I. OZONOLYSIS AND EPOXIDATION OF METHYL MALEOPIMARATE AND OTHER DITERPENOID ESTERS

II. ABSOLUTE CONFIGURATION OF (-)-METHYLISOPULEGONE

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GENERAL INTRODUCTION

This thesis consists of two parts. The first part describes the ozonolysis and epoxidation of methyl maleopimarate and other diterpenoid esters. The second part reports a study on absolute configuration of (-)-methylisopulegone and reductive methylation of (+)-pulegone and other flexible ketones. Due to the diversity of the two parts, each has its own subdivisions: historical and introduction, results and discussion, and experimental.

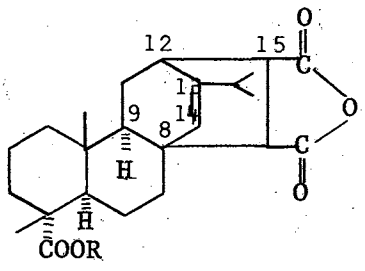
PART I

OZONOLYSIS AND EPOXIDATION OF METHYL MALEOPIMARATE AND OTHER DITERPENOID ESTERS

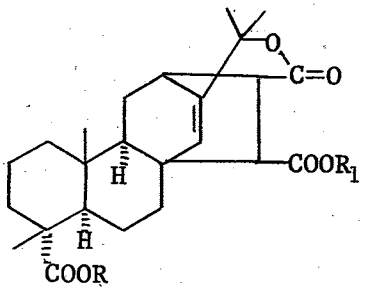
HISTORICAL AND INTRODUCTION

Oxidation of maleopimaric acid (1a), the Diels-Alder adduct obtained from levopimaric acid and maleic anhydride, with potassium permanganate has been studied by Arbuzov,[1] and by Ruzicka and LaLande.[2] Ozonolysis of methyl maleopimarate (1b) was first carried out by Weinhaus and Sandermann in 1936;[3] they claimed the isolation of a product (A) with formula $C_{25}H_{34}O_8$ and mp 250°.

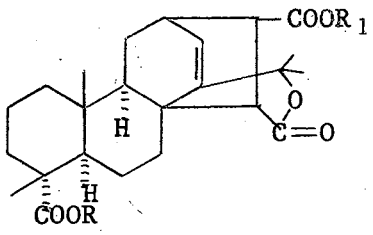
In 1940, Ruzicka and LaLande[2] repeated the ozonolysis of 1b, which yielded, in addition to A, two isomeric monomethyl esters of molecular formula $C_{25}H_{34}O_6$, melting at 290° (B) and 226° (C).[4] These workers found that the dimethyl ester (D), mp 184°, prepared from C was identical with a dimethyl ester prepared from the products obtained on oxidation of maleopimaric acid with alkaline potassium permanganate.



1a, R = H
1b, R = CH_3

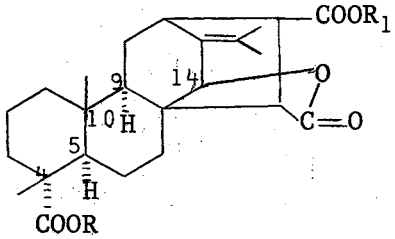


2a, R = R_1 = H
2b, R = CH_3, R = H
2c, R = R_1 = CH_3



3a, R = R_1 = H
3b, R = CH_3, R_1 = H
3c, R = R_1 = CH_3

They assigned either structure 2b or 3b to C. Zalkow and co-workers[5] also encountered C as an esterification product after the alkaline permanganate oxidation of 1a. These latter workers[5] rejected Ruzicka and LaLande's structures 2b or 3b, and instead proposed 4b as the structure for C. However, the structures of A and B remained uncertain, although structure 7 had been proposed by Ruzicka and LaLande[2] for A and 2b or 3b for B.

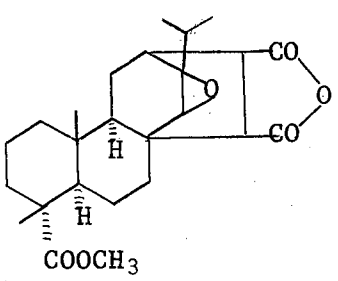


4a, R = R_1 = H
4b, R = CH_3, R_1 = H
4c, R = R_1 = CH_3

The present investigation was thus undertaken to study the course of the reaction of ozone with 1b and establish the structures of the reaction products. We[6] repeated the ozonolysis of methyl maleopimarate, 1b, as described previously[2] and obtained three products, A, B, and C as reported.

C, upon esterification with diazomethane, indeed gave D. This latter compound was shown to be identical with 4c since a mixture of

the products from the alkaline permanganate and the ozone oxidation of 1b showed no depression in melting point. B was reassigned structure 5 instead of 2b or 3b and A was assigned structure 6 instead of 7.



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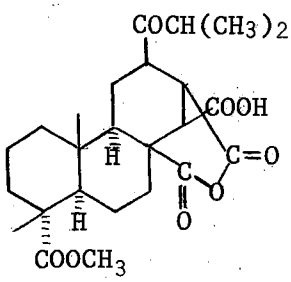

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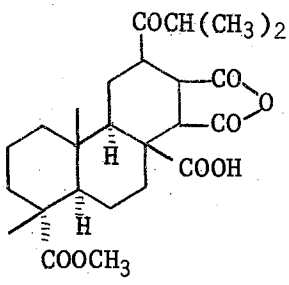
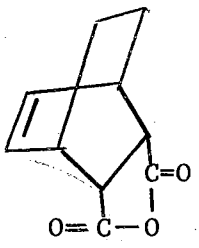


7

Compound 5, besides being obtained as one of the products of ozonolysis of 1b, was independently synthesized as a single product by epoxidation of 1b with peroxytrifluoroacetic acid. To account for the stereospecificity of the reaction, we proposed a peroxide intermediate[6] which satisfactorily accounts for the formation of 5. Henbest[7] has pointed out several reaction paths which are in accord with our proposal.[6]

Later, it seemed desirable to extend the epoxidation reaction to systems containing structures closely resembling the C/D ring junction in 1b. We selected bicyclo(2.2.2)oct-5-ene-endo-cis-2,3-dicarboxylic anhydride (8), an adduct of 1,3-cyclohexadiene and maleic anhydride, as a model compound for the epoxidation studies. Thus, when 8 was treated with peroxytrifluoroacetic acid, the product arising from cis-attack, namely 5,6-endo-epoxy-bicyclo(2.2.2)octane-cis-2,3-dicarboxylic anhydride (9), was preponderant over the hydroxy lactone 10. The precursor to lactone 10 could be either 9 or 11. The only evidence in favor of 11 is that the epoxidation of the olefin 8 with other peroxy

acids, such as m-chloroperphthalic acid, results exclusively in the formation of hydroxy lactone 10; and since this peroxy acid is bulky, the electrophilic attack on the double bond should occur from the less hindered side (exo). Thus, the epoxy anhydride 11 may serve as an intermediate in the formation of 10 from 8.



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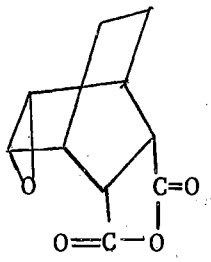

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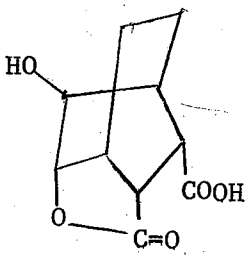

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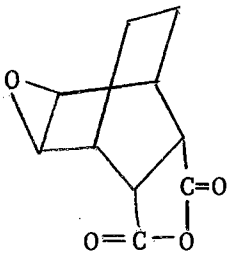

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RESULTS AND DISCUSSION

Ozonolysis and Epoxidation of Methyl Maleopimarate (1b) and Other Related Compounds

Ozonolysis of 1b was carried out in glacial acetic acid at room temperature and products were isolated according to the procedure of Ruzicka and LaLande.[2] Three products, 4b (=C), 5 (=B), and 6 (=A) were isolated.

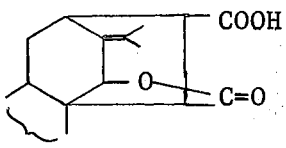
Structural Assignment to 4a

Ruzicka and LaLande[2] originally proposed structure 2b or 3b for B. Later, Zalkow and co-workers,[5] while studying the oxidation of 1a with alkaline potassium permanganate, isolated the lactone $C_{24}H_{32}O_6$ (E), mp 212°; this gave a dimethyl ester $C_{26}H_{36}O_6$ (F), mp 184°, that was identical with the methyl ester of the lactonic acid $C_{25}H_{34}O_6$, mp 227°, obtained by Ruzicka and LaLande.[2]

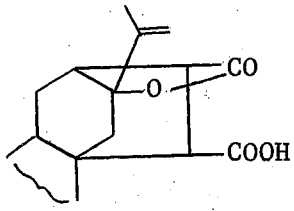
The latter workers,[5] using data from chemical, infrared (IR), and

nuclear magnetic resonance (nmr) studies, proposed structures 4a and 4b; these contradict the structures 2a or 3a and 3b originally proposed by Ruzicka and LaLande.[2] The IR spectra, for example, of both E and F showed a strong band at 1780 cm^{-1}, indicating the presence of a γ-lactone function. Since Ruzicka's structures (2a, 2b and/or 3a, 3b) contain δ-lactone groups, these structures cannot be correct.

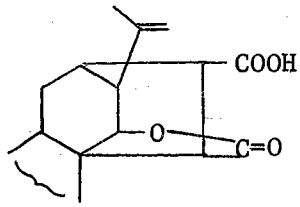
Nevertheless, three structures each containing a γ-lactone ring and one double bond may be written, viz., 4a, 4d, and 4e. The hindered nature of the double bond for E was revealed when it gave a positive



4a



4d

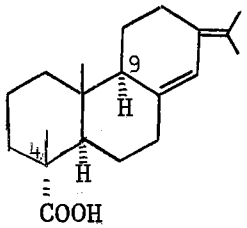


4e

test with tetranitromethane but a negative one with bromine in carbon tetrachloride. Structures 4d and 4e are inconsistent with the hindered nature of the double bond, and furthermore, the IR spectrum of E lacks the strong band at 890 cm^{-1} to be expected for the isopropenyl group in either 4c or 4d. The nmr spectrum of 4a distinguishes it from structure 4d and 4e.[5] The nmr spectrum of E showed only a single hydrogen signal at τ 4.92 and a sharp six-hydrogen signal at τ 8.22 in addition to a signal for the methyl hydrogen at C_{10}.

These nmr signals of E are incompatible with structures 4d and 4e but in full agreement with 4a.[5] Furthermore, when the nmr spectrum of this lactone, 4a and/or 4b, was compared with that of model compounds such as 1a and 1b, the C-14 proton showed a small upfield shift, whereas the deshielding of the protons of the isopropyl methyl (0.8 ppm)

of 4a and 4b compared to those in 1a and 1b was almost identical with the deshielding (0.7 ppm) in neoabietic acid (12) and abietic acid (13).[5] Had Ruzicka's structures 2a, 2b, 3a, and 3b been correct, the



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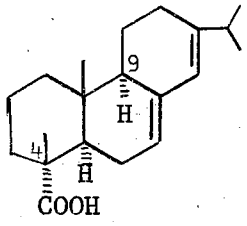


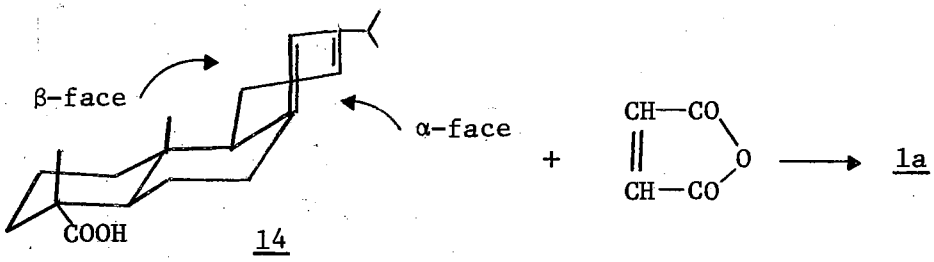
13

signals for the C_{14} proton in each case would have been expected to appear at about the same field position as in 1a or 1b, whereas the signals for the isopropyl methyl protons should occur at lower field as compared to those for the model compounds 1a and 1b, since the lactone function in 2a and 3a would exert its influence.

Absolute Configuration of 4b

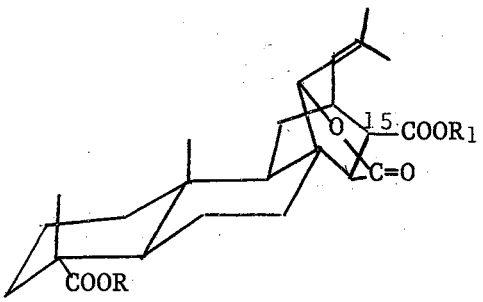
The stereochemistry at C-4, C-5, and C-10 for 4a and 4b has been shown to be the same as in other related resin acids;[4] furthermore, according to recent reports,[8,9] both abietic acid (13) and levopimaric acid (14) have an α hydrogen at C_9.

The absolute configuration at C_8 and C_{12} of 1a was predicted through the Diels-Alder reaction used to form 1a from 14 and maleic anhydride,[10] since the approach of the dienophile toward the α-face of 14 is preferred over that of the β-face as illustrated. Burgstahler



14

and co-workers[9] have shown that the C-ring in levopimaric acid is skewed in such a manner that the β-face is shielded by the angular methyl group at C-10 while the α-face is free for attack by the dienophile. Thus, the lactone 4a should properly be represented as shown below:



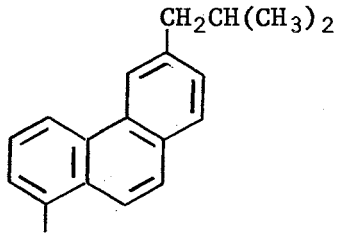
4a, R = R_1 = H
4b, R = R_1 = CH_3

The carbomethoxy group at C-15 in 4a or 4b has been assigned the β-configuration with certainty because the corresponding α-C_{15} isomer has recently been described[11] and was compared with 4b.

We also isolated 4b during the ozonolysis of 1b and have shown that its methyl ester is identical with 4b by comparison of melting point and infrared and nuclear magnetic resonance spectra.

Structure of the Anhydride 6

Since dehydrogenation of A did not give the expected 6-isobutyl-1-methylphenanthrene (15), structure 7 was discarded and structure 16a or 16b was substituted after the presence of a ketone carbonyl group was confirmed.



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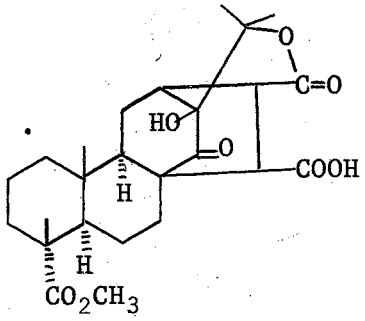
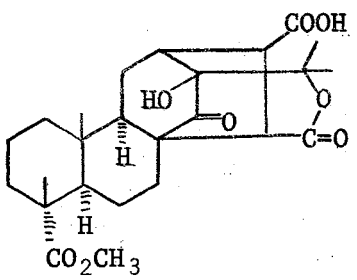
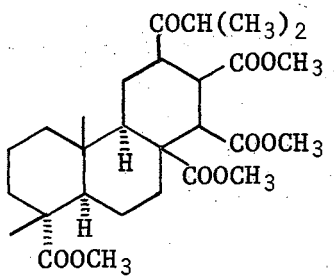


16a



16b

We also encountered A and confirmed the previously reported[3] molecular formula, $C_{25}H_{34}O_6$. This compound did not correspond to either 7, 16a, or 16b, and we suggested the structure 6 for the following reasons.[6] The infrared spectrum of A showed a characteristic glutaric anhydride band at 1764 and 1802 cm^{-1}. Further evidence was obtained by converting A to the tetramethyl ester 17 with methanolic diazomethane.



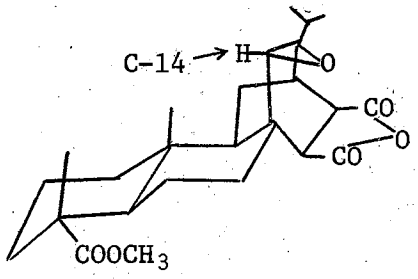
17

That 17 was a tetramethyl and not a trimethyl ester was shown by its nmr spectrum and its saponification equivalent. The anhydride 6 apparently arises by cleavage of the double bond as originally surmised[12] but the more stable six-membered anhydride ring is formed in preference to the five-membered ring during isolation.

Structure of the Epoxy Anhydride 5

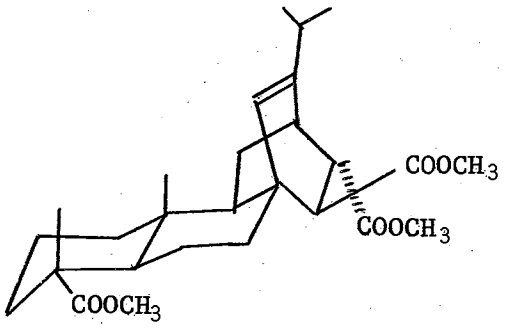
Structure 5 was proposed[6] as a substitute for 2a or 3b[2] to account

for the molecular formula, chemical properties, and nmr and IR data for B.



