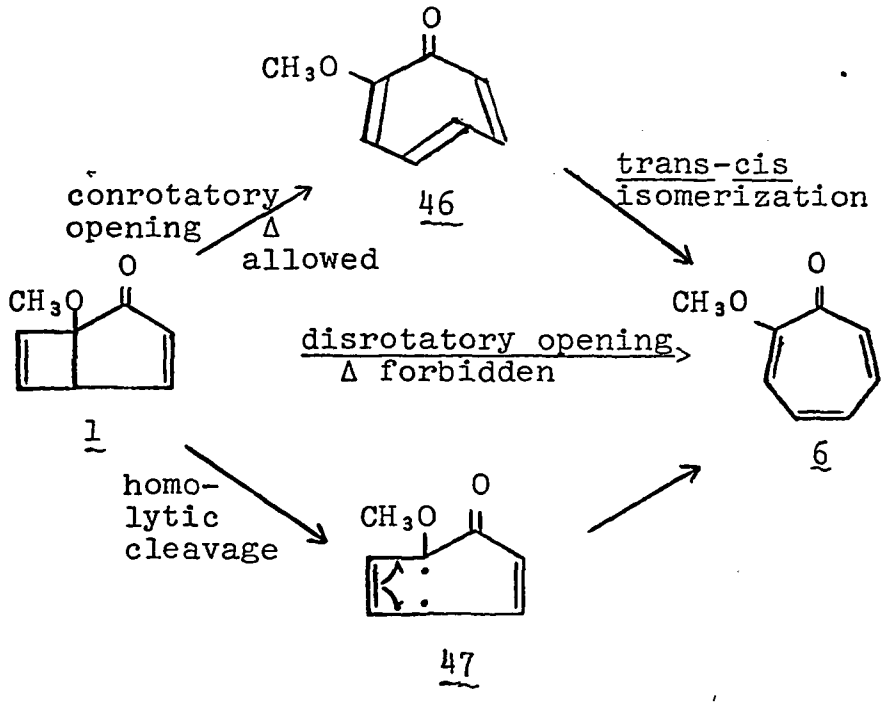
44a. R=R′=H	420°	45a. R=R′=H	14.
44b. R=H; R′=CH_3	415°	45b. R=H; R′=CH_3	14.
44c. R=Cl; R′=H	430°	45c. R=Cl; R′=H	7.

PART I. THE THERMAL REARRANGEMENT OF 1-METHOXYBICYCLO[3.2.0]HEPTA-3,6-DIEN-2-ONE

DISCUSSION OF RESULTS

The Mechanism of the Rearrangement of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) to 2-Methoxytropone (6)

The cycloreversion of the cyclobutene moiety of bicyclo-[3.2.0]hepta-3,6-diene derivatives to the butadiene equivalent in their cycloheptatriene precursors is a quite general reaction. Three distinct pathways might be conceived for this transformation, as illustrated below.



Both the conrotatory and disrotatory pathways are governed by orbital symmetry rules[1-5] and must be concerted. Each has two directions in which the conrotatory or disrotatory mode may theoretically occur. Only the conrotatory process is thermally allowed. However, inspection of molecular models reveals that of these four possible concerted modes, only one is sterically

feasible. The thermally allowed conrotatory process in which the 1,7 and 5,6 bonds rotate clockwise forms a cycloheptatrienone with a trans-Δ^4 double bond, as illustrated in structure 46. The alternate, counter-clockwise rotation of these bonds would result in a trans-Δ^2 double bond with the methoxyl substituent inside the ring. Not only would a trans double bond be difficult to accommodate in the seven membered ring intermediate, but even the initial rotation is difficult in the rigid bicyclic starting material. The thermally forbidden disrotatory opening in which the 1,7 and 5,6 bonds rotated inward (counter-clockwise and clockwise, respectively) would produce a trans configuration at both double bonds, which would be sterically impossible. In contrast, the disrotatory opening in which these bonds open outward is quite easy and produces 2-methoxytropone (6) directly. This mode would clearly prevail if it were a thermally allowed process.

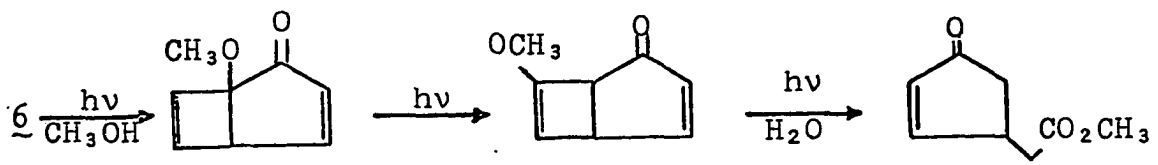
The biradical pathway is not concerted and the intermediate, 47, allows the orbitals to adjust to new bonding situations. Orbital symmetry rules are therefore not applicable. This process requires fission of the weakest bond in the bicyclic system as the initial event. The activation energy of the fission is lowered further by the electron donating character of the methoxyl substituent which stabilizes one site of the incipient biradical. Once the bond is broken, the ring opens quite naturally in a motion similar to the disrotatory process described above, and the biradical could

isomerize to 2-methoxytropone (6) as rapidly as bridgehead orbitals could rehybridize. The aromatic stabilization of the tropone ring would draw the reaction rapidly to its conclusion, allowing a very brief existence of the biradical, 47.

It is reported that simple, alkyl substituted cyclobutenes which can undergo the thermally allowed conrotatory processes proceed in this manner as first order reactions with no radical components at temperatures of 150-200°.[30-32] Since temperatures 350° to 500° are required to open the bicyclo[3.2.0]hepta-3,6-diene derivatives, it appears that the cyclopentene ring provides sufficient steric constraint that the reaction is forced to proceed by an alternate, less energetically favorable process. Both the biradical pathway and the thermally forbidden disrotatory process in which the 1,7 and 5,6 bonds rotate clockwise and counter-clockwise, respectively, opening the ring outward, pass the steric constraints of the rigid bicyclic system. The author favors the biradical process because of the high temperature requirement and the experimentally demonstrated validity of orbital symmetry rules as applied to concerted processes.[33] However, the disrotatory process can not be eliminated on the basis of available data.

Preparation of 1-Methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1)

In the process of purification of 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1) a new compound was isolated which proved to result from a thermal rearrangement of 1 competitive with the conversion to 2-methoxytropone (6) described above. To study this rearrangement in detail required a method to prepare 1 in gram quantities, free from other isomers. The sequential photochemical transformations in the 2-methoxytropone series had been established by Chapman and Smith, and Dauben and Koch to be the following:[14]



1 48 49

Formation of the photo-ester, 49, could readily be prevented by conducting the irradiation under anhydrous conditions. The secondary transformation of 1 to 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48) was less easily eliminated. The relative absorption of 1 at long wavelengths and the relative efficiency of its conversion to 48 were sufficient that the secondary product began appearing in a conventional irradiation through Pyrex before 5% conversion of 6 had been achieved. Irradiation through Corning 0-52 or 0-51 cut-off filters which absorb light below 340 and 355 nm, respectively, allowed 48 to form at even

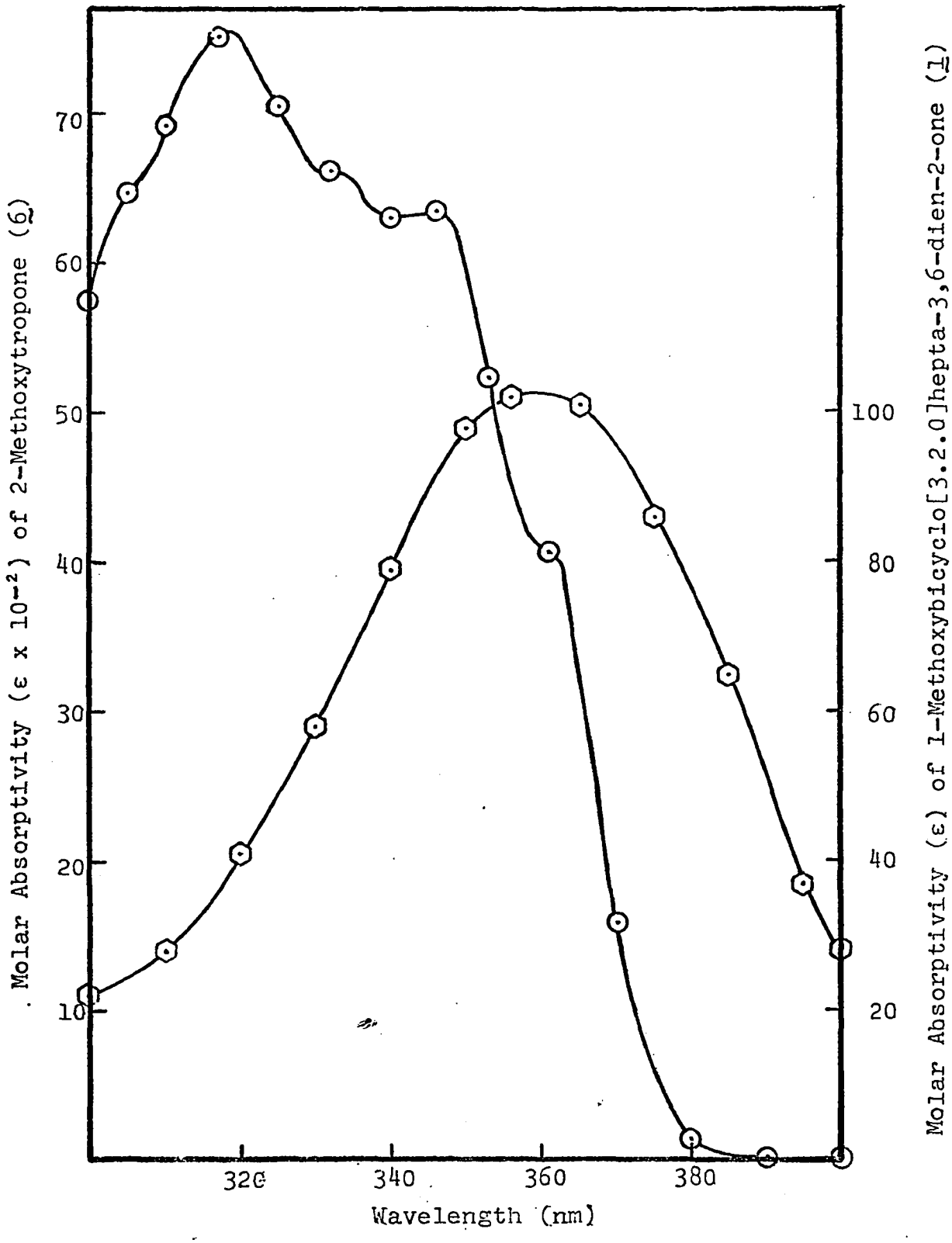
lower conversion of 6 to 1. Some improvement was achieved by using the commercially available "black light" lamps in a Rayonet Photochemical Reactor (emission band 310-400 nm, with the maximum at 350 nm), but still only 8-10% completion was possible.

The relative absorptivities of 2-methoxytropone (6) and 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1), plotted as a function of wavelength in Figure 7 (p 28), support the above results. The absorption of 1 increases steadily from a relative minimum at 300 nm to its maximum at 356 nm (ε=102) and drops more slowly, still having a significant value at 400 nm (ε=28). 2-Methoxytropone (6) overwhelmingly dominates the lower portion of this region with a maximum at 317 nm (ε=7510) and shoulders at 332 (ε=6610), 346 (ε=6350), and 361 nm (ε=4080). However, its absorption drops rapidly to a molar absorptivity of 140 at 380, 15 at 390, and only 2 at 400 nm. Obviously, light at the upper portion of this range, particularly above 380 nm, would be absorbed by 1 in a constantly increasing ratio and would increase the probability of 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48) being formed. For quantum yield studies the 313 nm mercury band would be ideal, but the required four component filter system[34] was impractical for preparative work. Alternatively, it would be desirable to cut out the longer wavelength light. This was achieved by the filter system shown in Figure 8 (p 31). A 550 watt Hanovia medium pressure mercury arc was inserted

Figure 7. Plot of molar absorptivity of 2-methoxytropone (6) and 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) vs. wavelength

⊙= 2-methoxytropone (6)

⊙= 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)


Molar Absorptivity (ε x 10⁻²) of 2-Methoxytropone (6)
Molar Absorptivity (ε) of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)
Wavelength (nm)
10
20
30
40
50
60
70
20
40
60
80
100
320
340
360
380

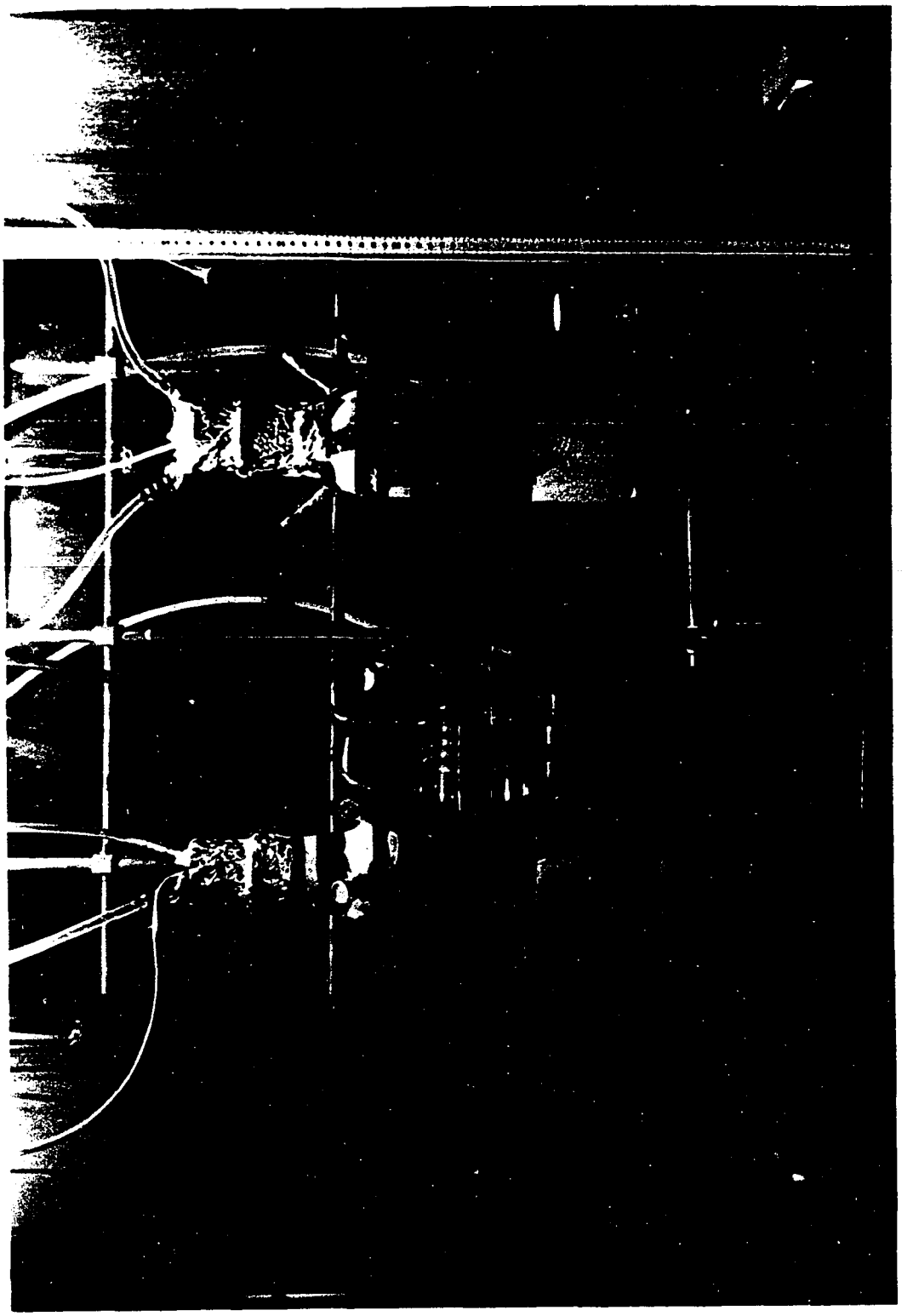
into the central Pyrex cooling jacket and the opening covered with aluminum foil so that the only exit was through the Corning 7-37 window. The external Pyrex flask was filled with a saturated cupric sulfate solution. A model showed the transmission maximum to be 25% at 362 nm. The band width was 330 to 376 nm. Accordingly, this system allowed a 35% conversion of 2-methoxytropone (6) to 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) with no appreciable (<1%) secondary product. The reaction progress was monitored by vpc and 6 was found to decrease linearly with time, correlating directly to the increase in 1 for the extent to which the reaction was carried. Simple distillation separated 1 from 6 and the latter was recycled in a subsequent irradiation. If 48 were present in more than 1 or 2% it was necessary to separate the isomers at great loss by preparative vpc. The bicyclic isomers have been characterized[10,11,14] and are easily distinguishable by their nmr (Figure 17, p 64) and ir (Figure 18, p 66) spectra.

Preparation of Isopropyl Substituted Derivatives of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

Separation and methylation of isomeric thujaplicins

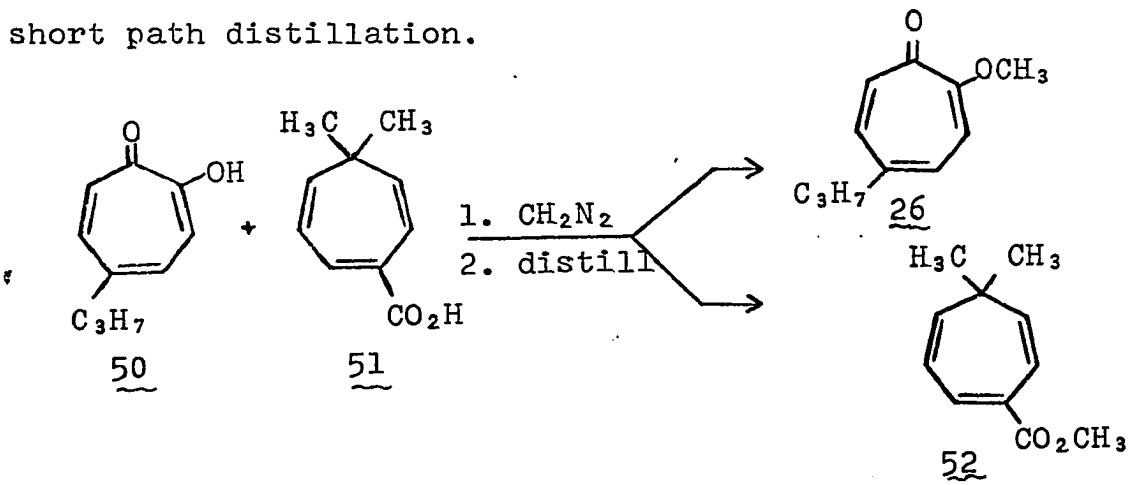
The pathway of the photochemical transformation of 2-methoxytropone (6) had been traced using 4-, and 6-methyl-2-methoxytropone (41b and 41c, respectively) synthesized by Chapman and Smith in a laborious sequence from purpurogallin.[35] A similar method of labeling by alkyl substitution was desired

Figure 8. Preparative irradiation apparatus

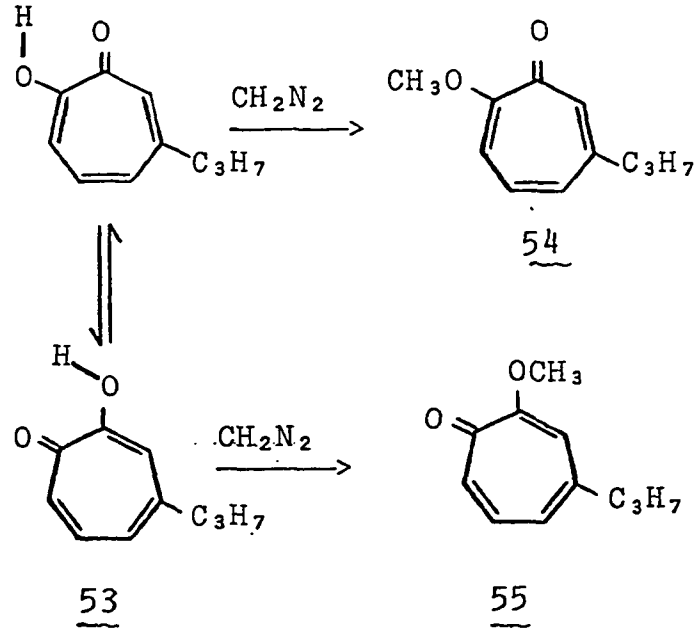


for the rearrangement of 1. For this purpose, γ- and β-thujaplicin (50 and 53, respectively) were chosen. These materials are extractable from the heartwood of the Western Red Cedar (Thuja plicata) and are available as a crude, reddish brown oil which also contains the α-isomer and thujic acid (51). The components could be separated by careful spinning band distillation and the methyl ethers readily prepared by treatment with diazomethane.

γ-Thujaplicin (50) was the most difficult isomer to isolate from the crude oil. It was the highest boiling of the three isomers, but the thujic acid (51), usually present in an equal amount, boiled even higher. γ-Thujaplicin could therefore not be easily collected in the later fractions without some contamination. This problem was overcome when it was found that the methylated derivatives differed in boiling points by over 60°. It was therefore expedient to methylate the two component mixture in ether with diazomethane and isolate methyl thujate as a valuable by-product by a simple, short path distillation.



The work with β-thujaplicin (53) was simplified by the availability of an authentic sample. This was methylated, the isomeric products isolated, and reference spectra obtained.

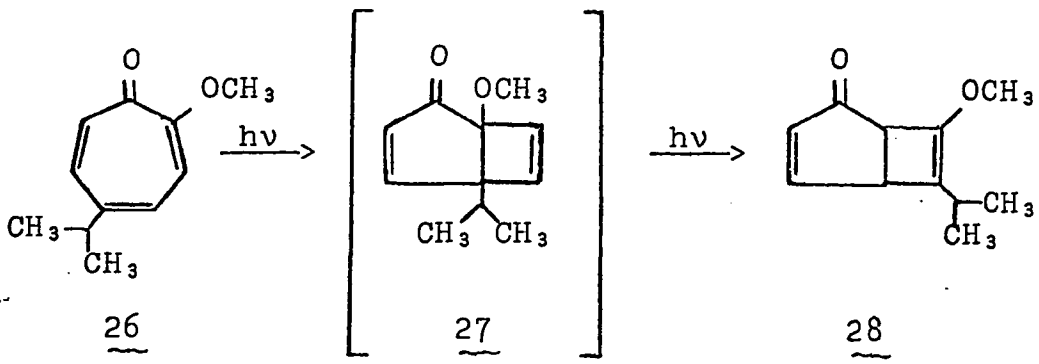


Since both isomers distilled at 107-112° (0.10 torr), they could be separated effectively only by preparative vpc. 6-Isopropyl-2-methoxytropone (54) had a slightly shorter retention time than its isomer, 4-isopropyl-2-methoxytropone (55) whose retention on diethylene glycol succinate (DEGS) or Carbowax 20M liquid phases was approximately the same as 5-isopropyl-2-methoxytropone (26). An interesting temperature dependence was observed in the product ratio. When β-thujaplicin (53) was treated with diazomethane in ether at room temperature, the ratio of 54 to 55 was 1.1:1.0; when the

reaction was carried out at the temperature of an ice-methanol bath (-10°C) the ratio increased to 2.1:1.0. The three thujaplicin methyl ethers may be readily distinguished by their nmr (Figure 9, p 36) and ir (Figure 10, p 38) spectra.

Photochemistry of 5-isopropyl-2-methoxytropone (26)

The irradiation of 5-isopropyl-2-methoxytropone (26) was approached with a great deal of care. W. G. Dauben and K. Koch had reported the isolation of a single product, 28, from the irradiation of 26.[14] 6-Isopropyl-7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (28) was postulated to have formed by way of 5-



26 27 28

isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27), but no evidence was presented for the existence of the latter as an isolable intermediate. It is conceivable that the substituents at both bridgehead positions might destabilize 27 sufficiently that, if it did not proceed photochemically to 28, it would revert to 26 by the mechanism previously proposed for the ring opening of 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1) (pp 22, et seq.). In addition the incipient radical at C-5 would be stabilized by the alkyl

Figure 9. Nuclear magnetic resonance spectra

Top - 5-isopropyl-2-methoxytropone (26)

Middle - 6-isopropyl-2-methoxytropone (54)

Bottom - 4-isoproply-2-methoxytropone (55)

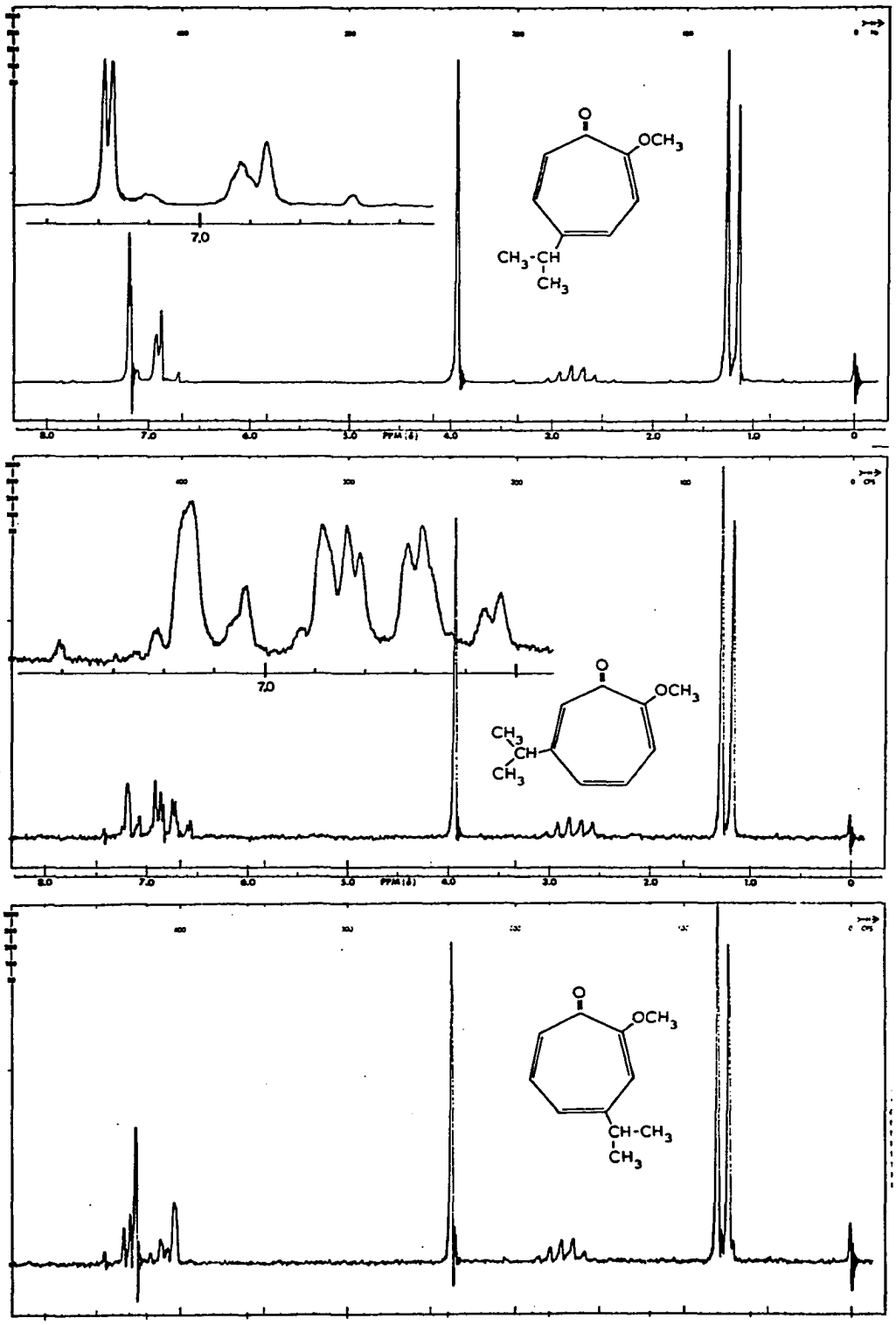
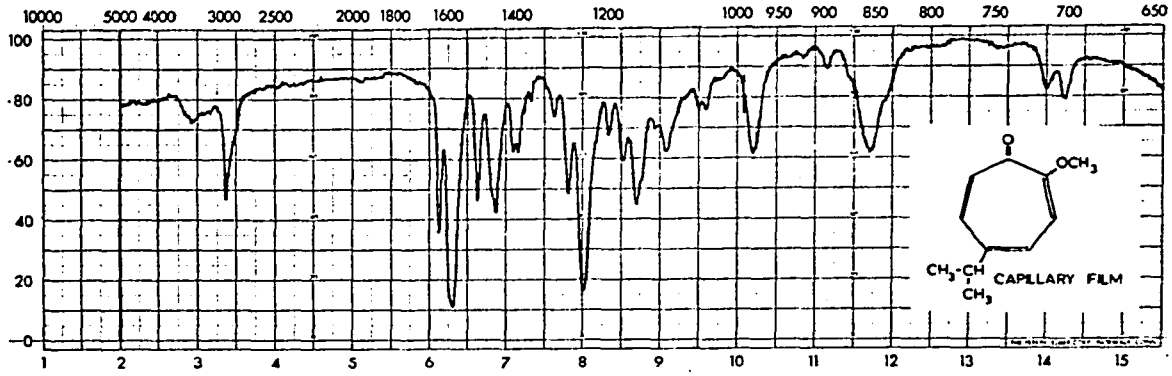

7.0
OCH3
CH3-CH
CH3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
7.0
OCH3
CH3
CH
CH3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
OCH3
CH-CH3
CH3

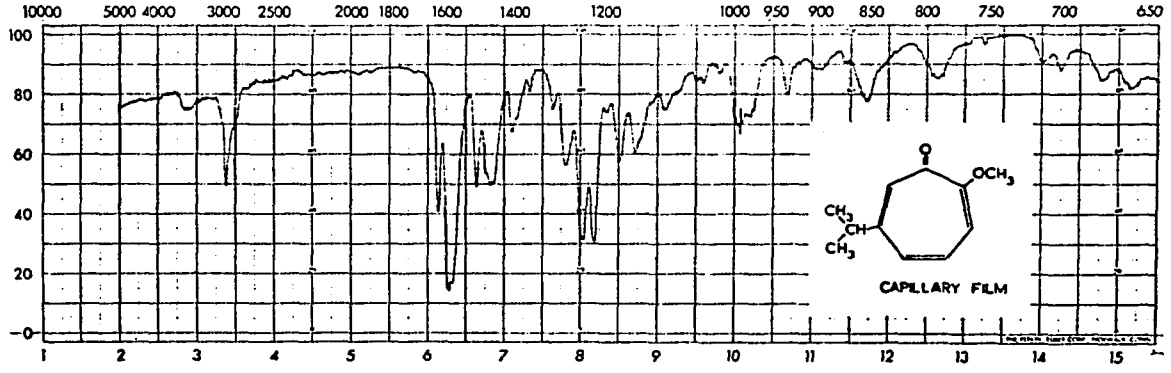
Figure 10. Infrared spectra

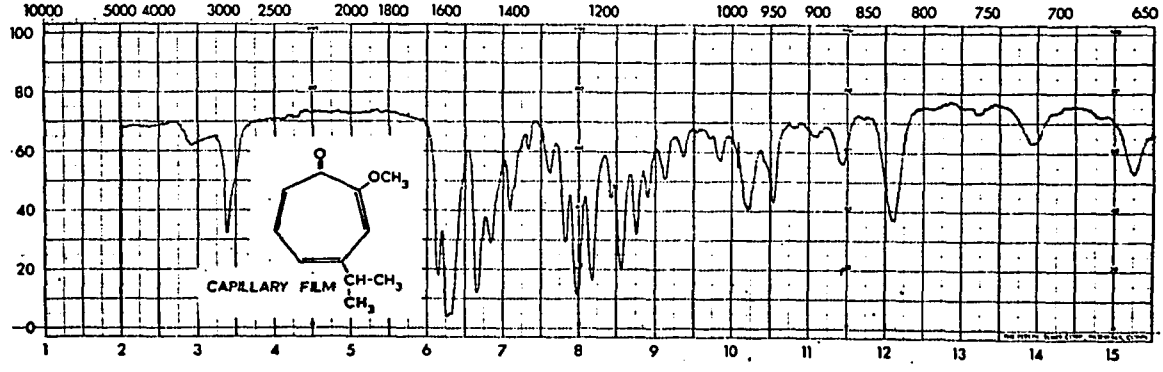
Top - 5-isopropyl-2-methoxytropone (26)

Middle - 6-isopropyl-2-methoxytropone (54)

Bottom - 4-isopropyl-2-methoxytropone (55)


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
OCH3
CH3-CH
CH3
CAPILLARY FILM


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
OCH3
CH3
CH
CH3
CAPILLARY FILM


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
OCH3
CAPILLARY FILM
CH-CH3
CH3

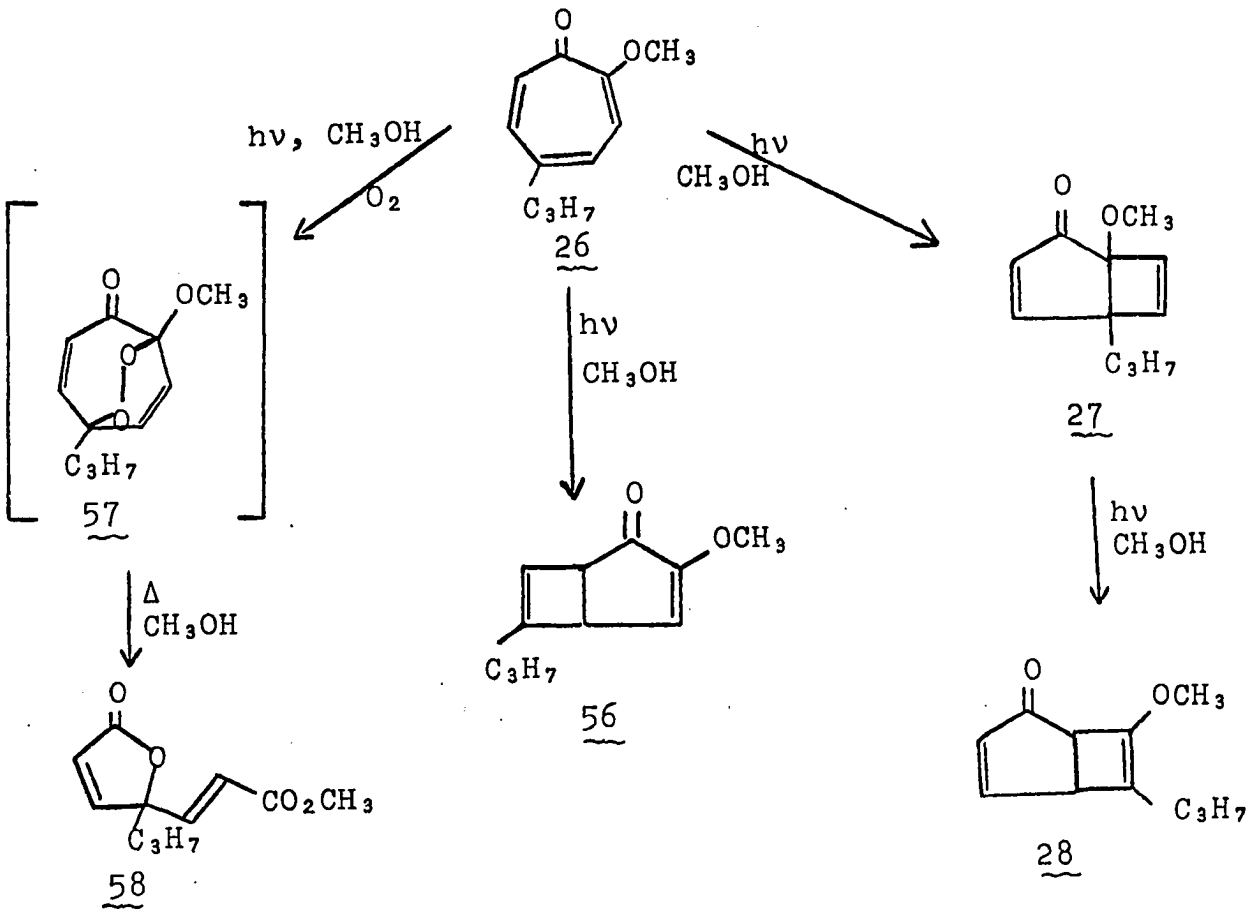
substituent resulting in a further decrease in the activation energy for bridgehead bond rupture.