5

The IR spectrum of B showed the characteristic succinic anhydride-type carbonyl absorption at 1720 and 1777 cm^{-1}; and, in addition, its nmr spectrum showed the proton at C-14 as a singlet centered at τ 6.8. Both these observations are inconsistent with structures 2b or 3b. The most convincing evidence for structure 5 came from the observation that B could also be prepared from 1b by treatment with peroxytrifluoroacetic acid.[13] However, other peracids such as monoperphthalic acid or m-chloroperbenzoic acid were ineffective. Recently, it has been shown that one of the products obtained in the alkaline permanganate oxidation of trimethyl fumaropimarate (18) is 19, arising by double-bond migration (but not in the absence of permanganate) followed by hydroxylation.[14]



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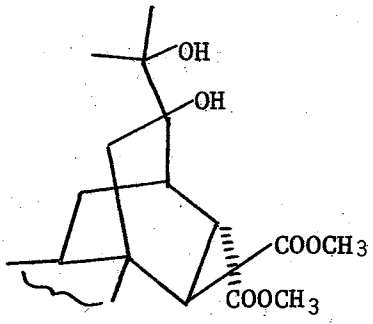
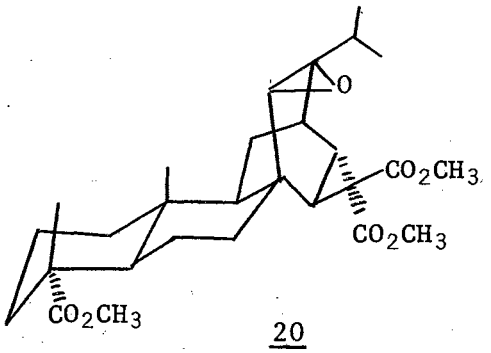


19

That the double bond in 1b did not rearrange in a similar manner in the formation of B was evident from the nmr spectrum of B, which showed the isopropyl methyl signals as a pair of doublets (J = 7 cps) centered at τ 9.28 and 8.93. Had the double bond migrated prior to epoxidation, these methyl signals would have appeared as a pair of singlets much farther downfield.[15] In addition, the presence of the low-field C-14 proton signal supports structure 5. The stereochemistry of the epoxide ring in 5 is assigned on the basis of the argument presented below (see Fig. 1 and 2).

The epoxide 5 was converted into epoxy triester 20 by heating in refluxing alkali, followed by re-esterification with diazomethane. The ester 20 was also prepared by epoxidation of trimethyl fumaropimarate (18) with peroxytrifluoroacetic acid. A comparison of the nmr spectra of 5 and 20 was of interest. Surprisingly, one of the isopropyl methyl groups in 20 is deshielded to a considerable extent (τ 8.68) as compared to those in 5. The anhydride ring in 5 was opened only with great difficulty, whereas the apparently similar anhydride ring in 1b was readily opened with methanolic diazomethane to yield triester 21.



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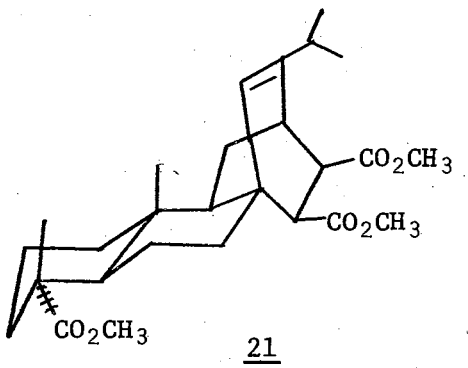
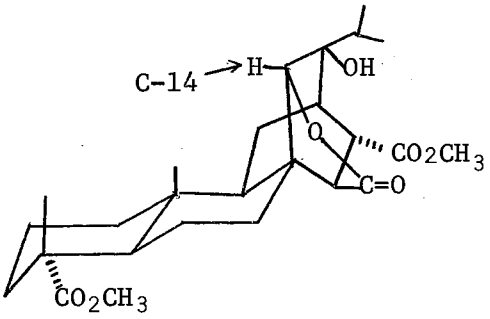


21

In contrast to 18, the isomeric trimethyl maleopimarate (21) when treated with peroxytrifluoroacetic acid under identical conditions, did

not give an epoxide but rather a hydroxy lactone ($C_{26}H_{38}O_7$). This product has been assigned structure 22 because its IR spectrum is characteristic of a hydroxy-γ-lactone (3400 and 1762 cm^{-1}) and its nmr spectrum established the presence of two methyl ester groups (τ 6.36 and 6.29). Of particular importance was the appearance of a one-proton singlet at τ 6.16 which arises from the C-14 proton of 22. This proton absorption was not affected by D_2O. The alternative γ-lactone structure 23 is considered less likely on both mechanistic and steric



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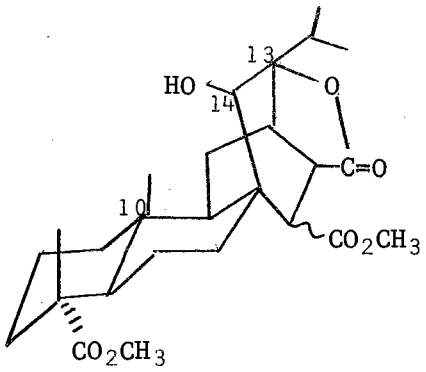
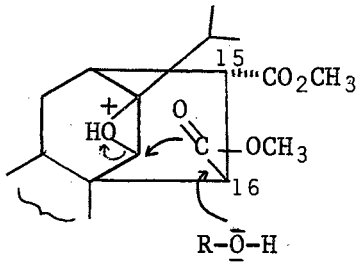


23

grounds. Examination of a Dreiding model indicates that the C_{10} methyl group of 23 would suffer severe interaction with the C_{13} isopropyl group and the C_{14} hydroxyl group; thus the C_{10} methyl group would be expected to be highly shielded. In fact, the nmr spectrum showed only a normal C_{10} bridgehead methyl group (τ 9 or 8.87).

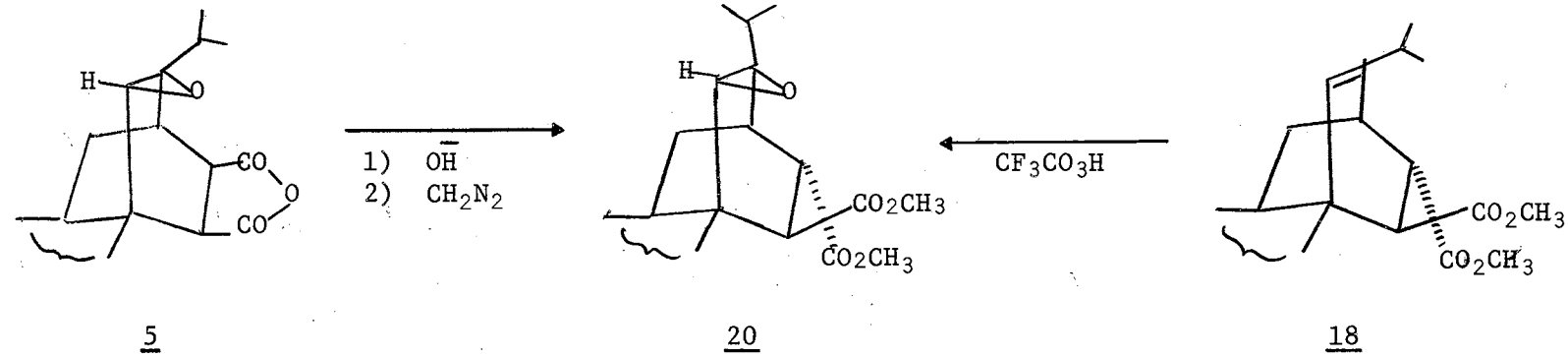
The formation of the hydroxy lactone 22 undoubtedly occurs via the intermediate epoxide 24 (see Fig. 1) which, in the presence of peroxytrifluoroacetic acid, undergoes ring opening by the β-oriented C_{16} carbomethoxy group as depicted in 25. The nucleophile ROH may arise from peroxytrifluoroacetic acid or water, the latter being present in the 90% hydrogen peroxide. Since 22 was unchanged after heating in



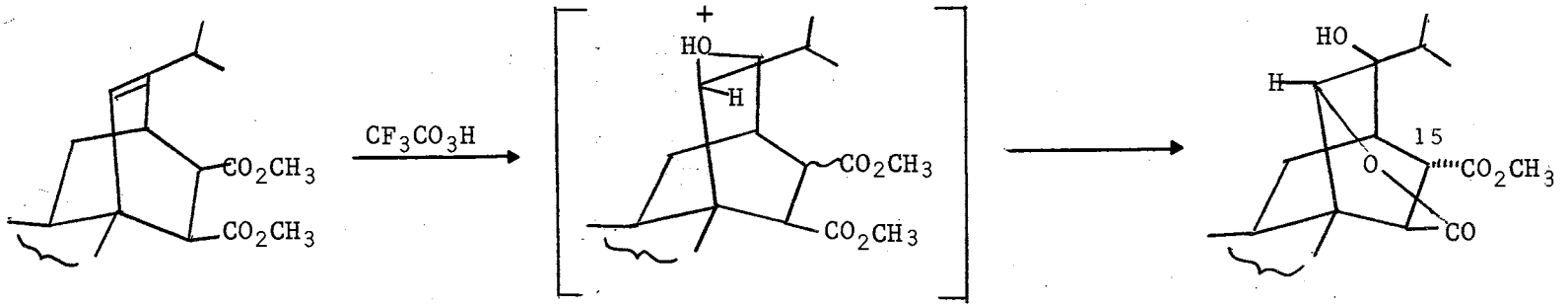
25

refluxing alkali followed by re-esterification with diazomethane, the C-15 carbomethoxy group is assigned the more stable α-configuration.[14] Thus, the epoxide ring in 5 or 20 must be *trans* to the C_{10} bridgehead methyl group, since it is not cleaved by hot alkali or under acidic conditions.

An explanation for the observed stereospecificity in the epoxidation of 1b, 18, and 21 follows. In 18, the face of the double bond *anti* to the C_{10} bridgehead methyl group is less hindered than the *syn* face, since the C_{15} carbomethoxy group is down, whereas in 21 the *syn* face is relatively less hindered than the *anti* face. Thus, the reaction of peroxytrifluoroacetic acid with 18 and 21 respectively yields 20 and 22 as shown in Fig. 1. Finally, considering the epoxidation of 1b with peroxytrifluoroacetic acid to yield 5, the observed stereospecificity appears to be more stereoelectronic rather than steric in origin. An apparent structural difference between 1b and both 18 and 21 is that 1b has an anhydride ring while 18 and 21 have carbomethoxyl groups at C_{15} and C_{16}. This, in conjunction with Henbest's observation[7] of stereospecific epoxidation of properly oriented olefinic anhydride moieties explains why 1b leads to 5. It states, "The directive effect of some kind may be caused by association of the reagent with the substituent by some form of partial bonding; the reagent would then be



5 20 18



21 24 22

Figure 1. Epoxidation of Trimethyl Maleopimarate (21) and Maleofumarate (18)

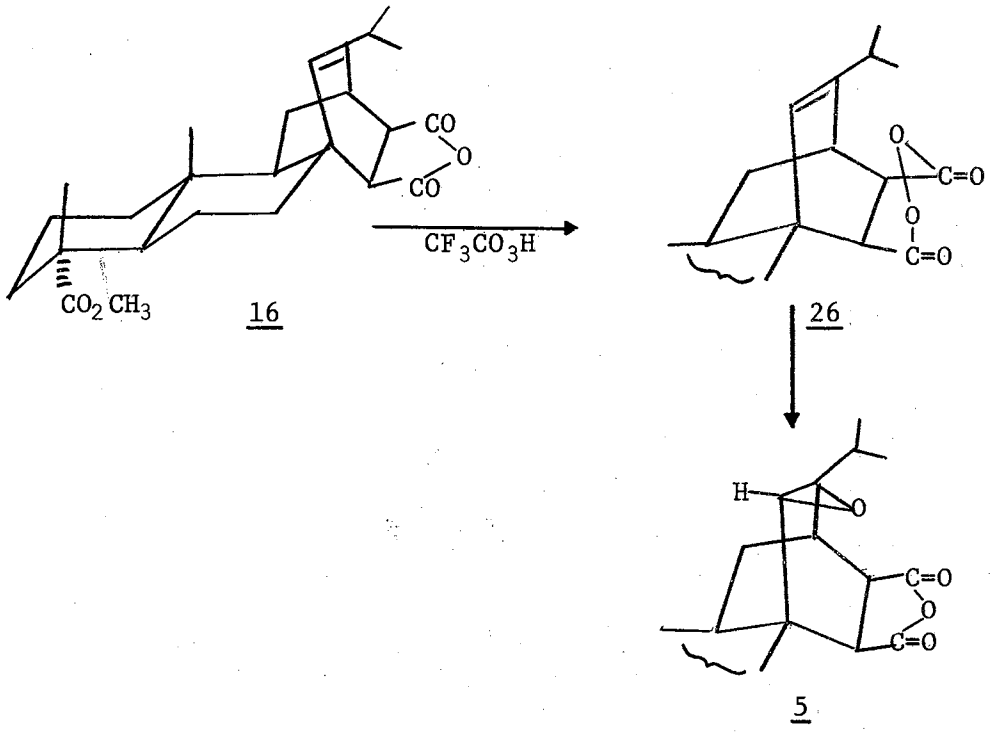


Figure 2. Epoxidation of Methyl Maleopimarate (1b)

held, albeit temporarily, on the same side of the ring as the substituent, and the probability of cis attack could be increased."[7] In view of this observation,[7] the proposal[6] that the anhydride ring in 16 is converted by reagents such as peroxytrifluoroacetic acid or ozone in acetic acid into the intermediate peroxide 26 (see Fig. 2), which then reacts intramolecularly to give 5, appears logical.

Finally, it is interesting to compare the results of ozonolysis of 1b and its corresponding trimethyl ester 21 under the same conditions. In the latter case, eight crystalline products were isolated, none of which arose by cleavage of the double bond.[16] However, such an oxidation product might very well have been present to a small extent in the non-crystalline residue. A possible mechanistic pathway for the formation of products 4b, 5, and 6 is outlined in Fig. 3.

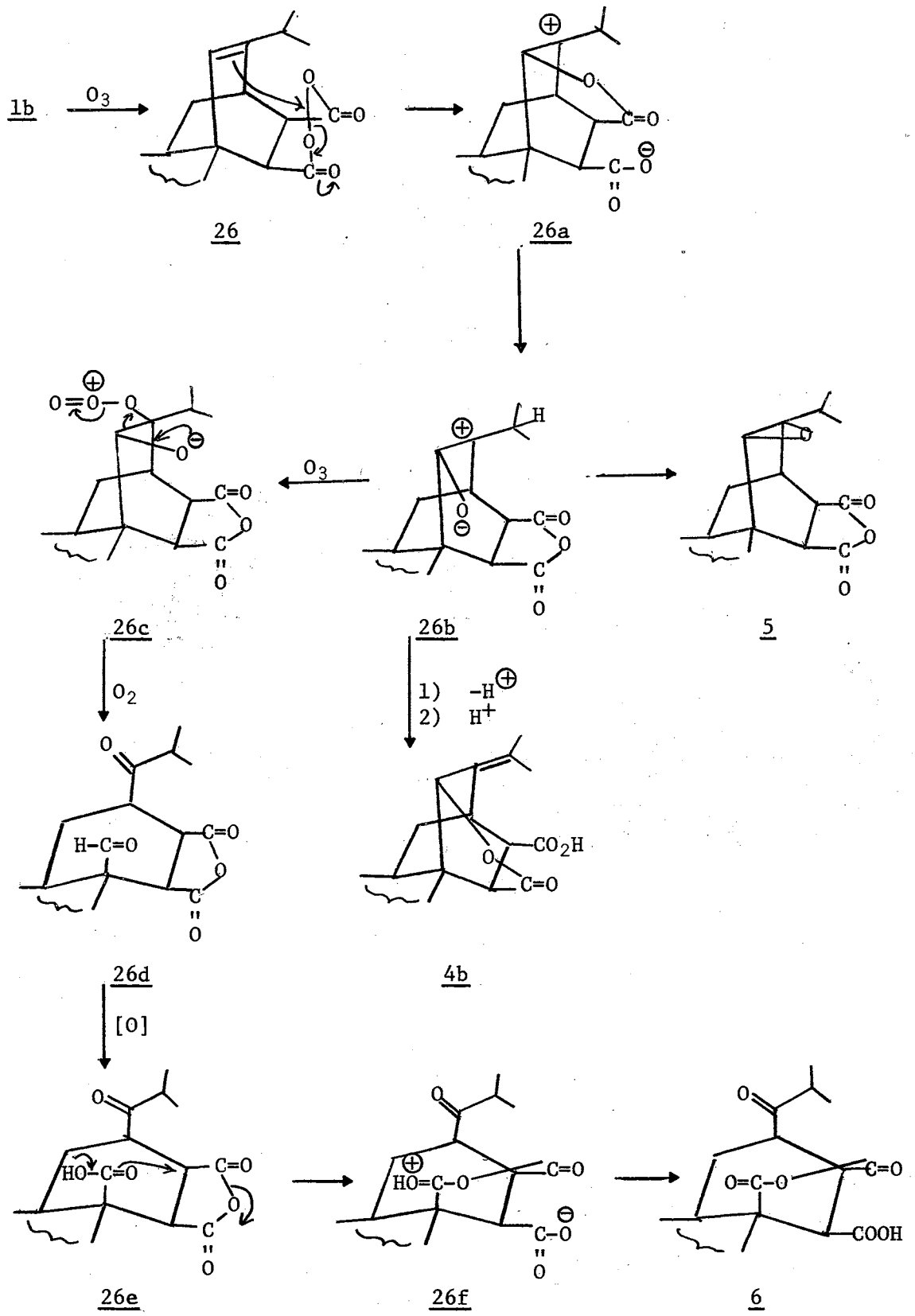
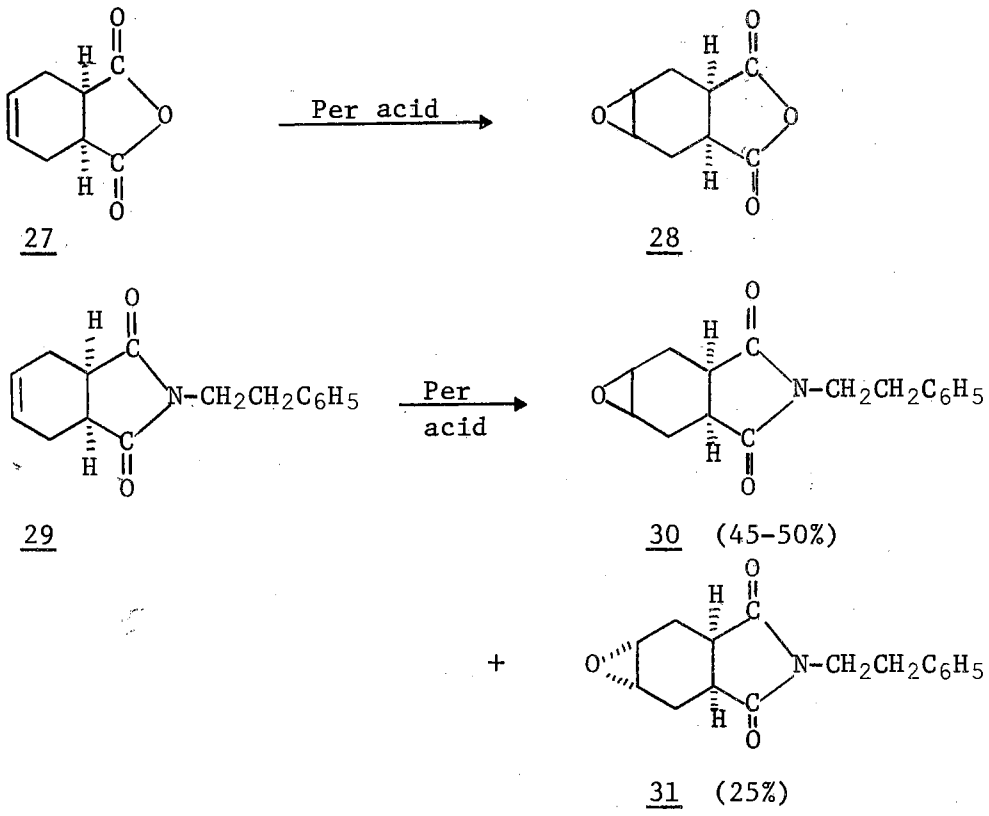


Figure 3. Ozonolysis of Methyl Maleopimarate (1b)

Reaction of Peroxytrifluoroacetic with Bicyclo[2.2.2]oct-5-ene-endo-cis-2,3-dicarboxylic Anhydride (8)

To test the generality of the reaction of peracids to give endo-epoxy anhydride by way of cis-attack on the olefinic anhydride, we treated peroxytrifluoroacetic acid with 8, an adduct of 1,3-cyclohexadiene and maleic anhydride. Endo-epoxy anhydride, 9, as expected was obtained as the major product, while the minor one was identified as the hydroxy lactone 10. Epoxidation reaction of olefins with per acids, in most cases, is stereospecific, leading to a cis-addition of the oxygen atom to the double bond.[17] Such a generalization, though, should be extended with caution because of the presence of other functional groups in the olefin which may alter the stereochemistry of the epoxide ring. The role of properly oriented olefinic anhydride to yield the stereospecific epoxy anhydride is now clear.[6,7] It has been observed[18] that the ability of the olefinic anhydride in which the anhydride ring forms a peroxide intermediate by reacting with peroxy acid, yielding cis epoxy anhydride, is unique. If, for example, the anhydride ring is replaced by imide, the stereospecificity is lost. Thus, Gray and co-workers[18] found that epoxidation of Δ^4-tetrahydrophthalic anhydride (27), with per acids, gave exclusively cis-epoxide 28, but when Δ^4-tetrahydro-N-phenethylphthalimide (29) was epoxidized with per acid, a mixture of both the epoxides 30 and 31 was obtained. The same authors found that when the anhydride ring is opened to prepare dimethyl ester 32, the epoxide ring obtained in 33 is exclusively trans to the carbomethoxyl groups.

We[6] have encountered a similar case as pointed out in earlier discussion (Structure of the Anhydride 5, page 8). Thus, when 1b,



containing an anhydride function, was epoxidized, the product was 5, while the corresponding trimethyl ester 21 on epoxidation gave hydroxy lactone 22, probably resulting from the precursor 24.

32 33

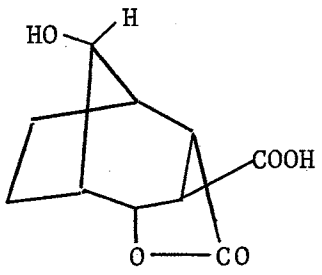
Structural Assignment to 9

The olefin 8, when treated with peroxytrifluoroacetic acid, gave two products. The IR spectrum of the major component showed the characteristic anhydride band (1852 and 1786 cm^{-1}) and its nmr spectrum showed three singlets at τ 6.3, 6.5, and 6.9 and a broad multiplet

between τ 8.6 and 7.9. Had the epoxide ring been exo as in 11, it would have cleaved easily owing to most favorable participation of the anhydride ring. This would result in the formation of hydroxy lactone 10 exclusively, which was not observed. Berti[19] has documented several cases involving intramolecular cleavage of a C-O bond in epoxides by the carbonyl or hydroxyl group, leading to hydroxy lactone. It is interesting to point out at this stage that the stereochemistry of the epoxide of 8 was governed by the size of the peroxy acid used. Thus, unlike peroxytrifluoroacetic acid, which, with olefin 8, gave as the major product 9 and the minor product hydroxy lactone 10, m-chloroperbenzoic acid gave exclusively hydroxy lactone 10. The apparent difference in reaction of these two per acids toward 8 might be steric rather than electronic in origin. Thus, m-chloroperbenzoic acid, being bulkier than peroxytrifluoroacetic acid, cannot approach the olefin 8 from the endo side owing to the hindrance from the anhydride ring. Instead, there is observed an exo-attack, resulting in the formation of 11, which, with concomitant intramolecular displacement by the anhydride gives 10.

Structure of the Hydroxy Lactone 10

The hydroxy lactone 10 was obtained as a minor component during the epoxidation of the olefin 8 with peroxytrifluoroacetic acid. Its structure, 10, as is outlined in Fig. 4, is assigned on the basis of its IR spectrum, which shows the characteristic bands for hydroxyl (3425 and 2941 cm^{-1}), γ-lactone (1770 cm^{-1}), and carboxyl groups (1709 cm^{-1}). These infrared data, unfortunately, fail to distinguish hydroxy lactone 10 from another hydroxy lactone, 34, resulting from Wagner-Meerwein 1,2 shift.



34

In order to exclude the possibility of a rearranged product such as 34, the hydroxy lactone was further esterified with diazomethane, and the resulting ester 35 was oxidized by chromic acid to yield the keto lactonic ester 36. Its infrared spectrum (1802, 1751, and 1721 cm^{-1}), which shows keto carbonyl absorption at 1721 cm^{-1}, discounted the possibility of cyclopentanone-type structure and thus ruled out structure 34.

The stereochemistry of the hydroxyl group at C-6 in 10 could easily be inferred, in view of the knowledge[17] that the opening of the epoxide, if sterically possible, proceeds with inversion of configuration with nucleophilic reagents (in the formation of 10, it is the carboxylate ion from anhydride ring) at the carbon atom attacked, resulting in an overall trans addition to the double bond, as exo.

Incidentally, as mentioned above, when the olefin 8 was epoxidized with m-chloroperbenzoic acid, formation of 10 was exclusive. Hydroxy lactone 10 obtained by two different routes (peroxytrifluoroacetic and m-chloroperbenzoic acid epoxidation of olefin 8) was shown

to be the same from each source, and as expected, the infrared spectra were superimposable.

The reaction of ester 37 with per acid 8 was also studied, and the results are in accord with those of Gary and co-workers.[18] Thus, on treating the olefin 8 with methanolic diazomethane, the dimethyl ester 37 was obtained, which, when epoxidized with m-chloroperbenzoic acid, gave a single epoxy ester, 38. Its structure is based on its IR (1751 and 1429 cm^{-1}) and nmr spectra: multiplet at τ 8.85 (4H), singlet at 6.45 (6H), two singlets at 7.0 (2H) and 7.7 (2H), and broad multiplet at 7.5 (2H).

The assignment of the stereochemistry of the epoxide ring of 38 is again based on steric consideration. The endo-cis carbomethoxy groups of 37 offer steric hindrance to the approaching m-chloroperbenzoic acid so that exo orientation is favored.

An attempt to prepare endo-epoxide from the dimethyl ester 37 through a bromohydrin was not successful.

Thus, when the olefin 8 was treated under strongly acidic conditions with N-bromosuccinimide and sulfuric acid, it gave a bromo lactonic acid, 39, which, when treated with alkali, gave its C-2 epimer 40. This epimer 40 was also obtained when dimethyl ester 37 was treated with N-bromosuccinimide and sulfuric acid, and the intermediate bromohydrin 41 treated with alkali. Milder bases, such as pyridine at 90°, had no effect on the bromohydrin. These reactions are outlined in Fig. 5.

Thus the reaction of peroxytrifluoroacetic acid on the olefinic anhydride 8, again unique in giving epoxy anhydride 9 and in line with views[6,7] discussed earlier, can be analogously rationalized through a

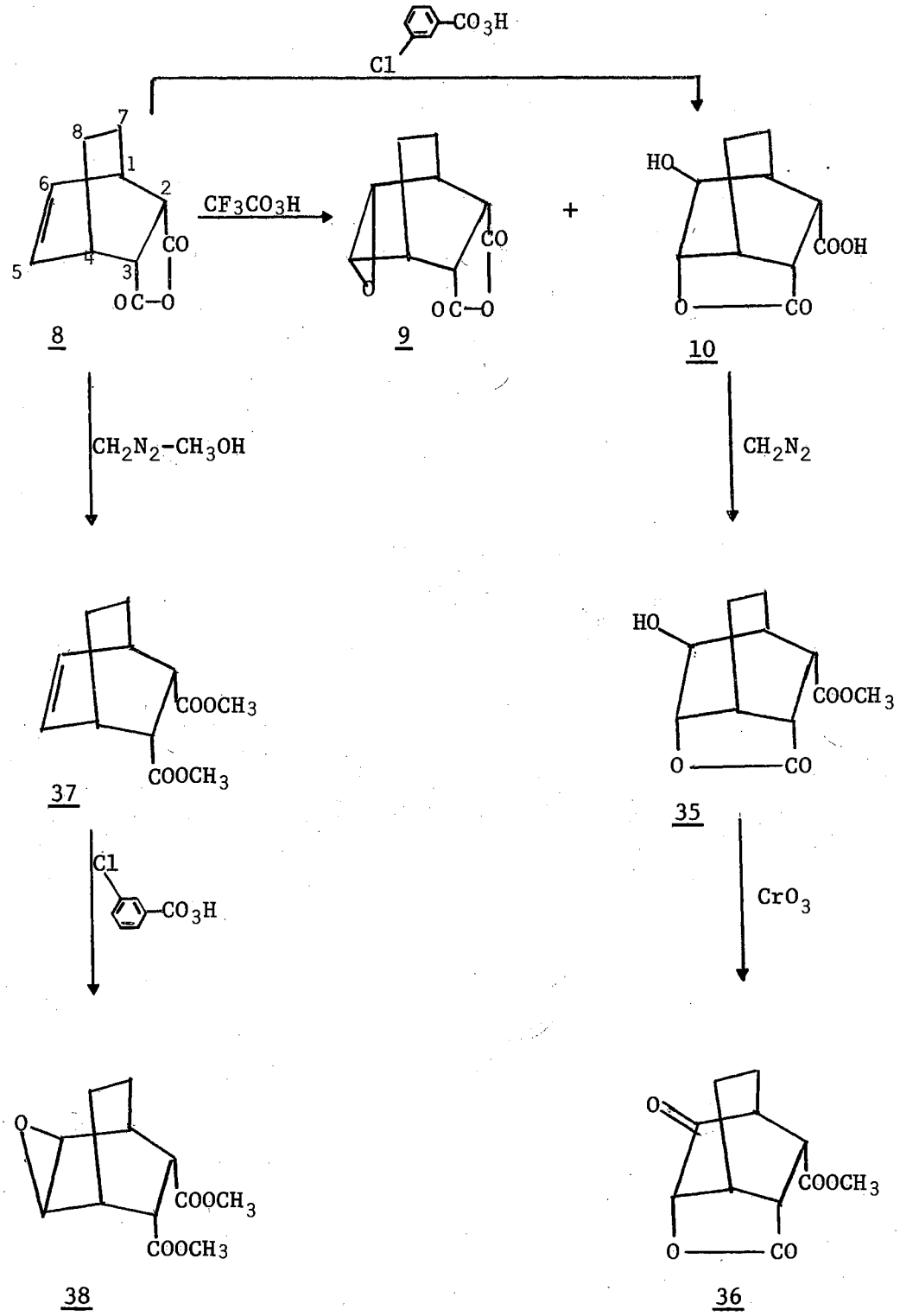


Figure 4. Epoxidation of Bicyclo[2.2.2]oct-5-ene-endo-cis-2,3-dicarboxylic Anhydride (8)

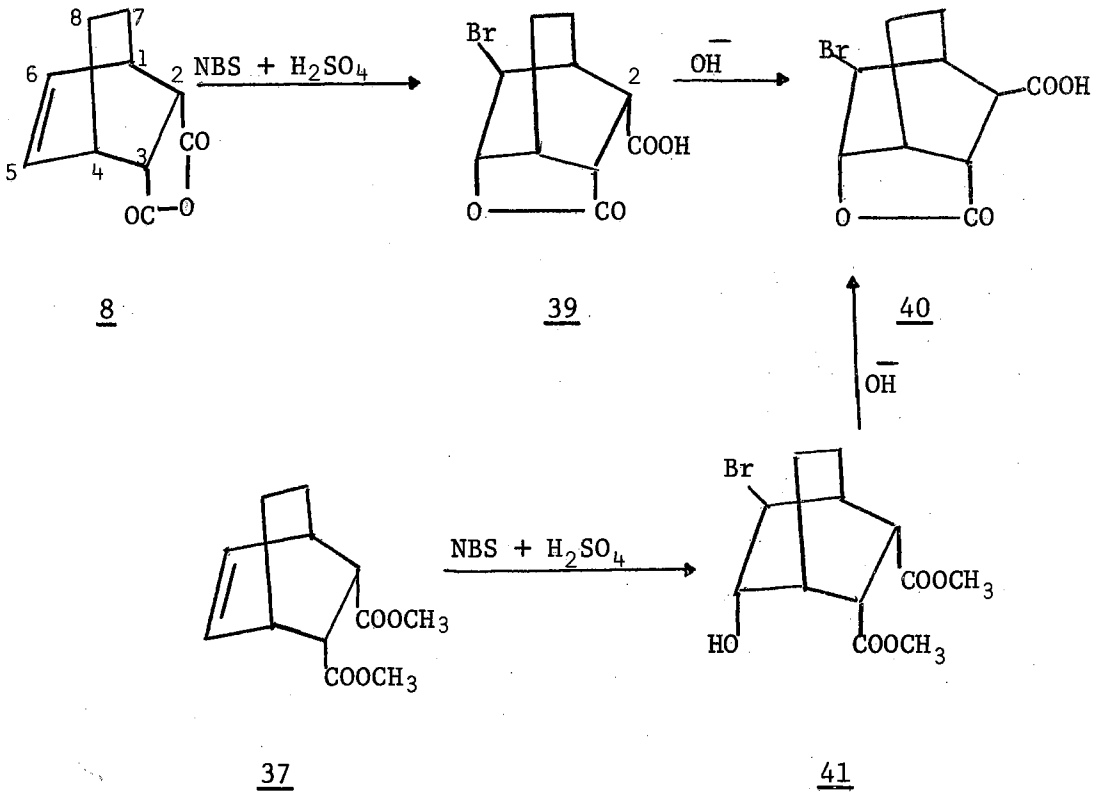
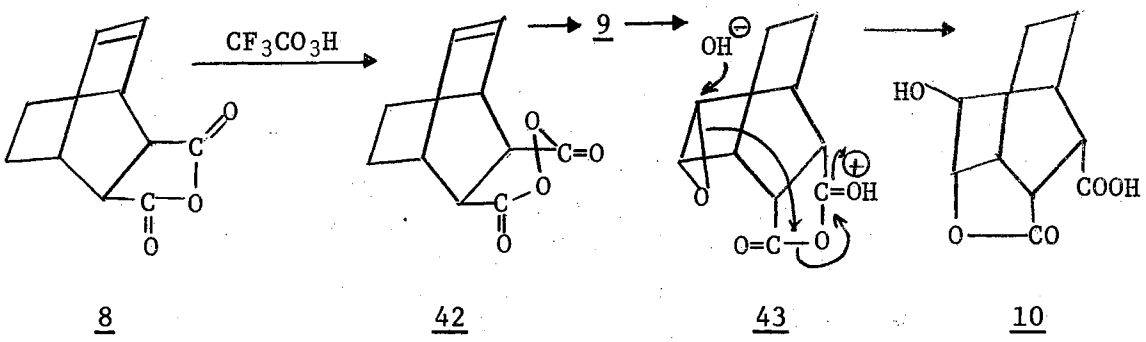


Figure 5. Reaction of N-Bromosuccinimide with 8 and 37.

similar peroxide intermediate 42 as represented in Fig. 6.