To optimize the possibility of obtaining 27 in an isolable amount, the first irradiation was conducted under a prepurified nitrogen atmosphere in degassed, anhydrous methanol. The solution was maintained below 15° and the cupric sulfate and Corning 7-37 filter system was used to restrict the irradiation band to the region where the absorptivity of 5-isopropyl-2-methoxytropone (26) should far exceed that of 5-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27). The progress of the irradiation was monitored by vpc and the results are summarized in Table 1.

Table 1. Irradiation of 5-isopropyl-2-methoxytropone (26); change in reaction mixture composition with time

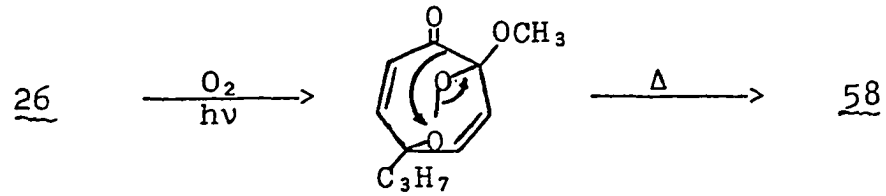
Elapsed Time (hr)	Relative areas of component vpc peaks (% of total)				
	26	27	28	56	Other
0	100	0	0	0	0
19 1/2	92	4.4	0	3.6	0
44	80	11.2	0	8.8	0
66 1/2	69	17	trace	14	0
85 1/3	61	20	0.7	18	0
136 3/4	33	31	3	33	0
158 3/4	25	36	5	34	0
181 1/2	12	38	7	42	1

Figure 11. Photochemical transformations of 5-isopropyl-2-methoxytropone (26)


hν, CH3OH
O2
hν
CH3OH
hν
CH3OH
Δ
CH3OH
hν
CH3OH
OCH3
C3H7
CO2CH3
26
27
28
56
57
58

It was encouraging to observe the formation of two products in roughly equal amounts early in the irradiation. On the basis of Dauben's work it would appear reasonable that one would be 28 and the other, hopefully, would be 27. When a third, then a fourth peak appeared in the chromatogram, the irradiation was terminated. The liquor was concentrated by rotary evaporation and the components separated by preparative vpc. Surprisingly, the secondary product, 28, was the minor product which began forming during the latter third of the irradiation period. One of the initial products was 27, as hoped, but the other was a new isomer, 6-isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (56). This is very significant because 5-isopropyl-2-methoxytropone (26) is thus the only simple, alkyl substituted troponoid which undergoes type C cyclization to an extent equal to type B. It shows that the balance between type B and C cyclization modes is very delicate and would normally favor type B, but that it can be shifted toward type C cyclization by steric impedances as well as by the electronic factors already discussed in the Historical section of this thesis.

In instances where less care was taken to maintain a nitrogen atmosphere over the irradiation solution, still another product, 6-carbomethoxy-4-isopropylhexa-2,5-dien-4-olide (58) was isolated. This was very likely formed by 1,4 addition of oxygen across the 2,5 positions of 26 to give the intermediate, 57, which readily rearranges under the reaction

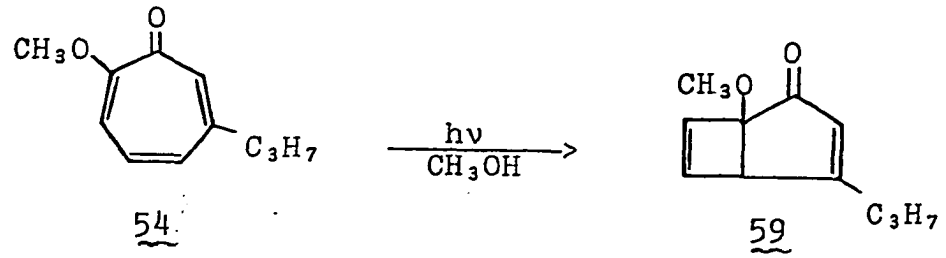


57

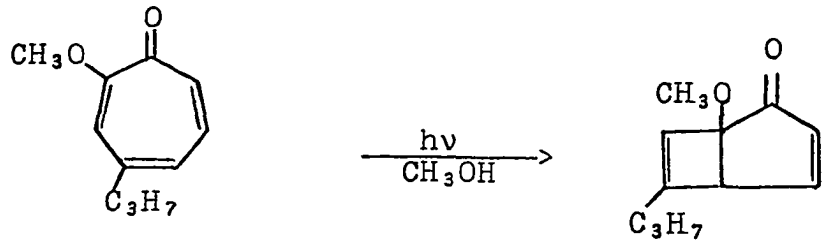
conditions to 58. The mechanism is consistent with the work of Forbes and Griffiths in which analogous products were obtained from tetra-o-methylpurpurogallin,[36] 4',5'-dimethoxy-6,7-benztropolone methyl ether,[37] and 2-methoxytropone[38,39] (6). Singlet oxygen was shown to be the reactive species which adds in a Diels-Alder manner to the tropone ring. In the cases of tetra-o-methylpurpurogallin and 2-methoxytropone (6) the intermediate peroxides were isolated using low temperature techniques and observed to decompose thermally to γ-lactones above 0°.

Photochemistry of 6-isopropyl-2-methoxytropone (54) and 4-isopropyl-2-methoxytropone (55)

The photochemistry of the isomeric products obtained by methylation of β-thujaplicin (53) is completely analogous to that of the parent, 2-methoxytropone (6). Hence the irradiation of 54 or 55 in the manner described for 6 (p 25 et seq.) produced the appropriately substituted 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one, 59 or 60. The retention time of the photoproducts on Carbowax 20 M or diethylene glycol succinate (LAC 728) proved to be sufficiently different (ratio of 1.26:



54 59



55 60

1.00 for 59 to 60) that the mixture of 54 and 55 from the methylation of β-thujaplicin (53) could be irradiated and the photoproducts separated and purified in a single preparative vpc separation.

Characterization of the Photoproducts of the Isopropyl Substituted 2-Methoxytropone Isomers

5-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27)

The nmr spectrum (Figure 12, p 46) of 27 is distinguished by its four vinyl hydrogen doublets resulting from elimination of all but vicinal coupling between the two pairs of vinyl hydrogens by substituents at both bridgehead positions. The hydrogens α(C-3) and β(C-4) to the carbonyl appear at 5.97 and 7.57 ppm, respectively, with a common coupling of 6.2 Hz. The cyclobutene hydrogens are less widely separated, at 6.55 (C-7) and 6.87 ppm (C-6), split by a 2.8 Hz coupling. The methoxyl

Figure 12. Nuclear magnetic resonance spectra

Top - 5-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (27)

Middle - 6-isopropyl-3-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (56)

Bottom - 6-carbomethoxy-4-isopropylhexa-2,5-dien-4-olide (58)

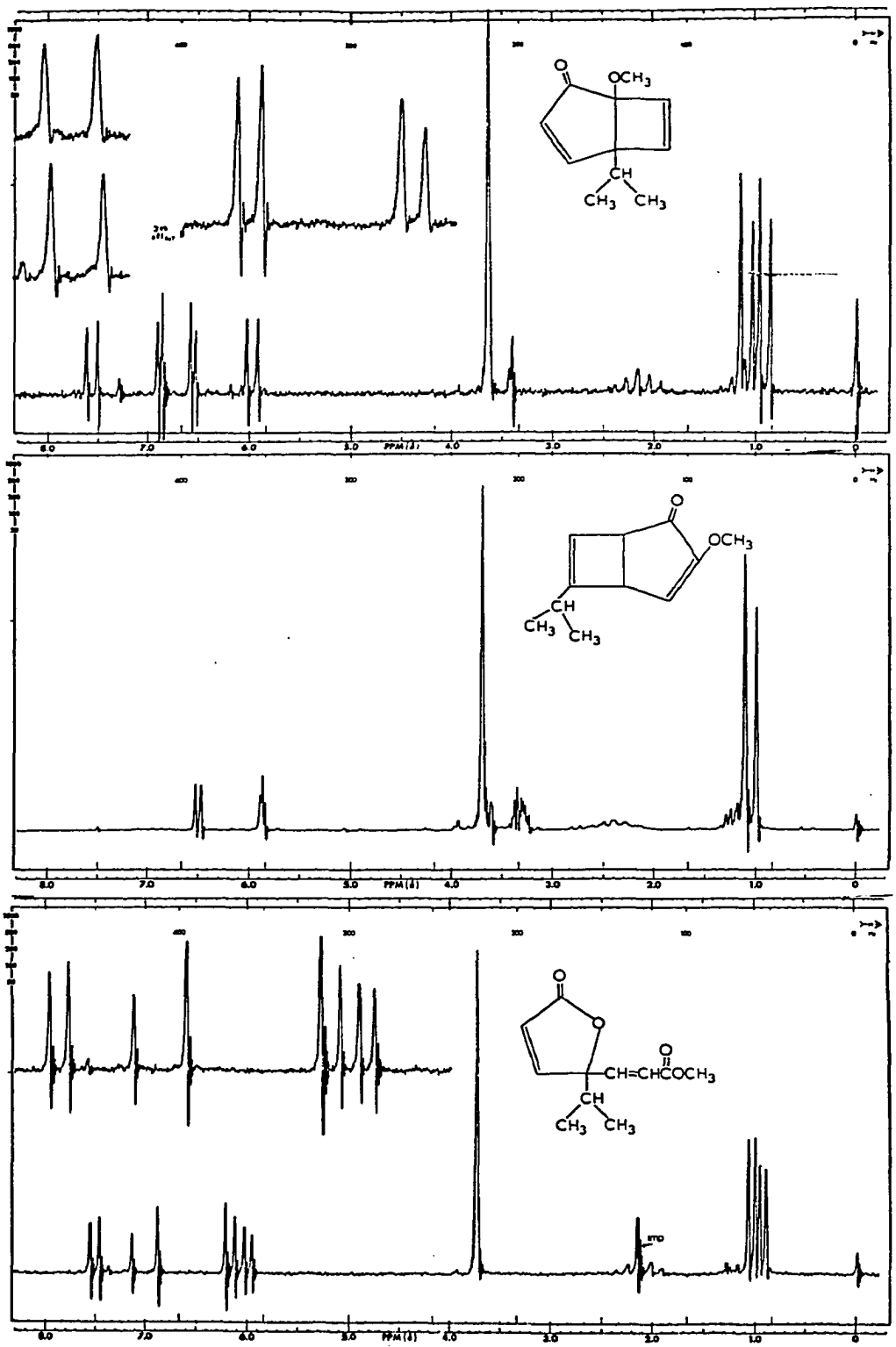
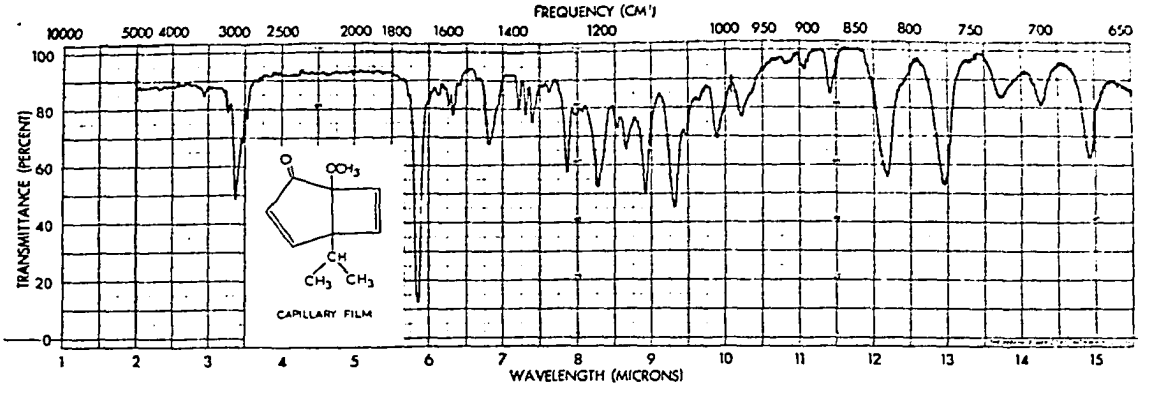

OCH3
CH
CH3 CH3
PPM (δ)
OCH3
CH
CH3 CH3
PPM (δ)
CH=CHCOCH3
CH
CH3 CH3
PPM (δ)

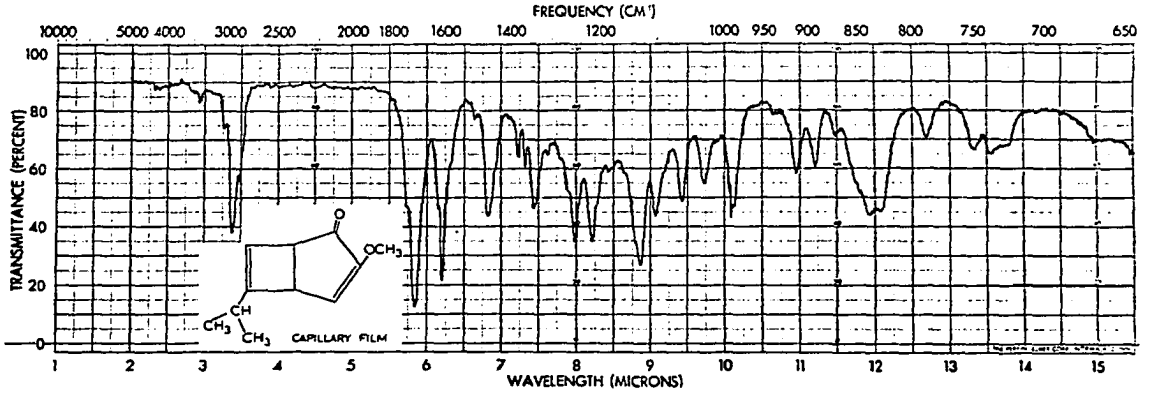
Figure 13. Infrared spectra

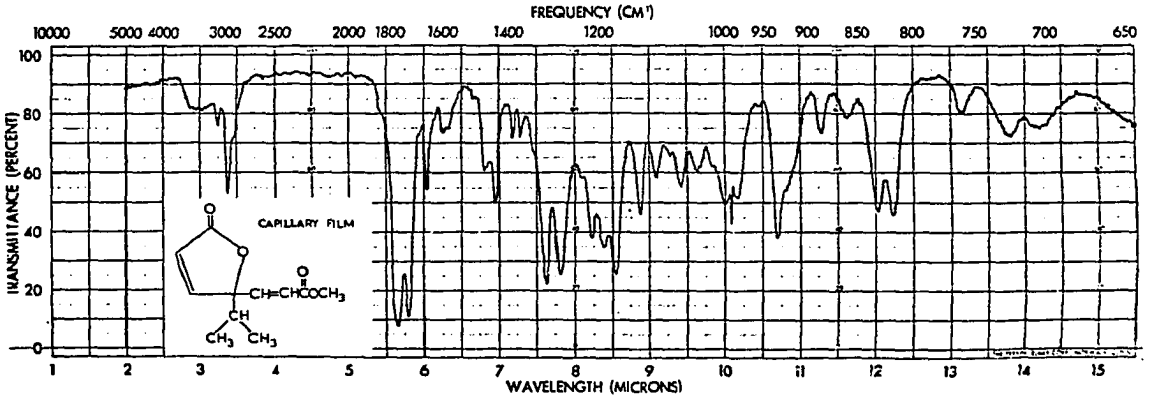
Top - 5-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (27)

Middle - 6-isopropyl-3-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (56)

Bottom - 6-carbomethoxy-4-isopropylhexa-2,5-dien-4-olide (58)


FREQUENCY (CM⁻¹)
10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OCH3
CH
CH3 CH3
CAPILLARY FILM


FREQUENCY (CM⁻¹)
10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OCH3
CH
CH3 CH3
CAPILLARY FILM


FREQUENCY (CM⁻¹)
10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
CAPILLARY FILM
CH=CHCOCH3
CH
CH3 CH3

group singlet is next, at 3.63 ppm. The methyne hydrogen of the isopropyl substituent is at 2.15 ppm, split by a 7.0 Hz coupling to the methyl hydrogens into a heptet, the outer peaks of which are discernable only in concentrated samples. The signals of the geminal methyl groups appear as doublets at 1.08 and 0.90 ppm. An anomalous signal appears at 3.42 ppm in the spectrum, but since the same signal is also present in the nmr spectra of the other two products from this irradiation, 56 and 28, it is likely due to a trace impurity.

The carbonyl absorbance at 1710 cm^{-1} is the dominant peak in the ir spectrum (Figure 13, p 48). Its 30 cm^{-1} shift from the normal cyclopentanone absorbance is evidence for the α,β-double bond, as is the small 1635 cm^{-1} band. The 1580 cm^{-1} absorbance is assigned to the cyclobutene double bond. A strong methyl band is present at 1470 cm^{-1}, and the characteristic gem-dimethyl doublet is at 1388 and 1370 cm^{-1}. The assignment of the ether bands is less clear, but two relatively intense bands are in the specified range, at 1122 and 1075 cm^{-1}.

6-Isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (56)

The coproduct of 27, 6-isopropyl-3-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (56), displays only two vinyl hydrogen signals in its nmr spectrum (Figure 12, p 46) indicating that the other two vinyl positions are substituted. They are also sufficiently separated that their major couplings are to the bridgehead hydrogens. The β-hydrogen (C-4) is shifted upfield

to 6.50 ppm by substitution of the methoxyl group at C-3. It is coupled by 3.2 Hz to the bridgehead hydrogen (C-5) at 3.33 ppm. This hydrogen is perturbed by the other bridgehead hydrogen (C-1) at 3.63 ppm, but the coupling constant was not obtainable since the latter signal is partially obscured by the methoxyl singlet at 3.70 ppm. The C-7 vinyl hydrogen at 5.87 ppm is coupled to both the C-1 hydrogen and the methyne hydrogen of the isopropyl group, as it is an unsymmetrical triplet with a 1.6 Hz splitting. This interaction causes the methyne heptet at 2.40 ppm to have broader peaks, but the pattern is still dominated by the 7 Hz coupling to the hydrogens of the geminal methyl groups. The latter's signal appears as a doublet at 1.05 ppm with several small peaks on its low field side in this spectrum, due to traces of 27.

The ir spectrum (Figure 13, p 48) of 56 differed from that of 27 in several important aspects. Most noticable is a tremendous increase in the intensity of the olefin band at 1612 cm^{-1}, relative to the carbonyl at 1710 cm^{-1}, defining the presence of the enol ether. The number and relative intensity of the bands in the C-O stretch region had also increased, being dominated by the 1128 cm^{-1} band. Other characteristic bands have already been discussed above, and are listed in the Experimental section (p 94).

6-Carbomethoxy-4-isopropylhexa-2,5-dien-4-olide (58)

The final product, 58, of 5-isopropyl-2-methoxytropone

(26) could be obtained in an amount nearly equal to 27 and 56 by simply omitting the nitrogen purge. It displayed one of the most novel 60 MHz nmr spectra (Figure 12, p 46) encountered in this work. Again, there are two pairs of vinyl hydrogens. One of each of these pairs has almost the same resonance position, 6.10 and 6.07 ppm, but their widely different coupling constants result in a nearly evenly spaced four line pattern. The outer two lines belong to the α-hydrogen of the acrylate chain (C-6), and share a 15.5 Hz coupling with the β-hydrogen resonance at 6.98 ppm. The inner two lines are of the α-hydrogen of the lactone (C-2), with a 5.8 Hz coupling to the β-hydrogen at 7.50 ppm. The methoxyl singlet stands alone at 3.73 ppm, and the methyne heptet appears at 2.12 ppm, coupled by a value of 7 Hz to the methyl groups which appear as doublets at 1.00 and 0.93 ppm. The large coupling between the acrylic vinyl hydrogens requires that the bond be trans substituted, whereas the mechanism of formation predicts a cis double bond. It is likely that the isomerization occurred during the irradiation, since no evidence was obtained for any other possible products.

The strongest bands in the ir spectrum, at 1770 and 1725 cm^{-1}, are due to the lactone and ester carbonyl, respectively. Their α,β double bonds absorb at 1658 and 1600 cm^{-1}. The broad 3450 cm^{-1} band is additional evidence for an α,β-unsaturated ester.[39] The 1440 cm^{-1} methyl band and 1393 and 1382 cm^{-1} gem-dimethyl doublet again are present, as are

several bands characteristic of C-O stretching vibrations, notably the one at 1170 cm^{-1}. A strong band not present in the other two spectra is at 936 cm^{-1} which may be assigned to the trans double bond.

6-Isopropyl-7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (28)

Although this isomer has been reported by Dauben[14] it is being included because the nmr spectrum is not entirely consistent with the published data. The nmr and ir spectra are in Figure 14 (p 54) and Figure 15 (p 56), respectively. The cyclopentenone structure has two vinyl hydrogens at 7.73 (C-4) and 5.95 ppm (C-3), with a common coupling of 6 Hz. The signal of the former is a quartet due to a second 2 Hz coupling to the C-5 bridgehead hydrogen at 3.47 ppm. This signal should also be a quartet, since the other bridgehead hydrogen at 3.18 ppm is a doublet (J=5 Hz), but it is obscured by the ubiquitous impurity previously mentioned and a possible trace of methanol so that its multiplicity cannot be clearly determined. The remaining signals are assigned to the methoxyl group, 3.67 ppm, and the isopropyl group, 2.50 (methyne) and 1.03 ppm (gem-dimethyl) (J=7 Hz).

The 1700 cm^{-1} carbonyl band dominates the infrared spectrum and is followed by the 1577 cm^{-1} cyclobutene absorption. The bands characteristic of the methyl (1455 cm^{-1}), gem-dimethyl (1382 and 1360 cm^{-1}), and ether (1289 and 1252 cm^{-1} groups are also present.

Figure 14. Nuclear magnetic resonance spectra

Top - 6-isopropyl-7-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (28)

Middle - 4-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (59)

Bottom - 6-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (60)

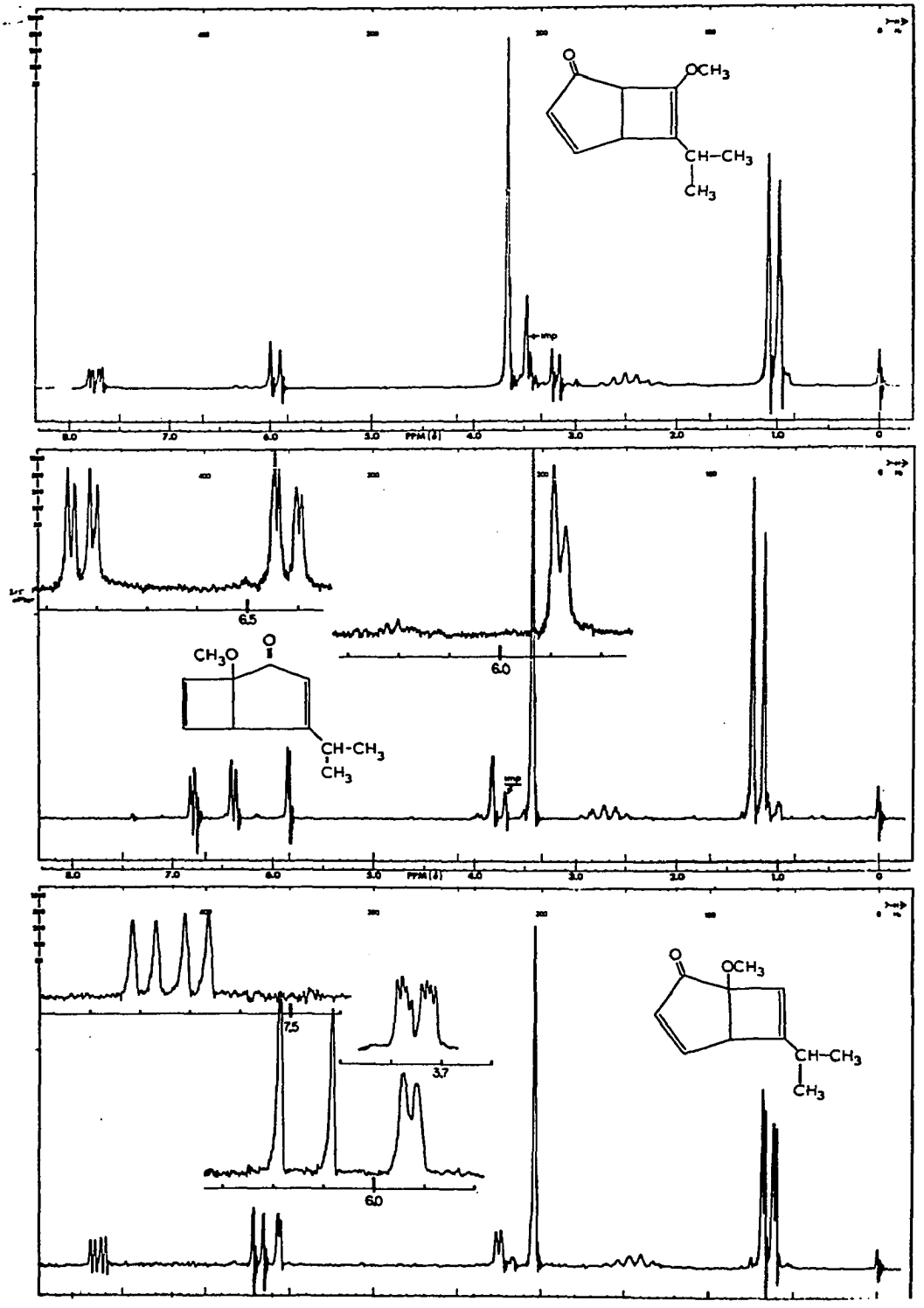
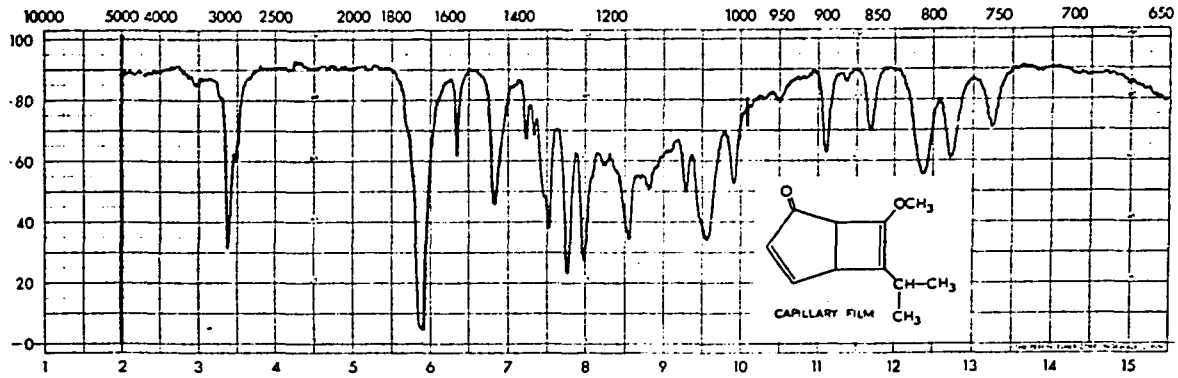

O
OCH3
CH-CH3
CH3
TMS
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
6.5
6.0
CH3O
O
CH-CH3
CH3
7.5
3.7
6.0
OCH3
CH-CH3
CH3

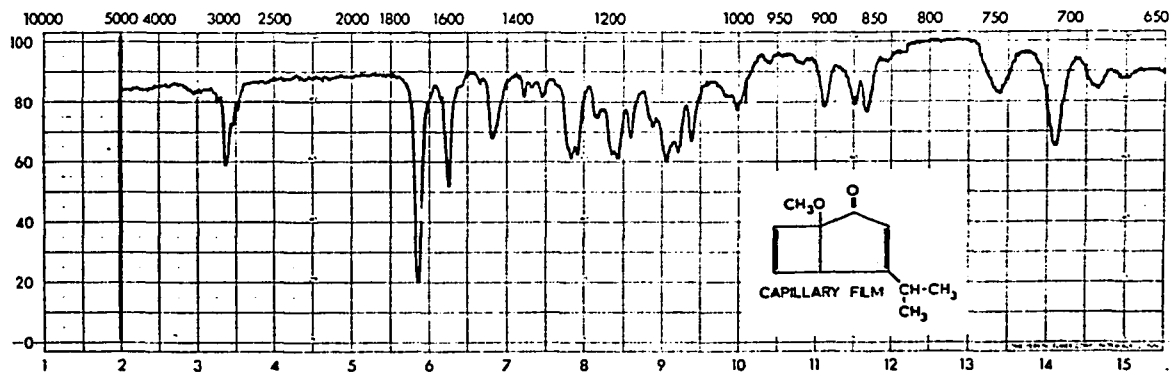
Figure 15. Infrared spectra

Top - 6-isopropyl-7-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (28)

Middle - 4-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (59)

Bottom - 6-isopropyl-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (60)


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
O
OCH3
CH–CH3
CH3
CAPILLARY FILM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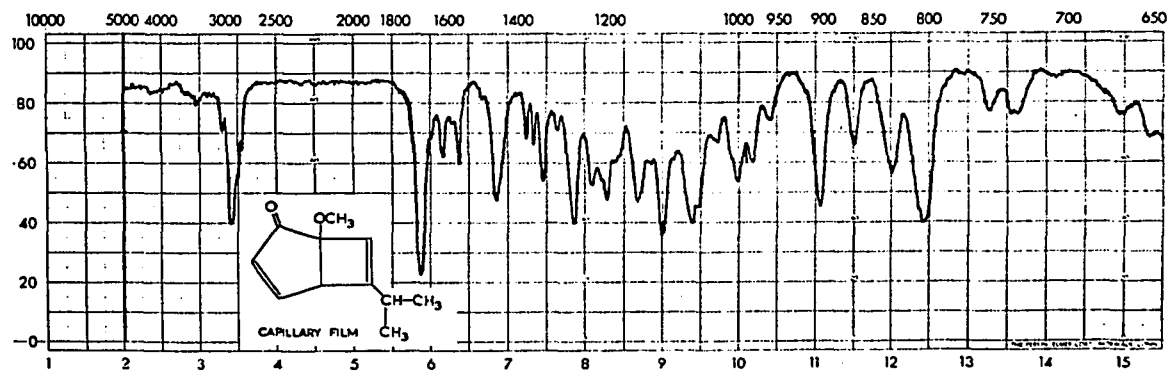
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CH3O
O
CAPILLARY FILM
CH-CH3
CH3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100 80 60 40 20 0
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O
OCH3
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CAPILLARY FILM
CH3

4-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (59)

Since 6-isopropyl-2-methoxytropone (54) was the major product from methylation of β-thujaplicin (53), 4-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (59) was more readily obtainable in workable quantity than its 6-isopropyl isomer (60). A brief outline of spectral data for 59 has been published[29] which supports the assignments. The nmr and ir spectra are included for reference (Figure 14, p 54, and Figure 15, p 56, respectively).