The formation of hydroxy lactone 10 during trifluoroperacetic acid epoxidation of 8 still remains to be explained. This may be due to protonation of the anhydride carbonyl group followed by rear-side attack by hydroxyl ion, generated through ionization of water, at C_6 to give 10. The overall process may be concerted or stepwise; further mechanistic aspects were not pursued.



8 42 43 10

Figure 6. Formation of Hydroxy Lactonic Acid (10) During the Epoxidation of 8 with Peroxytrifluoroacetic Acid.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were performed by Midwest Microlabs, Inc., Indianapolis, Indiana. Infrared spectra were obtained with a Beckman IR-5 spectrometer and nmr spectra were recorded with a Varian A-60 spectrometer and are reported as dimensionless "chemical shift" units relative to tetramethylsilane (τ = 10).

Ozonolysis of Methyl Maleopimarate (1b). Isolation of 4b, 5, and 6.

Maleopimaric acid (1a), when treated with ethereal diazomethane, gave 1b, mp 212-213° (lit.[5] mp 214-215°). Methyl maleopimarate (1b) (15 g) in 500 ml acetic acid was ozonized as previously described by Ruzicka and LaLande,[2] and the products 4b, 5, and 6 were isolated as by the earlier workers. The anhydride 6 (0.3 g, mp 250-251°, lit.[2] mp 252-253°) precipitated from the acetic acid solution and gave a negative tetranitromethane test, ν_{max}^{KBr} 1802, 1764, and 1725 cm^{-1}.

Anal. Calcd. for $C_{25}H_{34}O_8$: C, 64.99; H, 7.42. Found: C, 65.27; H, 7.38.

Addition of water to the acetic acid filtrate caused precipitation of 0.2 g of 4b, mp 224-225°, (lit.[2] mp 226-227°) ν_{max}^{KBr} 1730, 1758 cm^{-1}.

The dimethyl ester 4c was prepared from 4b with ethereal diazomethane and found to be identical with 4c obtained by permanganate oxidation of maleopimaric acid (1a) followed by esterification as previously described.[5] The identity was established by melting point of an admixture which showed no depression, and comparison of infrared and nmr spectra.

The epoxide 5 was isolated from the aqueous acetic acid filtrate as previously described,[2] and after crystallization from hot acetone, gave 100 mg, mp 289-290°; ν_{max}^{KBr} 2950, 1777, and 1720 cm^{-1}; nmr ($CDCl_3$), τ 9.28 (doublet, J = 7 cps), τ = 9.15, 8.93 (doublet, J = 7 cps), 8.8, 6.8, 6.29, no olefinic protons were evident; negative tetranitromethane test.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.83; H, 7.97. Found: C, 69.77; H, 7.91.

Concentration of the filtrate after removal of 4b, 5, and 6 gave a residue which was found to be starting material 16 as shown by its melting point and infrared spectrum.

Preparation of the Tetramethyl Ester of 6

An ethereal solution of excess diazomethane was added to 250 mg of 6 dissolved in 30 ml of methanol. After standing overnight, the solution was filtered, and evaporation of the filtrate gave a 72% yield of the tetramethyl ester 17, mp 128-132° after recrystallization from water-methanol, ν_{max}^{KBr} 1754-1724 (broad), 1250-1176 cm^{-1}. The nmr spectrum of the tetramethyl ester 17, on integration, showed 30 $\pm$ 3% of the total hydrogen present as methoxyl hydrogen (theoretical value 28.5%) by the appearance of three peaks at τ 6.43, 6.37, and 6.31. The saponification equivalent found was 510 (calculated for $C_{28}H_{42}O_9$: 523)

assuming four carboxyl groups; if three carboxyl groups were assumed, the saponification equivalent found should be 382.

Preparation of 5 by Direct Epoxidation of 1b

A solution of 3 ml of trifluoroacetic anhydride and 1 ml of 90% hydrogen peroxide in 10 ml of methylene chloride was added dropwise over twenty minutes to a stirred suspension of 4 g of disodium hydrogen phosphate in 30 ml of of methylene chloride containing 2.5 g of methyl maleopimarate. The solution was heated at the reflux temperature for 45 minutes, stirred at room temperature an additional 48 hours, washed with sodium sulfite solution, and then filtered, and the filtrate further washed with 10% sodium bicarbonate solution and finally with water. After drying over anhydrous magnesium sulfate, the organic layer was concentrated with a rotary evaporator to give 2.1 g of crude product which, after recrystallization from acetone, gave 1.5 g of 5, mp 289-290°, which was found to be identical with 5 obtained by the ozonolysis of 1b through comparison of infrared and nmr spectra.

Preparation of 20

Trimethyl fumaropimarate, 18,[14] (1.08 g) was epoxidized with peroxytrifluoroacetic acid and hydrogen peroxide as described above to give 0.45 g of 20, mp 179-181°, after recrystallization from ether; ν_{max}^{KBr} 1738, 2950 cm^{-1}; nmr ($CDCl_3$), τ 9.29, 9.0 (doublet, J = 6 cps), τ 8.97, 8.68 (doublet, J = 6 cps), 6.82, 6.34, 6.46, 6.3, and 6.2.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.12; H, 8.47. Found: C, 68.37; H, 8.43.

A solution of 5 (0.33 g) in 10 ml of methanol and 10 ml of 25% aqueous sodium hydroxide was heated at the reflux temperature for 34 hours (a shorter reflux time resulted in complete recovery of 5). The

solution was diluted with water and acidified with dilute hydrochloric acid and the precipitate was taken up in ether. The ether extract, after drying, was evaporated to give 0.26 g of product, mp 185-198°, ν_{max}^{KBr} 2750-3500 (broad). This material (0.19 g) was dissolved in 30 ml of ether, and to this solution, ethereal diazomethane was added. Evaporation of the ether solution yielded 0.065 g of unreacted 5, mp 287-291°, and the remainder as a gummy mass which could not be crystallized. Thin-layer chromatography on 25μ thick silica gel-coated glass plates using 3:7 methyl acetate-n-hexane as the mobile phase and detection by iodine vapor showed that this gummy material was predominantly the same as 20 (R_f 0.45), the other components presumably being the C-15 epimer of 20 and unreacted 5.

Reaction of 21 with Peroxytrifluoroacetic Acid. Preparation of 22.

Trimethyl ester 21 (2.58 g) was treated with peroxytrifluoroacetic anhydride and hydrogen peroxide as described above. After the usual workup, 2.6 g of white glassy product was obtained, which, after three recrystallizations from methanol, gave 1.5 g of 22, mp 146-148°; ν_{max}^{KBr} 3400, 1762, and 1709 cm^{-1}; nmr (CCl_4), τ 9.0, 8.98 (doublet, J = 6 cps), 8.87, 8.8 (doublet, J = 6 cps), 6.36, 6.29, 6.16 (after addition of D_2O).

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.59; H, 8.29. Found: C, 67.42, H, 8.38.

The triester 21 was unchanged after heating in refluxing methanolic sodium hydroxide for 8 hours followed by acidification and re-esterification with diazomethane.

The adduct, bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (8), obtained by condensation of 1,3-cyclohexadiene and maleic anhydride,

was recrystallized three times from benzene to give crystals, mp 146-150°.

Reaction of Peroxytrifluoroacetic Acid with Olefin 8. Preparation of 5,6-Endo-epoxy-bicyclo[2.2.2]octane-cis-2,3-dicarboxylic Anydride 9.

To a well stirred suspension of 13 g of disodium hydrogen phosphate (dried at 100° in the oven for 36 hours before use) in 50 ml methylene chloride was added 3.6 g of olefin 8 in 40 ml methylene chloride. After the addition was over, a solution of 5 ml trifluoroacetic anhydride containing 1 ml of 90% hydrogen peroxide in 15 ml methylene chloride[13] was added dropwise over a period of 15 minutes. There was an exothermic reaction. After the addition was complete, the reaction mixture was heated at reflux temperature for 30 minutes and then stirred at room temperature for 24 hours. After cooling, the reaction mixture was washed with 10% sodium sulfite, 10% sodium bicarbonate and then twice with water. The organic layer was separated and dried, and the solvent was evaporated to give 2 g of the reaction product. Further recovery of 0.5 g was made through two extractions with ether. On recrystallization from hot acetone, pure 9 had mp 208-210°; ν_{max}^{KBr} 2985, 1852, and 1786 cm^{-1}; nmr (CF_3COOH) showing signals at τ 6.3, 6.5, 6.9, and a broad signal between τ 8.6 - 7.9 was obtained.

The mother liquor, after removing 9, gave 0.2 g of another product, mp 223-225°, identified as hydroxy lactone 10.

The remainder of the acetone solution, on concentration, gave 0.8 g of crystalline product, mp 141-144°, identical with olefin 8.

Epoxidation of Olefin 8 with m-Chloroperbenzoic Acid. Preparation of Hydroxy Lactone 10.

The adduct 8 (1.78 g), in 20 ml methylene chloride and 2.58 g of

m-chloroperbenzoic acid in 20 ml methylene chloride were stirred together for 24 hours at room temperature. Excess peracid was removed with 15% sodium sulfite. The methylene chloride layer was washed with 10% sodium bicarbonate and with water, dried over anhydrous magnesium sulfate, and on evaporation of the solvent, gave a crude product which was recrystallized from hot acetone to yield white crystals, mp 221-223°, ν_{max}^{KBr} 3425, 2941, 1770, and 1709 cm^{-1}. This product, 10, was shown to be identical with the one obtained from the mother liquor in the preparation described above of 9, using trifluoroperacetic acid. Their melting points were undepressed on admixture, and the infrared spectra were superimposable.

Preparation of 35 and 36 from 10.

Methyl ester 35 of the hydroxy lactonic acid 10 was prepared by taking 0.25 g of 10 in ether and treating with ethereal diazomethane; it showed ν_{max}^{film} 3448, 1792, and 1748 cm^{-1} and nmr ($CHCl_3$), doublet at τ 5.6 (2H), singlet at τ 6.3 (3H), and at τ 6.5 (OH), doublet around 7.1 τ (2H), broad signal at 7.7 τ (2H) and multiplet at τ 8.2 (4H). After exposing the sample to deuterium oxide, the signal at τ 6.5 disappeared.

The lactone 36 was prepared by dissolving 0.250 g of methyl ester 35 in 10 ml anhydrous acetone and adding 2 ml of the Jones' reagent while stirring the reaction mixture in an ice-bath. When a permanent orange color appeared, the entire reaction mixture was extracted with ether and dried over magnesium sulfate. On evaporation, 0.2 g of crude keto lactonic ester 36, ν_{max}^{film} 1802, 1751, 1721 cm^{-1}, was obtained.

Preparation of 37 and 38

The anhydride 8 (2.5 g) was dissolved in 10 ml methanol and treated

with ethereal diazomethane solution. After filtering, drying over magnesium sulfate, and evaporating the ether solvent, the residue obtained was recrystallized from ethyl acetate giving fine crystals of the dimethyl ester 37, mp 66-68° (lit.[21] 70-70.8°); nmr (CCl_4), multiplet at τ 8.5 (4H), broad peak at τ 7.1 (4H), broad singlet at τ 6.5 (6H), and multiplet at τ 3.75 (2H).

Epoxide 38 was prepared by dissolving 2.5 g of the dimethyl ester 37 in 25 ml of stirred methylene chloride at 25° and adding 3.0 g of m-chloroperbenzoic acid in 35 ml methylene chloride dropwise. After 12 hours, the reaction mixture was processed in the same manner as described in the preparation of 10, giving 2.65 g of the crude product 38. When recrystallized from ether, white crystals were obtained, mp 142-145°, ν_{max}^{Nujol} 1751 and 1429 cm^{-1}; nmr (CCl_4), multiplet at 8.85 τ (4H), singlet 6.45 τ (6H), two singlets at τ 7.0 (2H), and 6.7 τ (2H) and broad peak at τ 7.5 (2H).

Preparation of Bromo Lactonic Acid 39 from the Olefinic Anhydride 8.

N-Bromosuccinimide (7 g) was added to olefin 8 (5 g) dissolved in 60 ml of 1N sulfuric acid and 100 ml of tert-butyl alcohol. After being stirred at room temperature for 48 hours, the solution was diluted with 300 ml water and repeatedly extracted with ether and petroleum ether. The combined extracts, on drying and concentrating, gave 5.82 g of the crude product 39. On recrystallization from water, 39, mp 150-153°, ν_{max}^{Nujol} 3448, 2941, 1786, and 1730 cm^{-1}, was obtained. A Beilstein test was positive. The methyl ester melted at 132-134°.

Preparation of the Bromohydrin 41 of Dimethyl Ester 37.

N-Bromosuccinimide (0.8 g) was added to bicyclo[2.2.2]-oct-5-ene-2,3-dicarboxylic acid dimethyl ester 37 (0.9 g) dissolved in 7 ml of 1N

sulfuric acid and 4.4 ml of t-butyl alcohol. After being stirred at room temperature overnight, the solution was diluted with 30 ml water and exhaustively extracted with ether. The ether extract was washed with 10% sodium bicarbonate solution, washed with water, and then dried over magnesium sulfate. Evaporation of the solvent gave 1.1 g of the crude bromohydrin 41 which, on recrystallization from ether-chloroform, gave mp 108-110°, ν_{max}^{KBr} 3390 and 1739 cm^{-1}, and a positive Beilstein test.

This bromohydrin 41 was unaffected by heating in pyridine solution at 90° for 5 hours.

Preparation of 40, the C_2 Epimer of 39.

The bromo lactonic acid 39 (1.3 g) was dissolved in 15 ml of 15% sodium hydroxide and 10 ml methanol, and the solution was refluxed for 8 hours, diluted with water, acidified and extracted with ether on a continuous extractor for 16 hours. The ether extract was dried and the ether evaporated to give 0.92 g of 40, mp 240-244°, ν_{max}^{KBr} broad band at 2857 cm^{-1} and another at 1667 cm^{-1}, Beilstein test positive. The compound 40 was identical, both in its infrared and melting point (alone and on admixture), with the product obtained on the treatment of alkali with the bromohydrin 41 (preparation shown below).

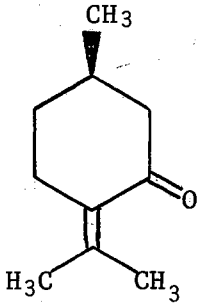
The bromohydrin 41 (10.6 g) was heated for 6 hours in a refluxing solution of 10 ml methanol and 0.4 g potassium hydroxide in 5 ml water, cooled and stored overnight, diluted, acidified, and extracted with ether to give 0.55 g of 40, mp 239-241°.

PART II

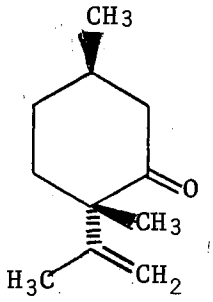
ABSOLUTE CONFIGURATION OF (-)-METHYLISOPULEGONE

HISTORICAL AND INTRODUCTION

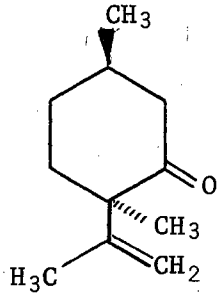
Methylation of (+)-pulegone (44), the major component of the commercial oil of pennyroyal, is known to lead in good yield to (-)-methylisopulegone (45a) (2,5-dimethyl-2-isopropenylcyclohexanone).[22,23] Except for a small amount of unreacted pulegone, the methylpulegones consisted of approximately 84% of 45a and 16% of 45b. While there is no question about the structure of (-)-methylisopulegone, its stereochemistry can be represented by either 45a or 45b.



(+)-44

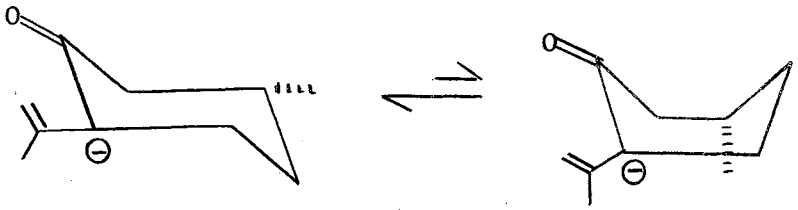


(-)-45a



(+)-45b

The stereochemical assignment of 45a to the major product was made by Swiss investigators[24] who used (-)-methylisopulegone (45a) in their preparation of (+)-trans-2,5-dimethylcyclohexanone. To explain the selection of 45a for the major compound, these workers suggested an axial attack of a methyl group upon 46a which is in equilibrium

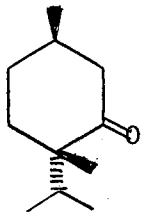


46a 46b

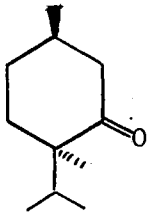
with 46b. Later, Djerassi and co-workers[25] expressed doubt about this earlier assignment to the stereochemistry of (-)-methylisopulegone (45a) and instead, proposed an alternate structure, 45b,[25] based on quasi-racemate studies. The use of quasi-racemates in determining absolute configurations has been discussed by Fredga.[26a] These quasi-racemate studies[25] provided an incorrect stereochemical assignment for 45a. The stereochemical studies involved (+)-2-isopropylglutaric acid (50a), which was related to (+)-2-isopropyl-2-methylglutaric acid derived from (+)-2-isopropyl-2-methyl-5-oxocaproic acid and (+)-2,5-dimethyl-2-isopropylcyclohexanone obtained by degradation of 45a. Consequently, 47b, 48b, and 49b also received an incorrect assignment. However, these structures have been revised and are correct as now written.

In 1962, Norin,[27] while studying the absolute configuration of the thujane group, degraded (+)-sabinene (51a) to 48a, which had previously been obtained from 45a.[25] The keto acid 48a was further degraded to 49a.[27] Norin[27] also converted (+)-sabinol (51b) and (+)-sabinyl acetate (51c) into (+)-2-isopropyl-2-methylsuccinic acid (52a), whose absolute configuration is well established.[28a-e]

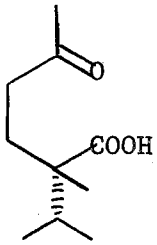
This apparent discrepancy[27] in the stereochemical assignment of



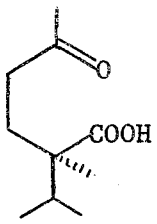
(+)-47a



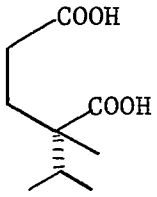
(-)-47b



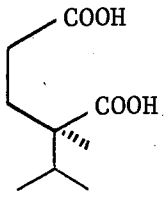
(+)-48a



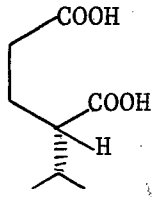
(-)-48b



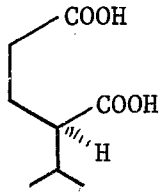
(+)-49a



(-)-49b

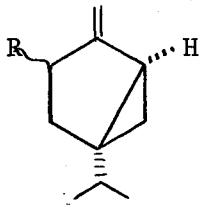


(+)-50a

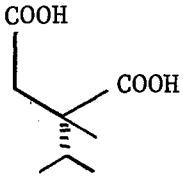


(-)-50b

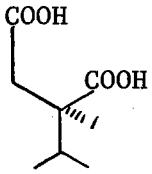
(-)-methylisopulegone prompted reinvestigation of the earlier work leading to structure 45b.[25] The reinvestigation was to include a partial repetition of the earlier work[25] and also additional research needed to clarify the problem. This involved degradation of (-)-methylisopulegone to 2-isopropyl-2-methylsuccinic acid (52a) or (52b),



51a, R = H
51b, R = OH
51c, R = OAC



(+)-52a

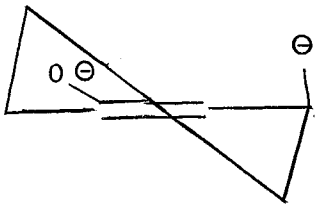


(-)-52b

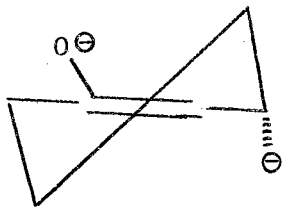
and comparison of the resulting acid with the known optically active succinic acid 52a to unequivocally establish the absolute configuration of (-)-methylisopulegone. We therefore converted (-)-methylisopulegone to 52a, mp 128-130°, which was found to be identical

with an authentic sample[28c] of 52a. The melting point of a mixture was not depressed and their infrared spectra were identical. A recent communication by Whalley and co-workers[28e] further adds confirmatory evidence in favor of 52a. Thus, the correct representation of (-)-methylisopulegone is 45a. The preparation of 45a involved alkylation reactions and thus prompted more extensive investigation.

Reductive methylation of flexible cyclic ketones as contrasted to methylation[29] has not been extensively studied. We examined several α,β-unsaturated ketones to learn more about the stereochemistry of the reductive methylation process. This involved the reaction of lithium metal dissolved in ammonia with α,β-unsaturated ketones followed by the addition of alkyl halides. Reductive methylation of rigid cyclic ketones has been extensively studied by several workers in recent years.[30-34] The overall reaction involves the protonation of the β-carbon (due to its high nucleophilicity) followed by the methylation of the α-carbon. The stereochemical outcome of this reductive alkylation was of particular interest to establish whether equilibrium or kinetic control was involved.[35,36] Some possible reaction intermediates and their conformations were considered, and experiments were designed to probe these proposals. The most likely conformations are those which offer maximum and continuous overlap of p-orbitals, and therefore the "equatorial anion"[34] is less likely. Since the ketones we selected are flexible cyclohexenones, the proton introduced at the β-carbon atom will be axial with respect to the six-membered ring containing the carbonyl.[37] In such cyclohexenone systems, there will normally be two conformations, 53a and 53b, that will permit axial protonation at the β-carbon atom.[38]

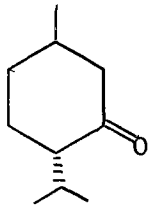


53a

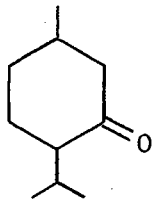


53b

Reductive methylation of (+)-pulegone (44) following the procedure of Stork and co-workers[39] gave four products as shown by gas chromatography. The major product, obtained in about 88% yield, was identified as (+)-dihydromethylisopulegone (47a). In contrast, methylation of an equilibrium mixture of 54a and 54b in the presence of sodium hydride using dimethyl sulfoxide solvent provided 47a.

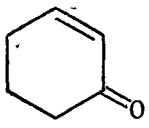


(-)-54a



(+)-54b

Other α,β-unsaturated ketones, 55, 56, 57, and 58, were included as model compounds to extend the reductive alkylation study.



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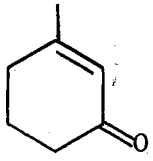

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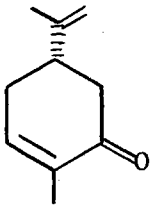

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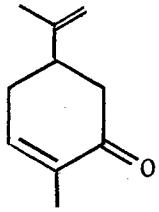


58

RESULTS AND DISCUSSION

Methylation of (+)-pulegone (44) with sodium pentyloxide and methyl iodide yields an unequal mixture of (+)- and (-)-methyl-

isopulegones[22,23] with the latter predominating. The determination of the absolute configuration of 45a has a bearing on the mechanism of alkylation of conformationally flexible systems. Tentative preference for 45a [(-)-methylisopulegone] was first expressed by Swiss workers;[24] 45a was assumed to be the principal product because its formation from anion 46a and alkyl halide would be expected to yield an axial methyl group at C_2.

Later Djerassi and co-workers,[40] while studying the optical rotatory dispersion (ORD) of polyalkylcyclohexanones, prepared (-)-methylisopulegone. Since a precise knowledge of stereochemistry at C_2 of 45a was essential to interpreting the ORD data, these authors[25] attempted degrading 45a to molecules of known absolute configuration. Pure 45a was obtained as a crystalline semicarbazone, mp 202°, from a mixture of methylation products of 44. The recrystallized semicarbazone was regenerated to 45a by steam distillation in the presence of oxalic acid. The degradation of 45a was accomplished through the sequence of reactions shown in Fig. 7 which involved hydrogenation of 45a to 47a and then bromination in aqueous solution to yield (-)-2-bromo-3,6-dimethyl-6-isopropylcyclohexanone (59), mp 79-81°. Dehydrobromination of 59 with lithium bromide and lithium carbonate in dimethylformamide solution produced (-)-3,6-dimethyl-6-isopropyl-2-cyclohexen-1-one (60), which was ozonized to yield (+)-2-isopropyl-2-methyl-5-oxocaproic acid (48a). This keto acid, 48a, was further oxidized with sodium hypobromite to (+)-2-isopropyl-2-methylglutaric acid (49a), which was purified through its anhydride, 61a. These two substances, 49a and 61a, were then related by Fredga's quasi-racemate method to (-)-2-isopropylglutaric acid (50a) and its anhydride 62a, whose absolute configurations

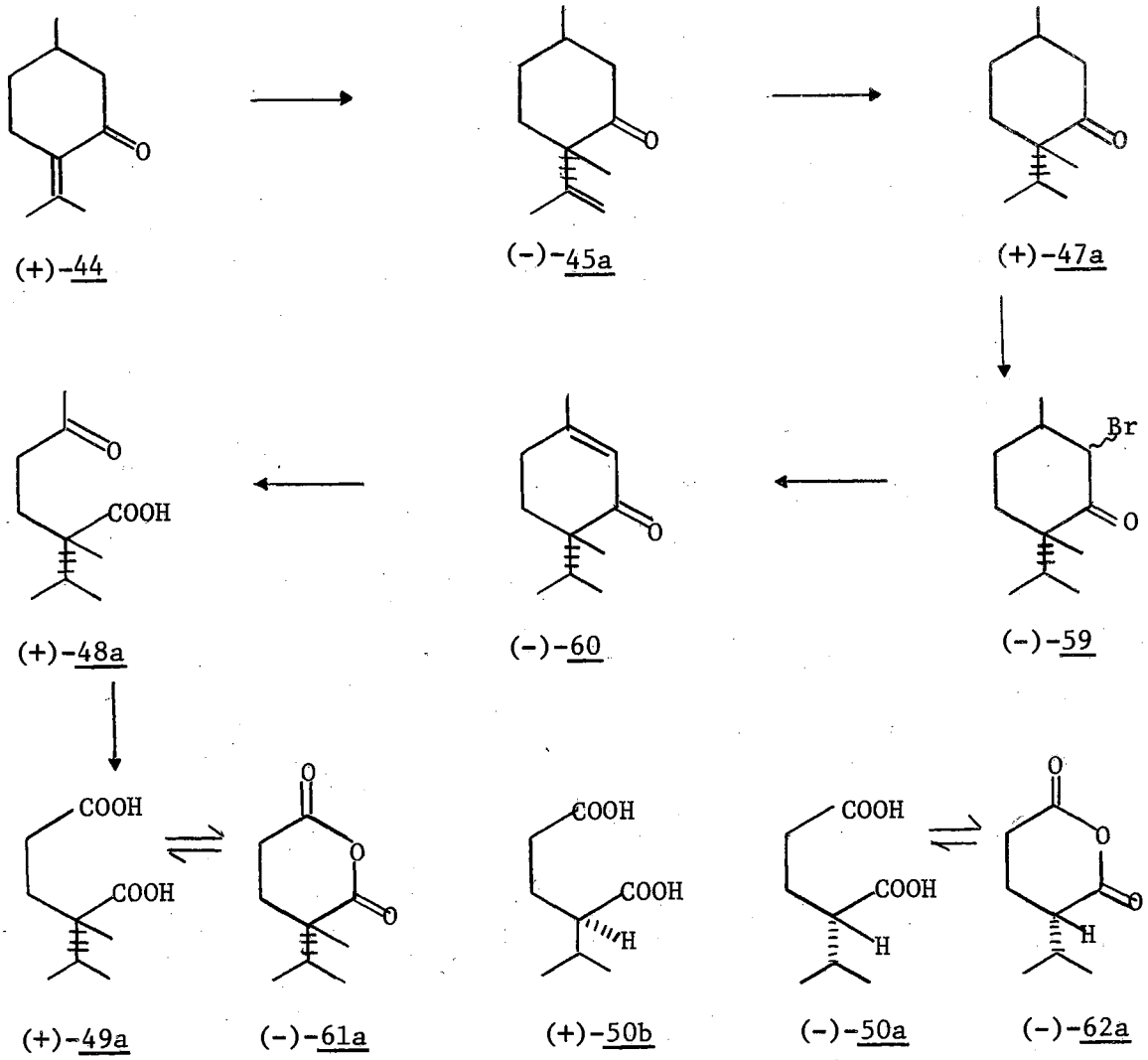


Figure 7. Degradation of (-)-Methylisopulegone (45a) to (+)-2-Isopropyl-2-methylglutaric Acid (49a).

were known.[41]

The structures shown in Fig. 7 corresponding to 49a and 61a represent the correct absolute configurations as established by recent X-ray analytical studies.[28e] Since antipodal structures were reported for 49a and 61a in the earlier work,[25] the quasi-racemate method has provided an incorrect absolute configuration assignment to this series. At this time, it is uncertain why the quasi-racemate method does not apply in this case. The application of these erroneous absolute

configuration assignments to (-)-methylisopulegone (45a) suggested that the methyl group at C_2 had an equatorial instead of axial configuration.

Norin's degradation of 51a, 51b, and 51c, which is shown in Fig. 8, provided 48a, 63, and 52a.[27] Comparison of the samples of 48a and 63 obtained from 44 and 51a was made and the data recorded in Table I. The new absolute configuration assignment made by Norin[27] was recently confirmed by X-ray analysis.[28e]

It thus became apparent that the stereochemical assignment for (-)-methylisopulegone required reinvestigation to determine which assignment was correct and to learn whether the quasi-racemate method was the source of the error. Our approach to the solution of this problem involved the degradation of 45a to one of the known enantiomers of 2-isopropyl-2-methyl succinic acid. In order to accomplish this, we repeated part of the earlier work[25] which involved methylation of 44 with methyl iodide in the presence of sodium pentyloxide.[22,23] This procedure afforded pure 45a as described previously.[25] The structure of 45a from the current work is well supported by IR, nmr, and ORD data (Table II).

Catalytic hydrogenation of 45a gave the previously described 47a. The structure of 47a was confirmed by instrumental studies including IR, nmr, and ORD (Table II). The mass spectrum of 47a showed the expected molecular ion (m/e = 168) and the fragmentation pattern confirmed the assigned structure. One of the important fragments (m/e = 126), but not the most intense peak, results from ring cleavage of 47a and loss of ketene by bond cleavage β to the carbonyl.

Bromination of 47a gave the known bromo ketone 59. Its IR spectrum showed a band at 1727 cm^{-1} for C-O stretch in carbon tetrachloride

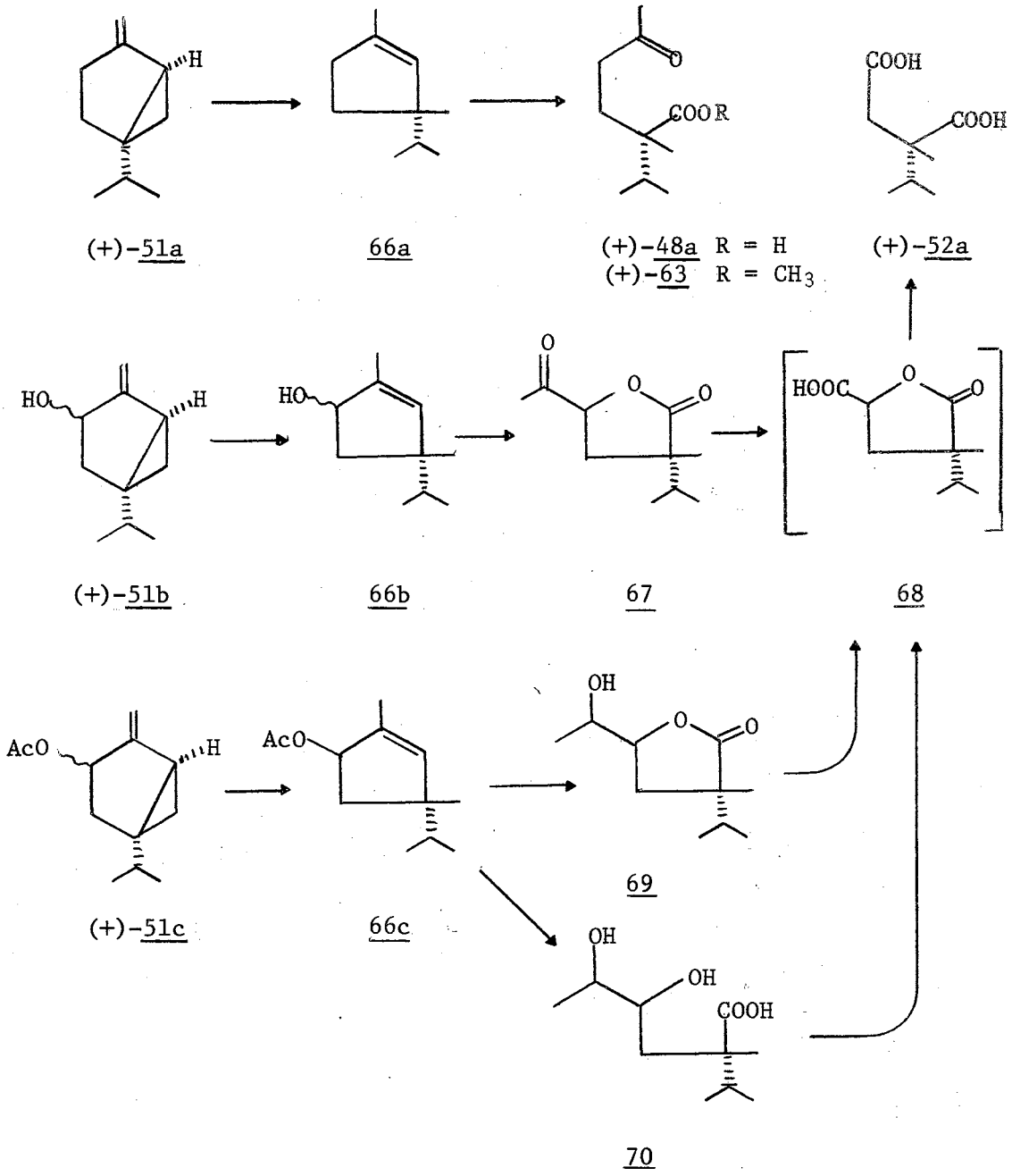


Figure 8. Degradation of (+)-Sabinene (51a), (+)-Sabinol (51b), and (+)-Sabinyl Acetate (51c) to (+)-2-Isopropyl-2-methyl-succinic Acid (52a).

(a shift of 15 cm^{-1}). In DMSO, this band appeared at 1712 cm^{-1}.