Several difficultly traceable splittings appear in the nmr signals of the vinyl hydrogens of 59. The cyclobutene hydrogens at 6.78 (C-6) and 6.38 ppm (C-7) are coupled by 2.6 Hz, but each is further split, by 0.9 and 0.6 Hz respectively, consistent with a small coupling to the bridgehead hydrogen at 3.82 ppm (C-5). The latter signal is a broad singlet adjacent to the methoxyl singlet at 3.43 ppm. The lone cyclopentenone hydrogen gives a peculiarly shaped doublet, likely caused by coupling to the methine hydrogen of the isopropyl group at 2.72 ppm. This 1.6 Hz coupling is not very distinct in the latter signal because the 7 Hz coupling to the methyl hydrogens results in a low intensity, broad heptet. The gem-dimethyl group gives a clean doublet at 1.18 ppm although its base is cluttered by a trace of the pyrolysis product of 59 which is also responsible for the singlet at 3.70 ppm.

The infrared spectrum has relatively few intense peaks. The carbonyl is in the normal position for a cyclopentenone,

1708 cm^{-1} and β-substitution obviously enhances the Δ^3 double bond absorption at 1600 cm^{-1}. This region is quite analogous to the 1800-1500 cm^{-1} region in the spectrum of 4-methyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one.[40] The 1470 cm^{-1} methyl band is prominent, and the gem-dimethyl doublet is discernable at 1385 and 1340 cm^{-1}.

6-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60)

The characteristic quartet-doublet pattern of the cyclopentenone hydrogens is readily recognizable at 7.70 and 6.13 ppm in the nmr spectrum (Figure 14, p 54) of the less abundant isomer, 6-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60). The common coupling constant is 6.4 Hz and the C-4 hydrogen is further coupled by 2.8 Hz to the C-5 bridgehead hydrogen at 3.73 ppm. This hydrogen has an eight line signal dominated by the 2.8 Hz splitting, to give it the appearance of a doublet of quartets. The assignment of the other spacings has not been worked out. The principal splitting, 1.5 Hz, of the cyclobutene hydrogen (C-6) at 5.93 ppm is due to an allylic coupling to the methine hydrogen of the isopropyl group, whose broad multiplet is centered at 2.43 ppm. The methoxyl singlet falls at 3.60 ppm and the gem dimethyl doublets at 1.08 and 1.05 ppm. The 7.0 Hz splitting of the latter is again due to coupling to the methine hydrogen.

In the infrared spectrum (Figure 15, p 56) the carbonyl band at 1705 cm^{-1} is at nearly the same position as that of its isomer, and the Δ^3 olefin band has returned to 1627 cm^{-1} and is of lower intensity, consistent with its unsubstituted nature. The cyclobutene band is now enhanced by alkyl substitution and

is clearly defined at 1573 cm^{-1}. The characteristic methyl and gem-dimethyl bands are present at 1470, 1382, and 1364 cm^{-1}, respectively.

Pyrolysis of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

As noted earlier, the first indication that 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) rearranged to give a product besides the parent, 2-methoxytropone (6), was obtained from preparative vpc data. To prepare this unreported isomer in quantity sufficient for characterization and to confirm that it resulted from a unimolecular thermal rearrangement, a series of pyrolyses were conducted by passing 1 in an inert solvent through a glass helix packed Pyrex column enclosed in a heating jacket. The apparatus is shown in Figure 16 (p 62).

Characterization of 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2)

The identity of the new isomer was deduced from the nmr (Figure 17, p 64) and ir (Figure 18, p 66) spectra. Its isomeric formula was confirmed by carbon hydrogen analysis. Retention of the bicyclic structure was suggested by the nmr spectrum, but there were now two saturated ring hydrogens and only three vinyl hydrogens, indicating a shift of the methoxyl group. Furthermore, the absence of the very characteristic quartet-doublet pattern of the cyclopentenone hydrogens limits it to one of these two positions. The distinct doublet at 6.42 ppm, coupled to the broad multiplet at 3.55 by 3.5 Hz, is assigned to the C-4 hydrogen since bridgehead-cyclobutene hydrogen couplings are normally of lower magnitude. The latter signal, then must be due to the C-5 hydrogen, and the

Figure 16. Pyrolysis apparatus

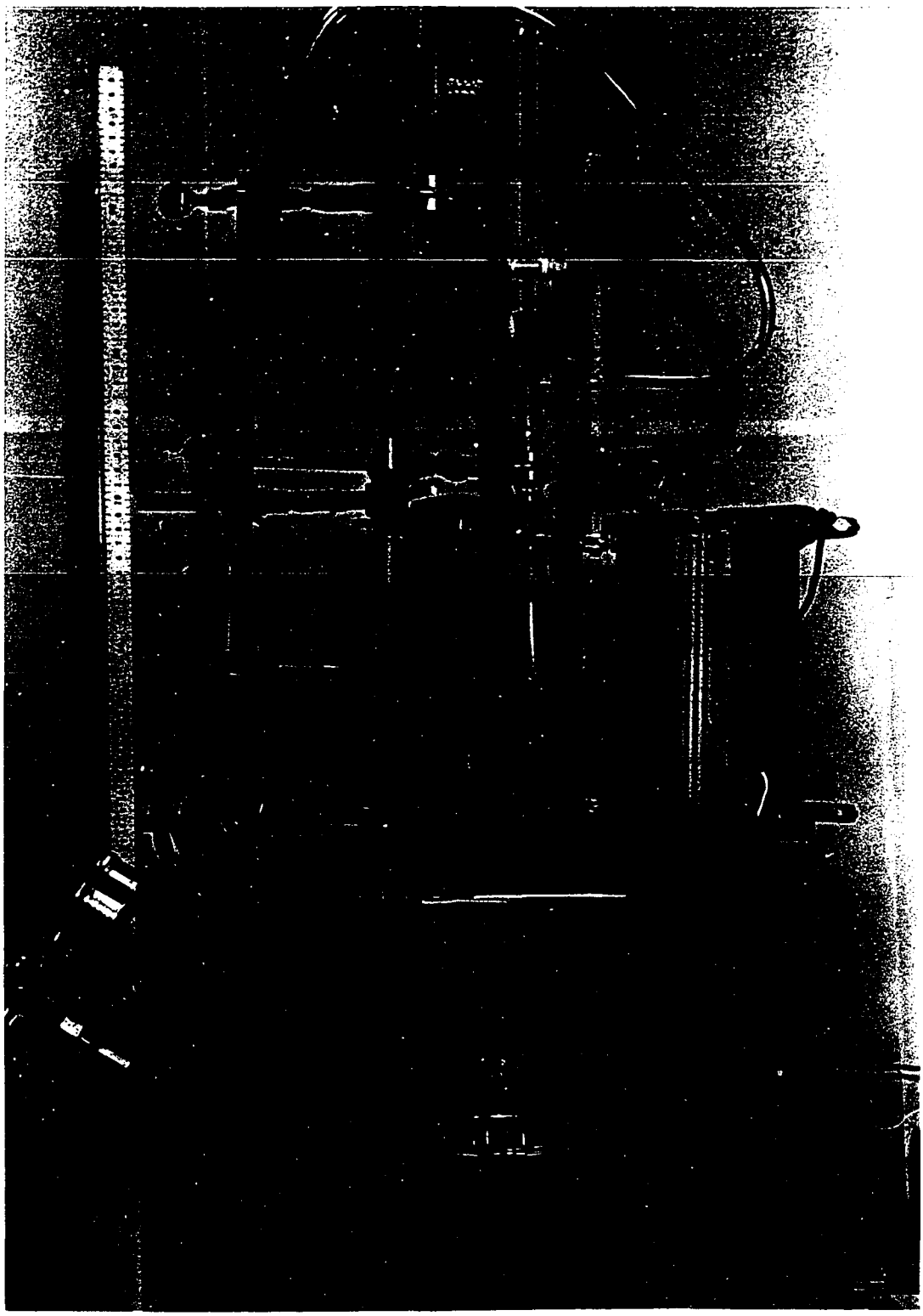


Figure 17. Nuclear magnetic resonance spectra

Top - 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

Middle - 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2)

Bottom - 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48)

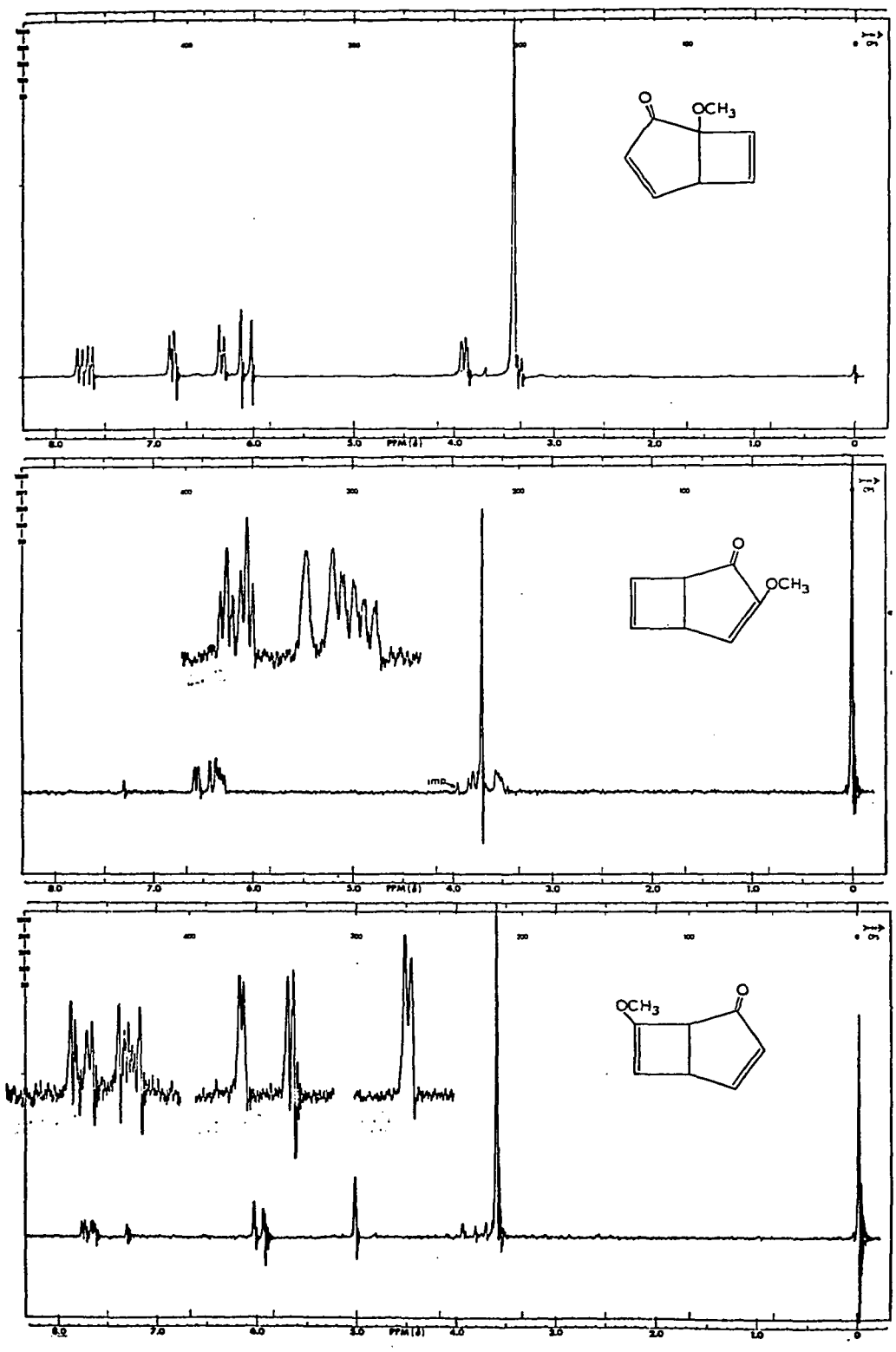
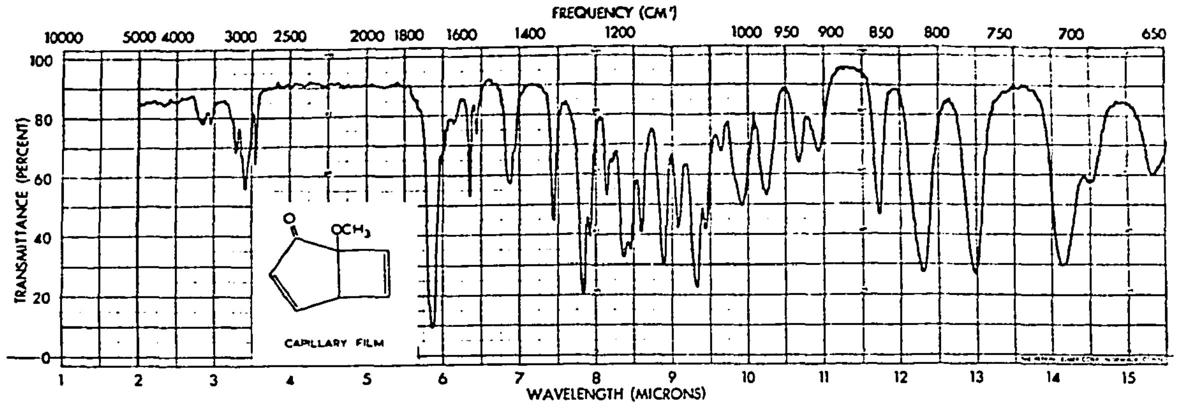

OCH3
OCH3
OCH3
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

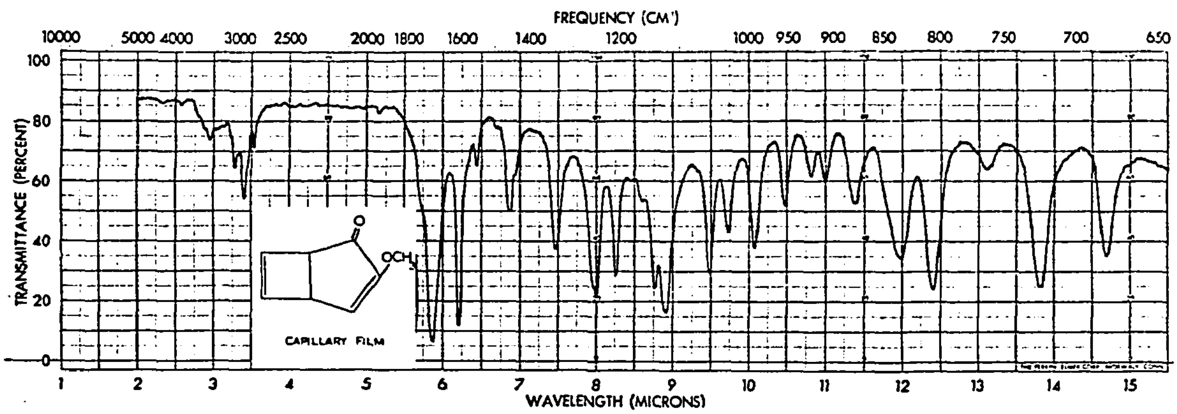
Figure 18. Infrared spectra

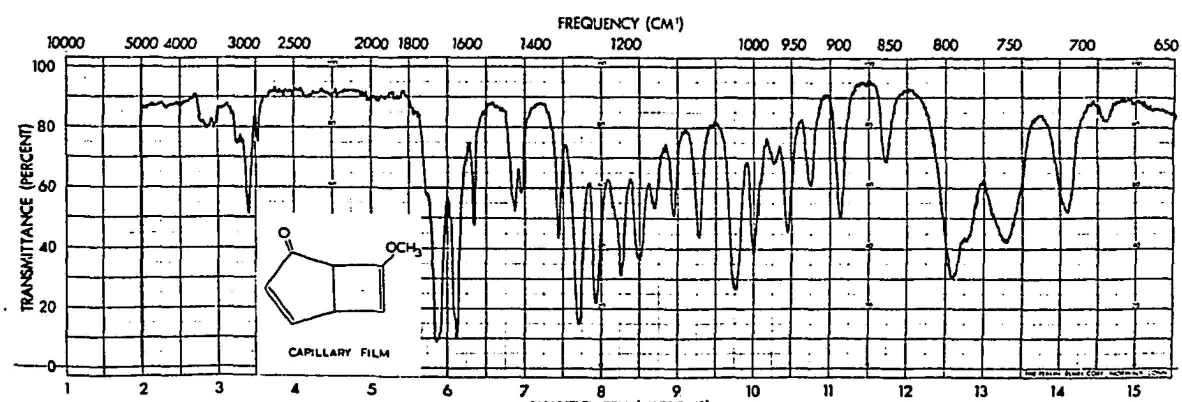
Top - 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

Middle - 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2)

Bottom - 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48)


FREQUENCY (CM⁻¹)
TRANSMITTANCE (PERCENT)
WAVELENGTH (MICRONS)
OCH3
CAPILLARY FILM


FREQUENCY (CM⁻¹)
TRANSMITTANCE (PERCENT)
WAVELENGTH (MICRONS)
OCH3
CAPILLARY FILM


FREQUENCY (CM⁻¹)
TRANSMITTANCE (PERCENT)
WAVELENGTH (MICRONS)
OCH3
CAPILLARY FILM

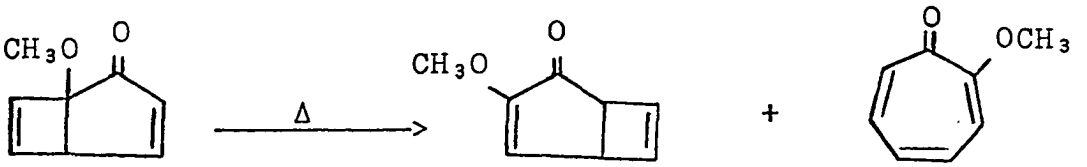
methoxyl group, a singlet at 3.70 ppm, must be at C-3. The other vinyl hydrogen signals at 6.58 and 6.33 ppm share a 2.5 Hz coupling and are assigned to the cyclobutene hydrogens at C-6 and C-7, respectively. The further splitting of these signals is very difficult to assign, since vicinal and allylic coupling to both bridgehead hydrogens is apparent. For the C-6 signal the splittings are of nearly equal magnitude, 0.8 Hz, giving a doublet of triplets. For the C-7 signal a quartet of narrow-doublets is observed, since one of the splittings, only 0.4 Hz, is hardly resolvable, while the other is 1.2 Hz. The final hydrogen, at C-1, is partially obscured by the methoxyl peak, so reliable values for splittings cannot be obtained.

Further evidence is provided by the infrared spectrum. The 1707 cm^{-1} carbonyl band is characteristic of a cyclopentenone and the strong 1610 cm^{-1} band confirms the enol ether. The cyclobutene double bond absorbs weakly at 1555 cm^{-1}. The 1250 cm^{-1} C-O stretch of enol ethers is present, with other bands characteristic of the methoxyl methyl, 1455 and 1340 cm^{-1}.

Temperature dependence of the product distribution

A series of pyrolyses was carried out in benzene to determine the temperature at which the yield of 3-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (2) was greatest so the isopropyl substituted bicyclic dienones could be pyrolyzed under optimum conditions. The product mixtures were analyzed by vapor phase

chromatography. The peak areas of the components, expressed as percentages of the total area, are plotted versus the column temperature in Figure 19 (p 71). The amount of starting material, 1, in the reaction mixture decreased rapidly to zero



1 2 6

over the range 180° to 265°. Both products were formed, but 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) was dominant, reaching its maximum concentration in the pyrolysis at 266°. Its coproduct, 2-methoxytropone (6), became the major product in higher temperature pyrolyses. Product recovery ranged from 82 to 99% at temperatures below 300° but dropped to 52% at 455°, the highest temperature studied. These data are summarized in Table 2 (p 69).

To determine whether 2-methoxytropone (6) originated directly from 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1), or could have formed from 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2), the latter was pyrolyzed at 225° and 300°. At

Table 2. Pyrolysis of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1): temperature dependence of the product distribution

Pyrolysis Temperature (°C)	Sample Weight (mg)	Pyrolysate Recovery (%)	Relative areas[a] of component vpc peaks (% of total) 1	2	6
179-183	132	99	98	2	0
208-209	259	93	39	45	16
233-240	604	87	16	48	36
264-268	3,725	82	0	54	46
273-284	528	82	0	52	48
452-458	350	52	0	9	91

[a] Adjusted for thermal conductivities determined relative to diethyl phthalate.

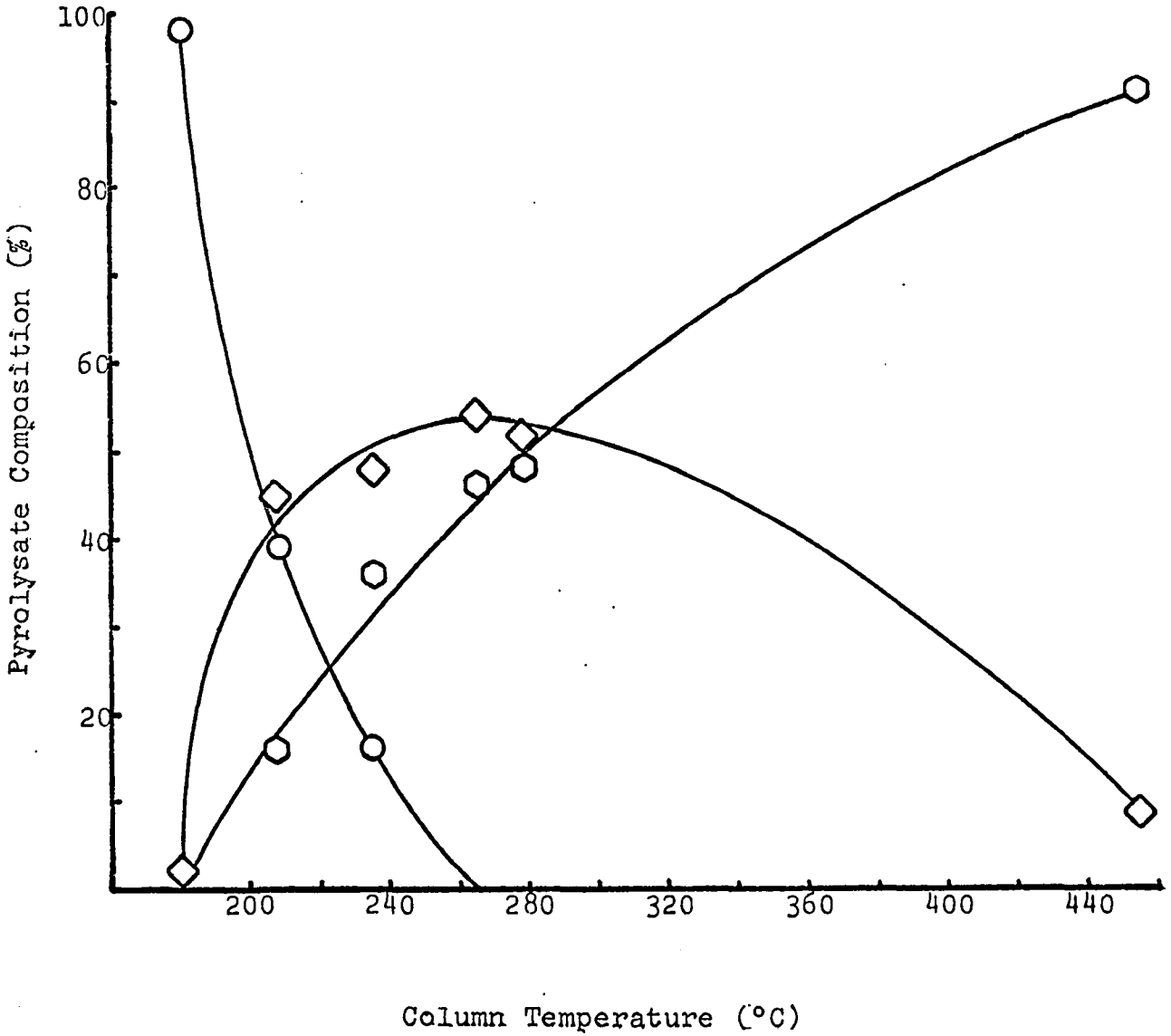
the lower temperature only a trace (4%) of 6 was detected, but at 300° 6 comprised 22% of the mixture, the rest being unreacted 2. The thermal stability of 2 is therefore shown to be considerably greater than 1, perhaps due to the absence of the methoxyl group at the bridgehead position. The amount of 6 formed at lower temperatures must thus come principally from 1. At higher temperatures, particularly above 300°, the secondary decomposition of 2 causes its yield to decrease rapidly.

Figure 19. Pyrolysate composition vs. column temperature

○ = 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

◇ = 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2)

⬡ = 2-methoxytropone (6)

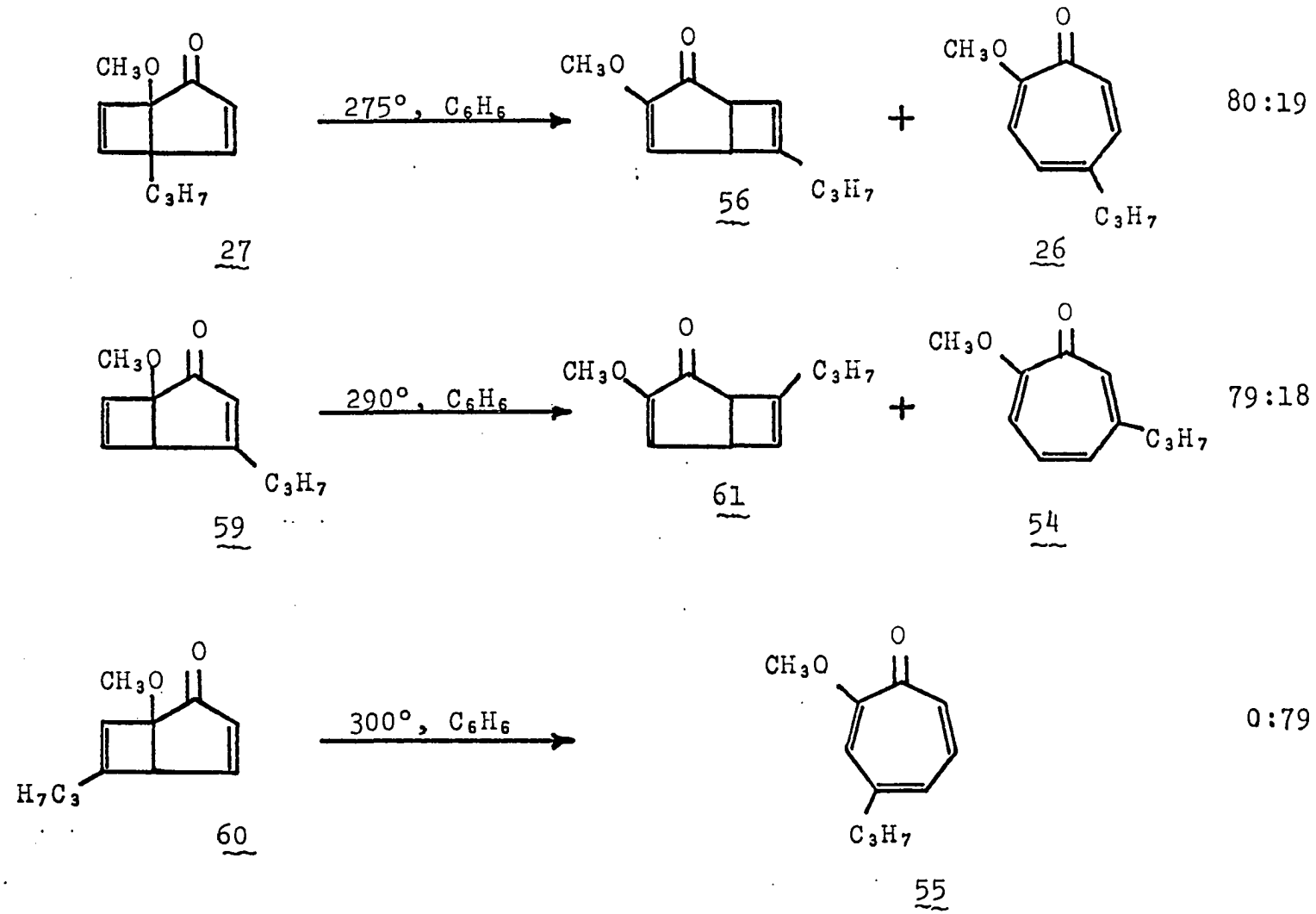

100
80
60
40
20
Pyrolysate Composition (%)
200
240
280
320
360
400
440
Column Temperature (°C)

Pyrolysis of Isopropyl Substituted 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ones (27), (59), and (60)

The three isopropyl substituted 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ones 27, 59, and 60 were pyrolyzed at temperatures in the range which gave a maximum yield of 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) from 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1) by the same procedure. The products, shown in Figure 20 (p 74) were isolated by preparative vapor phase chromatography and identified by comparison of their spectra to spectra of authentic samples. The relative amount of each product is indicated at the end of the equation by the area under its chromatographic peak, expressed as percent of the total area. The starting material was the only other component in the product mixtures.

The spectra of the troponoids, 26, 54, and 55 were easily recognizable, since these were the photochemical precursors to the 1-methoxybicyclic dienone isomers. Similarly, 6-isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (56) had been isolated as a coproduct of (27) in its photochemical preparation and was thus available for comparison. 7-Isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (61) had been independently prepared and characterized by Mukai and coworkers.[29] The spectra of 61, the bicyclic product isolated from the pyrolysis of 59, were in agreement with the published data. Surprisingly, no bicyclic product was isolated from the pyrolysis of 60. Subsequent pyrolyses were carried out on

Figure 20. Thermal rearrangements of isopropyl substituted 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ones

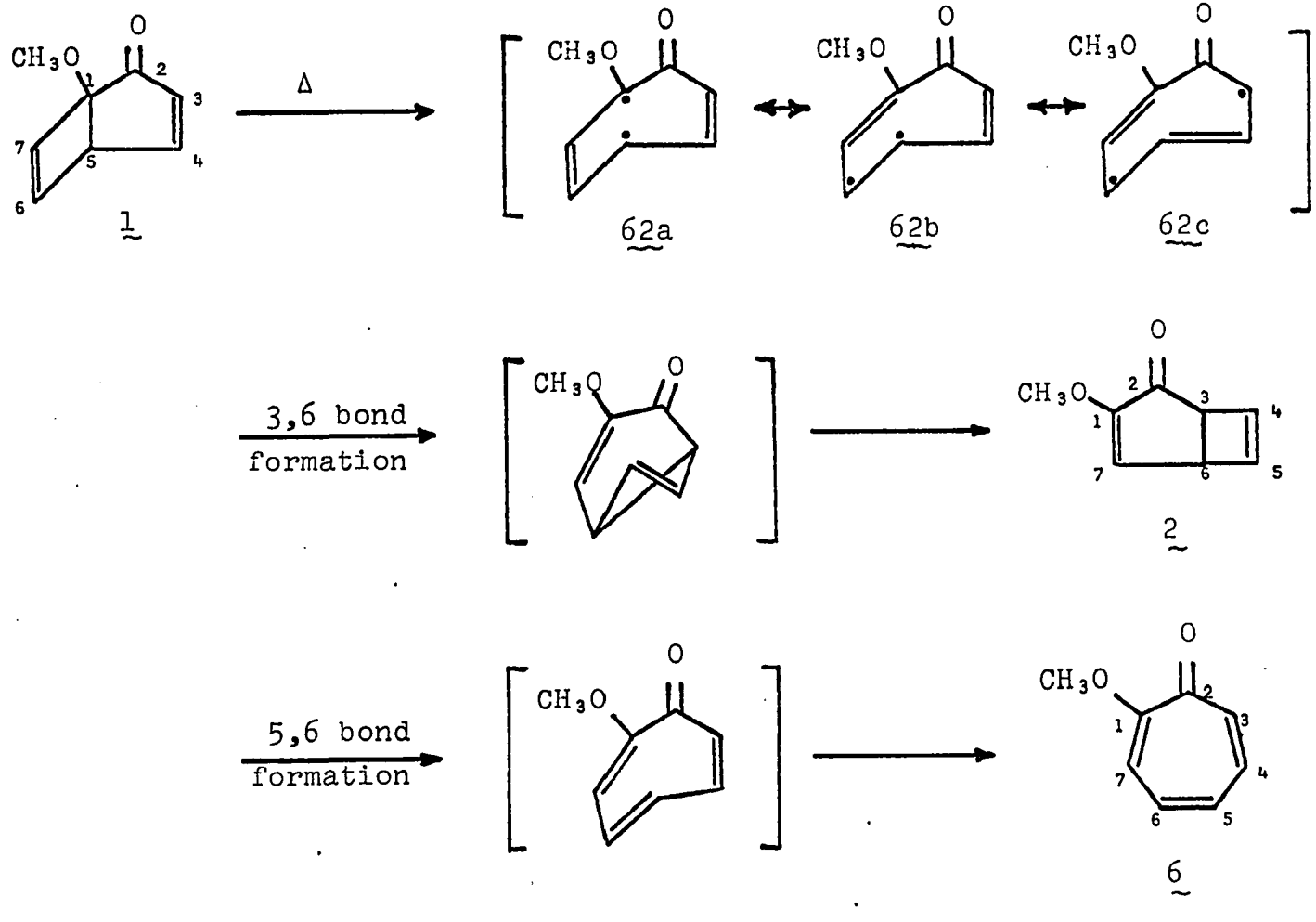

CH3O
O
C3H7
275°, C6H6
56
26
80:19
59
290°, C6H6
61
54
79:18
H7C3
60
300°, C6H6
55
0:79

benzene solutions of 60 in pressure bottles in order to allow longer reaction periods at lower temperatures. No detectable rearrangement occurred in 30 minutes at 180°, so the bottle was immersed in the oil bath at 190-200° for 120 minutes. In this case, 60 rearranged to a slightly greater extent than it had on the Pyrex helices packed column at 300°, and again, the only product was 4-isopropyl-2-methoxytropone (55). It is unlikely that a 3-methoxy bicyclic isomer, if formed, would have escaped detection. Since it should have greater thermal stability than 60, it would have persisted under the milder reaction conditions.

The Mechanism of the Rearrangement of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-one (1) to 3-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2)

The mechanism presented for the reversion of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) to 2-methoxytropone (6) (p 22 et seq.) can be readily adapted to its rearrangement to 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2). This is outlined as Mechanism I in Figure 21 (p 77). Homolytic cleavage of the bridgehead bond produces the biradical intermediate, 62a. The bi-allylic radicals can delocalize, giving resonance structures 62b and 62c. Bond formation between the radical sites of 62c (3,6 bonding) would give the bicyclic product, 2, and between the sites of 62b would give the monocyclic product, 6. Both products are numbered in accordance with the position

Figure 21. Thermal rearrangement of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) to 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2). Mechanism I



1

62a 62b 62c

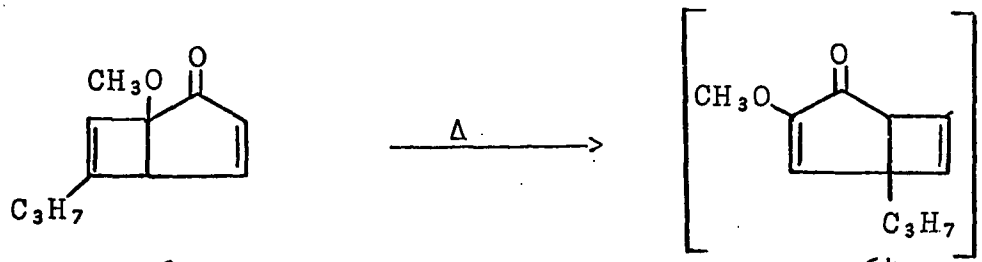
2

6

assignments of the starting material to indicate the movement of ring carbons.

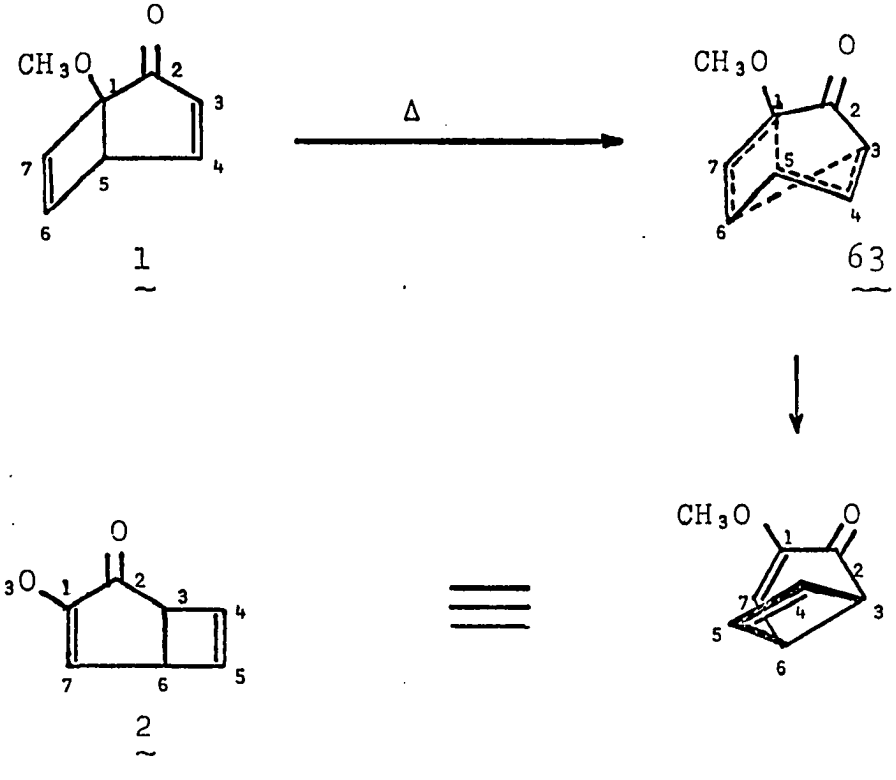
Alternately, a thermally allowed, concerted process is available for the conversion of 1 to 2. This is illustrated as Mechanism II in Figure 22 (p 80). The C-3 and C-6 carbons are termini of a 1,5-hexadiene moiety connected through the bridgehead bond. The rigid bicyclic skeleton holds the olefinic bonds in a nearly ideal geometry for an antarafacial-antarafacial [3,3] sigmatropic shift. As the C-1 and C-5 positions begin to separate, the C-3 and C-6 positions are brought closer together and interact, beginning the formation of a new bond, as represented in structure 63. The double bonds delocalize within the separate allylic halves and reform between the 4,5 and 6,7 positions as the rearrangement progresses. The bicyclic skeleton of 1 is literally turned inside out to yield 2.

Application of either of these mechanisms to the rearrangement of 6-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60) would predict 64 as the structure of the bicyclic product. It is quite conceivable that the isopropyl substi-



60 64

Figure 22. Thermal rearrangement of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) to 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2). Mechanism II


O
CH3O
1
2
3
4
5
6
7
Δ
1
63
2

tuent would interfere sterically with the approach of C-3 position enough to tip the delicate balance in favor of the troponoid product (55). The absence of 64 might therefore provide further support for the 3,6 bond formation required by the mechanisms.

Since both mechanisms are consistent with the observed substituent shifts, distinction between them must be made by analogy. The initial step of Mechanism I, rupture of the bridgehead bond, has also been proposed for the transformation of bicyclo[3.2.0]hepta-dienes, e.g. 1, to their monocyclic photochemical precursors. If the formation of the common biradical intermediate, 62a, were the rate determining step, then it would be expected that ratio of bicyclic to monocyclic products would not show the observed sensitivity to pyrolysis temperature. It is more reasonable that the formation of the separate products be the result of competition between a thermally allowed, concerted process such as Mechanism II to produce the bicyclic product and a less favorable biradical process which yields the monocyclic product. The higher temperatures required for formation of the monocyclic product reflects the necessity of breaking the bridgehead bond as the initial event. It seems unlikely that a sufficiently strong interaction could develop between the C-3 and C-6 positions at such temperatures to prevent the biradical intermediate from unfolding to the monocyclic product. The [3,3] sigmatropic

shift should proceed as the favored process under milder conditions, but due to its strict orbital symmetry requirements is very sensitive to conformational and steric effects. In instances where the conformational conditions are less ideal or steric interferences are present, the concerted rearrangement may not occur under conditions sufficiently milder than those required for the biradical process for it to compete effectively. Hence, as in the case of 6-isopropyl-1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-one (60), it is not formed.

EXPERIMENTAL

Irradiation Apparatus and Procedure

A front and side view of the filter systems are shown in the irradiation chamber in Figure 8, p 31. Also included are a Pyrex bottle (60 mm o.d. x 260 mm) and cylinder (100 mm o.d. x 100 mm) with cooling coils and standard taper 24/40 joint inlet. The cylinder is set up as it would be in an irradiation to illustrate the use of the various water lines, the nitrogen purge, and stirring system. The latter consists of a 1/2" brass rod bored for a 2" Teflon covered magnet bar and tapped to receive the shaft of the Waco motor. The bar and stirrer shaft were secured by set screws.

The filter systems were standard Pyrex irradiation flasks (81 mm o.d. x 350 mm) with water cooled Pyrex immersion wells (51 mm o.d.) to hold the 550 watt Hanovia medium-pressure mercury lamp. A 75 mm square Corning 7-37 filter was suspended even with the lamp, and the remainder of the flask was covered with 1/32" asbestos paper, and the immersion well head covered with aluminum foil to reduce stray light. The 17.5 mm space between the immersion well and flask was filled with a saturated aqueous cupric sulfate solution.

Since the third component of the recommended filter system,[41] an aqueous solution of 2,7-dimethyl-3,6-diazocyclohepta-1,6-diene perchlorate, could not be accommodated in the apparatus, an ultraviolet spectrum was obtained on a model of

the system to determine the width and intensity of its transmission band. The model, consisting of a 30 mm quartz cell of appropriately diluted aqueous cupric sulfate, a 6.0 mm Pyrex disc, and the 5 mm Corning 7-37 filter, had an absorbance value of two or greater beyond a narrow band between 330 and 376 nm, with a maximum transmission of 25% at 362 nm.

The starting material was dissolved in 500 to 700 ml absolute methanol (distilled from magnesium turnings[42]) in the irradiation cylinder and the inlet was sealed with a rubber septum. Oxygen was displaced from the solution by bubbling high purity nitrogen through it with vigorous stirring for approximately an hour before and continuing during the irradiation. Occasionally both filter systems were positioned with the Corning 7-37 filter flush against the cylinder faces, but more often only one was necessary, as shown in the picture.

The progress of the photochemical rearrangement was followed by vpc. A half-milliliter aliquot was concentrated approximately five-fold by rotary evaporation under reduced pressure for the analysis. When the appearance of secondary photoproducts made it necessary to terminate the irradiation, the solvent was removed by rotary evaporation and the residual oil vacuum distilled to separate the starting material from the bicyclic product. In cases where secondary products or several bicyclic isomers were present, the low boiling fraction was further purified by preparative vpc on a Hewlett-

Packard (F & M Scientific Division) Model 776 Prepmaster Jr.. The higher boiling fractions were simply recycled in a subsequent irradiation.

Pyrolysis Apparatus and Procedure

The assembled apparatus is shown in Figure 16, (p 62). The Pyrex column (22 mm o.d. x 255 mm) was packed to a depth of 220 mm with 1/8" Pyrex helices and suspended vertically in the cylindrical oven (core, 32 mm x 200 mm). The inlet was adapted with a female standard taper 19/38 ground glass joint and the outlet with a 12/5 ball joint. Oven temperature was empirically correlated with settings on a Variac with overnight equilibration and measured by an iron-constantan thermocouple positioned midway in the column. The e.m.f. was determined on a Leeds-Northrup potentiometer, just visible at the lower right corner of the picture.

The pyrolysis solution (5-10 ml) was dropped onto the preheated column from a 10 ml buret over a 15 to 20 minute interval and the vapors were swept by a continuous stream of prepurified nitrogen (flow rate ~ 20 cm^3/min) into a coiled receiver cooled in a salt-ice water bath. Approximately 5 seconds separated the time the solution dropped onto the column and the appearance of condensate in the collection tube.

The oven was opened as soon as the last vapors were swept from the column to permit rapid cooling. When cooled below

the solvent boiling point the column was rinsed with several 50 ml volumes of solvent, which were combined with the condensate and concentrated under reduced pressure (2.3 cm Hg, 60-80° bath temperature) by rotary evaporation. The resultant oil was analyzed by vpc, then purified by short-path vacuum distillation for spectral identification of the components.

Methylation of Tropolone (2-Hydroxy-2,4,6-cycloheptatrienone)

Commercially available tropolone (Aldrich Chemical Company) was purified by recrystallization from hexane to give 80% recovery of pale yellow needles: mp 50.5-51.5°, lit.[43] 50-51°. Diazomethane was prepared from p-tolylsulphonylmethylnitrosamide by procedures adapted from Vogel.[44] The precursor is commercially available as Diazald (Aldrich Chemical Company) or may be readily synthesized.[45] Extreme care was taken while working with diazomethane, as it is shock sensitive and highly toxic (threshold limit in air, 0.2 ppm[46]).

The diazomethane generator consisted of a 500 ml separatory funnel with a Teflon stopcock, a 250 ml Florence distilling flask with a Claisen side arm, a West condenser, and 105° adapter. The drip tip of the adapter had been extended to reach the liquid level in the 500 ml Erlenmeyer flask, used as receiver and reaction flask, to minimize escape of diazomethane. As a further precaution, the vent from the reaction flask was

connected directly to a Dry-Ice packed Dewar condenser which was vented into an aqueous formic acid solution. A Corning magnetic stirring hot plate served the dual purpose of agitating the distilling flask liquors and maintaining the water bath at 65°. An air-driven magnetic stirrer (G. Frederick Smith Chemical Company, Columbus, Ohio) taped to the reaction flask provided ample stirring with the flask immersed in an ice-methanol bath (-10°). All glassware was periodically annealed to guard against cracks or scratches and ground glass joints were strictly avoided.

Typically, the reaction flask was charged with 5-30 g of tropolone in 200 ml ether. The addition funnel and distilling flask were charged with an ethereal Diazald solution and alcoholic potassium hydroxide in specified ratios[44] in an amount necessary to produce a 10% molar excess of diazomethane, relative to tropolone. The Diazald was added to the potassium hydroxide solution over a 2-4 hour interval, depending upon the amount, to maintain a slow rate of distillation of diazomethane into the reaction flask and avoid any significant accumulation. Upon completion of the addition, the generator was rinsed with ether until the distillate was completely free of the yellow color characteristic of diazomethane. The reaction liquors were allowed to warm to room temperature overnight. Excess diazomethane was then distilled from the reaction liquor and destroyed in aqueous formic acid.

The reddish-orange oil obtained by rotary evaporation of the solvent was 95% (vpc) 2-methoxytropone (6). Vacuum distillation through a Kontes short-path distillation assembly gave a pale yellow, viscous oil, bp 93-95° (0.05 torr), which solidified upon standing into broad needles, 99% pure by vapor phase chromatography: mp 34-39°. This was sufficiently pure for preparative purposes. The yields varied from 75-98% with the greatest loss occurring during the distillation. This could be minimized by rapid distillation at as low temperature and pressure as possible, with a slow nitrogen purge. Recrystallization from ether produced white needles: mp 39.8-40.5°, lit.[47] 41°.

Separation of Isomeric Thujaplicins

A sample of mixed thujaplicin isomers (75 g) (Crown Zellerbach Co., Chemical Products Division, Camas, Washington) was vacuum distilled (0.1-0.6 torr) over a 16 hour period on a 1 meter Nester-Faust spinning band column. The low boiling fractions (52°-65°) were recrystallized from pentane at -25° yielding 15.5 g α-thujaplicin as colorless prisms: mp 29.0-30.5°, lit.[48] 32-24°. Recrystallization of intermediate fractions (65-72°) from 1:1 mixture of pentane and hexane yielded 12.5 g of colorless prisms of β-thujaplicin (53): mp 46-48°, lit.[48] 47°. A second batch of pale yellow prisms (28 g) was obtained by partial evaporation of the solvent and refrigeration (-25°) of the liquors: mp 36-44°. Overnight

refrigeration (15°) of the high boiling fractions (79-85°) resulted in partial solidification of the oil. The solid was collected by vacuum filtration and recrystallized from ether at -25°, affording 3.4 g of γ-thujaplicin (50) as white needles: mp 78-79.5°, lit.[48] 78°. Roughly 10 g of yellow oil comprised of γ-thujaplicin (50) and thujic acid (51) remained which could not be separated (cf p 90).

The three isomers have distinctive nmr spectra. α-Thujaplicin has the most complex vinyl pattern, from 7.65 to 6.70 δ($CDCl_3$). A broadened hydroxyl signal appeared at 9.38 ppm, and the isopropyl group at 3.75 (heptet, 1H) and 1.25 ppm (doublet, 6H). β-Thujaplicin's vinyl pattern is dominated by a singlet at 7.22 ppm, presumably the α-hydrogen, with multiplets above (7.05-6.80 ppm, 1H) and below (7.40-7.25 ppm, 2H) it. The hydroxyl is a sharp singlet at 9.18 ppm and the isopropyl group appears at 2.90 (heptet, 1H) and 1.25 ppm (doublet, 6H). A standard spectrum of γ-thujaplicin is available.[49]

Methylation of Isomeric Thujaplicins

γ-Thujaplicin (50)

γ-Thujaplicin (50) (2.03 g, 12.4 mmole) in ether (50 ml) was treated with diazomethane (0.59 g, 14.0 mmole) generated from p-tolylsulphonylmethylnitrosamide (4.30 g) by procedure "a" of Vogel[44] in the apparatus described under methylation of tropolone (p 86 et seq.) Distillation of excess

diazomethane and concentration of the reaction liquors under reduced pressure produced an amber oil which showed only starting material and a single product peak, area ratios 8:92, respectively, by vapor phase chromatography. Vacuum distillation gave a pale yellow, viscous oil (2.01 g , 91%). The small amount of fore-run was discarded. The product oil, analyzed by vpc, was 97.4% pure 5-isopropyl-2-methoxytropone (26) which was sufficient for preparative purposes. The nmr and ir spectra are available in Figures 9 (p 36) and 10 (p 38) respectively: bp 108-112° (0.05 torr); nmr ($CDCl_3$) δ 7.20 (d, 2H, vinyl), 6.90 (AB, 2H, vinyl), 3.92 (s, 3H, OCH_3), 2.80 (heptet, 1H, $C\underline{H}(CH_3)_2$), and 1.20 (d, 6H, $-CH(C\underline{H}_3)_2$); ir (cap film) 1632, 1588, 1508, 1456, 1247, 1150, 980, and 855 cm^{-1}; uv max (SpectrAR CH_3OH) 363 (ε 4930), 347 (ε 7520), 319 (ε 9490), and 234 nm (ε 24200).

The principal impurity in subsequent samples of γ-thujaplicin (50) was thujic acid (51). Separation of these isomers by distillation was impractical, but it would be an effective method for separating their methylated products. Therefore the mixture was methylated as though it contained only γ-thujaplicin, and the methyl thujate (52) (bp 45° @ 0.05 torr) was separated in the vacuum distillation. It was easily identified by comparing its nmr and ir spectra to those of an authentic sample.[50]

β-Thujaplicin (53)

Commercially available β-thujaplicin (53) (5.0 g, 3.1 mmole) (Aldrich Chemical Company, 99% pure) in ether (100 ml) was treated with diazomethane (1.5 g, 3.5 mmole) generated from p-tolylsulphonylmethylnitrosamide (10.75 g) by the procedure described for tropolone (p 86 et seq.) except that the reaction flask was at room temperature. Vapor phase chromatography analysis of the crude oil confirmed that the reaction had gone to completion, with the product peak areas in the ratio of 48:54, in order of retention time, for 4-isopropyl-2-methoxytropone (55) and 6-isopropyl-2-methoxytropone (54), respectively. Vacuum distillation on a Nester-Faust 12" silvered spinning band column effected very little separation. To obtain pure samples for identification it was necessary to use preparative vpc. Although the reaction was nearly quantitative, the techniques required to separate the isomeric products reduced the combined yield to 1.7 g (31%). Nuclear magnetic resonance and infrared spectra of both isomers are provided in Figures 9 (p 36) and 10 (p 38), respectively. For 6-isopropyl-2-methoxytropone (54): bp 108-110° (0.05 torr); nmr ($CDCl_3$) δ 7.70 (broad sing., 1H, vinyl), 7.13-6.53 (m, 3H, vinyl), 3.93 (s, 3H, OCH_3), 2.80 (heptet, 1H, $-CH(CH_3)_2$), and 1.22 (d., 6H, $-CH(CH_3)_2$); ir (cap film) 1630, 1595 (d), 1506, 1438, 1244, 1223, 989, and 853 cm^{-1}; uv max (SpectrAR CH_3OH) 320 (ε 8230), and 238 nm

(ε 26,270). For 4-isopropyl-2-methoxytropone (55): bp 108-110° (0.05 torr); nmr ($CDCl_3$) δ 7.10 (s, 1H, vinyl), 7.20 (m, 1H, vinyl), 6.83 (m, 1H, vinyl), 6.70 (m, 1H, vinyl) 3.97 (s, 3H, OCH_3), 2.88 (heptet, 1H, $-CH(CH_3)_2$), and 1.28 (d , 6H, $-CH(C\underline{H}_3)_2$); ir (cap film) 1626, 1595 (d), 1500, 1252, 1224, 1169, 980, 948, and 826 cm^{-1}; uv max (SpectrAR CH_3OH) 360 (sh) (ε 6100), 345 (ε 8900), 335 (ε 8,860), and 320 nm (sh) (ε 8240).

Irradiation of 2-Methoxytropone (6)

The apparatus and procedures described earlier in this section (p 83 et seq.) were designed for this system. Typically, 10 to 15 g of 2-methoxytropone (6) was dissolved in 500 ml absolute methanol in the 10.0 x 10.0 Pyrex cylinder and irradiated as shown in Figure 8, p 31 . Due to the low intensity of the filtered ultraviolet light, the irradiation was generally run for several days. It was desirable to continue as long as possible, until the amount of the secondary photoproduct, 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48) exceeded 1% of the mixture, as determined by vpc, to gain maximum conversion (usually greater than 20%). The bicyclic products (bp 48-50°, 0.06 torr) could be easily separated from 2-methoxytropone (6) by vacuum distillation. If the small amount of 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (48) was detrimental to the intended application of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) it was necessary

to separate the isomers by preparative vpc. The recovered 2-methoxytropone (6) was recycled in a subsequent irradiation.

Nuclear magnetic resonance and infrared spectra of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) and its 7-methoxy isomer (48) are shown in Figures 17 (p 64) and 18 (p 66), respectively, and are consistent with published spectra.[11]

Anal. Calc. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.99 for 1.

Irradiation of 5-Isopropyl-2-Methoxytropone (26)

A solution of 5-isopropyl-2-methoxytropone (26) (2.01 g, 11.3 mmole) in absolute methanol (475 ml) was irradiated in the 10.0 x 10.0 cm Pyrex cylinder by the standard procedure (p 83 et seq.). Special care was taken to maintain the solution temperature below 15° by a rapid flow of the cooling water and vigorous stirring, and to keep the system under nitrogen throughout the irradiation period. The irradiation was terminated at 88% conversion because the relative amount of a secondary product appeared to be increasing with a corresponding decrease in the rate of formation of one of the primary products. The kinetic data are summarized in Table 1 (p 39).

It was necessary to use diethylene glycol succinate (LAC 728) (15%) as the liquid phase for the preparative vpc separation since the product with the shortest retention time

rearranged completely if Carbowax 20 M were used. This thermally labile compound was identified as 5-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27) from its spectra: bp 42-44° (0.03 torr); nmr ($CDCl_3$) δ 7.57 (d, 1H, vinyl), 6.87 (d, 1H, vinyl), 6.55 (d, 1H, vinyl), 5.97 (d, 1H, vinyl) 3.63 (s, 3H, OCH_3), 2.15 (heptet, 1H, $-CH(CH_3)_2$), and 1.08 and 0.90 (dd, 6H, $-CH(CH_3)_2$); ir (cap film) 1710, 1635, 1600, 1580, 1470, 1388, 1370, 1272, 1208, 1122, 1075, 822, 772, and 670 cm^{-1}; uv max (SpectrAR CH_3OH) 343 (ε 240) and 227 nm (ε 5,860).

Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.99.

The other primary photoproduct, also the pyrolysis product of 5-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27), was 6-isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (56): bp 45-48° (0.03 torr); nmr ($CDCl_3$) δ 6.50 (d, 1H, vinyl), 5.87 (t, 1H, vinyl), 3.70 (s, 3H, OCH_3), 3.63 (m, 1H), 3.33 (m, 1H), 2.40 (heptet, 1H, $CH(CH_3)_2$), and 1.05 (d, 6H, $CH(CH_3)_2$); ir (cap film) 1710, 1612, 1466, 1383, 1366, 1344, 1253, 1218, 1128, 990, 838 and 828 cm^{-1}; uv max (SpectrAR CH_3OH) 324 (ε 180) 265 (ε 2,000), and 224 nm (ε 4,300).

Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.03; H, 7.92.

If the irradiation were not carefully degassed (as in a subsequent irradiation) a third product, 6-carbomethoxy-4-isopropylhexa-2,5-dien-4-olide (58) was formed in an isolable

amount: nmr ($CDCl_3$) δ 7.50 (d, 1H, vinyl), 6.98 (d, 1H, vinyl), 6.10 (d, 1H, vinyl), 6.07 (d, 1H, vinyl), 3.73 (s, 3H, OCH_3), 2.12 (heptet, 1H, $C\underline{H}(CH_3)_2$), and 1.00 and 0.93 (dd, 6H, $CH(C\underline{H}_3)_2$); ir (cap film) 1770, 1725, 1658, 1600, 1440, 1393, 1382, 1310, 1280, 1170, 936, 832, and 818 cm^{-1};

Anal. Calc. for $C_{11}H_{14}O_2$: C, 62.85; H, 6.71. Found: C, 62.87; H, 6.67.

Nuclear magnetic resonance and infrared spectra of the above products are collected in Figure 12 (p 46) and Figure 13 (p 48), respectively, accompanied by more detailed assignment of peaks. The secondary product, 6-isopropyl-7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (28) was the sole product isolated and identified in a previous report.[14] Its nuclear magnetic resonance and infrared spectra are included in Figure 14 (p 54) and Figure 15 (p 56), respectively, for reference.

Irradiation of 6-Isopropyl-2-methoxytropone (54) and 4-Isopropyl-2-methoxytropone (55)

Pure 6-isopropyl-2-methoxytropone (54) and 4-isopropyl-2-methoxytropone (55) were obtained in such low yield from the preparative vapor phase chromatography separation that purification prior to irradiation was impractical on the synthetic scale desirable. It was more efficient to irradiate the mixture and isolate the isomeric products in a final preparative vpc separation. Thus 18 g of distilled product

oils from the methylation of β-thujaplicin (53) was irradiated in 600 ml abs. methanol in the standard manner (p 83 et seq.) for 110 hours and worked up by distillation and preparative vpc separation of the fractions rich in the bicyclic products. Only 0.7 g was lost as a tarry residue in the distillation, but the losses in the preparative separation were nearly 50%. Again, diethylene glycol succinate (LAC 728) (15%) was used in preference to Carbowax 20 M. The nuclear magnetic resonance and infrared spectra of both isomers are in Figure 14 (p 54) and Figure 15 (p 56), respectively; peak positions are listed below.

For 4-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (59): nmr ($CDCl_3$) δ 6.78 (dd, 1H, vinyl), 6.38 (dd, 1H, vinyl), 5.85 (d, 1H, vinyl), 3.82 (broad s, 1H), 3.42 (s, 3H, OCH_3), 2.72 (heptet, 1H, $C\underline{H}(CH_3)_2$), and 1.18 (d, 6H, $CH(C\underline{H}_3)_2$); ir (cap film) 1708, 1600, 1470, 1386, 1364, 1340, 1270, 1190, 1164, 1105, 1064, 1002, 900, 868, 856, 747, and 708 cm^{-1}; uv max (SpectrAR CH_3OH) 340 (ε 340) and 226 nm (ε 6,500).

Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.97; H, 7.73.

For 6-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60): nmr ($CDCl_3$) δ 7.70 (q, 1H, vinyl), 6.13 (d, 1H, vinyl), 5.93 (broad d, 1H, vinyl), 3.73 (m, 1H), 3.60 (s, 3H, OCH_3), 2.43 (heptet, 1H, $C\underline{H}(CH_3)_2$), and 1.08 and 1.05 (dd,

6H, $CH(C\underline{H}_3)_2$); ir (cap film) 1705, 1627, 1573, 1460, 1380, 1340, 1272, 1208, 1153, 1112, 1065, 1002, 905, 868, 833, 805, 754 and 735 cm^{-1}; uv max (SpectrAR CH_3OH) 348 (ε 260) and 226 nm (ε 5400).

Anal. Calc. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.00; H, 7.87.