The observed shift of 15 cm^{-1} in the infrared spectrum of 59 due to change of solvent polarity is typical of ketones having a bromo function in an equatorial conformation.[25,57] The observed negative

TABLE I

COMPARISON OF DEGRADATION PRODUCTS OF (+)-DIHYDROSABINENE (66a) AND (-)-METHYLISOPULEGONE (45a)

		M.p.° C	$[\alpha]_D$° C	C in Chloroform	Comments
(+)-2-Methyl-2-isopropyl-5-oxocaproic acid (48a)	A[a]	Oil	+ 3.3	1.52	Identical infrared
	B[b]	Oil	+ 16.0	1.0	
2,4-Dinitrophenylhydrazone of 48a	A	122	--	--	Mixed mp 122° and identical infrared
	B	122	--	--	
(+)-Methyl 2-Isopropyl-2-methyl-5-oxocaproate (63)	A	Oil	+ 14.1	1.07	
	B	Oil	+ 29.0	2.8	
2,4-Dinitrophenylhydrazone of 63	A	66-67	+ 32.0	0.93	
	B	66-67 (77-78)[c]	+ 34.0	0.94	
(+)-α-Methyl-α-isopropyl-glutaric acid (49a)	A	60-62	+ 8.7	0.8	
	B	60-62 (68-70)[d]	+ 9.5	0.65	
(-)-α-Methyl-α-isopropyl-glutaric anhydride (61a)	A	55-56	- 6.1	0.99	
	B	56-57	- 5.5	0.94	

[a]Derived from 45a.

[b]Derived from 66a.

[c]Dimorphous needles, mp 77-78; leaflets, mp 66-67°.

[d]Recrystallized from water. The dried product melted at 60-62°.

TABLE II

COTTON EFFECTS OF KETONES RELATED TO 45a

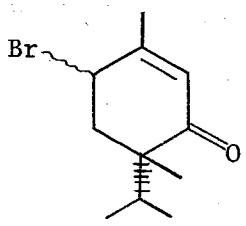
Compound	Rotatory Dispersion		
	Peak [α]	Trough [α]	Amplitude
45a	$[\alpha]_{277}$ + 2580°	$[\alpha]_{323}$ - 3180°	5760
47a	$[\alpha]_{320}$ + 1380°	$[\alpha]_{275}$ - 1560°	2940
59	$[\alpha]_{265}$ + 2040°	$[\alpha]_{316}$ - 1950°	3990
60	$[\alpha]_{378}$ + 450°	$[\alpha]_{305}$ - 1710°	2160

*In dioxane solutions.

Cotton effects $[\alpha]_{316}$ - 1950°, $[\alpha]_{265}$ + 2040° also supports the equatorial assignment to the halogen. The presence of protons at C_5 and C_6 was confirmed by the presence of a doublet at 4.9 τ (J = 5 cps) in the nmr spectrum of 59 using $CDCl_3$ as solvent.

Dehydrobromination of 59 gave the known α,β-unsaturated ketone 60. The structure of 60 was confirmed by UV, IR, nmr, mass and ORD spectral data.

Bromination of 60 with N-bromosuccinimide in carbon tetrachloride yielded the bromo enone 71. The structure 71 is favored over 72 for



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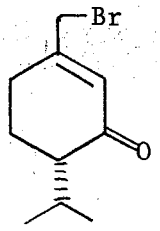

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the bromination product of 60 because the absorption due to the C_3 allylic methyl protons persists in the nmr spectrum of the bromination product, and this absorption is the same as the nmr absorption of the parent ketone at the same field.

Oxidation of 71 with alkaline potassium permanganate gave 52a, mp 128-130°. The melting point of a mixture of 52a and an authentic sample of (+)-2-isopropyl-2-methyl succinic acid,[28c] $[\alpha]_D$ + 15° (c 0.8, EtOH), showed no depression. The sequence of reactions is shown in Fig. 9.

The infrared spectra of these samples were identical and the mass fragmentation patterns supported the structure assignment to 52a. The acid was converted to the dimethyl ester 52e through use of diazomethane.

Since the absolute configuration of the isopropylmethylsuccinic acids is known, it is possible unequivocally to assign the absolute configuration of (-)-methylisopulegone (45a) as shown.

The conversion of 71 to 52a presumably proceeds through 4-hydroxy-3,6-dimethyl-6-isopropyl-2-cyclohexen-1-one (73) since 73 may be conveniently prepared by treating 71 with a refluxing suspension of aqueous calcium carbonate. Further oxidation to 52a may be rationalized as a typical permanganate oxidation. Whalley, et al., recently published a communication describing X-ray crystallographic studies of the rubidium salt of the monomethyl ester 52d,[28e] which provides the same absolute configuration assignment and confirms Norin's observation[27] that the absolute configuration assignment from the quasi-racemate work[25] is in error.

Other attempts to prepare 52a by degradation of 48a and 60 were made. These degradations were directed towards introducing unsaturation

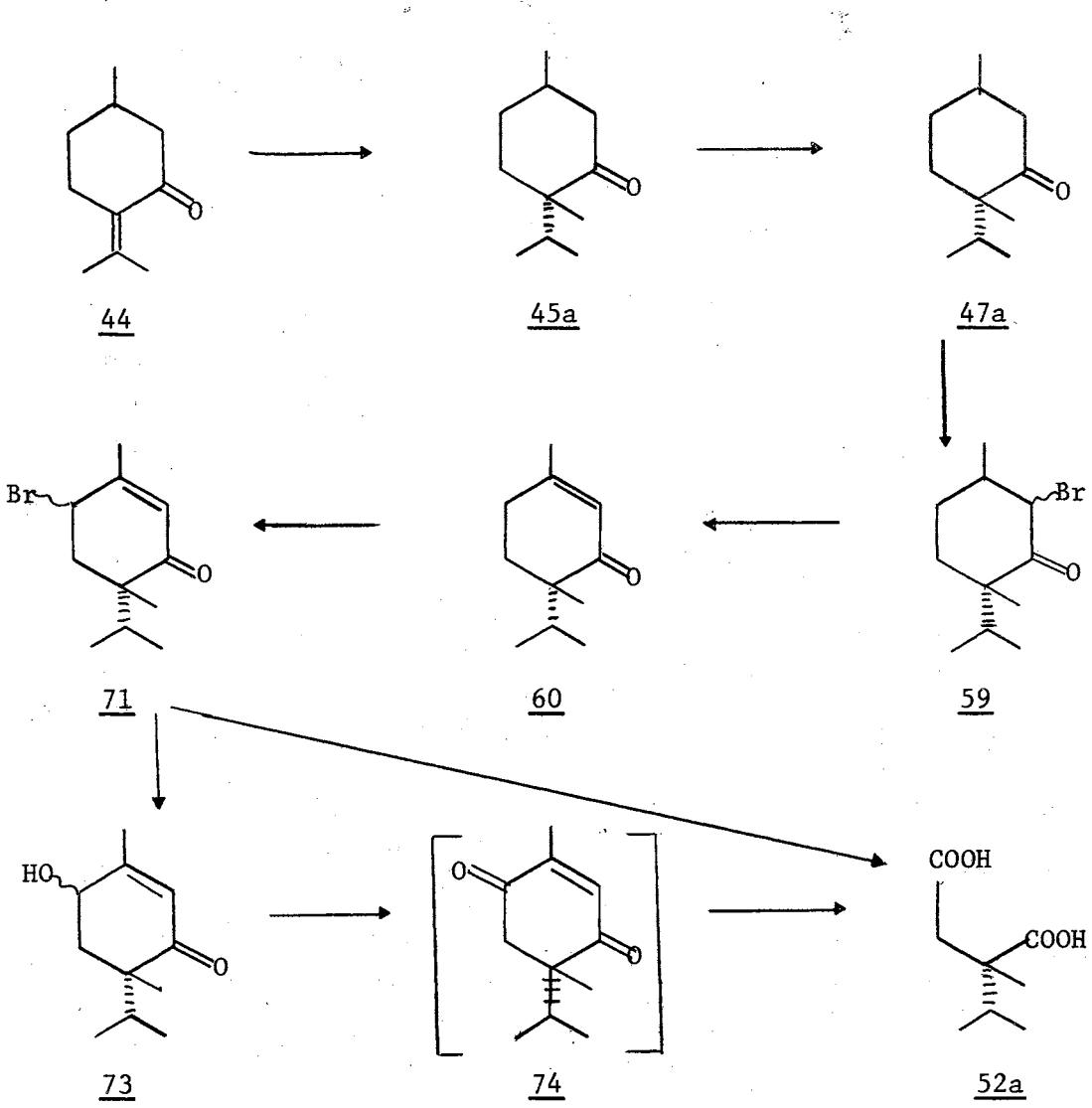
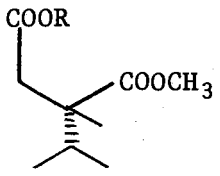
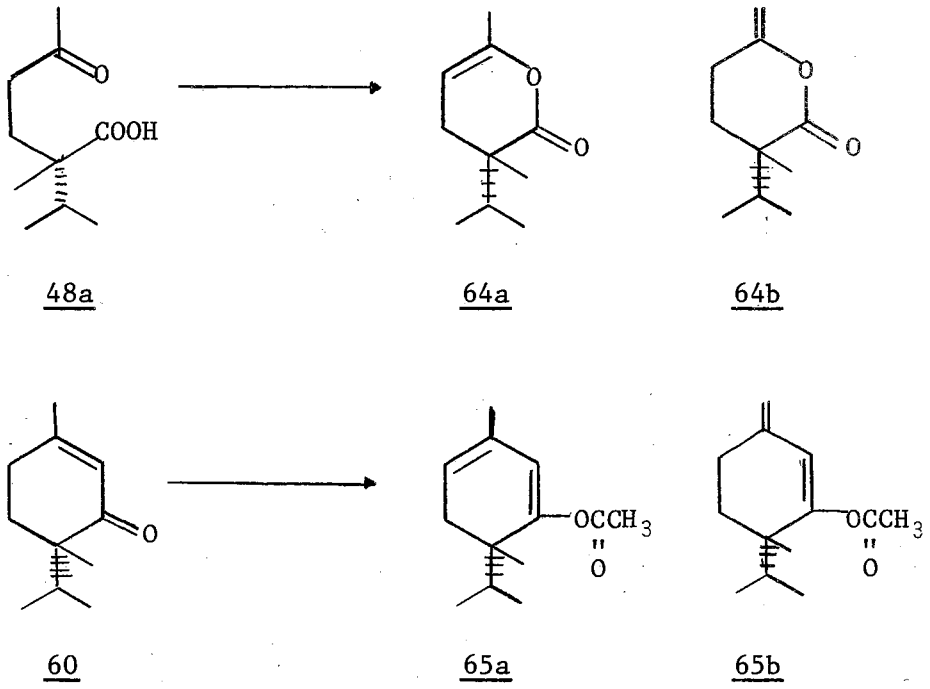


Figure 9. Degradation of (-)-Methylisopulegone (45a) to (+)-2-Isopropyl-2-methylsuccinic Acid (52a).

between carbons 4 and 5 of 48a and 60 to provide intermediates which would be susceptible to oxidation. These reactions are shown in Fig. 10.



52c, R = H
52d, R = Rb
52e, R = CH_3



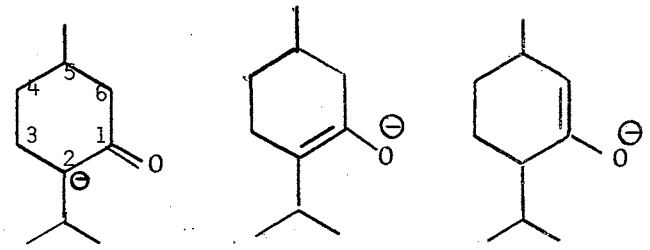
48a 64a 64b

60 65a 65b

Figure 10. Proposed Degradation Routes for 48a and 60.

Several attempts to convert 48a to 64a, using sodium acetate and acetic anhydride or acetyl chloride and finally by direct pyrolysis, were made, but 64a or 64b could not be isolated. The use of isopropenyl acetate in the presence of a catalytic amount of p-toluenesulfonic acid or acetic anhydride in the presence of a catalytic amount of sulfuric acid similarly failed to give 65a and 65b.

The methylation of an equilibrium mixture of menthones is generally carried out with a sodium alkoxide catalyst and results in a complex mixture of C_2 and C_6 methylation products. This reaction is usually of little synthetic value since the separation of products is difficult. To achieve product control in favor of C_2 methylation, the polarity of the reaction medium was increased by using DMSO as solvent. Sodium hydride was used as base in this reaction. It was assumed that under these conditions, the enolate 76 would be favored



75 76 77

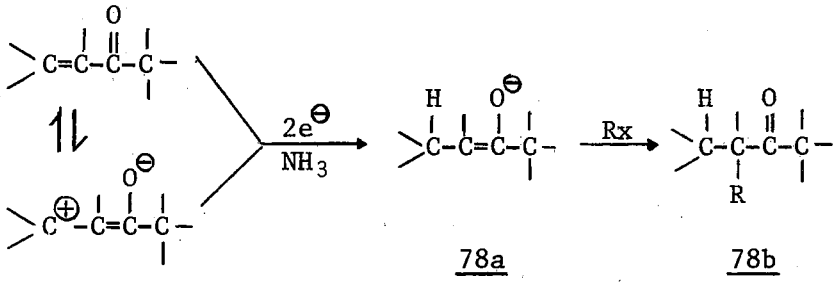
over 77 and a higher percentage of C_2 methylation would result. When the methyl iodide/menthone ratio was 1.5 and the ratio of sodium hydride/menthone was 1, clean methylation at C_2 to give a 45% yield of 47a was observed. Since the absolute configuration of 47a is known, the methyl group must react with the enolate anion 76 to give axial alkylation. It is of interest that no C_6 methylation product was observed. These results are in agreement with modern views[44-46] on alkylation which specify that the stereochemistry during the ketonization-enolization process is controlled by the developing p-orbital on the α-carbon atom and the requirement of maximum overlap of orbitals in the transition state is fulfilled. The product which results from the methylation of the enolate would be expected to have the methyl group in an axial orientation.

Reductive methylation of conformationally flexible α,β-unsaturated ketone systems was also studied. This involves the reaction of lithium metal in ammonia with the α,β-unsaturated ketone followed by addition of methyl iodide or isopropyl iodide. This reaction has been extensively studied with rigid systems in the steroid and triterpenoid field.[31,35,36] An important property of lithium-ammonia reaction is that in it the enolate formed from α,β-unsaturated ketone should undergo slow equilibration, and this has been demonstrated[33,43] by

enolate trapping. The alkylation with lithium and ammonia was also found to be faster than enolate equilibration.[32] The reaction sequence for lithium-ammonia reductive alkylation of α,β-unsaturated ketones is summarized in equations (1) and (2).[30,35] Thus the reaction of lithium

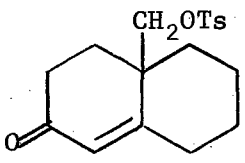
(1) $$Li \underset{}{\overset{NH_3}{\rightleftharpoons}} Li^+ + e^-\text{---}(NH_3)_n$$

(2)

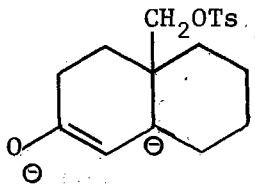


78a 78b

with ammonia and an α,β-unsaturated ketone involves transfer of two electrons and an abstraction of a proton from ammonia by the more nucleophilic β-carbon with the formation of an enolate species, 78a, which leads, after reaction with suitable alkylating agent, to the ketone 78b. That the proton abstracted by the β-carbon indeed comes from ammonia has been supported by similar reductions in deuterated liquid ammonia which caused addition of a deuterium atom to the β-carbon atom.[48] Stork and Tsuji[49] showed that the tosylate of 79 when treated with lithium and ammonia gave a cyclopropane ring and resulted in the formation of 81. This demonstrates that the β-carbon anion is sufficiently nucleophilic to displace the tosylate group.



79



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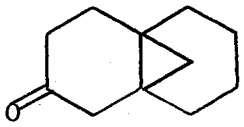
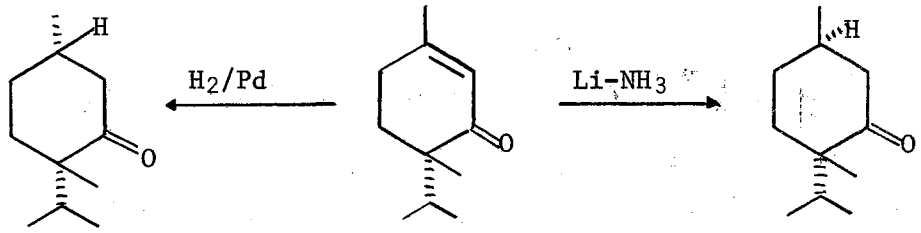


81

Barton and Robinson[36] proposed that protonation of the β-carbon is under thermodynamic control and this results in formation of the more stable epimer at that carbon, which means that in the reduction of enones, thermodynamic stability of the ketonic reduction products would determine the product ratio. Later, Stork and co-workers[34] questioned this concept[36] and instead offered an alternate proposal involving stereoelectronic requirements for the transition state for the addition of a proton to the β-carbon. They[34] have shown that the saturated ketone formed by such a reduction is not simply the more stable of the two possible epimers at the β-carbon but the one that results from stereoelectronically allowed transition states. Such a requirement would, in turn, imply that equilibration could take place only between those transition states in which maximum p-orbital overlap with the carbon-carbon double bond of the enolate system is maintained. Thus, despite the considerable tetrahedral character at the β-carbon atom, the developing orbital at that carbon atom will be expected to overlap continually with the double bond between α and β carbon atoms and the p-orbital must remain perpendicular. During reduction of α,β-unsaturated ketones with lithium in ammonia, the most rapidly formed isomer will be the one having the newly introduced hydrogen in an axial conformation. It has been suggested[50,51] that this hypothesis holds true for ketones having either flexible or rigid ring systems.