Pyrolysis of 1-Methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1)

A series of pyrolyses of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) in benzene was carried out by the procedure already described (p 85 et seq.). The results are tabulated in the Discussion, Figure 19 (p 71) and Table 2 (p 68). The components were isolated from the 264-268° pyrolysis and identified from their spectra. The infrared spectrum of the higher boiling product (bp 93-95° @0.05 torr) was identical to the spectrum of an authentic sample of 2-methoxytropone (6). Nuclear magnetic resonance and infrared spectra of the lower boiling product (bp 49-51° @ 0.05 torr), 3-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (2), are included in Figure 17 (p 64) and Figure 18 (p 66), respectively: nmr ($CDCl_3$) δ 6.58 (dt, 1H, vinyl), 6.42 (broad d, 1H, vinyl), 6.33 (q, 1H, vinyl), 3.80 (m, 1H), 3.70 (s, 3H, OCH_3), and 3.55 (m, 1H); ir (cap film) 1707, 1610, 1555, 1456, 1340, 1248, 1210, 1122, 1055, 992, 834, 806, 724, and 680 cm^{-1}; uv max (SpectrAR CH_3OH) 318 (ε 210), 265 (ε 5500) and 226 nm (ε 4020).

Anal. Calc. for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.36, H, 5.99.

Pyrolysis of 3-Methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (2)

Two samples of 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) (92 and 113 mg), isolated by distillation from the pyrolysis (264-268°, p 69) of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1), were pyrolyzed in benzene (3 ml) by the standard procedure (p 85 et seq.). The first sample (92 mg) was pyrolyzed at 219-232°. The pyrolysate (73 mg, 79%) was 96% starting material (2), 4% 2-methoxytropone (6), based on vpc peak areas, corrected for thermal conductivity differences. The second sample (113 mg) was pyrolyzed at 293-301° with 99% recovery. Analysis of the pyrolysate showed it to be 78% 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) and 22% 2-methoxytropone (6). The identity of the components was confirmed by nuclear magnetic resonance spectroscopy.

Pyrolysis of Isopropyl Substituted 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ones

5-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27)

5-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27) (90 mg) in benzene (5 ml) was pyrolyzed at 269-279° according to standard procedures (p 85 et seq.). Vapor

phase chromatography analysis showed two major product peaks comprising 80% and 19% of the total area. The remaining 1% was attributed to residual starting material. The crude residue (71 mg , 79%) was separated by short path vacuum distillation and the identities of the major product, 6-isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (56), and minor product, 5-isopropyl-2-methoxytropone (26), were determined by comparison of their nuclear magnetic resonance spectra to those of authentic samples available from previous work.

4-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (59)

A solution of 4-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (59) (201 mg) in benzene (5 ml) was pyrolyzed at 285-290° in the standard manner (p 85 et seq.). Vapor phase chromatography analysis of the product mixture (187 mg, 93%, but the sample contained a small silicon grease residue) was complicated by the major product having nearly the same retention time as the starting material. This peak accounted for 79% of the total area. The longer retention product area was 18% of the total. A trace component, amounting to only 3%, with an unusually long retention time was also present, but could not be isolated in sufficient amount for identification. The nuclear magnetic resonance spectrum of the distilled mixture gave evidence for a small amount (<10%) of starting material (59) and monocyclic product, 6-isopropyl-2-

methoxytropone (54) by comparison to spectra of authentic samples. The nmr spectrum of the major product, purified by collection from an analytical scale vpc column (10% diethylene glycol succinate (LAC 728)), was consistent with the published data[29] for 7-isopropyl-3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (61).

6-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60)

6-Isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60) (250 mg) in benzene (6 ml) was pyrolyzed at 295-302° in the standard manner (p 85 et seq.). Only a single product, 4-isopropyl-2-methoxytropone (55), was found in the vpc analysis of the crude residue. The area ratio between the starting material (60) and product (55) was 21 to 79. Component identities were established by comparing the nmr spectrum of the vacuum distilled products to spectra of authentic samples. A second pyrolysis of 6-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (60) (362 mg) in benzene (30 ml), conducted in a sealed Pyrex pressure bottle immersed in a 178-182° oil bath for 30 minutes, did not result in any detectable rearrangement of starting material. The pyrolysis was repeated at 197-203° for 120 minutes, resulting in an 86% conversion of starting material to 6-isopropyl-2-methoxytropone (55), determined from relative vpc peak areas. Component identities were confirmed by nuclear magnetic resonance spectroscopy.

PART II. THE THERMAL REARRANGEMENT OF EXO-1-METHOXYBICYCLO[3.2.0]HEPTA-3,6-DIEN-2-OL

DISCUSSION OF RESULTS

Preparation of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Sodium borohydride is given as the reagent of choice for the reduction of α,β-unsaturated carbonyl compounds to allylic alcohols.[51, 52] Lithium aluminum hydride, a more reactive, less selective reagent, has been reported to also reduce the conjugated double bond.[53,54] However, by avoiding an excess of hydride and by adding it as a slurry to the enone solution (inverse addition) at ice bath temperatures the double bond reduction may be minimized.[55]

Initial experiments with sodium borohydride and lithium aluminum hydride using 2-cyclopentenone as a model for 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) gave results contrary to those expected. Only cyclopentanol and varying amounts of an uncharacterized material which, from its nmr spectrum appeared to be a mixed borate of ethanol (solvent) and cyclopentanol were isolated from the sodium borohydride reduction. The latter product was eliminated by use of glyme in place of ethanol as solvent. In the lithium aluminum hydride reduction, however, the desired product, 2-cyclopentenol, was obtained together with unreacted starting material. No cyclopentanol was detected by vpc. These abnormal results supported by recent developments in this area[56] prompted a brief study of the product distribution of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) as a function of reducing agent. The

results are summarized in Figure 23 (p 105), and the product distributions as a function of reaction conditions are tabulated in Table 3. The difference between the sum of the percentages reported in the table and 100% is comprized of trace impurities, unidentified side products, and, in some cases, unreacted starting material.

The first three reductions were run with aged lithium aluminum hydride (34% active hydride) to determine whether greater selectivity might be obtained from a less reactive reagent. In the fourth reduction a commercially available, standardized lithium aluminum hydride solution in ether was used. 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) was the major product in all cases with 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65) and 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66) being obtained in varying amounts. The latter two compounds could not be separated sufficiently by vpc to obtain accurate integrals, so their areas are combined in the cases where both were present. The relative amount of 66 increased at the expense of 65, based upon nmr signal integrals, with increasing excess hydride.

Although sodium borohydride had been used to successfully reduce a related bicyclo[3.2.0]hepta-3,6-dien-2-one to the allylic alcohol,[57] in the reduction of 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1) the tetrahydro derivative, 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66) was the major product. The minor product, 1,4-dimethoxybicyclo[3.2.0]hept-6-en-2-ol (67),

Figure 23. Hydride reduction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

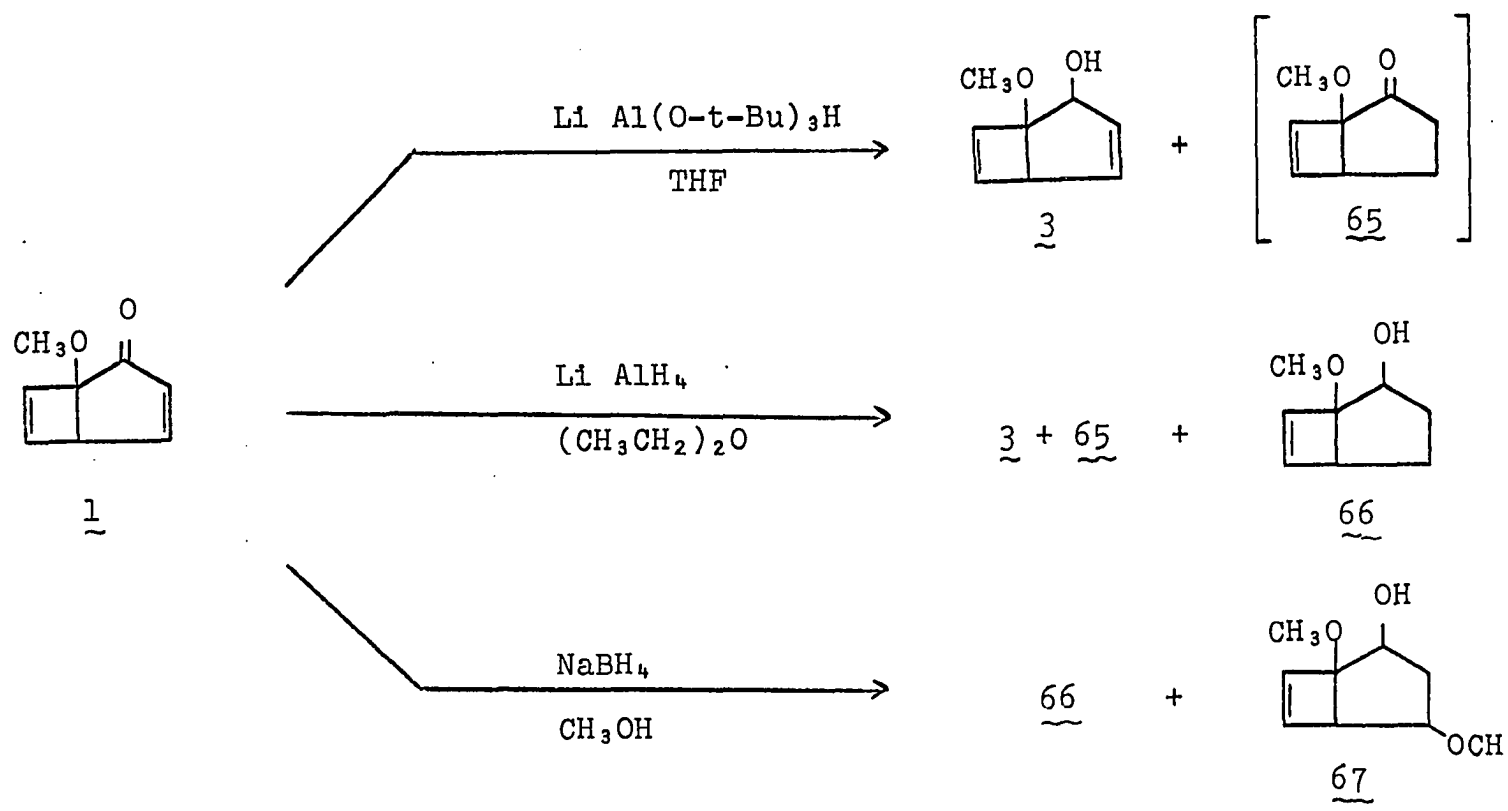

CH3O
O
1
Li Al(O-t-Bu)3H
THF
CH3O
OH
3
+
CH3O
O
65
Li AlH4
(CH3CH2)2O
3 + 65
+
CH3O
OH
66
NaBH4
CH3OH
66
+
CH3O
OH
OCH3
67

Table 3. Reduction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1): product distribution as a function of reaction conditions

Reducing agent and reaction conditions	Overall yield[a], %	Product distribution[b], % 3	65	66
$LiAlH_4$ (6 eq/mole 1)[c] 0.24 M in $(CH_3CH_2)_2O$	80	68	23	
$LiAlH_4$ (4 eq/mole 1)[c] 0.66 M in $(CH_3CH_2)_2O$	47	71	21	
$LiAlH_4$ (3 eq/mole 1)[c,d] 0.16 M in $(CH_3CH_2)_2O$	54	64	17	
$LiAlH_4$ (1.1 eq/mole 1)[e] 0.03 M in $(CH_3CH_2)_2O$	86	75	19	0
$NaBH_4$ (4.5 eq/mole 1)[f] 0.16 M in CH_3OH	68[g]	0	0	64
$LiAl(OC_4H_9)_3H$ (1.0 eq/mole 1)[e] 0.042 M in tetrahydrofuran	76[h]	24	68	0

[a]Represents total weight of oil recovered from reaction/weight of starting material x 100.

[b]Component peak areas as a % of total peak areas; ratios were confirmed by nmr signal integrals.

[c]Equivalence ratio uncorrected; hydride source was aged, only retained 34% active hydride.

[d]Inverse addition, hydride to dienone.

[e]Active hydride >98%.

[f]Activity not determined.

[g]1,4-dimethoxybicyclo[3.2.0]hept-6-en-2-ol comprised 33% of mixture.

[h]Starting material comprised 8% of product mixture.

might represent the amount of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) formed in the reduction which then underwent base catalyzed addition of methanol. Even in this case, lithium aluminum hydride still would be a more suitable reagent for the conversion of 1 to 3. The observed reduction of the conjugated double bond is consistent with current literature reports.[58-60]

The reduction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) with lithium tri-t-butoxyaluminum hydride had been carried out in an independent attempt to synthesize 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65) for irradiation. The results were useful to this work because the major product, (65), was present as a minor product in the lithium aluminum hydride reductions and the availability of a relatively pure sample aided in its detection in the product mixtures. Contrary to earlier reports,[27,56,58,59] the minor product was not the tetrahydro derivative, 66, but rather the allylic alcohol, 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3).

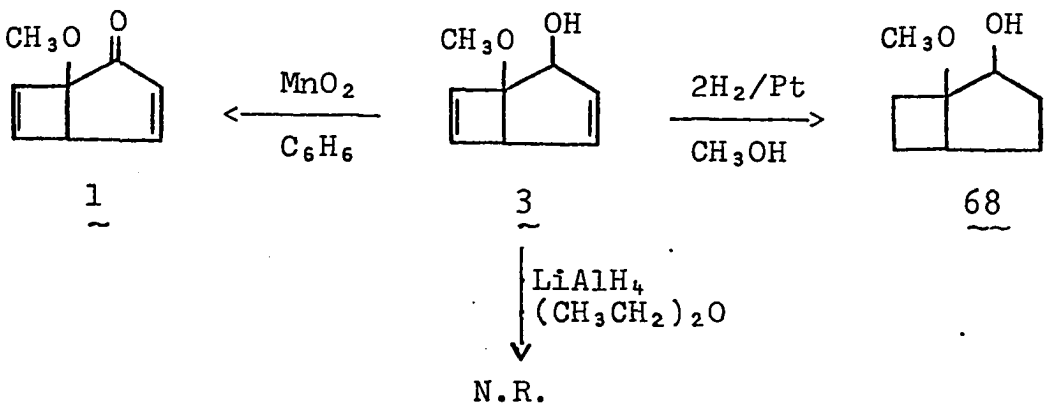
Other reagents, notably aluminum hydride[61] and diisobutylaluminum hydride,[62] have recently been recommended for the preparation of allylic alcohols from conjugated cyclopentenones, but the results obtained in this system with the 3.9 M standardized solution of lithium aluminum hydride were comparable. In retrospect, further improvement might have been obtained by using the 3.9 M solution with the inverse addition technique. However, this technique did not appear to

offer any advantages when it was attempted with lithium aluminum hydride powder, and was therefore not considered to be desirable at the time.

Characterization of the Hydride Reduction Products of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Chemical evidence for the structure of 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-ol (3) is provided by its oxidation to its precursor, 1, and by its uptake of 2.0 moles of hydrogen per mole to give 1-methoxybicyclo[3.2.0]heptan-2-ol (68). It has also been shown to be inert to further reduction by lithium aluminum hydride.



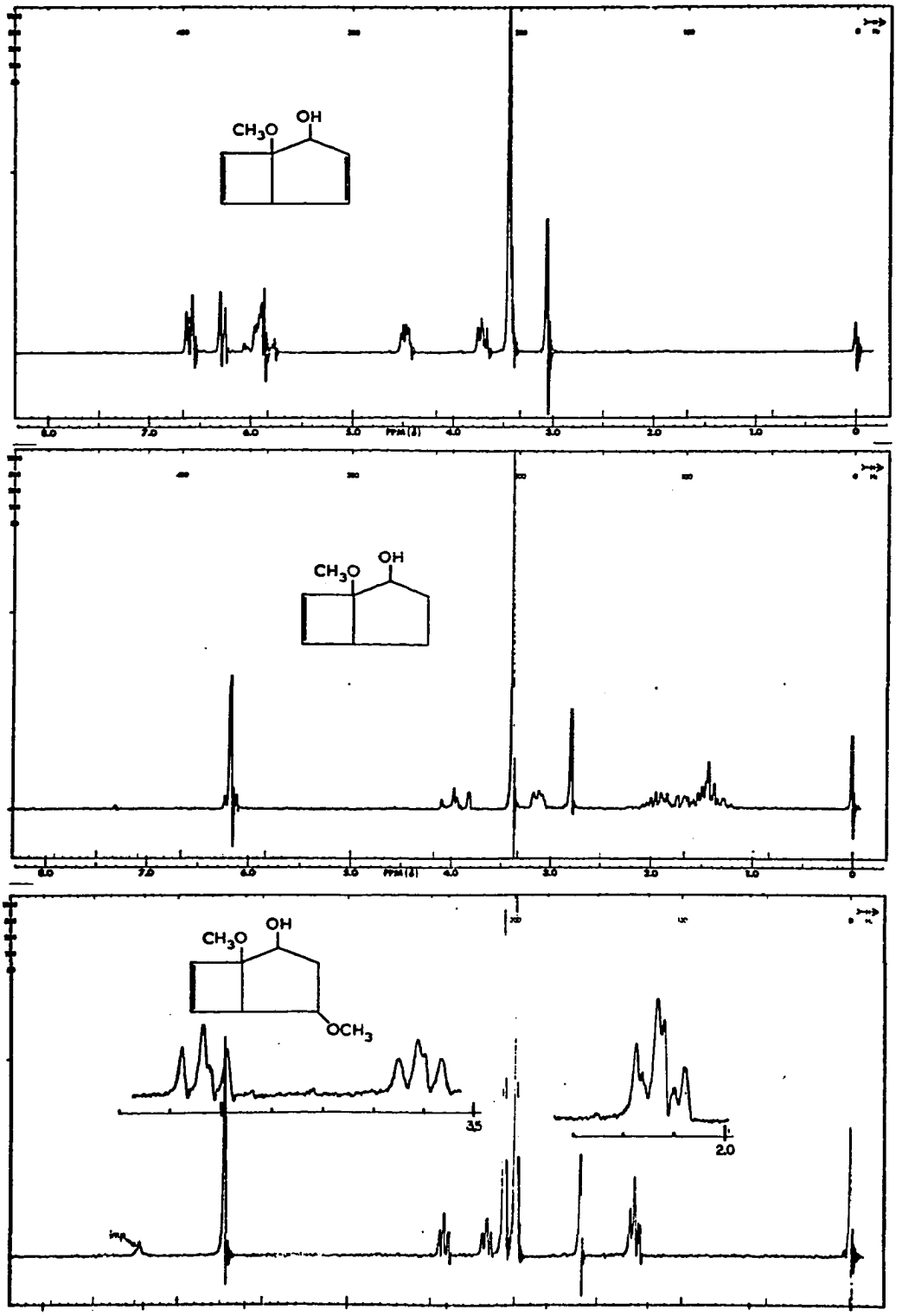
The nmr spectrum (Figure 24, p 110) has four vinyl hydrogen signals at 6.60, 6.28, and a multiplet stretching from 6.07 to 5.73 ppm. The first two signals are clearly due to the cyclobutene hydrogens (C-6 and C-7), and have a common coupling

Figure 24. Nuclear magnetic resonance spectra

Top - 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Middle - 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66)

Bottom - 1,4-dimethoxybicyclo[3.2.0]-hept-6-en-2-ol (67)


CH3O
OH
CH3O
OH
CH3O
OH
OCH3
3.5
2.0

of 3.0 Hz. The multiplet is analogous in pattern and position to that of the vinyl hydrogens in the nmr spectrum of 2-cyclopentenol and is therefore assignable to the hydrogens at C-3 and C-4. By a similar analogy the signal at 4.47 ppm may be assigned to the C-2 hydrogen. The bridgehead hydrogen (C-5) signal is at its characteristic position, 3.72 ppm, just below the methoxyl singlet at 3.46 ppm. The hydroxyl hydrogen signal appears as a ringing singlet at 3.05, but its position can vary over a ± 0.5 ppm range, depending upon concentration, and is frequently under the methoxyl signal. It is also washed out by treatment with deuterium oxide.

The hydroxyl band is very prominent at 3440 cm^{-1} in the infrared spectrum (Figure 25, p 113). Several bands are present which might be assigned to the C-O stretch of the ether and alcohol substituent, notably those at 1120 and 1050 cm^{-1}. The 710 cm^{-1} band is characteristic of a cis-disubstituted double bond.

The mass spectrum of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) presented special problems which will be discussed in a later section (p 147).

1-Methoxybicyclo[3.2.0]hept-6-en-2-one (65)

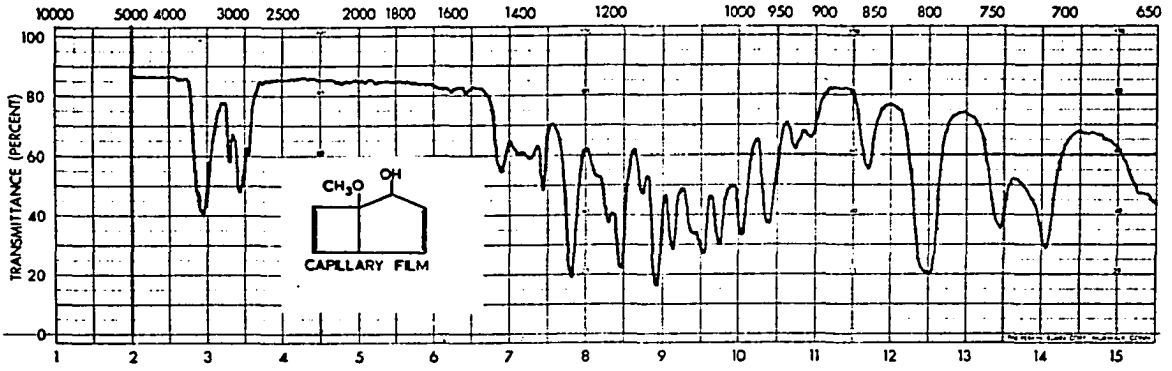
This compound could not be obtained in a state of greater than 90% purity. Therefore, the structural evidence is based on dominant peaks in the nmr and ir spectra after corrections had been made for the peaks attributable to the known impurity.

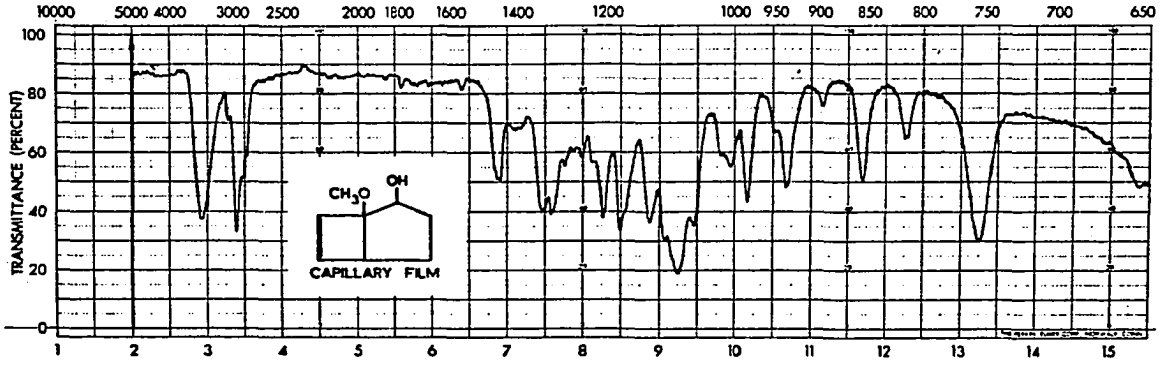
Figure 25. Infrared spectra

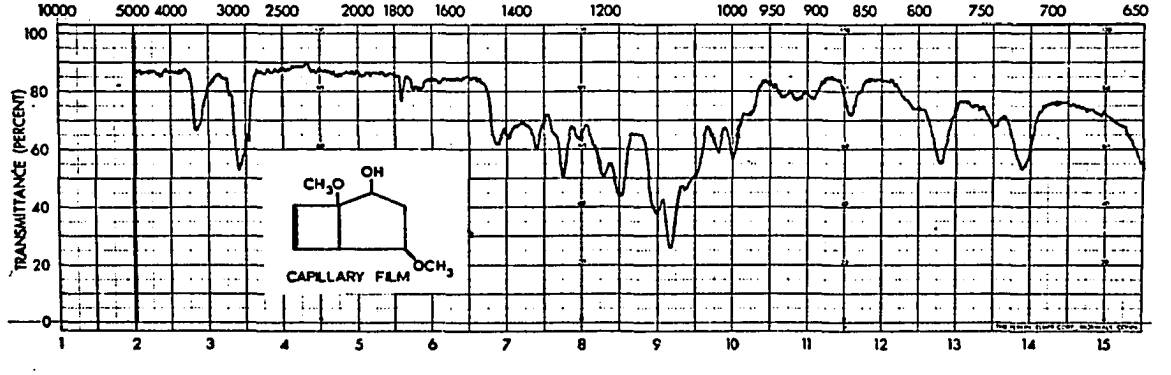
Top - 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Middle - 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66)

Bottom - 1,4-dimethoxybicyclo[3.2.0]-hept-6-en-2-ol (67)


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CH3O
OH
CAPILLARY FILM


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 800 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CH3O
OH
CAPILLARY FILM


10000 5000 4000 3000 2500 2000 1800 1600 1400 1200 1000 950 900 850 600 750 700 650
TRANSMITTANCE (PERCENT)
100 80 60 40 20 0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
CH3O
OH
CAPILLARY FILM
OCH3

The data are provided to serve as a guide for future work and to correlate with the minor product obtained in lithium aluminum hydride reductions.

The strongest evidence for the carbonyl structure was the infrared band at 1740 cm^{-1}, exactly the position for cyclopentanones and too high for acyclic carbonyl compounds or for the starting material (1). Evidence that the cyclobutene ring was intact was given by a distinct pair of characteristic doublets at 6.45 and 6.20 ppm, coupled by 3.0 Hz in the nmr spectrum. The characteristic methoxyl singlet (3.33 ppm) and bridgehead (C-5) hydrogen (3.55 ppm) are present also. The principal change in the nmr spectrum from that of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) was the disappearance of the α,β-unsaturated enone hydrogen signals and the appearance of multiplets at 2.24, 2.10-1.66, and 1.25 ppm, integrating for 1, 2, and 1 hydrogens, respectively, as a result of the reduction of the double bond.

1-Methoxybicyclo[3.2.0]hept-6-en-2-ol (66)

Saturation of the cyclopentenone ring had an interesting effect upon the nmr signal of the cyclobutene hydrogens. In carbon tetrachloride they gave a ringing singlet at 6.13 ppm; in deuterochloroform (the spectrum shown in Figure 24, p 110) the hydrogens become slightly non-equivalent (6.19 and 6.17 ppm) and were coupled by 3.0 Hz. The C-2 hydrogen signal appeared as a multiplet at 3.95 ppm. The saturated hydrogens'

(C-3 and C-4) signals formed a complex pattern from 2.1-1.6 (2H) and 1.6-1.2 (2H) ppm. The bridgehead hydrogen's multiplet was above the methoxyl singlet (3.38 ppm) at 3.13 ppm. The singlet at 2.80 ppm, which can be cancelled by treating the alcohol with deuterium oxide, was assigned to the hydroxyl hydrogen. Its position was concentration dependent and in the spectrum run in carbon tetrachloride the hydroxyl hydrogen signal was under the methoxyl singlet. The spectrum compares favorably with the published nmr spectrum of bicyclo[3.2.0]-hept-6-en-2-ol.[63]

The infrared spectrum, (Figure 25, p 113) gave evidence for the hydroxyl group (3440 cm^{-1}) and cyclobutene double bond (755 cm^{-1}). The major bands in the ether C-O stretch region were 1178 and 1080 cm^{-1}.

The mass spectrum was consistent with a molecular weight of 140 (M^+) and loss of water to give an ion of m/e 122 (M-18).

1,4-Dimethoxybicyclo[3.2.0]hept-6-en-2-ol (67)

The principal evidence for the structure of 1,4-dimethoxy-bicyclo[3.2.0]hept-6-en-2-ol (67) was provided by the nmr spectrum (Figure 24, p 110). The ringing singlet at 6.22 ppm was assigned to the cyclobutene hydrogens, consistent with the assignment in 66. This singlet separates into an AB quartet (J=3 Hz) in the 100 MHz nmr spectrum. A pair of triplets at 4.03 and 3.60 ppm were due to the methine hydrogens at C-2 and C-4, respectively, coupled by 2.4 Hz to the methylene hydrogens

at C-3. The methylene hydrogen's signal was a six line pattern at 2.13 ppm. In the 60 MHz spectrum the bridgehead hydrogen is obscured by the upfield methoxyl singlet (3.32 ppm), but in the 100 MHz it appears as a distinct, broad singlet at 3.28 ppm. The second methoxyl signal (3.43 ppm) is assigned to the hydrogens of the bridgehead (C-1) substituent. The hydroxyl hydrogen, which exchanges with deuterium in heavy water, is assigned to the singlet at 2.68 ppm.

The infrared spectrum (Figure 25, p 113) is fairly similar to the spectrum of 65 in the 1400-1000 cm^{-1} region. The most definitive bands are at 3550 (O-H stretch), 1174 and 1089 (C-O stretch), and 720 cm^{-1} (C-H deformation of cis-olefin).

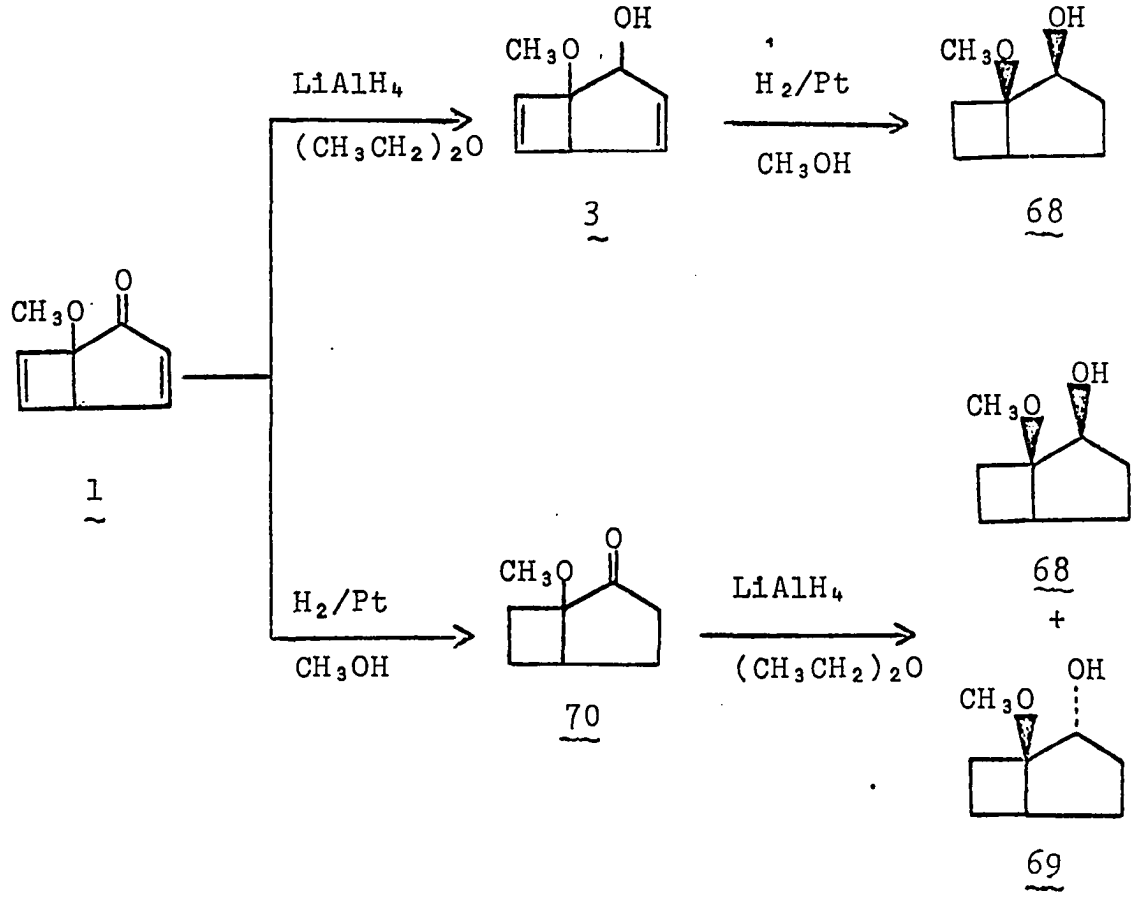
The approximate molecular weight was defined by the mass spectral molecular ion (170). In addition to the normal loss of water (152, M-18), the spectrum showed a significant loss of methanol (138, M-32), reflecting the presence of the second methoxyl group.

Determination of the Stereochemistry of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Preparation of the epimeric 1-methoxybicyclo[3.2.0]heptan-2-ols (68) and (69)

The epimeric alcohols of 1-methoxybicyclo[3.2.0]heptan-2-ol, (68) and (69), were prepared by the sequence outlined in Figure 26 (p 118). The hydrogenations both proceeded smoothly, consuming the theoretical amount of hydrogen and stopping. The rate of hydrogenation of 3 was over twice that of 1, even

Figure 26. Reaction sequence for the preparation of the epimers of 1-methoxybicyclo[3.2.0]heptan-2-ol

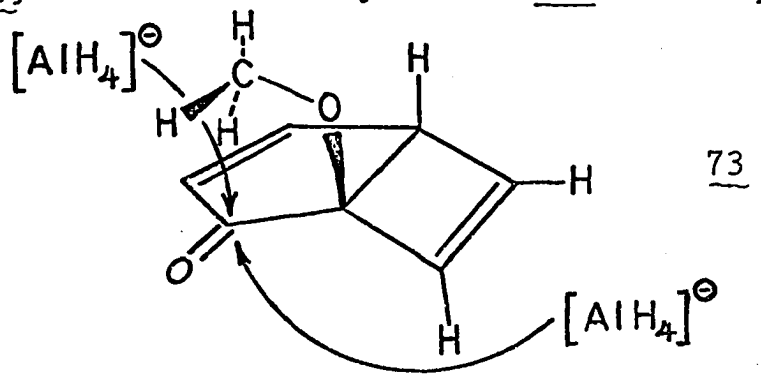

CH3O
O
1
LiAlH4
(CH3CH2)2O
CH3O
OH
3
H2/Pt
CH3OH
CH3O
OH
68
H2/Pt
CH3OH
CH3O
O
70
LiAlH4
(CH3CH2)2O
CH3O
OH
68
+
CH3O
OH
69

though only half as much catalyst was used. 1-Methoxybicyclo-[3.2.0]heptan-2-one (70) was more resistant to lithium aluminum hydride reduction than its precursor, 1, and gave a mixture of epimers, 68 and 69 in a 15:85 ratio.

These results can be easily explained in terms of steric hindrance to hydride attack. In the case of the unsubstituted bicyclo[3.2.0]hepta-3,6-dien-2-one (37), lithium aluminum hydride shows a slight distinction between endo and exo attack of the carbonyl position. The epimeric alcohols, 71 and 72

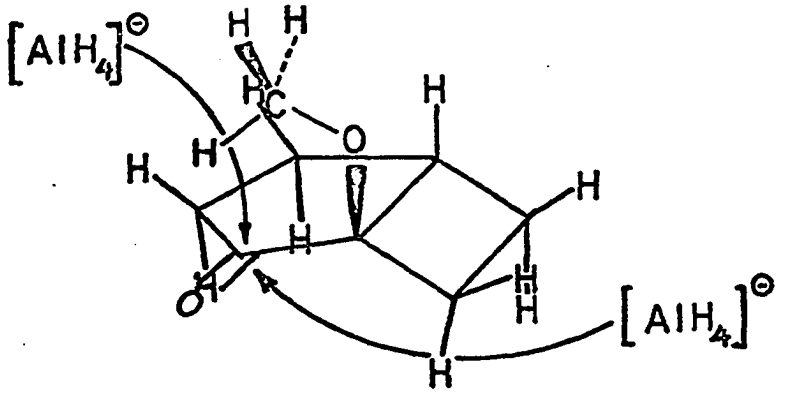
37 71 72

were formed in nearly equal amounts, with the endo-epimer predominating.[27] The presence of the methoxyl substituent at the bridgehead position alters the access to the carbonyl sufficiently that only one of the epimeric 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-ols, 3, is produced. As shown in the structure 73, this would likely be the exo-alcohol, produced



73

by attack from the more exposed endo side of the bicyclic structure. Hydrogenation of the double bonds to give 70 causes access to either side of the carbonyl to be more cluttered. However, the relative change is considerably greater on the endo side. This is represented in structure 74, although it may be seen more clearly with molecular models. The methoxyl group still presents the most serious impedance to exo attack



74

when in the position shown, but it can rotate to other conformations where it is less in the way, as before. The endo hydrogens, however, protrude into space in which, before, there were no atoms, and, due to the rigid bicyclic skeleton, they can not rotate out of the way. The balance is shifted towards exo attack, and the increased steric hindrances on both sides of the carbonyl reflects itself in a reduced

reactivity. The endo-alcohol would therefore be predicted to be the major product.

Product development control would predict the formation of the endo-alcohol in the reduction of both the dienone, 1, and its tetrahydro derivative, 70, as the more stable product. In the case where approach to one side of the carbonyl is clearly more hindered, such as for 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1), steric control is dominant. In the case of bicyclo[3.2.0]hepta-3,6-dien-2-one (37) product development may be controlling. For 1-methoxybicyclo[3.2.0]heptan-2-one (70), the steric approach discussed is more intuitive, but product development may also contribute, depending upon how nearly the steric hindrances are balanced.

Characterization of the epimeric 1-methoxybicyclo[3.2.0]-heptan-2-ols (68) and (69)

The nmr spectrum of exo-1-methoxybicyclo[3.2.0]heptan-2-ol (68) (Figure 27, p 124) showed some very complex splitting patterns. The C-2 hydrogen was still distinct at 3.70 ppm and the methoxyl singlet easily identified at 3.28 ppm. Exchange with deuterium oxide helped to assign the hydroxyl peak at 2.50 ppm. However, the additional couplings reduced the bridgehead hydrogen to a broad hump centered at roughly 2.60 ppm, and the eight methylene hydrogens gave a complex pattern from 2.38 to 1.00 ppm for which individual assignments were not attempted.

The most distinctive features of the ir spectrum (Figure 28, p 124) were the broad, unsymmetrical hydroxyl absorption (3550 and 3440 cm^{-1}) and the strong bands in the C-O stretch region (1099, 1048 and 1021 cm^{-1}). Instrumental evidence for the exo-configuration was provided by its relative retention time being considerably shorter than its epimer[64] and by the demonstration of intramolecular hydrogen bonding in the following section.

Several differences were observed in the nmr spectrum (Figure 27, p 124) of endo-1-methoxybicyclo[3.2.0]heptan-2-ol (69). The C-2 hydrogen's multiplet had broadened considerably and shifted downfield to 3.93 ppm, and the broad hydroxyl singlet (3.40 ppm) was downfield of the methoxyl signal (3.22 ppm). The bridgehead hydrogen's signal (2.50 ppm) had changed little. The bulk of the methylene signals (2.40-1.10 ppm) appears to have shifted downfield, but they are still too complex for individual assignments.

The ir spectrum of 69 was not sufficiently different, qualitatively, from that of 68 to merit its inclusion. The absorption bands are listed in the experimental section (p 161). The vpc retention time of this epimer was nearly three times that of 68, which is consistent with its inability to form an intramolecular hydrogen bond,[64] as clearly demonstrated in the following section.

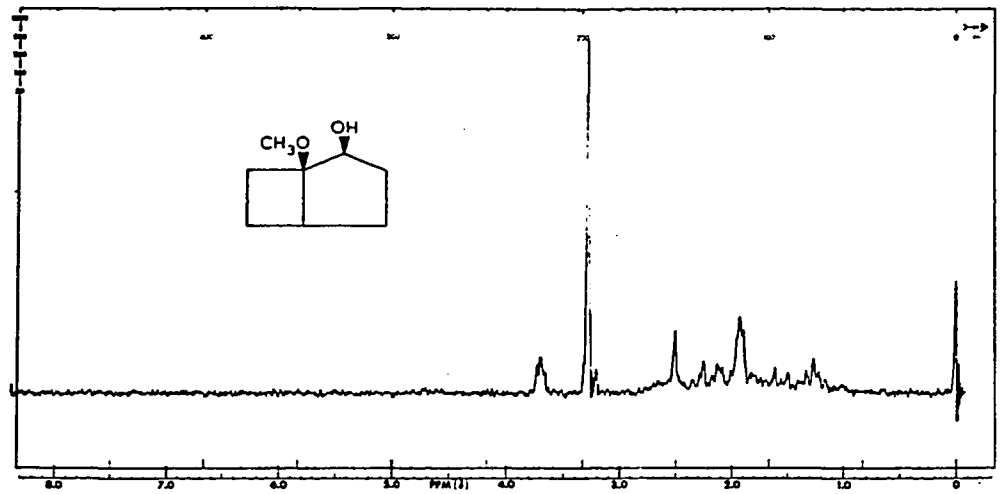
Figure 27. Nuclear magnetic resonance spectra

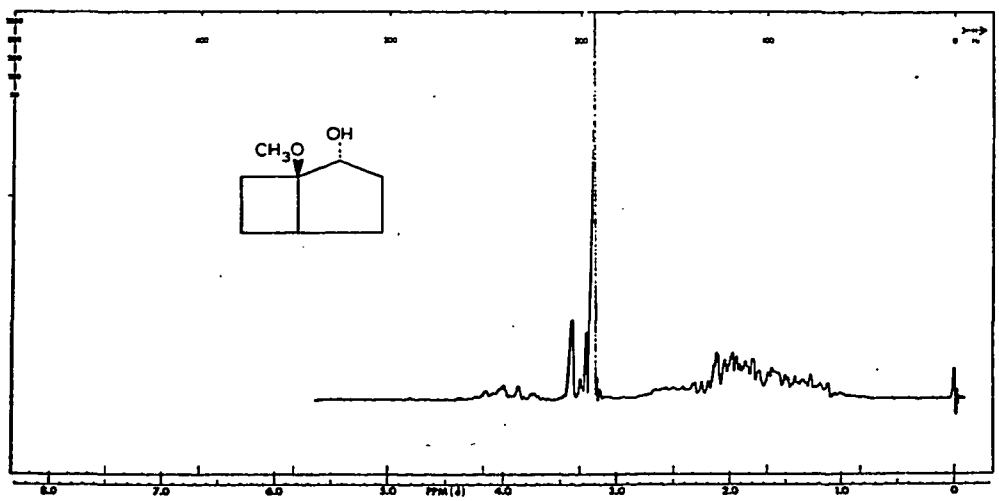
Top - Exo-1-methoxybicyclo[3.2.0]heptan-2-ol (68)

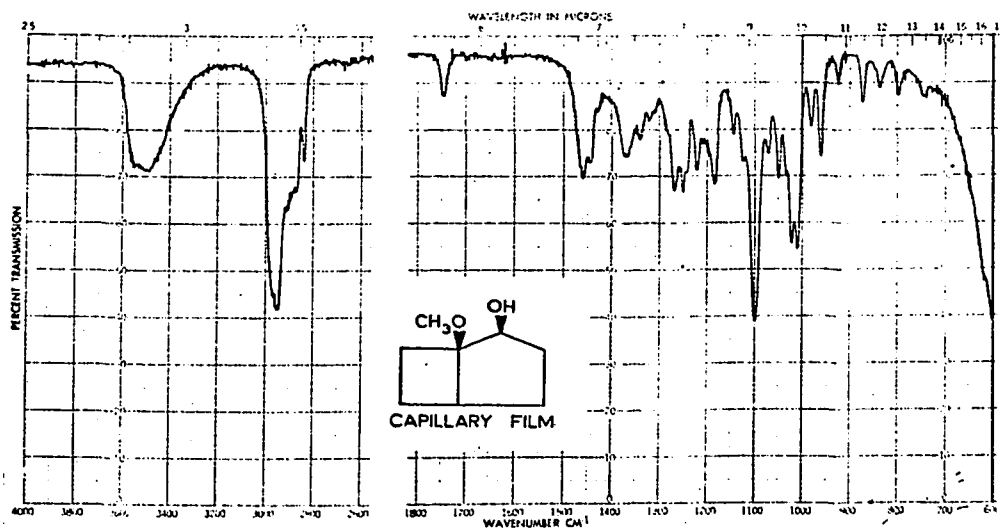
Middle - Endo-1-methoxybicyclo[3.2.0]heptan-2-ol (69)

Figure 28. Infrared spectrum

Bottom - Exo-1-methoxybicyclo[3.2.0]heptan-2-ol (68)


CH3O
OH
PPM (δ)

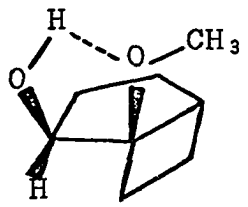

CH3O
OH
PPM (δ)


PERCENT TRANSMISSION
WAVELENGTH IN MICRONS
WAVENUMBER CM-1
CH3O
OH
CAPILLARY FILM

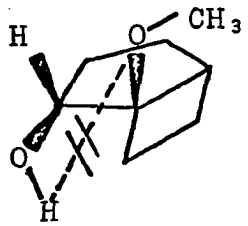
Study of hydrogen bonding in the epimeric 1-methoxybicyclo-[3.2.0]heptan-2-ols (68) and (69) by infrared spectroscopy

The stereochemistry of the epimeric alcohols, 68 and 69, has been tentatively assigned on the basis of steric arguments (pp 116 et seq.) and vpc data.[27,64] To confirm this assignment the changes in hydroxyl band position and shape in the 3200-3700 cm^{-1} region was studied as a function of concentration. This has been shown to be a powerful technique for proof of the stereochemistry of epimeric alcohols in which the hydroxyl group of one of the epimers is significantly closer to an electron donating center than in the other.[65]

The saturated epimers, 68 and 69, are ideal for such a study. Although 68 can not adopt a six membered conformation which allows maximum hydrogen bonding,[66] it should still show significant intramolecular hydrogen bonding. The cyclopentane ring is sufficiently rigid that the hydroxyl hydrogen and



68



69

methoxyl oxygen in 69 can never come within the 3.3Å required for observation of intramolecular hydrogen bonding.[67] Therefore, it should display only intermolecular bonding.

The infrared spectroscopic data are summarized in Table 4 (p 126) and examples of selected absorption bands are provided in Figure 29 (p 128) and Figure 30 (p 130) for 68 and 69,

Table 4. Concentration dependence of hydroxyl absorption band maxima[a] of exo- and endo-1-methoxybicyclo[3.2.0]heptan-2-ol (68) and (69)

Epimer	Solvent	Molar Concentration	Path Length (mm)	Free ν_{O-H}	Bonded ν_{O-H} (±2 cm^{-1})		Intensity Ratio
					Intermolecular	Intramolecular	
68	Neat	7.52	Film	-	3495	3550	1.0:1.0
"	CCl_4	3.76	0.05	-	3500	3557	1.4:1.0
"	"	2.51	0.05	-	3500(sh)	3557	1.7:1.0
"	"	1.00	0.10	-	Unresolved shoulder	3560	2.1:1.0
"	"	0.57	0.20	-	"	3558	2.5:1.0
"	CH_2Cl_2	0.10	1.00	-	-	3547	-
"	"	0.01	10.0	-	-	3550	-
69	CCl_4	3.76	0.05	3618(sh)	3440	-	1:47
"	"	1.00	0.20	3618	3445	-	1.0:3.8
"	"	0.33	0.20	3620	3468	-	1.0:1.8
"	"	0.10	1.00	3622	3469	-	1.1:1.0
"	"	0.03	1.00	3624	3478	-	3.5:1.0
"	"	0.01	10.0	3626	-	-	-

[a]Data were obtained on a Beckman IR-9 Infrared Spectrometer (grating), at nominal scan rates of 20 and 40 cm^{-1}/min. with scale expansion.

Figure 29. Selected hydroxyl absorption bands of exo-1-methoxybicyclo[3.2.0]heptan-2-ol (68)

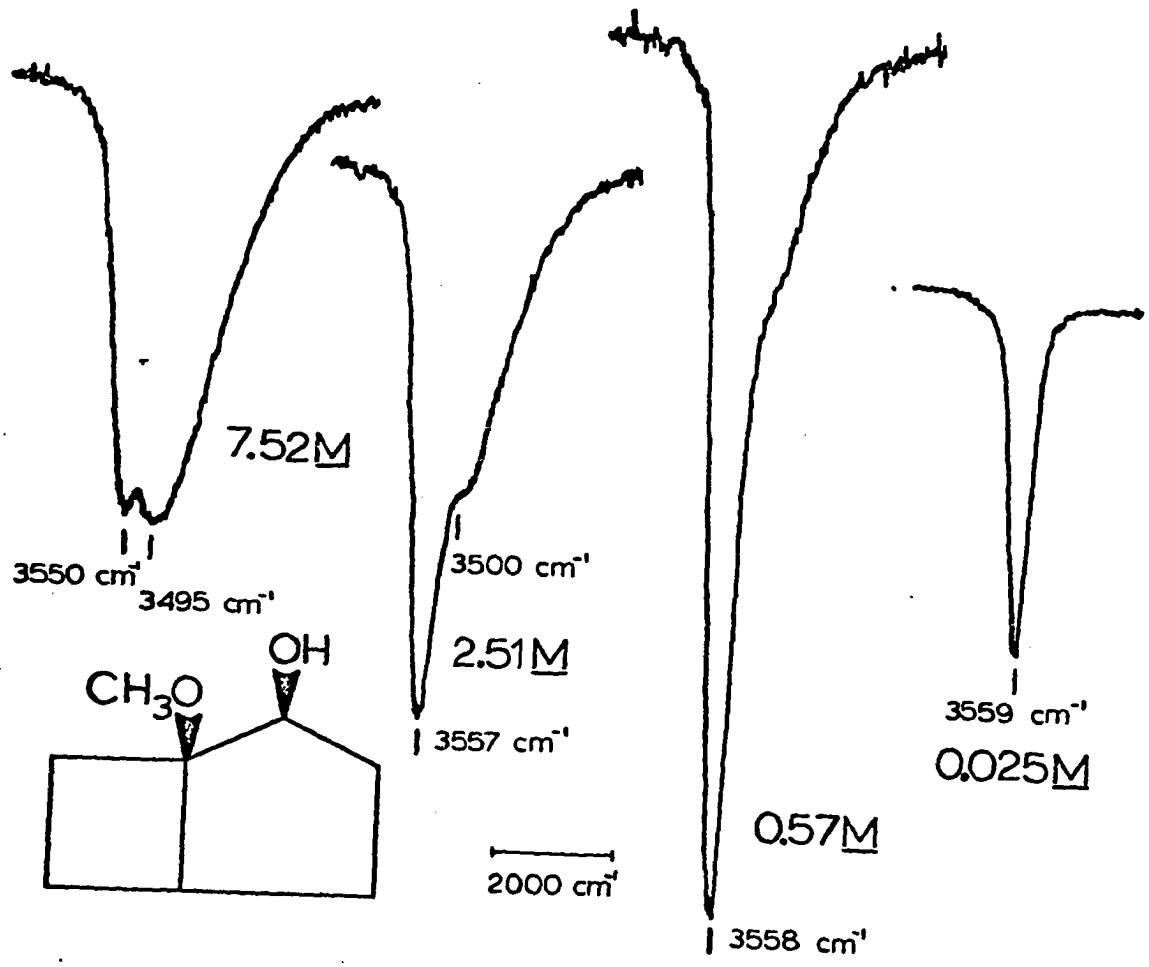
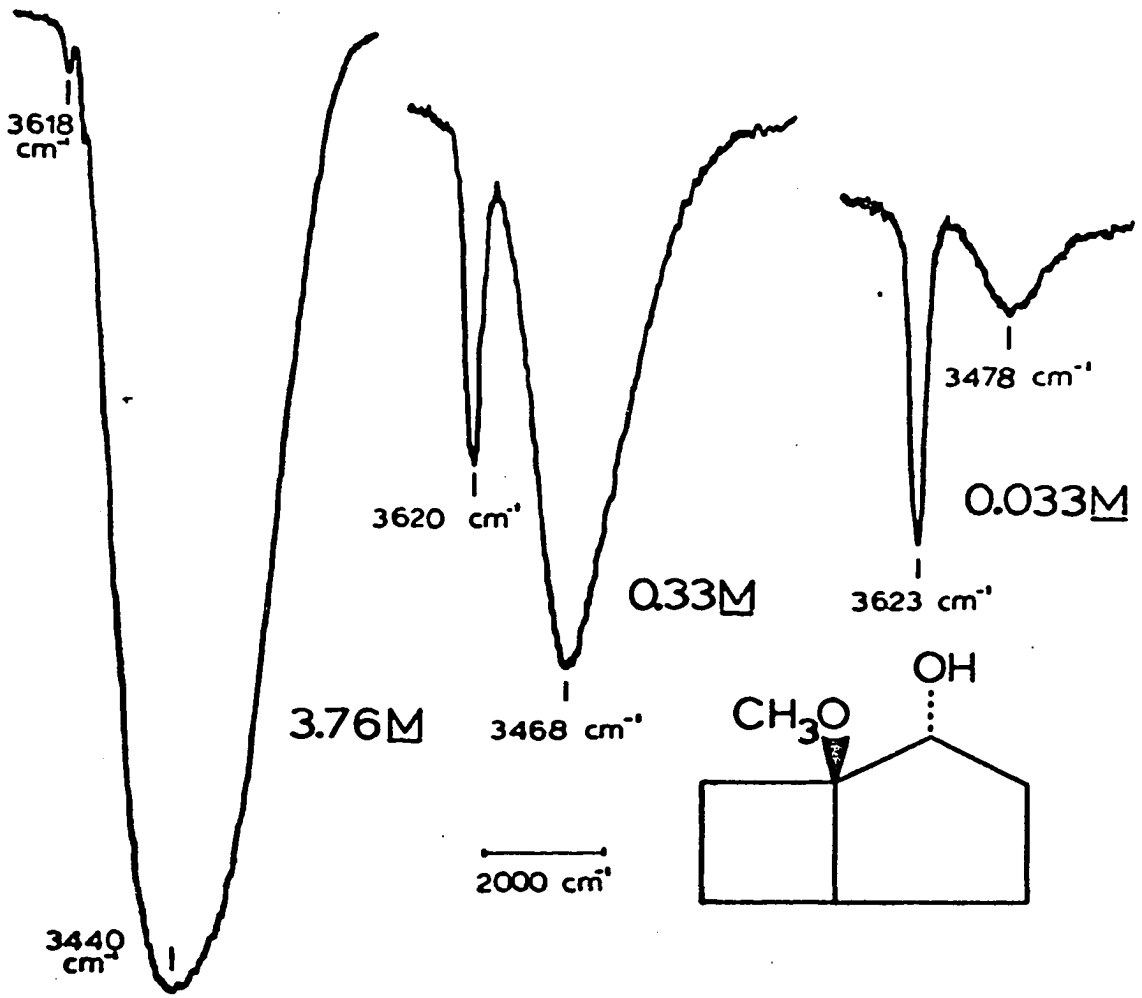

7.52M
3550 cm⁻¹
3495 cm⁻¹
OH
CH3O
3500 cm⁻¹
2.51M
3557 cm⁻¹
2000 cm⁻¹
0.57M
3558 cm⁻¹
3559 cm⁻¹
0.025M

Figure 30. Selected hydroxyl absorption bands of endo-1-methoxybicyclo[3.2.0]heptan-2-ol (69)


3618 cm⁻¹
3440 cm⁻¹
3.76M
3620 cm⁻¹
3468 cm⁻¹
0.33M
2000 cm⁻¹
3478 cm⁻¹
3623 cm⁻¹
0.033M
OH
CH3O

respectively. Shifts of only 3 cm^{-1} over a seven and ten-fold dilution in carbon tetrachloride or chloroform for the 3550 cm^{-1} band of (68) provide good evidence for intramolecular hydrogen bonding. The band position of 3557 cm^{-1} in carbon tetrachloride correlates reasonably with the 3572 cm^{-1} value reported for cis-cyclopentane-1,2-diol.[68] Band shifts of the epimer, (69), followed a normal pattern for a non-intramolecularly hydrogen bonded alcohol. The intermolecular hydrogen bond absorption shifted substantially and a free hydroxyl stretch band appeared upon dilution. The value at intermediate concentrations, 3620 cm^{-1}, was identical to that reported for trans-cyclopentane-1,2-diol.[68]

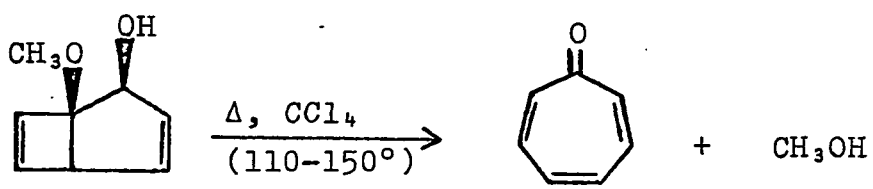
With the stereochemistry of the 1-methoxybicyclo[3.2.0]-heptan-2-ol (68) isolated from the catalytic hydrogenation of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) clearly established as exo, it follows that the stereochemistry of (3) must also be exo.

Pyrolysis of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Initial attempts to pyrolyze 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (3) on Pyrex helices, as was done for 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (p 85 *et seq.*) were not successful. The high temperatures required to offset the short residence time resulted in a low recovery of dark, tarry product residues. A more satisfactory procedure

was to heat a solution of 3 in a sealed Pyrex tube. This allowed the solution to be degassed more effectively and retained volatile products. The milder temperatures also lessened the possibility of rearrangement of bicyclic products which might be formed.

A sample of exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) in carbon tetrachloride was sealed in an nmr tube and heated for 30, 60, and 120 minute periods in a Woods Metal bath at temperatures from 99-150°. The tube was cooled between periods and an nmr spectrum was taken to monitor reaction progress and to detect signals which might be related to new products or intermediates. The lowest temperature at which net production of tropone (5) was observed was 106-112°. An hour at 99-104° actually resulted in a decrease in the ratio between 5 and 3. Apparently at 100-110° the



3 5

rate of degradation of 5 is competitive with its formation from 3 and higher temperatures are necessary for its efficient production. The two singlets characteristic of methanol appeared with the tropone signal and increased more rapidly, consistent with the gradual polymerization of tropone. The

relative integrals in the final mixture corrected for number of hydrogens, were 3.3:1.0. No evidence for any additional products was found at any point in the reaction.

In a separate experiment a toluene solution of (3) was pyrolyzed in the same manner at 165-174° in a Woods Metal bath for 100 minutes. The product mixture was separated on an analytical vpc column and the identity of the tropone product (5) confirmed by comparison of its nmr and ir spectra to those of an authentic sample. The coproduct, methanol, was lost with the solvent in the work-up.

Preparation and Characterization of 2-Deuterio-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (75)

1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) was reduced with lithium alumnium deuteride (99% deuterium) to yield 2-deuterio-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (75) and, as a minor product, 1-methoxybicyclo[3.2.0]hept-6-en-2-ol-d_2 (76). Due to the instability of the parent ion (cf p 147 et seq.) a reliable isotope enrichment value could not be obtained from the mass spectrum (Table 5, p 134). However, the 4.47 ppm signal (CHOH) in the nmr spectrum of the undeuterated compound, 3, (Figure 24, p 110) was completely absent in the nmr spectrum of 75 (Figure 32, p 142), even when the region was scanned at increased amplitude. The integrals of the remaining signals were normal and approximately the same as those of 3. On the basis of the nmr

Table 5. Mass spectra of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) and 2-deuterio-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (75) at 70 ev

m/e	3[a]	75[a]
140	-	-
139	-	2.8
138	1.1	3.4
137	2.1	21.0
136	17.0	8.3
135	9.3	10.3
111	0.9	9.7
110	9.6	6.4
109	7.1	10.5
108	10.5	13.3
107	8.5	59.5
106	52.4	19.5
105	32.6	26.2
80	1.6	22.6
79	15.7	100.0
78	100.0	40.3
77.5	m*[b]	-
77	52.5	37.2
76	8.3	6.6
75	3.7	4.8
74	7.4	5.1
56.5	m*	-
54	1.3	3.1
53	5.1	25.7
52	31.6	34.5
51	41.2	38.3
50	28.8	22.9
49	4.2	3.4

[a]Relative intensity, expressed as per cent of base peak.

[b]Metastable ion.

spectrum, then, the deuterium appears to have been incorporated entirely in the C-2 position and the per cent incorporation is near 100.

Pyrolysis of 2-Deuterio-1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-ol (75)

The pyrolysis mixtures were generally contaminated with tarry residues and vpc would be a convenient method of isolating the volatile products. However, there was a possibility that the labeled product, deuteriotropone (77), might undergo exchange with the polar liquid phase and lose part of its deuterium content. Since 3 was known to rearrange readily to tropone (5) in preparative vpc separations, an on-column pyrolysis of 75 on a 10% diethylene glycol succinate column was carried out at 180° to clear this method for the separation of the standard sealed tube pyrolysis mixture. The isotope enrichment of the deuterated tropone (77) collected was determined by standard methods of comparison between the mass spectra (Table 6, p 136) of the labeled material and an unlabeled reference run concurrently.[69] The value, 99.0% d_1, 1.0% d_2, indicated that there was essentially no loss of deuterium in the separation. Therefore, the remainder of the sample of 75 was pyrolyzed in a sealed Pyrex tube in toluene at approximately 160-170°. The pyrolysate, consisting of starting material (75) and product (77) (relative vpc peak areas 38:62), was separated on an analytical vpc column to

Table 6. Mass spectra of tropone (5) (reference) and deuteriotropone (77) at 20 ev

m/e	5[a]	77[a,b]	77[a,c]
109	-	1.1	1.5
108	0.7	8.4	9.1
107	6.1	92.8	100.0
106	77.4	3.6	3.8
105	3.0	0.5	1.5
80	-	8.8	-
79	8.4	100.0	-
78	100.0	9.2	-
77	10.0	2.5	-
76	2.6	-	-
75	-	-	-
74	m*[d]	-	-
57-58	m*[d]	m*[d]	-

[a]Relative intensity, expressed as per cent of base peak.

[b]Recovered from on-column pyrolysis.

[c]Recovered from sealed tube pyrolysis; spectrum below 100 m/e not recorded.

[d]Metastable ion.

minimize further conversion of 75. A portion of the deuteriotropone (77) collected from the center of several vpc peaks was submitted with a reference for mass spectral analysis (data are included in Table 6, p 136). The amount of deuterium retained, 98.4%, was slightly less than the value found for the deuteriotropone (77) collected directly from the on-column pyrolysis (vide supra), but the difference is not serious and the additional loss could have occurred during the extensive pyrolysis period.

Preparation and Characterization of the Maleic Anhydride-Deuteriotropone Adduct (79)

A flow diagram of the deuterium labeling experiment is provided in Figure 31 (p 139). The Diels-Alder adduct, 79, was prepared to separate the tropone hydrogen nmr signals to determine the position of the deuterium. Maleic anhydride was selected in preference to other common dienophiles[70] because of ease of preparation in an aprotic solvent, high yield[71], and good separation of the vinyl hydrogen nmr signals for accurate integration.