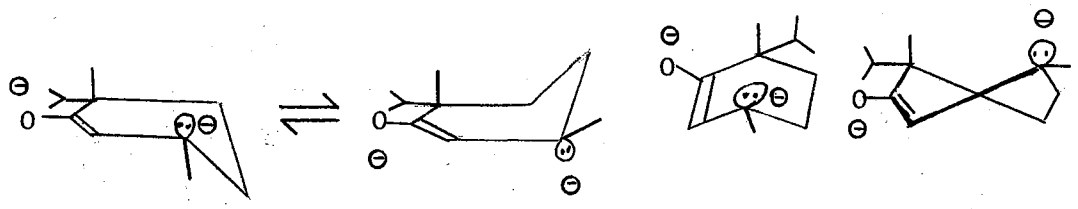
Lithium-ammonia reduction of 60 provides 47a and 82 in 75% and 25% yields respectively.[40] However, catalytic reduction of 60 gives 47a and 82 in 30% and 70% yield. These data can be explained by applying Stork's axial lithium-ammonia reduction proposal[34] and assuming that the catalytic hydrogenation[40] of 60 proceeds so that hydrogen becomes attached

at the least hindered side of the β carbon of 60, which is in keeping with the observed stereochemistry of 82.



82 60 47a

Four transition states,[34] 83a, 83b, 83c, and 83d, may be written to explain lithium-ammonia reduction of 60. Of these, 83c appears to be energetically favorable because a twist-boat conformation has less internal steric interactions and the particular conformation selected allows a tetrahedral arrangement for the β carbon, which is the probable location of the ammonia charge. The transition states 83a and 83b have favorable ground-state energies because a chair conformation is used. However, 83a and 83b are less likely transition states due to interaction of the isopropyl group and the enol oxygen.[51]



83a 83b 83c 83d

Another aspect of reductive alkylation concerns the attachment of alkyl group at the α carbon atom. As previously pointed out, the slow equilibration of lithium enolate permits alkylation at the α carbon before ketonization takes place and enolization occurs at the

α' position. This has been substantiated by enolate-ion trapping experiments.[39] It has also been shown that replacement of ammonia with the more polar DMSO prior to addition of alkyl halide causes equilibration of enolate and results in the formation of products of equilibrium control.

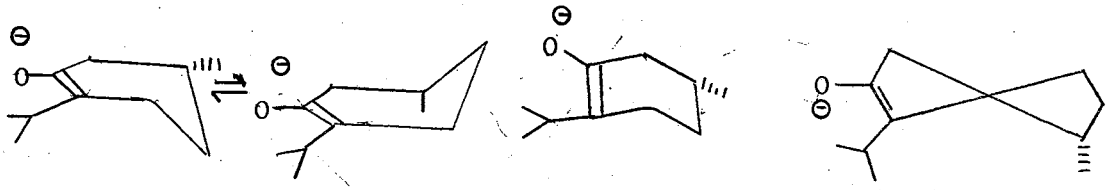
In contrast, when lithium and ammonia are used, a kinetically controlled reductive alkylation takes place and axial alkylation at the α position results. This can be compared to lithium-ammonia reduction, which has been shown to be a kinetically controlled protonation of the enolate anion from a direction perpendicular to the plane of the enolate and generally from the less hindered side.[44-47]

Recently[52] it has been pointed out that the steric course of alkylation of enolates of substituted cyclohexanones is in general the result of a balance of steric repulsions between the alkylating agent and proximate groups on one hand, and the developing oxo group on the other. The net stereochemical outcome depends on the magnitude of these effects characteristic of the given system.

We selected the cyclic α,β-unsaturated ketones 44, 55, 56, 57, and 58 as model compounds for reductive alkylation studies. Of these, 44, 57, and 58 are substituted at the α carbon and present the possibility of determining conclusively whether alkylation is axial.

The most definite case was 44 since we had already established the structures and stereochemistry of the reaction products, of which 47a is the major component when lithium metal, ammonia, and methyl iodide are used. Since 47a was obtained as the major product, it can be concluded that the methyl group is added in an axial orientation. We also established that enolate trapping occurred because there was no

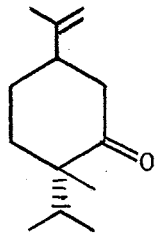
alkylation at C_6, which would result if equilibration of the enolate anion took place. However, since more than one methyl menthone is formed in the reductive methylation of 44, some ring flipping must occur as illustrated in the series of transition states 84a, 84b, 84c, and 84d. It is not possible to exclude formation of 47a by direct



84a 84b 84c 84d

methylation of 54a or 54b formed in the reaction.

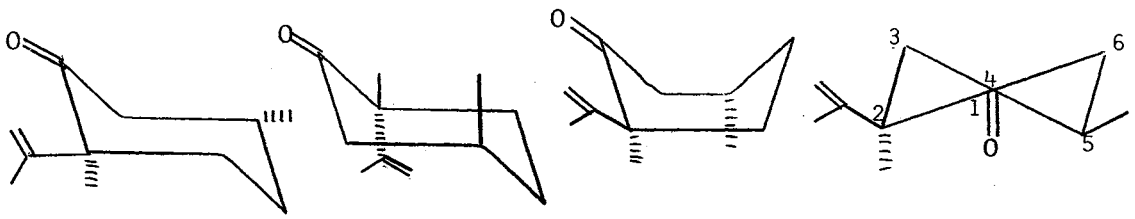
The evidence for absence of C_6 methylation in the product assigned structure 47b is the absence of the fragment m/e = 112 in its mass spectrum (due to loss of $CH_3CH{=}C{=}O$). Instead, the fragment m/e = 126 (due to loss of ketene) was observed. The reductive alkylation study was extended to the reductive isopropylation of the carvones 57 and 58 with lithium metal, ammonia and isopropyl iodide. A gas chromatography analysis of the reaction product mixture from 57 or 58 on a 10 ft x 1/4 in. column of 60-80 mesh, acid-washed Chromosorb W coated with 20% Carbowax 20M at 190° showed 3 peaks. The two leading peaks corresponded in retention times to the expected dihydrocarvones. The last peak was shown to be due to material having both an isopropyl and an isopropenyl group; therefore, isopropylation had occurred. If we assume that kinetically controlled reductive isopropylation takes place, structure 85 represents the reaction product from (-)-carvone (58). The area ratio of these three peaks was 52:20:28 respectively.



85

Both reductive isopropylation and methylation reactions were carried out on 56. However, a complex mixture of products resulted. In the case of 55, considerable polymerization was observed and no useful products were obtained.

The optical rotatory dispersion studies carried out on these ketones related to 45a are worthy of comment. In view of the recent crystallographic evidence[28e] and our chemical degradation of 45a, the absolute configuration of 45a is firmly established. Hence, it was considered that ORD studies could furnish valuable information regarding its conformation. For example, 45a can have conformations such as A, B, C, and D.

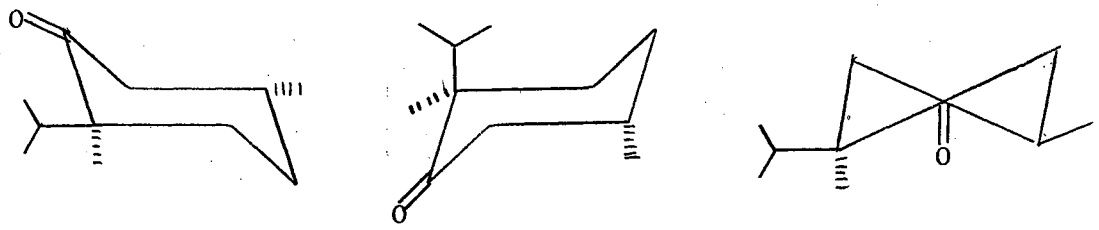


A B C D

Since 45a exhibits a negative Cotton effect, conformations such as A and B may be ruled out because according to the octant rule[54] they are expected to exhibit a positive Cotton effect. An earlier prediction[40] that 45a should exhibit a positive Cotton effect was probably based on the assumption that the molecule exists in a chair

conformation. Also, precise quantitative application of the octant rule[54] to 45a is not possible because free rotation of the isopropyl group must be considered as well as all the intermediate forms between chair and boat conformations. Recent quantitative studies of the Cotton effect associated with α-equatorial alkylcyclohexanones have indicated that an equatorial isopropyl group provides a positive contribution to the molecular amplitude of about 17 whereas an axial isopropyl group contributes about 98 to the molecular amplitude,[55] and therefore the isopropyl group does not lie in the nodal plane passing through carbons 1, 2, and 6.

The ORD curve of 47a exhibited a positive Cotton effect, and favors conformation E over F because the latter has the isopropyl group axial, while in E this group is equatorial; at the same time, the twist form G cannot be ignored.



E F G

The bromo ketone 59 showed a negative Cotton effect. Here the conformational equilibrium is governed by the nature of solvent and is temperature-dependent. The conformer H is preferred over I because it has been shown that an equatorial bromine predominates over an axial bromine.[57] Twist conformations such as J must also be considered.

The ORD curve of the α,β-unsaturated ketone 60 showed a positive Cotton effect. These observations are recorded in Table II and the

TABLE III

MASS SPECTRAL DATA FOR KETONES RELATED TO 45a

	45a		47a		60	
	Mass	%	Mass	%	Mass	%
M	166	2.0	168	0.7	166	0.7
M-15	151	1.6	153	1.2	151	0.6
M-28					138	1.0
M-29	137	3.0				
M-33			135	0.5		
M-41			127	0.7	125	0.7
M-42	124	1.7	126	8.1	124	8.7
M-43	123	7.7	125	1.2	123	2.1
M-44	122	0.8				
M-57					109	3.1
M-84					82	26.5
M-85	81	4.2				
M-99	67	5.4	69	6.7		
M-113			55	9.9		
M-125	41	8.2	43	4.7	41	6.8
M-127	39	6.0	41	9.5	39	6.3
M-139	27	4.4			27	5.0
M-141			27	5.1		

Optical Rotatory Dispersion Curves for Ketones Related to 45a

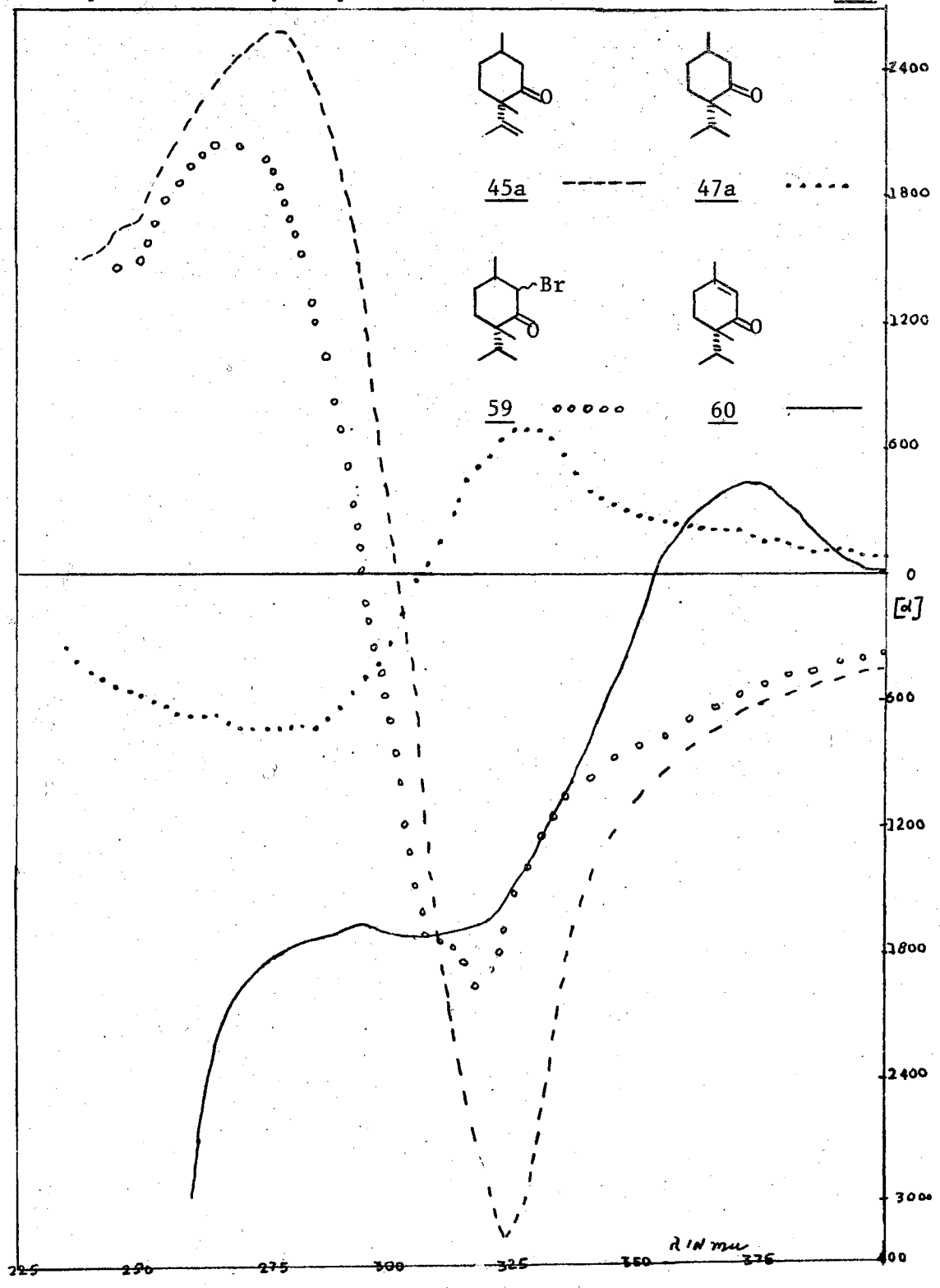
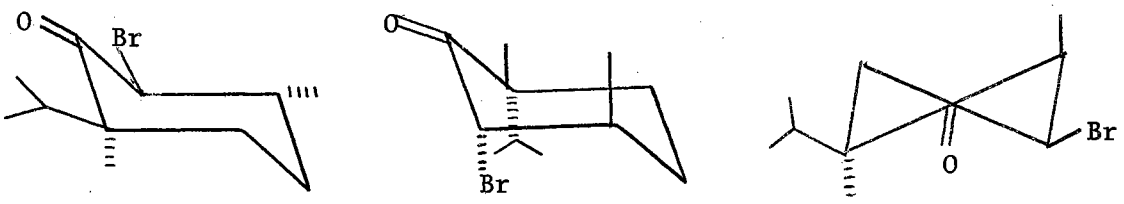


PLATE I



H I J

curves are shown on Plate I.

This ORD study of 45a, 47a, and 59 along with their absolute configurations help to predict their most probable conformation.

EXPERIMENTAL

For the gas chromatography studies, a Beckman GC-2A or an F&M Model 700 gas chromatography apparatus was used. The columns used for analytical gas-phase chromatography were 10 ft x 1/4 in. and were packed with acid-washed Chromosorb W 60-80 mesh coated with LAC 886 or Carbowax 20M. The column temperature was usually 180-190°. Infrared spectra were obtained with a Beckman IR-5A spectrometer; the nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as the internal standard (τ = 10) and carbon tetrachloride as the solvent. Melting points were obtained in capillary tubes and are uncorrected.

Isolation of (+)-Pulegone (44) from Oil of Pennyroyal

Commercial oil of pennyroyal (600 ml) was distilled through a column packed with steel grids and equipped with a variable reflux take-off head. Distillation fractions weighing 290 g and boiling at 72-75° (0.65 mm) and 75-80° (0.7 mm) were combined and purified by preparative gas chromatography using a column packed with Chromosorb W coated with LAC 886. The column temperature was 180°. This gave 44

in 98.7% purity. It was redistilled and the material with the following constants was used for methylation: bp 74-75° (0.65 mm), $[\alpha]_D$ + 22.9° (neat), λ_{max}^{EtOH} 251 (ε 7370). Its nmr showed a doublet at 9.0 τ (3H), doublet around 8.7 τ (1H), singlet at 8.2 τ (6H), singlet at 8.1 τ (4H), and a multiplet at 7.6 τ (2H).

Preparation of (-)-Methylisopulegone (45a)

To (20.3 g) sodium sand in 336 ml dry benzene was added 87.5 ml of tert. pentyl alcohol and the entire mixture was heated under reflux for 30 hours until all the sodium sand was dissolved. The hot solution was then slowly added to a stirred solution of 106.4 g of 44. After addition of sodium tert.-pentyloxide was complete, 61.6 ml of methyl iodide in 560 ml dry ether was added carefully while cooling the reaction flask in an ice-bath. The mixture was heated under reflux for 3 hours after all the methyl iodide was added. Water was then added to the reaction mixture and the organic layer was separated. The organic layer was washed with water and the solvent was evaporated. Distillation of the crude product afforded 90 g of a mixture of 45a and its epimer at C_2, bp 81-86°/11 mm. This crude methylisopulegone fraction (85 g) was added slowly to an aqueous solution containing 108 g semicarbazide hydrochloride and 170 g sodium acetate in 750 ml water. The turbid solution was clarified by adding ethanol. After 12 hours crystallization time, 53 g of semicarbazone were collected and recrystallized three times from isopropyl alcohol to give 36 g of the pure semicarbazone of 45a, mp 200-202° C. The literature value is 201-202.5°.[40]

In order to obtain pure 45a, 26 g of the pure semicarbazone was steam distilled in the presence of 52 g of oxalic acid. The steam distillate was extracted with ether, and the ether layer dried and

evaporated. Distillation of the product gave 15 g of 45a, bp 89-93° (11.5 mm); $[\alpha]_D$ - 123.4° (neat); λ_{max}^{EtOH} 294 mμ (ε 51); $\lambda_{max}^{CCl_4}$: 3000 cm^{-1}, 1720 cm^{-1}, 1560 cm^{-1}, 1470 cm^{-1}, 1390 cm^{-1}, and 1650 cm^{-1}; nmr signals at 5.05 τ [2H(d)], between 7.3 to 8.2 τ [6H(m)], 8.3 τ [3H(s)], 8.7 τ [1H(d)], 8.9 τ [3H(s)], and 9.0 τ [3H(d)]; ORD showed negative Cotton effect: RD (c 0.13, dioxane) $[\alpha]_{400}$ - 450°; $[\alpha]_{323}$ - 3180°; $[\alpha]_{277}$ + 2580°; $[\alpha]_{250}$ + 1680°; $[\alpha]_{235}$ + 1500°.