The mass spectrum of the deuterium labeled adduct (79) compared to that of an authentic sample (78) (Table 7, p 140) showed that only a few per cent of the deuterium had been lost. The 60 MHz nmr spectra of the reference and deuterium labeled adduct are shown in Figure 32 (p 142) and their 100 MHz spectra are in Figure 33 (p 144). The assignment of the signals

Figure 31. Deuterium labeling experiment

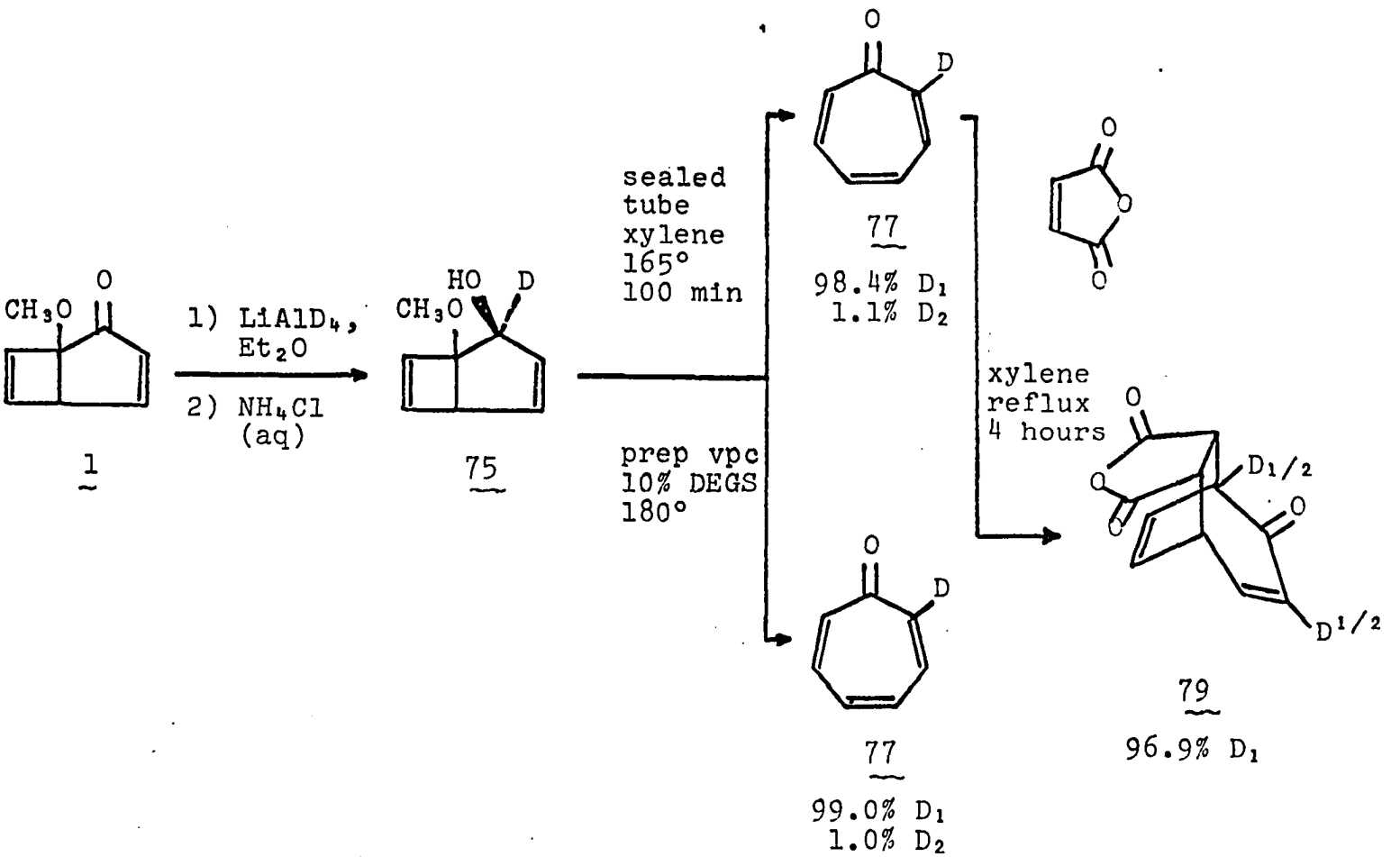

CH3O
O
1) LiAlD4, Et2O
2) NH4Cl (aq)
HO
D
CH3O
sealed tube xylene 165° 100 min
prep vpc 10% DEGS 180°
O
D
77
98.4% D1
1.1% D2
77
99.0% D1
1.0% D2
xylene reflux 4 hours
D1/2
D1/2
79
96.9% D1

Table 7. Mass spectra of Diels-Alder adducts of maleic anhydride with tropone (78) (reference) and deuteriotropone (79) at 70 ev

m/e	78[a]	79[a]
207	-	0.8
206	0.4	4.9
205	2.5	34.4
204	16.6	1.2
135	-	0.7
134	0.4	5.5
133	5.6	56.5
132	51.7	100.0
131	100.0	8.8
130	4.4	-
106	0.7	4.9
105	8.1	40.0
104	55.4	26.0
103	35.2	5.8
102	5.8	1.2
101	0.8	-
98-1/2	-	m*[b]
97-1/2	m*[b]	-
82	-	m*[b]
81	m*[b]	-
79	3.6	22.7
78	46.2	26.2
77	25.8	10.9
76	5.6	3.3
58-1/2	m*[b]	-

[a]Relative intensity, expressed as per cent of base peak.

[b]Metastable ion.

Figure 32. Nuclear magnetic resonance spectra

Top - 2-Deuterio-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (75)

Middle - Diels-Alder adduct of maleic anhydride with tropone (78)

Bottom - Diels-Alder adduct of maleic anhydride with deuteriotropone (79)

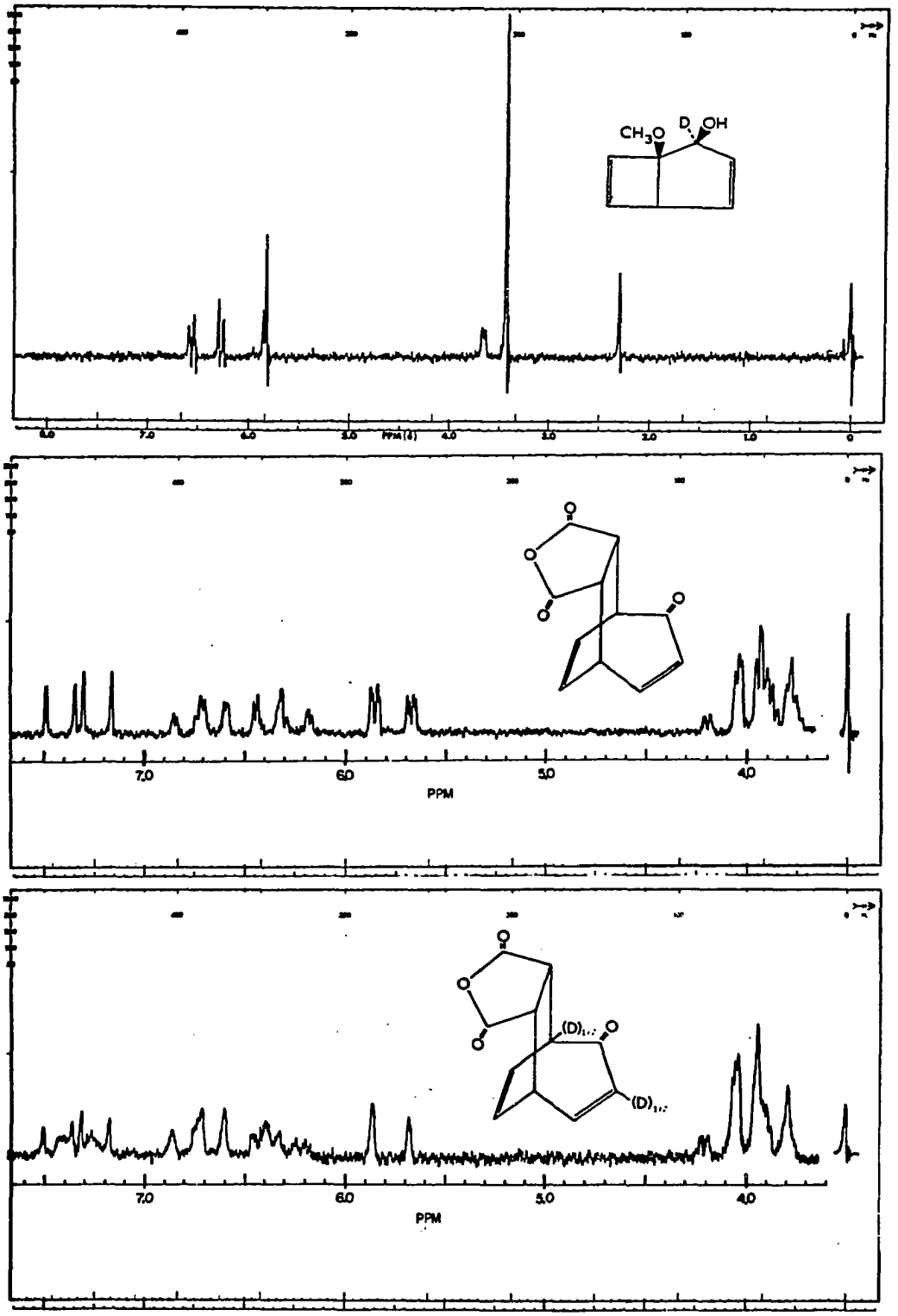

CH3O
D
OH
7.0
6.0
5.0
4.0
PPM
(D)1.2
(D)1.2
7.0
6.0
5.0
4.0
PPM

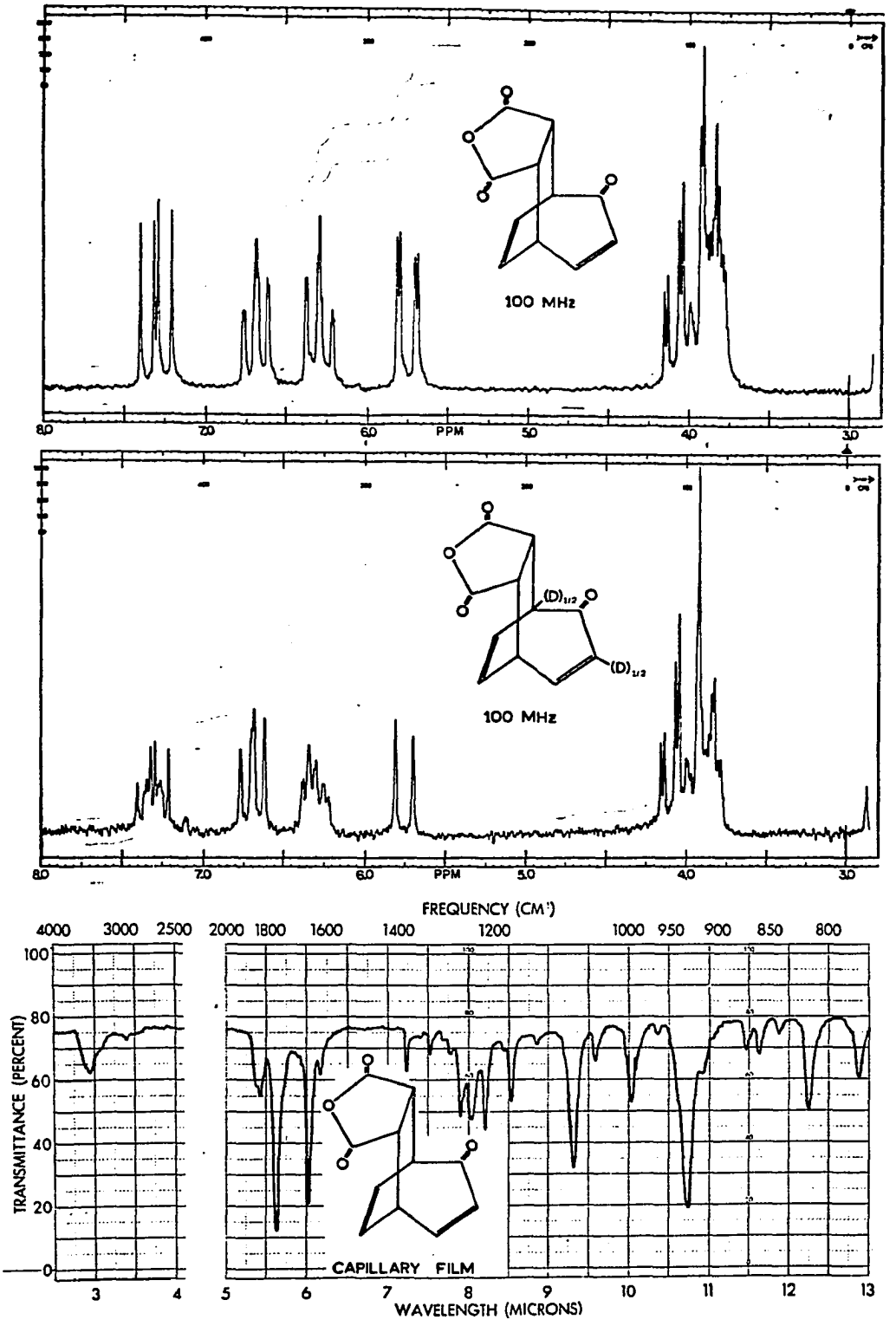
Figure 33. Nuclear magnetic resonance spectra (100 MHz)

Top - Diels-Alder adduct of maleic anhydride with tropone (78)

Middle - Diels-Alder adduct of maleic anhydride with deuteriotropone (79)

Figure 34. Infrared spectrum

Bottom - Diels-Alder adduct of maleic anhydride with tropone (78)


100 MHz
8.0
7.0
6.0
PPM
5.0
4.0
3.0
(D)1/2
(D)1/2
100 MHz
8.0
7.0
6.0
PPM
5.0
4.0
3.0
FREQUENCY (CM-1)
4000
3000
2500
2000
1800
1600
1400
1200
1000
950
900
850
800
TRANSMITTANCE (PERCENT)
100
80
60
40
20
0
CAPILLARY FILM
3
4
5
6
7
8
9
10
11
12
13
WAVELENGTH (MICRONS)

with their relative integrals are listed in Table 8, below.

Table 8. Relative nmr signal integrals of Diels-Alder adducts of maleic anhydride with tropone (78) (reference) and deuteriotropone (79) in acetone-d_6

Position	Chemical Shift (δ)	Relative signal integrals 60MHz 78	60MHz 79	100 MHz 78	100 MHz 79
4	7.32	1.0	1.2	1.0	1.0
6	6.72	1.0	1.0	1.0	1.0
7	6.33	1.1	0.9	1.0	1.0
3	5.77	1.1	0.5	1.0	0.5
9	4.10	4.1	3.5	4.2	3.7
1	3.95				
8	3.86				
5	3.85				

Within the limits of accuracy of the integration, the signal ratios are comparable between the reference and the deuterium labeled adduct (78 and 79) for all vinyl positions except the one α to the carbonyl. In both spectra of 79, the C-3 hydrogen signal integrates for only 1/2 hydrogen. The bridge-head hydrogen signals could not be separated adequately for accurate integration of the individual multiplets, so the total integral is reported. This value was also seen to decrease by 1/2 hydrogen in the spectra of the labeled adduct

(79), meaning that the deuterium is at either the C-1 or C-5 position. Considering that the maleic anhydride would add to the original tropone (77) across either of the α,δ positions and that one-half of the label is in the C-3 position, it is more likely that the remainder of the deuterium would be at the other α position, C-1. Further proof that the deuterium is at either the C-1 or C-3 position, but not both simultaneously, is the complete absence of the 2 Hz coupling observed between the hydrogens on these positions in the reference (78). Other perturbations include the superposition of the normal quartet ($J_{3,4}$ = 11 Hz, $J_{4,5}$ = 9Hz) of the C-4 hydrogen upon a doublet (J = 9 Hz) of broad triplets (J ~ 1 Hz). The quartet would arise from those molecules in which the deuterium was at the C-1 position, and the broadened multiplet from those in which the deuterium was at C-3. A less discernable broadening occurred in the C-7 signal. Changes in the bridgehead hydrogen signals were too difficult to analyze due to overlap. These results also clearly establish that the deuterium was not scrambled by thermal 1,5 hydride shifts such as might be expected of a cycloheptatrienol intermediate.

Preparation and Characterization of 2-(^{18}O-Hydroxy)-1-methoxybicyclo[3.2.0]hepta-3,6-diene (81)

The carbonyl oxygen of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) was exchanged with oxygen-18 enriched water in absolute methanol. A distinct 1744 cm^{-1} band with the normal

1710 cm^{-1} carbonyl band in the infrared spectrum of the re-isolated oil confirmed that a significant amount of oxygen-18 had been incorporated.[72] A small portion of the product, 80, was reserved for mass spectral analysis while the rest was promptly reduced with lithium aluminum hydride. The reduction product was confirmed to be the dienol, 81, by comparison of its nmr spectrum to one of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3).

Determination of the isotope content of 2-(^{18}O-hydroxy)-1-methoxybicyclo[3.2.0]hepta-3,6-diene (81) was complicated by its instability to high temperature and, apparently, to electron bombardment. Attempts to minimize the M-2 loss by sample introduction at lower temperature on an inert support were unsuccessful. The main cause of the low intensity of the molecular ion region in the mass spectrum of 3 (Table 5, p 134) is the facile loss of methanol, which is analogous to its thermal rearrangement and is supported by a metastable ion at m/e 77-78. The second metastable ion, m/e 56-57, is from the loss of carbon monoxide from the m/e 106 fragment. (An analogous rearrangement occurs in tropone.[73])

A routine mass spectrum of 2-(^{18}O-hydroxy)-1-methoxybicyclo[3.2.0]hepta-3,6-diene (81) is provided in Table 9 (p 148). The fragmentation pattern is similar to 3, as expected, but it also shows that all of the oxygen-18 is retained in the C_7H_6O fragment after loss of methanol. Mass spectra were run of the molecular ion region of the reference,

Table 9. Mass spectrum of 2-(^{18}O-hydroxy)-1-methoxy-bicyclo[3.2.0]hepta-3,6-diene (81) at 20 ev

m/e	Rel. Int.
140	2.7
139	5.4
138	10.8
137	9.5
136	16.2
135	10.8
110	16.2
109	12.2
108	45.9
107	24.3
106	48.6
105	27.0
80	5.4
79	18.9
78	100.0
77[a]	37.8

[a]Lowest mass scanned.

3, and oxygen labeled material, 81, at expanded scale to determine the isotope content (Table 10, below). The

Table 10. Mass spectra (molecular ion region) of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) (reference) and 2-(^{18}O-hydroxy)-1-methoxybicyclo[3.2.0]hepta-3,6-diene (81) at 20 ev

m/e	3[a]	81[a]
140		6.7
139		9.3
138	9.9	58.7
137	18.3	44.0
136	100.0	100.0
135	49.3	53.3
134	2.8	6.7

[a]Relative intensity, expressed as per cent of m/e 136 peak.

oxygen-18 enrichment of 81 was calculated to be 26% from the M-2 region. A similar calculation based on the M-32 region gave a value of 34%. An attempt to determine the isotope enrichment of the dienone, 80, which would reflect the maximum value which 81 could have, failed due to obvious loss of label over the several months between its preparation and analysis.

Pyrolysis of 2-(^{18}O-hydroxy)-1-methoxy-bicyclo[3.2.0]hepta-3,6-diene (81)

The nmr sample used to confirm the identity of 81 was sealed in its tube and pyrolyzed in a 167-168° Woods Metal bath. The tropone 82 was separated from the brown residue by vpc and analyzed by mass spectroscopy. Since the molecular ion region is strong in the tropone spectrum (Table 11, below), a reliable value of 29% oxygen-18 enrichment could be calculated. Details of the oxygen-18 labeling experiment are summarized in Figure 35 (p 152).

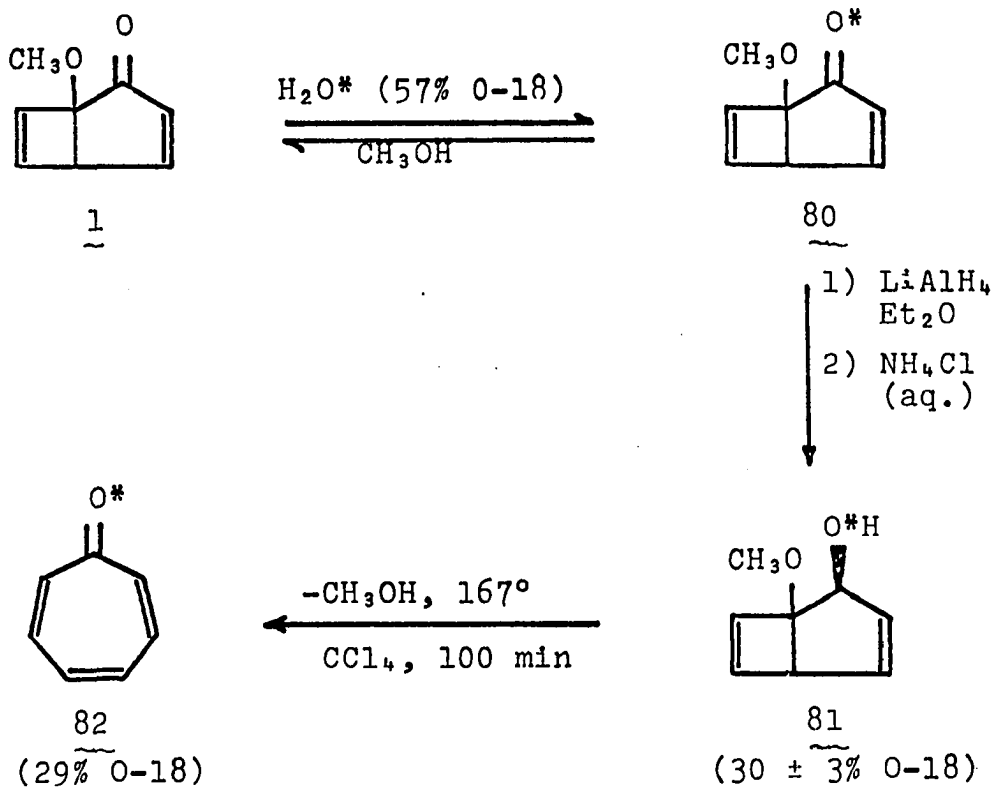
Table 11. Mass spectra (molecular ion region) of tropone (5) (reference) and carbonyl-^{18}O-tropone (82) at 20 ev

m/e	5[a]	82[a]
109		6.1
108	0.9	44.3
107	8.1	11.4
106	100.0	100.0
105	3.8	6.1

[a]Relative intensity, expressed as per cent of the molecular ion peak.

The principal uncertainty in the experiment arises from the inability to accurately determine the amount of oxygen-18 incorporated in 81. However, the amount of oxygen-18 retained

Figure 35. Oxygen-18 labeling experiment

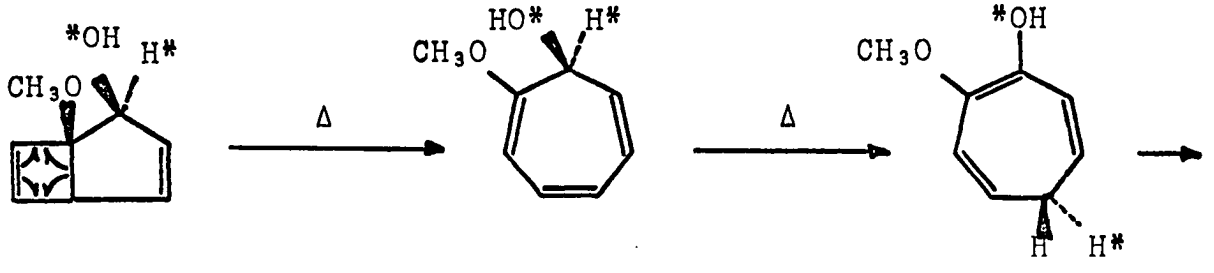

CH3O
O
H2O* (57% O-18)
CH3OH
CH3O
O*
1
80
1) LiAlH4
Et2O
2) NH4Cl
(aq.)
O*
-CH3OH, 167°
CCl4, 100 min
CH3O
O*H
82
(29% O-18)
81
(30 ± 3% O-18)

in the pyrolysate, 82, was within the range determined by approximate calculations for 81, and considering that retention of oxygen-18 with the tropone-like fragment rather than loss with the methanol was clearly evident in the mass spectrum of 81, it may be concluded with reasonable certainty that the hydroxyl oxygen, not the methoxyl oxygen, is retained in the tropone.

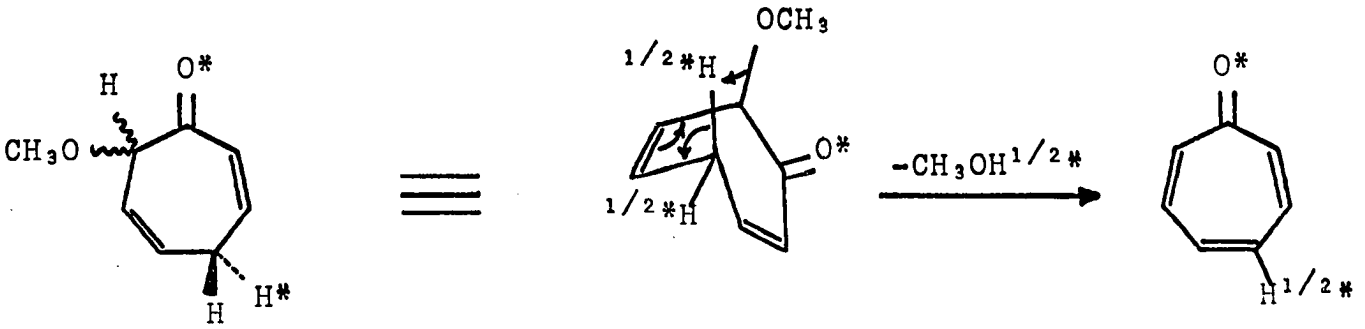
The Mechanism of the Rearrangement of exo-1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) to Tropone (5)

The intuitive mechanism, initiated by homolytic cleavage of the bridgehead bond of exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) is outlined as Mechanism I in Figure 36 (p 155). The atoms labeled in the preceding experiments are indicated by an asterisk. Since the cycloheptatrienol intermediates are susceptible to further 1,5-hydride shifts[74,75,76] before ketonization, this mechanism would predict an uneven scrambling of the deuterium label.[74] If ketonization occurred rapidly after the initial 1,5 shift, the methoxyl group would appear cis or trans to the deuterium at the γ-position with equal probability. It is likely, then, that up to one-half of the label could be lost in the elimination of methanol. Since neither of these possibilities was observed in the deuterium labeling experiment, this mechanism is eliminated. The remaining two mechanisms to be considered are consistent with the results of both isotope labeling experiments.

Figure 36. Thermal rearrangement of exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) to tropone (5). Mechanism I


*OH
H*
CH3O
Δ
HO*
H*
CH3O
Δ
CH3O
*OH
H
H*

3* 82 83

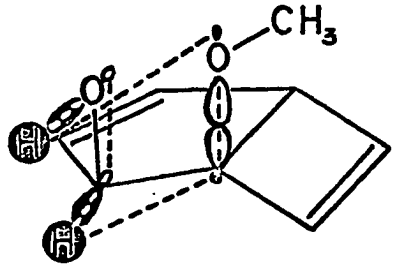

H
O*
CH3O
H*
OCH3
1/2*H
O*
1/2*H
-CH3OH1/2*
O*
H1/2*

84 85 5*

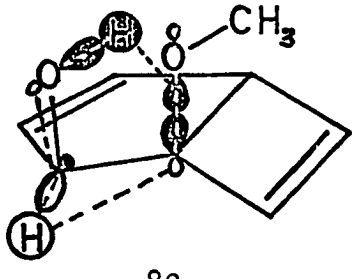
The first of these, Mechanism II, is illustrated in Figure 37, (p 158). A 1,5-hydride shift, which is quite facile in cyclopentadienes[77], is proposed as the initial event. Concomitant scission of the bridgehead bond of exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3*) produces the monocyclic cycloheptatrienol, 86, which promptly undergoes 1,8-elimination of methanol to give tropone. The transformations are symmetry allowed and the strong intramolecular bonding demonstrated in 3 (p 125 et seq.) should be retained in 86, favoring the stereochemical requirements for elimination. The stability of the non-benzenoid aromatic product, 5, would provide a strong driving force to draw the reaction to completion.

The final mechanism is presented in Figure 38 (p 158). The first transformation is a thermally allowed, concerted $[_{\sigma}2_a + _{\sigma}2_a + _{\sigma}2_s]$ cycloaddition.

A cyclohexane boat (88) or chair (89) transition state



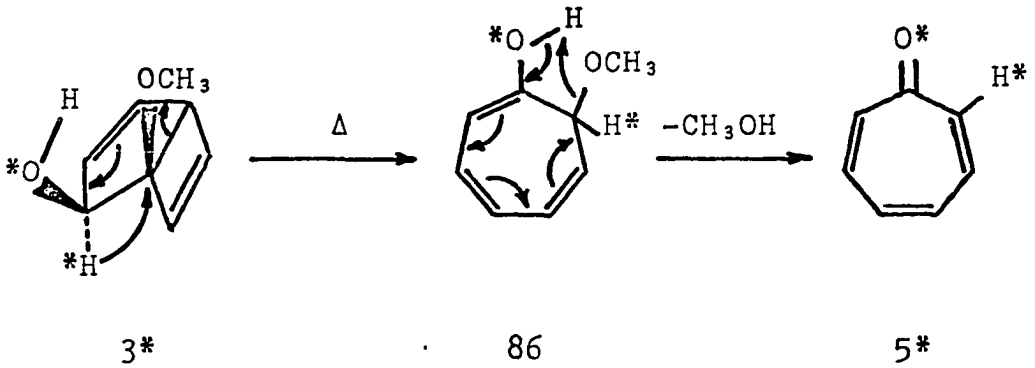
88



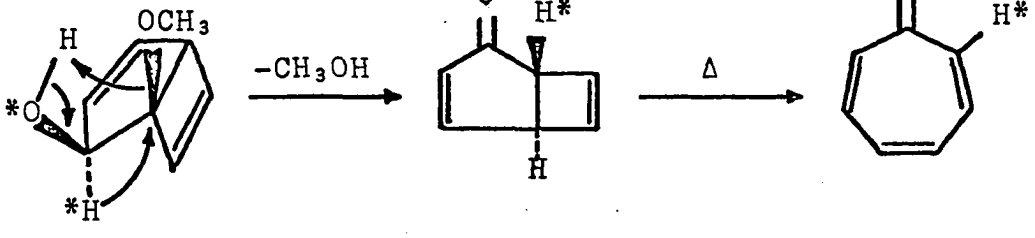
89

Figure 37. Thermal rearrangement of exo-1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-ol (3) to tropone (5). Mechanism II

Figure 38. Thermal rearrangement of exo-1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-ol (3) to tropone (5). Mechanism III



3* 86 5*



3* 87 5*

can be visualized. In the former, the mode of addition to the methoxyl bond would be suprafacial to the methoxyl bond and antarafacial to the hydroxyl hydrogen and C-2 hydrogen bonds. As the methoxyl bond ruptures, its minor sp^3 lobes interact with the hydrogen atoms departing from the C-2 carbon and the hydroxyl oxygen. The cycle is completed by the simultaneous enlargement and bonding interaction of the minor sp^3 lobes of the C-2 carbon and hydroxyl oxygen. The chair transition state, 89, would be more consistent with the anticipated movement of the atomic centers. In this case, the suprafacial addition would occur to the C-2 hydrogen bond and antarafacial additions would occur to the methoxyl and hydroxyl hydrogen bond. The bonding arguments are similar to those for the boat conformation (88). The product formed in both cases would be trans-bicyclo[3.2.0]hepta-3,6-dien-2-one (87). This intermediate would be very strained at the bridgehead bond and could readily undergo a thermally allowed conrotatory cycloreversion to tropone (5).

Distinction between mechanisms II and III cannot be made on the basis of available data. Both propose distinct intermediates which are not sufficiently stable under the required reaction conditions to be detected. However, 1,5 hydride shifts are well established thermal rearrangements,[77,78] and aided by the strong intramolecular hydrogen bonding to maintain the required conformation, elimination of methanol from 86 could conceivably take place in preference to enol-ketone

tautomerization. On the other hand, there is no precedent to support the discrete existence of trans-bicyclo[3.2.0]hepta-3,6-dien-2-one, and it cannot be constructed, for instance, from Dreiding models. Mechanism II therefore appears to be more reasonable for the observed transformation.

EXPERIMENTAL

Metal Hydride Reduction of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

Lithium aluminum hydride (3.9 M standardized solution)

Optimum yields of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) with the least number of side products were obtained using lithium aluminum hydride in the form of a standardized solution in ether (Foote Mineral Company, Eaton, Pennsylvania). This solution has several advantages over the conventional powder form, such as higher purity, greater shelf life, easier handling, greater measurement accuracy, and no residue in the solution. The latter factor is particularly important in the inverse addition technique.

The procedure in Vogel was used as a guide for the reduction technique and apparatus.[79] Thus 100 ml ether was distilled under nitrogen from lithium aluminum hydride powder into a 200 ml three-necked flask equipped with an overhead stirrer, and a 25 ml pressure equilizing addition funnel capped by a Dewar condenser and drying tube. The distillation apparatus was replaced by a nitrogen purge line. The lithium aluminum hydride solution (0.70 ml of 3.9 M solution, 2.75 mmole) was transferred from a septum capped vial (filled from the supply cylinder under nitrogen in a glove bag) to the round bottomed flask with a 1 ml syringe. The addition funnel was charged with neat 1-methoxybicyclo[3.2.0]hepta-3,6-

dien-2-one (1) (1.363 g, 10.0 mmole) against a positive flow of nitrogen. The condenser was packed with ice and the hydride solution cooled in an ice-methanol (-10°) bath with stirring for 10 minutes prior to the addition of the ketone, 1. Dropwise addition of 1 to the rapidly stirring hydride solution required only 2 minutes and was followed by several 15-20 ml volumes of ether to wash residues in the funnel into the reaction flask. This was accomplished in about 10 minutes without opening the system by increasing the nitrogen flow rate to sweep ether vapors into the Dewar condenser where they were condensed and returned to the addition funnel. The ice bath was removed and the liquor allowed 40 minutes to warm to room temperature. A saturated ammonium chloride solution (aq.) (0.20 ml) was then added, dropwise, and the pale yellow solution became opaque. Gravity filtration readily removed the slight, yellow precipitate and the colorless filtrate was washed with 25 ml saturated salt solution, dried over magnesium sulfate, and the ether removed by rotary evaporation at reduced pressure (10-20 torr). The resultant oil (1.17 g, 86% recovery) consisted mainly of 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (3) (75 parts) and two minor products (19 and 6 parts). A nuclear magnetic resonance spectrum of the mixture gave evidence for the presence of 1-methoxybicyclo-[3.2.0]hept-6-en-2-one (65) by comparison to a spectrum of the major product of the lithium tri-t-butoxyaluminum hydride reduction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

(p 168). Peaks characteristic of 1-methoxybicyclo[3.2.0]-hept-6-en-2-ol (66) were absent from the spectrum, implying that the second largest vpc peak could be attributed entirely to 65. The third component was not present in sufficient amount to show up in the spectrum. Separation of the mixture on an analytical scale vpc column (10% diethylene glycol succinate) resulted in recovery of only the major component in sufficient quantity and purity for characterization. The data for 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) follow. The nmr (Figure 24, p 110), ir (Figure 25, p 113), and mass spectra (Table 5, p 134) are included in the text: bp 52-54° (3.0 torr); nmr ($CDCl_3$) δ 6.60 (d, 1H, vinyl), 6.28 (d, 1H, vinyl), 6.07-5.73 (m, 2H, vinyl), 4.47 (m, 1H, CHOH), 3.72 (m, 1H), 3.46 (s, 3H, OCH_3), and 3.05 (s, 1H, OH); ir (cap film) 3440, 1452, 1344, 1279, 1180, 1121, 1094, 1048, 1027, 996, 964, 855, 800, 744, and 711 cm^{-1}; mass spectrum (70 ev) m/e 138 (1), 137 (2), 136 (17), 106 (52), and 78 (100); uv max (SpectrAR CH_3OH) 313 (ε 14), 278 (ε 17), 210 (end absorption, ε 1800).

Anal. Calc. for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.69; H, 7.47.

Lithium aluminum hydride (powder)

Three reductions of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) were carried out in ether with an aged sample of lithium aluminum hydride (Metal Hydrides Incorporated, Beverly,

Massachusetts). The active hydride was determined by the hydrogen evolution method[80] to be 34%. Accordingly, the equivalent excess reported for these preparations should be reduced by roughly a factor of 3 to get the actual excess hydride.

In the first preparation, 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (2.39 g , 17.5 mmole) in ether (60 ml) was added to a slurry of lithium aluminum hydride (1.01 g, 106 meq.) in ether (50 ml) according to the procedure previously described (p 161). The excess hydride was hydrolyzed with saturated ammonium chloride (8 ml) and worked up as before to yield a pale yellow oil (1.9 g , 80% recovery). Analysis by vpc showed three components whose areas were in the ratio 68:23:9, in order of retention time. The oil was distilled on a Nester-Faust 12" silvered spinning band column, with fractions cut at 52°, 54°, and 56° (3.0 torr), with a loss of 0.3 g. (1.6 g, 65%). The major reduction product comprized 95% of the 52-54° fraction and could be tentatively identified from its nmr spectrum as 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3). The fractions were further purified by intermediate scale preparative vapor phase chromatography on a 15% Carbowax 20 M column. The major product completely rearranged to two new compounds which were identified as tropone (5) and benzaldehyde by comparison of their nmr and ir spectra to those of authentic samples. The amount of benzaldehyde varied in successive injections, but its peak area was never more than

15% of the tropone peak area. The second component was a mixture of two compounds with nearly identical retention times. Spectra of the mixture contained all peaks characteristic of 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66) which had been isolated and identified from the sodium borohydride reduction of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (p 167). The remaining peaks were attributable to 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65) present in less than 1/4 the amount of 66, based on nmr signal integrals. The third component was not isolated in sufficient amount for identification.

The second preparation was conducted on a larger scale with a smaller excess of hydride. 1-Methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1) (9.00 g, 66.1 mmole) in ether (60 ml) was reduced by lithium aluminum hydride (2.51 g , 264 meq) in ether (100 ml). The excess hydride was hydrolyzed with saturated ammonium chloride (10 ml) and worked up to yield only 4.25 g (47% recovery) of yellow oil. Analysis by vpc showed four peaks of relative areas of 71:21:6:2. A spinning band vacuum distillation was attempted, as above, but the bulk of the product mixture solidified during the prolonged period at 80-100°. A total of 0.78 g (8.7% recovery) was obtained which had to be further purified by intermediate scale preparative vpc (15% diethylene glycol succinate). This time the major product, 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol

(3) was isolated. The second component again was a mixture of 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66) and 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65), based upon the nuclear magnetic resonance spectrum, whose integrals for the cyclobutene hydrogens were in the ratio 1.5:1.0. The nmr and ir spectra of the third component were identical to those of the minor product in the sodium borohydride reduction (p 167), 1,4-dimethoxybicyclo[3.2.0]hept-6-en-2-ol (67). The source of methanol necessary for formation of this product might have been a small amount used to rinse the filter cake prior to the removal of ether from the product oils. The fourth component was lost in the separation.

In the final reduction the inverse addition technique was used. Thus a slurry of lithium aluminum hydride (600 mg , 63.1 meq) in 50 ml ether was added dropwise to a rapidly stirring, cold ether solution (50 ml) of 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1) (2.73 g , 20.0 mmole) by the established procedure (p 161). Excess hydride was destroyed with saturated ammonium chloride (5 ml) and the mixture worked up as before. Vapor phase chromatography analysis of the resultant oil (1.47 g , 54% recovery) showed four components whose peak areas were in the ratio 64:17:13:6. The nuclear magnetic resonance spectrum of the crude mixture supported the assignment of the major component to 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (3). The second component peak was

principally 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65) with a detectable amount of 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66). The third peak was assigned to unreacted starting material, based on its retention time and presence of the characteristic signals in the spectrum. Since inverse addition did not appear to offer any improvement over normal addition, no attempt was made to separate the components or identify the fourth component.

Sodium borohydride

A solution of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (920 mg , 6.75 mmole) in methanol (25 ml) was added dropwise in 5 minutes to a vigorously stirring methanolic solution (25 ml) of sodium borohydride (Callery Chemical Company, Pittsburgh, Pennsylvania) (302 mg , 8.0 mmole). The apparatus described above (p 161) was used except that a smaller, 125 ml flask was used and the ice bath was omitted. The mixture was allowed to stir overnight at room temperature. The solution was neutralized by the dropwise addition of 10% hydrochloric acid (6 ml) and concentrated to approximately 25 ml under reduced pressure. A heavy, gray suspension formed on the first attempt to wash the product liquors with ether (25 ml), but this was broken by the addition of water (20 ml). The aqueous layer was drawn off and washed with ether (2 x 25 ml). The combined ether volumes were washed in turn with a saturated salt solution (25 ml) and dried over magnesium

sulfate. Flash distillation of the ether yielded a yellow oil (623 mg , 68% recovery). Analysis by vpc showed two components, in the ratio 64:33, the remaining 3% being divided among three trace impurities. The ratio was confirmed by an nmr spectrum of the mixture. The products were separated by preparative vpc (15% diethylene glycol succinate) and identified from nmr (Figure 24, p 110) and ir (Figure 25, p 113) spectral data.

For the major product, 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66): nmr ($CDCl_3$) δ 6.19 and 6.17 (AB, 2H, vinyl), 3.95 (m, 1H, C<u>H</u>OH), 3.38 (s, 3H, OCH_3), 3.13 (m, 1H), 2.80 (s, 1H, OH) and 2.12-1.18 (m, 4H, CH_2CH_2); ir (cap film) 3440, 1450, 1340, 1320, 1209, 1178, 1080, 984, 938, 855, 816, and 755 cm^{-1}; mass spectrum (70 ev) m/e 140 (13), 122 (35), 79 (100).

For the minor product, 1,4-dimethoxybicyclo[3.2.0]hept-6-en-2-ol (67): nmr ($CDCl_3$) δ 6.22 (s, 2H, vinyl), 4.03 (t, 1H, C<u>H</u>OH), 3.60 (t, 1H, C<u>H</u>OCH_3), 3.43 (s, 3H, OCH_3), 3.32 (s, 3H, CHO<u>CH</u>$_3$), 3.28 (broad s, 1H), 2.68 (s, 1H, OH), and 2.13 (m, 2H, CH_2); ir (cap film) 3550, 1452, 1352, 1290, 1174, 1089, 784, and 720 cm^{-1}; mass spectrum (70 ev) m/e 170 (2), 152 (6), 138 (26), 109 (100).

Lithium tri-t-butoxyaluminum hydride

By the procedure already described (p 161) 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (670 mg, 4.92 mmole) in tetrahydrofuran (20 ml) was added in 5 minutes to a THF slurry (100 ml) of lithium tri-t-butoxyaluminum hydride

(1.27 g , 5.00 mmole) prepared by the method of Brown and McFarlin.[81] The excess hydride was hydrolyzed with saturated ammonium chloride solution (2.0 ml) and the product worked up as before. Vapor phase chromatography analysis of the crude oil (560 mg , 84% recovery) showed three peaks in the ratio of 68:24:8. Vacuum molecular distillation improved the appearance of the oil, but did not effect significant separation. An nmr spectrum of the pale yellow oil (510 mg, 76% overall recovery) confirmed the vpc data, showing the smallest peak to be starting material and the minor product to be 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) by comparison to spectra of authentic samples. A preparative vpc separation of the product mixture failed to produce a sample of the major product sufficiently free from the starting material, 1, for characterization. However, the compound was tentatively identified as 1-methoxybicyclo[3.2.0]hept-6-en-2-one (65) on the basis of the following data obtained from its spectra after subtracting peaks due to starting material: nmr (CCl_4) δ 6.45 (d, 1H, vinyl) 6.20 (d, 1H, vinyl), 3.55 (m, 1H), 3.33 (s, 3H, OCH_3), 2.30-2.17 (m, 1H), 2.10-1.66 (m, 2H), and 1.33-1.17 (m, 1H); ir (cap film) 1740 cm^{-1}. These data are supplied as a guideline for future work should this compound be desired, and to define its presence in reduction mixtures encountered in this study.

Treatment of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) with Lithium Aluminum Hydride

1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) (70 mg, 0.50 mmole) in ether (25 ml) was added to an ether solution (10 ml) of lithium aluminum hydride (0.5 ml of 3.9 M solution, 1.95 mmole) at room temperature by the normal procedure (cf p 161). After 3 hours stirring, the excess hydride was hydrolyzed with ammonium chloride (aq., 0.70 ml) and worked up to yield a yellow oil (52 mg, 74% recovery). Comparison of the product mixture to starting material by vpc showed the area under peak of 3 had decreased only 3.5% relative to the internal standard. The composition was confirmed by nuclear magnetic resonance spectroscopy.

Manganese Dioxide Oxidation of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

A mixture of activated manganese dioxide[82,83] (200 mg, 2.30 mmole) and 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) (100 mg) in benzene (30 ml) was stirred at room temperature for 36 hours. The solution was filtered and concentrated under reduced pressure to yield a yellow oil (67 mg , 67% recovery). Analysis of the mixture by vpc showed a single product peak of the same retention time as 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1). The ratio of peak areas of 3 to 1 were 47:53. Comparison of the nmr spectrum of the mixture to spectra of authentic samples of 1 and 3 supported

the vpc data. The integrals and peak intensity of the methoxy singlets were equal. The product oil was separated by vpc and the identities of 1 and 3 confirmed by their ir spectra.

Catalytic-Hydrogenation of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Adams catalyst (platinum oxide, 50 mg) in absolute methanol (20 ml) was charged to the reaction flask of a conventional atmospheric hydrogenation apparatus and pre-reduced. To the rapidly stirring slurry, a methanolic solution (5 ml) of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) (98 mg, 0.71 mmole) was added, an additional volume of methanol (5 ml) being used to rinse residues into the flask. After a brief induction period, the hydrogen uptake began and was compensated for by displacement of hydrogen in a burett with mercury to maintain atmospheric pressure. Hydrogen uptake proceeded linearly with time past 1.1 mmole, then tapered off and stopped abruptly at a consumption of 1.43 mmole. The solution was filtered and the solvent evaporated under reduced pressure. The pale yellow oil (96 mg, 98%) showed a single product peak in the vpc with a trace (<1%) of starting material. This was easily purified by a short path distillation (0.05 torr) at room temperature to give a colorless liquid.

The product was identified as exo-1-methoxybicyclo[3.2.0]-

heptan-2-ol (68) on the basis of its nmr (Figure 27, p 124) and ir (Figure 28, p 124) spectra: nmr (CCl_4) δ 3.70 (m, 1H, CHOH), 3.28 (s, 3H, OCH_3), 2.60 (broad m, 1H, methyne), 2.50 (broad s, 1H, OH), 2.38-1.00 (m, 8H, methylene); ir (cap film, Beckman IR-12) 3550 (sh), 3440, 1460, 1445 (sh), 1368, 1340 (w), 1269, 1250, 1221, 1184, 1143 (w), 1099, 1071 (w), 1048, 1021, 1009, 981 (w), 961 (w), 923 (w), 872 (w), 797 (w), and 744 (w) cm^{-1}.

Anal. A sample submitted for C,H analysis was broken in transit. Analysis by a high resolution mass spectrometer was substituted. Calc. for $C_8H_{14}O_2$: 142.199. Found: 142.1009.

Catalytic Hydrogenation of 1-Methoxybicyclo-[3.2.0]hepta-3,6-dien-2-one (1)

1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (882 mg, 6.48 mmole) was reduced over Adams catalyst (100 mg) by the preceeding procedure (p 171). The hydrogen uptake proceeded at slightly less than half the rate observed above in the early stages of the reaction, tapered off more slowly and stopped at 12.8 ± 0.2 mmoles (uncertainty due to necessity to refill hydrogen reservoirs during reaction). Analysis of the pale yellow product oils by vpc showed a single product peak and confirmed the absence of starting material. The nmr spectrum contained no vinyl hydrogen signals, and retention

of the cyclopentanone structure was verified by the 1740 cm^{-1} infrared absorption: nmr (neat) δ 3.35 (m, 1H, methyne) 3.17 (s, 3H, OCH_3), 2.57-1.30 (m, 8H, methylene). The product, 1-methoxybicyclo[3.2.0]heptan-2-one (70), was carried directly to the next step in the synthesis, described below.

Lithium Aluminum Hydride Reduction of 1-Methoxybicyclo[3.2.0]heptan-2-one (70)

The sample of 1-methoxybicyclo[3.2.0]heptan-2-one was subjected to three successive reductions by the procedure (p 161) used for 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) before complete reduction was achieved. The product from the catalytic hydrogenation of 1 (860 mg , 6.32 mmole) was treated in successive experiments, with lithium aluminum hydride (34% active hydride) at ice methanol bath temperature (175 mg , 4.62 mmole), at room temperature (100 mg , 2.64 mmole), and in refluxing ether (100 mg , 2.64 mmole) to complete the reduction. The final product was vacuum distilled (0.05 torr, 35-40° oil bath) to yield a colorless liquid (480 mg , 55%). Analysis by vpc showed two product peaks of relative areas 15:85. The mixture was separated on an analytical vpc column and the minor product was shown to have identical vpc retention time, nmr, and ir spectra to the exo-1-methoxybicyclo[3.2.0]heptan-2-ol (68) prepared by the reverse reduction sequence (cf. Figure 25, p 113). The major product was assigned the epimeric structure, endo-1-

methoxybicyclo[3.2.0]heptan-2-ol (69) on the basis of its nmr (Figure 27, p 124) and ir spectra: nmr (CCl_4) δ 3.93 (m, 1H, CHOH), 3.40 (broad s, 1H, OH), 3.22 (s, 3H, OCH_3), 2.50 (broad m, 1H, methyne), 2.40-1.10, (m, 8H, methylene); ir (cap film, Beckman IR 12) 3435, 1462, 1410 (w), 1345, 1298, 1256, 1242, 1202 (w), 1183, 1146 (w), 1122, 1082, 1048, 1025 (w), 908 (w), 796, and 772 cm^{-1}.

Anal. Calc. for $C_8H_{14}O_2$: C, 67.54; H, 9.92. Found: C, 67.45; H, 9.76.

Pyrolysis of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3)

Freshly distilled 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3), (200 mg , 1.45 mmole) in carbon tetrachloride (0.25 ml) was degassed by three freeze-thaw cycles and sealed in a Varian A-60 nmr tube under vacuum. The first thirty minute immersion in the Woods Metal bath (142-150°) resulted in the appearance of a broad peak at 7.00 and a sharp singlet at 3.30 ppm in the nmr spectrum characteristic of tropone and the methyl group of methanol, respectively. The ratio between one-sixth of the 7.00 peak integral and the average proton integral of 3 was 19:100. The following hour at 120-124° increased the ratio to 26:100. An hour at 99-104° actually decreased the ratio (23:100), but two hours at 106-112° raised it again (27:100). The reaction was terminated at this point because the sample had deteriorated so much that the integrals

were becoming unreliable. The ratio of the integral between the methoxyl signals of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) and methanol (54:46) implied that over 1/2 of the tropone (5) formed during the experiment had polymerized.

In the same manner a fresh sample of 1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-ol (3) (400 mg , 2.92 mmole) was pyrolyzed in toluene (5 ml) at 165-174° for 100 minutes. Analysis by vpc showed essentially complete conversion to a single product. This material was collected from the analytical column effluent and confirmed to be tropone (5) by comparison of its nmr and ir spectra to those of an authentic sample.

Lithium Aluminum Deuteride Reduction of 1-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1)

A neat sample of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (2.733 g, 20.0 mmole) was added to an anhydrous ether solution (100 ml) of lithium aluminum deuteride (2.0 g, 48 mmole) (Bio-Rad Laboratories, Richmond, California. Lot 61415, anal. 99% deuterium) by the procedure described for the 3.9 M standardized solution (p 161). The exceptions were that the lithium aluminum deuteride was added to the reaction flask through a powder funnel, since it was not in solution form, and the reaction time was extended to 60 minutes, followed by 45 minutes at reflux temperature. The unintentionally large excess of lithium aluminum deuteride (decimal

point error in calculations) was hydrolyzed with saturated ammonium chloride (3.6 ml). Analysis of the crude oil (1.52 g,, 56% recovery) by vpc showed two products whose peak areas were in the ratio 73:27. It is noteworthy that the ratio of 1,2 to 1,4 reduction was not significantly different in this case than in those where only a 10% excess was used (cf. Table 3, p 106). The products were separated on an analytical vpc column (10% diethylene glycol succinate) with relatively little losses due to decomposition. The minor product was tentatively identified as 2,4-dideuterio-1-methoxybicyclo[3.2.0]hept-6-en-2-ol (76) by comparison of its nmr and mass spectra to spectra of 1-methoxybicyclo[3.2.0]hept-6-en-2-ol (66): nmr (CCl_4) δ 6.12 (s, 2H, vinyl), (~3.95, CHOH is absent), 3.32 (s, 3H, OCH_3), 3.05 (m, 1H, methyne), 2.18 (s, 1H, OH), and 1.92-1.17 (m, 3H, methylenes-d_1); mass spectrum (70 ev) m/e 142 (22), 141 (3), 140 (3), and 79 (100).

Similarly, the major product, 2-deuterio-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (75) was identified by comparison of its nmr (Figure 32, p 142) and mass spectra (Table 5, p 134) to the spectra of 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (3): nmr (CCl_4) δ 6.57 (d, 1H, vinyl), 6.28 (d, 1H, vinyl), 5.83 (m, 2H, vinyl), (~4.47, CHOH is absent), 3.65 (m, 1H), 3.43 (s, 3H, OCH_3), and 2.30 (s, 1H, OH); mass spectrum (70 ev) m/e 139 (3), 138 (3), 137 (21), 107 (60), and 79 (100).

Pyrolysis of 2-Deuterio-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (75)

On column (vpc) pyrolysis

Roughly 200 µl of 2-deuterio-1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-ol (75) was dissolved in benzene (0.30 ml) and injected in 50-80 µl aliquots onto an intermediate scale preparative vpc column (10% diethylene glycol succinate, 180° column temperature, 200° injection port). The rearrangement was complete, as no short retention peaks which might represent (75) were observed. The product peak was collected and submitted with a reference sample of tropone (5) for mass spectral analysis. The fragmentation patterns were comparable, with the labeled compound's peaks generally being one mass unit higher (Table 6, p 136). From the relative ratios the deuterium content of the pyrolysis sample was found to be 99.0%-d_1, 1.0%-d_2.

Sealed tube pyrolysis

A toluene solution (5.0 ml) of 2-deuterio-1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-ol (75) (500 mg , 3.60 mmole) was degassed by a 10 minute nitrogen purge and sealed under vacuum in a Pyrex tube (60 mm x 13 mm od) fused to a length of tubing (8 mm). The bulb was immersed in a 171° Woods Metal bath for 100 minutes, during which the temperature dropped to 161°. Analysis of the concentrated, brown reaction liquors by vpc showed two peaks, of the retention times of starting material (75) and tropone (77), whose areas were in

the ratio 38:62. The mixture was separated on an analytical vpc column (10% diethylene glycol succinate) and a portion of the tropone collected (77) was submitted with a reference sample (5) for mass spectral analysis (Table 6, p 136). From the relative peak ratios of the parent ion region the deuterium content of the tropone (77) (pyrolysate) was calculated to be 98.4-d_1, 1.1%-d_2. The remainder of the product (95 mg, 25%) was carried over to the preparation of the maleic anhydride adduct, 79 (p 179).

Preparation of Tropone (5)

The reference sample of tropone was prepared by the method of Radlick[84] in 42% yield: nmr ($CDCl_3$) δ 7.05 (m, aromatic); ir (cap film) 3425, 3020, 1634, 1575, 1522, 1475, 1253, 1215, 897, 832, and 783 cm^{-1}; mass spectrum (70 ev) m/e 106 (55), and 78 (100).

Preparation of the Diels-Alder Adduct of Maleic Anhydride and Tropone (5)

Reference sample (78)

According to the procedure of Nozoe et al.[71] tropone (5) (500 mg, 4.72 mmole) in xylene (3.0 ml) was combined with a xylene slurry (2.0 ml) of maleic anhydride (982 mg, 10.0 mmole) and refluxed for 4-1/2 hours. Overnight storage of the reaction liquors at -25° resulted in the precipitation of light brown crystals (844 mg, 87%): mp 177-178°. A single

recrystallization from acetone gave white needle crystals (448 mg,, 53% recovery): mp 180-181°, lit[71] mp 181.5-182.5°. A portion of the crystals were further purified by sublimation (0.02 torr, 120° oil bath) for reference infrared (Figure 34, p 144), nmr (Figures 32 and 33, p 142 and 144), and mass spectra (Table 7, p 140) for the deuterium labeling experiment: nmr (acetone-d_6) δ 7.32 (dd, 1H, vinyl), 6.72 (broad t, 1H, vinyl), 6.33 (broad t, 1H, vinyl), 5.77 (dd, 1H, vinyl), and 4.10-3.73 (m, 4H); ir (KBr) 3400, 1842, 1774, 1662, 1624,(w), 1266, 1245, 1218, 1172, 1073, 997, 931, 817, 777, 747, 714, and 684 cm^{-1}; mass spectrum (70 ev) m/e 204 (17), and 131 (100).

Deuterium labeled sample (79)

The tropone-d_1 (77) (95 mg , 0.90 mmole) separated by vpc from the sealed tube pyrolysis of 2-deuterio-1-methoxybicyclo-[3.2.0]hepta-3,6-dien-2-ol (75) was refluxed with maleic anhydride (164 mg , 1.67 mmole) in toluene (1.0 ml) for 4 hours. The product was precipitated by cooling the solution at -25° for 4 hours and collected by filtration. The pale yellow crystals (165 mg , 90%, mp 170-174°) were further purified by sublimation (0.02 torr, 120° oil bath) and nmr (Figures 32 and 33, p 142 and 144) and mass spectra (Table 7, p 140) were obtained: mp 179-180°; nmr (acetone-d_6) δ 7.34 (m, 1H, vinyl), 6.72 (broad t, 1H, vinyl), 6.36 (m, 1H, vinyl), 5.78 (d, 1/2H, vinyl), and 4.10-3.73 (m, 3-1/2H); mass spectrum (70 ev) m/e 205 (34), and 132 (100).

Oxygen-18 Enrichment of 1-Methoxybicyclo[3.2.0] hepta-3,6-dien-2-one (1)

A sample of 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (1) (250 mg , 1.84 mmole) was combined under nitrogen with oxygen-18 enriched water (150 µl, approx. 7.5 mmole) (Yeda Research and Development Co. Ltd., Weizmann Institute of Science, Rehovoth, Israel) in the minimum amount of methanol (100 µl) required to give a homogenous solution. Mass spectral analysis of the water showed it to be enriched in deuterium (4.9%) as well as oxygen-18 (57.5%, assuming no d_2 contribution). The methanol and water were removed at room temperature under vacuum after 66 hours at room temperature and the incorporation of oxygen-18 confirmed by infrared spectroscopy.[72] The mass spectrometer was not available during the course of this experiment and the small sample of the oxygen-18 enriched dienone, 80, which was reserved for analysis had lost much of its label by the time it could be run. The remainder of the product oil (200 mg , 79%) was carried immediately into the next step in the synthesis (vide infra).

Lithium Aluminum Hydride Reduction of Carbonyl-^{18}O-labeled 1-Methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (80)

An ether solution (10 ml) of the oxygen-18 enriched dienone (80) (200 mg , 1.47 mmole) was added to 0.50 ml (1.95 mmole) of the 3.9 M standardized lithium aluminum hydride

solution diluted with additional ether (10 ml) at -10° by the procedures already described (p 161). The mixture was hydrolyzed with saturated ammonium chloride (0.8 ml) and worked up as usual. The product mixture (approximately 150 mg) was roughly 50% (by relative vpc peak areas) 2-(^{18}O-hydroxy)-1-methoxybicyclo[3.2.0]hepta-3,6-diene (81). The mixture was separated on an analytical vpc column and the identity of 81 (62 mg , 30% overall) confirmed by comparison of its nmr spectrum to that of an authentic sample of the unlabeled dienol, 3. The oxygen-18 content was determined from the mass spectrum (Tables 9 and 10, p 148 and 149).

Pyrolysis of 2-(^{18}O-Hydroxy)-1-methoxybicyclo[3.2.0]-hepta-3,6-diene (81)

The nmr sample of the vpc purified dienol, 81, (62 mg, 0.45 mmole) in carbon tetrachloride was degassed and sealed under vacuum in its nmr tube and immersed in a 167-168° Woods Metal bath for 105 minutes. Analysis (vpc) of the dark brown product oil showed the ratio of the areas of the starting material (81) and tropone product (82) peaks to be 15:85. The center portion of several product peaks were collected from the analytical vpc column and submitted with a reference sample of tropone (5) for mass spectral analysis (Table 11, p 150). A value of 29% oxygen-18 enrichment was calculated from the spectra.

SUMMARY

The thermal rearrangement of 1-methoxybicyclo[3.2.0]-hepta-3,6-dien-2-one (1) to 3-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) has been studied. A mechanism has been proposed based upon the results of analogous rearrangements of 5-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (27), synthesized from γ-thujaplicin, and the 4, and 6-isopropyl-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one isomers (59 and 60), synthesized from β-thujaplicin.

Reduction of the carbonyl group of 1 has been shown to yield only the exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol epimer (3). Although the structural characteristics implicated in the rearrangement of 1 to 2 are retained in 3, it undergoes a unique rearrangement to tropone (5) at even lower temperatures than appear to be required for the Cope rearrangement of 1. The mechanism of this rearrangement was elucidated by deuterium and oxygen-18 labeling experiments.

APPENDIX

Instrumentation and Analysis Techniques

Nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Varian Associates A-60 spectrometer. Instances where different solvents were used are so indicated. In several clearly defined cases, supplementary spectra were run on a Varian Associates HA-100 spectrometer to separate signals of similar chemical shift for accurate integration, or to define coupling. All chemical shifts are reported as parts per million (δ) from TMS.

Routine infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer. However, Beckman Models IR-9 and IR-12 spectrophotometers were used interchangeably in the intramolecular hydrogen bonding studies because of their greater resolution and expanded scale capability. In this study the samples of known concentration were prepared by mixing a known weight of solute (by difference) with a volume of solvent measured between visible graduations of an appropriate size Hamilton microliter syringe. Subsequent dilutions were carried out by combining volumes of a known solution with solvent, both having been measured in separate syringes. The infrared spectrophotometer was operated in accord with recommended procedures, variable settings being SB/DB ratio, 1.0; select/standard slit width ratio, 1.5; period, 2; and gain, 4.4-6.0. Path lengths were varied from a capillary film to

10.0 mm to obtain acceptable band intensities.

Samples were submitted for mass spectral analysis on an Atlas CH-4 single-focusing spectrometer (MAT). Liquids were commonly vaporized in the heated inlet system. However, to reduce the possibility of pre-rearrangement of 1-methoxy-bicyclo[3.2.0]hepta-3,6-dien-2-ol (3) this liquid was absorbed on silica and introduced directly into the inlet chamber.

Analytical vapor phase chromatography was carried out on a Varian Aerograph Model 1520 dual column chromatograph with thermal conductivity detectors. Diethyl phthalate was used as an internal standard and corrections were made for differences in thermal conductivities in the first part of this thesis, but not in the second part. Thus, in the latter case, only peak area ratios (not necessarily molar ratios) are reported. The areas under the peaks were obtained by a Disc integrator and were corrected for baseline drift. Carbowax 20 M (10% w/w) was used as liquid phase on Chromsorb W, acid washed, DMCS (dimethyl-dichloro silane) treated, 60/80 mesh support in the very early phases of this research, but was replaced with diethylene glycol succinate (LAC 728) (10% w/w) after isomerization of the bicyclic products was observed on preparative scale columns of Carbowax 20 M.

Temperature programming was necessary to obtain satisfactory separation of the 2-methoxytropone photoproducts or their isopropyl substituted analogs. A rate of 4°/minute from 130° (140° for the isopropyl substituted compounds) to 180°

(hold at limit) was standard. Injection port temperatures ranged from 190-210°. Milder conditions were used in analysis of the compounds discussed in Part II of this thesis. Port temperatures of 170-180° and oven temperatures of 130-140° (isothermal) were sufficient. No thermal rearrangement of any of the bicyclic compounds was observed on the analytical scale (1/4" x 60") copper columns with LAC 728 under these conditions.

Separation of the bicyclic isomers encountered in Part I could be effected only by preparative vapor phase chromatography. Special 1" x 96" and 1/2" x 84" copper columns (15% LAC 728 with a layer of 10% SE-30 on effluent end to minimize liquid phase bleeding into the collectors) were prepared for the Hewlett-Packard (F & M Scientific Division) Model 776 Prepmaster Jr. chromatograph for this purpose. The alcohol studied in Part II, exo-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-ol (3) was far too unstable to survive the lengthy separation period required by preparative scale vpc, so it was separated, as necessary, on the analytical columns (vide supra). Intermediate scale preparative vpc columns (3/8" x 144") were packed with 15% LAC 728 and Carbowax 20 M, respectively, for the Aerograph Model 1520 chromatograph. These received heavy use before the Prepmaster Jr. was available and served in special applications thereafter.

Ultraviolet spectra were recorded on a Cary 14 spectrophotometer.

Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillary tubes. Neither the melting points nor boiling points reported are corrected.

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