Preparation of (+)-Methyldihydroisopulegone (47a)

a) By Catalytic Hydrogenation of 45a. Catalytic hydrogenation of 14 g of 45a in the presence of 1 g of 10% palladized charcoal catalyst in 150 ml of 95% ethanol resulted in the uptake of one equivalent of hydrogen within 45 minutes. The catalyst was filtered out and the solvent was evaporated. Distillation of the product afforded 10 g of 47a, bp 85-88°/23 mm; $[\alpha]_D$ + 18.75° (neat); $\lambda_{max}^{CCl_4}$: 2825 cm^{-1}, 1710 cm^{-1}, 1450 cm^{-1}, and 1375 cm^{-1}; nmr signals at 9.2 τ [3H(d)], 9.1 τ [2H(s)], 9.0 τ [6H(2d)], 8.4 τ [1H(d)], 8.2 τ [1H(d)], 8.0 τ [2H(s)], and a multiplet between 7.5 and 7.85 τ [4H]. Its mass spectrum (see Table III) showed a molecular ion at m/e 168 (0.6%), and other prominent fragments at m/e = 55 (9.9%), m/e = 41 (9.5%), m/e = 126 (8,1%). Its ORD curve showed a positive Cotton effect, RD (c, 0.174, dioxane) $[\alpha]_{400}$ + 150°; $[\alpha]_{320}$ + 1380°; $[\alpha]_{275}$ - 1560°; $[\alpha]_{240}$ - 660°.

b) By Methylation of a Mixture of (-)-54a and (+)-54b. A typical procedure followed to accomplish this was that of Bloomfield.[53] Sodium hydride (2.4 g, 0.1 mole) was heated in 50 ml of dry refluxing dimethyl sulfoxide under a nitrogen atmosphere (2 hrs). The reaction mixture was cooled, 15.4 g (0.1 mole) of menthone, bp 67°/1.25 mm, added, the mixture refluxed for another hour and cooled, and 22 g (0.15 mole) of

methyl iodide added. After stirring at room temperature for 4 hours, the entire mixture was diluted with water and extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and evaporated. Distillation gave 14.4 g of the product, bp 75°/0.8 mm. Gas chromatography analysis at 160° on Carbowax 20M showed three peaks, two of which were found to be 54a and 54b while the third peak was identified as 47a by its comparison with pure 47a. Furthermore, the nmr of the reaction mixture showed the characteristic singlet at 9.1 τ for the C_2-methyl group. The yield of 47a estimated by gas chromatography was about 45%.

c) By Reductive Methylation of (+)-Pulegone (44). A 2000-ml, three-necked flask fitted with a stirrer and dry ice condenser was heated for 15 minutes. Dry nitrogen was swept through the system and then 1000 ml of ammonia, distilled over sodium metal, was introduced into the reaction flask and 7.5 g, 2.5 gram atoms of lithium metal was added and stirring begun. To the resulting blue solution, 76 g (0.5 mole) of 44 in 200 ml of freshly distilled tetrahydrofuran was slowly added through a Hirshberg dropping funnel. The blue solution was allowed to stir for 1 hr. The excess ammonia was then displaced by adding 250 ml of tetrahydrofuran and the dry ice condenser was replaced by a water condenser. A complete removal of ammonia was further accomplished by refluxing the solution for 1 hr. The reaction mixture was then cooled and 710 g (5 mole) of methyl iodide were slowly added. After the addition of methyl iodide, the entire mixture was refluxed for 1 hr. and kept overnight at room temperature and then poured into water and extracted with ether. The ether layer was dried over magnesium sulfate, filtered and evaporated. Distillation of the

product gave 60 g product, bp 60-65°/1.8 mm. Gas chromatography analysis on a 10 ft x 1/4 in. column at 160° showed four peaks; the first two peaks were identified as due to 54a and 54b, while the third peak corresponded to 47a. The IR spectrum of the mixture showed bands at $\lambda_{max}^{CCl_4}$ 1710 cm^{-1}, 1460 cm^{-1}, and 1380 cm^{-1}. Its ORD curve showed a positive Cotton effect comparable to authentic 47a, but the amplitude was reduced; RD (c, 0.1 dioxane) $[\alpha]_{400}$ + 90°; $[\alpha]_{325}$ + 690°; $[\alpha]_{275}$ - 720°; $[\alpha]_{235}$ - 330°. Its mass spectrum showed most prominent fragments at m/e = 41 (8.9%), m/e = 55 (8.8%), m/e = 28 (6.8%), m/e = 126 (6.7%), m/e = 69 (6.3%), m/e = 27 (4.5%).

Preparation of (-)-2-Bromo-3,6-dimethyl-6-isopropylcyclohexanone (59)

To a stirred suspension of 4.58 g of 47a in 16 ml of water was added dropwise over a period of 3 hrs 4.76 g of bromine. After complete decoloration (ca. 8 hrs.), the reaction mixture was extracted with ether; the ether layer was washed with water and dried over magnesium sulfate. After filtration, the ether was removed and the residue was distilled from a trace of magnesium oxide to give a colorless distillate, bp 140-142°/0.9 mm, which solidified (6.2 g). On recrystallization from n-hexane, the solid melted at 79-81°; $[\alpha]_D$ - 148.7° (c, 1.2; $CHCl_3$); $\lambda_{max}^{CCl_4}$ 1727 cm^{-1}, 1460 cm^{-1}, 1400 cm^{-1} λ_{max}^{DMSO} 1712 cm^{-1}. There was no shift in the carbonyl stretching frequency of the parent ketone 47a when the spectra in DMSO were compared. The nmr spectrum (in $CDCl_3$) showed τ 9.3 (C_2 methyl protons), 9.2 τ (C_5 methyl protons, doublet, J = 3 cps), 8.95 τ (isopropyl methyl protons, doublets, J = 5 cps), τ 7.6 - 8.5 (six protons), τ 4.9 (C_6 proton, doublet, J = 5 cps). Its ORD curve exhibited a negative Cotton effect, RD (c, 0.1 dioxane) $[\alpha]_{400}$ - 360°; $[\alpha]_{316}$ - 1950°; $[\alpha]_{265}$ + 2040°; $[\alpha]_{245}$ + 1500°.

Preparation of (-)-3,6-Dimethyl-6-isopropyl-2-cyclohexan-1-one (60)

A mixture of 1.64 g of bromo ketone 59, 1.2 g of anhydrous lithium carbonate, 1 g of anhydrous lithium bromide, and 28 ml of freshly distilled dimethylformamide was heated at 90-95° for 18 hrs while a current of nitrogen was passed through the system. Water was added and mixture was steam distilled until about 200 ml of distillate were collected. It was repeatedly extracted with ether. The ether extract was dried over $MgSO_4$, filtered, and evaporated. The residue, on distillation at bath temperature (110°/1.25 mm) gave 0.8 g of 60; $[\alpha]_D$ - 81° (c 1.4, in $CHCl_3$); λ_{max}^{EtOH} 235 and 320 mμ (log ε 4.12 and 1.85); $\lambda_{max}^{CCl_4}$ 2950 cm^{-1}, 1665 cm^{-1}, 1550 cm^{-1}, 1440 cm^{-1}, and 1380 cm^{-1}; its ORD curve exhibited a positive Cotton effect. RD (c 0.1235, dioxane), $[\alpha]_{400}$ + 6°, $[\alpha]_{378}$ + 450°; $[\alpha]_{305}$ - 1710°; nmr (CCl_4), 9.1 - 9.3 τ (9 protons of isopropyl methyl and C_6 methyl), 8.8 τ (isopropyl proton, doublet, J = 3.5 cps), 8.1 τ (three allylic methyl protons), 7.8 τ (four methylene protons), 4.3 τ (olefinic proton). Its mass spectrum (refer to Table III) showed molecular ion at m/e = 166 (0.7%). The most intense peak was due to m/e = 82 (28.5%).

Preparation of Bromo Ketone 71 from 60

N-Bromosuccinimide (1.35 g) in 25 ml carbon tetrachloride with 1 g of 60 was heated for 1 hr under a nitrogen atmosphere. The hot solution was filtered and the solvent was evaporated. Distillation (bath temperature 85°) (1.2 mm) of the residue gave 0.75 g of 71; λ_{max}^{DMSO} 1650 cm^{-1}, 1430 cm^{-1}, 1380 cm^{-1}; nmr ($CHCl_3$) showed τ 9.05 - 9.25 (two isopropyl methyl and C_6 methyl protons), 8.75 τ (isopropyl proton, doublet) 8.15 τ (three allylic methyl protons), 7.8 τ (two methylene protons, doublet) and 4.35 τ (one vinylic proton and one C_4 proton,

multiplet).

Preparation of 73 from 71

Bromo ketone 71 (0.5 g) was added to a stirred suspension of 2 g of calcium carbonate[59] in 20 ml water and the mixture was boiled for 1 hr, cooled and extracted with ether. The ether extract was dried with magnesium sulfate, filtered, and concentrated. The viscous liquid (0.250 g), $\lambda_{max}^{CCl_4}$ 3400 cm^{-1}, 2950 cm^{-1}, 1650 cm^{-1}, and 1050 cm^{-1}; nmr (CCl_4), τ 9.1 - 9.2 (9 protons due to isopropyl methyls and C_6 methyl), 8.05 τ (3 protons for allylic methyl), 7.85 τ (2 methylene protons, doublet), 6.4 τ (one proton at C_4), 6.1 τ (one proton of allylic hydroxyl) and 4.35 τ (vinylic proton), was directly oxidized with alkaline potassium permanganate.

Preparation of (+)-2-Isopropyl-2-methylsuccinic Acid (52a)

a) Permanganate Oxidation of 71. The bromo ketone 71 (0.35 g) was dissolved in 3 ml of 6% NaOH and cooled to 10° with ice water bath. To the cooled solution was added 10 ml of 0.17 Molar $KMnO_4$ solution. The suspension was then stirred overnight and the resulting manganese dioxide was filtered out. The filtrate was acidified with dilute HCl and was continuously extracted with ether. The ether layer was dried over $MgSO_4$, filtered and concentrated. The crude solid product was sublimed at 110° (0.8 mm) to give 150 mg of 52a. Recrystallization from 95% ethanol gave material melting at 128-130°. The IR spectrum of 52a showed λ_{max}^{KBr} 3000 cm^{-1}, 1758 cm^{-1}, 1710 cm^{-1}, 1440 cm^{-1}, and 1370 cm^{-1}. The melting point of this 52a was not lowered when it was mixed with an authentic sample; $[\alpha]_D$ + 15° (c, 0.8 in ethanol).

The dimethyl ester 52e, prepared by reacting 52a with diazomethane, was distilled at bath temperature 128° (2.3 mm); $[\alpha]_D$ + 29.5°

(c 0.83, $CHCl_3$); $\lambda_{max}^{CCl_4}$ 2920 cm^{-1}, 1743 cm^{-1}, 1550 cm^{-1}, 1440 cm^{-1}, 1360 cm^{-1}, and 1220 cm^{-1}; its ORD showed a positive plain curve RD (c 0.50, CH_3OH) $[\alpha]_{393}$ + 24°; $[\alpha]_{345}$ + 78°; $[\alpha]_{290}$ 208°; nmr (CCl_4) signals appeared between 8.7 - 9.2 τ (9 protons due to isopropyl methyls and C_2-methyl), 7.9 τ (single proton), 7.45 τ (two protons) and 6.3 τ (six methoxyl protons, doublet).

b) Permanganate Oxidation of 73. The oxidation procedure previously described was used to oxidize 150 mg of 73 in 2 ml of 6% NaOH and 5 ml of potassium permanganate. The reaction gave 70 mg of 52a.

All the reductive methylations and isopropylation described below were carried out like the reductive methylation of 44.

Reductive Methylation of 2-Cyclohexen-1-one (55)

To 150 ml of ammonia containing two equivalents of lithium metal (0.38 g) was added 2.5 g (0.0266) mole) of 55. The blue solution was stirred for 1 hr. Methyl iodide (16 g, 0.11 mole) was then added and the resulting reaction mixture was stirred for 30 min. The ammonia was allowed to evaporate. After the usual workup, a gas chromatography analysis of the reaction product showed two peaks corresponding to 2-methylcyclohexanone and cyclohexanone. During distillation of this product, some viscous residue was observed which did not distill. The IR spectrum of the residue showed λ_{max}^{film} 3450 and 1700 cm^{-1}.

Reductive Methylation of 3-Methyl-2-cyclohexen-1-one (56)

The procedure was analogous to the one described for the reductive methylation of 44. Quantities used were 150 ml ammonia, 0.4 g lithium, 3.5g (0.027 mole) of 56 and 16 g (0.11 mole) methyl iodide. After the usual workup, the residue was analyzed by gas chromatography and this analysis showed a complex mixture of products. The nmr (CCl_4) spectrum

gave the expected signals for methyl and methylene protons showing that the reductive methylation had indeed occurred.

Reductive Isopropylation of 3-Methyl-2-cyclohexen-1-one (56)

The experimental details were similar to those described for the reductive methylation of 44. The following quantities were used: 500 ml ammonia, 1.4 g (0.2 g atom) of lithium, 7.2 g (0.066 mole) of 56, 34 g (0.2 mole) of isopropyl iodide, and 150 ml tetrahydrofuran. The reaction mixture on distillation gave 4 g of liquid, distilling at a bath temperature of 90° (0.5 mm). Gas chromatography analysis showed a complex mixture had formed. The IR spectrum showed $\lambda_{max}^{CCl_4}$ 2900 cm^{-1}, 1710 cm^{-1}, 1670 cm^{-1}, 1440 cm^{-1}, 1380 cm^{-1}, and the nmr (CCl_4) showed the isopropyl methyl and C_3 methyl protons at their usual position.

Reductive Isopropylation of l-Carvone (58)

Reductive isopropylation was carried out in the same way described for reductive methylation of 44. The following quantities were used: 500 ml ammonia, 1.4 g lithium (0.2 g atom), 10.1 g of 58 120 ml tetrahydrofuran, and 34 g (0.2 mole) of isopropyl iodide. After the usual workup, the reaction mixture yielded 7.2 g of product, distilling at 116° (0.26 mm). Gas chromatography analysis on Carbowax 20M at 190° showed three peaks in the ratio 52:20:28. The last peak is tentatively assigned to 85 while the first two peaks are believed to be due to reduction of 58. The IR spectrum of 85 showed $\lambda_{max}^{CCl_4}$ 2800 cm^{-1}, 1710 cm^{-1}, 1675 cm^{-1}, 1650 cm^{-1}, 1450 cm^{-1}, 1380 cm^{-1}, and 890 cm^{-1}, and the nmr spectrum in CCl_4 showed multiplet of isopropyl methyl and C_2 methyl protons appeared at 9.0 τ, allylic methyl protons appeared at 8.3 τ, and isopropyl protons at 8.1 τ, complex signals showing methylene protons and methine proton at C_5 appeared between 7.5 and 7.95 τ and

vinylic protons around 5.3 τ.

Reductive Isopropylation of d-Carvone (57).

Reductive isopropylation of 57 was carried out in an analogous manner to that described for 44. The following quantities were used: 250 ml ammonia, 0.7 g (0.1 g atom) of lithium, and 17 g (0.1 mole) of isopropyl iodide. After the usual workup, 3.2 g of product was obtained. The gas chromatography analysis showed the same peaks as observed for 58.

Lithium Ammonia Reduction of l-Carvone (58)

To the blue lithium-ammonia solution formed by 2.1 g (0.3 g atom) of lithium in 250 ml dry ammonia was added 3 g of 58 and 60 ml tetrahydrofuran, followed by slow addition of 20 g (0.374 mole) of ammonium chloride in small portions over a period of four hours. The ammonia was evaporated, water was added and the product extracted with ether. The ether extract was dried over $MgSO_4$ and the solvent removed. The residue on distillation gave 2 g of product which distilled at a bath temperature of 95° (0.54 mm). The gas chromatogram showed four peaks. It appears that the carbonyl group was reduced to hydroxyl as a side reaction because the IR spectrum of the mixture showed $\lambda_{max}^{CCl_4}$ 3500 cm^{-1}, 2800 cm^{-1}, 1712 cm^{-1}, 1680 cm^{-1}, 1640 cm^{-1}, 1370 cm^{-1}, and 890 cm^{-1}, and the nmr spectrum in CCl_4 showed the expected signals for C_2 methyl protons appearing at 9.0 τ, C proton at 8.7 τ, allylic methyl protons at 8.3 τ, methylene protons at 7.6 and 8.2 τ, and vinylic protons at 5.3 τ.

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