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Synthesis and reactivity of small ring bicyclic compounds

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SYNTHESIS AND REACTIVITY OF SMALL RING BICYCLIC COMPOUNDS

by

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INTRODUCTION

Although the bicyclopentane ring system was first synthesized over ten years ago, work in the area of bicyclopentane chemistry at first proceeded slowly because of the lack of a general synthetic route for the preparation of substituted bicyclopentanes. Syntheses for a number of specifically substituted bicyclopentanes were found, but these procedures could not easily be extended to the preparation of other compounds. In particular, the introduction of substituents at the bridgehead position was hampered by the lack of synthetic procedures. Until 1967, only the 1-methyl and 1-isopropyl compounds were available with substituents at this position. Since the chemistry of the bicyclopentane molecule centered primarily about the reactivity of the central 1-4 bond, the preparation of a variety of 1-substituted bicyclopentanes was of considerable interest. This work presents a general synthesis of bridgehead-substituted bicyclopentanes, examines the limitations of chemical conversions of these bridgehead substituents, the effects of these substituents on 1-4 bond breaking reactions, and their utility for the generation of reactive intermediates at the bridgehead position in the ring system. The mass spectral behavior of a number of these compounds will also be discussed.

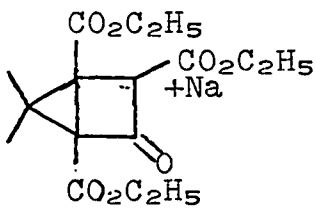
HISTORICAL

Syntheses of Bicyclopentanes

The first claim for the synthesis of a compound containing the bicyclopentane ring system appeared in the literature in 1901. Perkin and Thorpe (1) reported that the treatment of ethyl α,α'-dibromo-β,β-dimethylglutarate with sodium diethyl malonate, followed by treatment with sodium in boiling xylene yielded a yellow sodium salt which they characterized as 5,5-dimethyl-1,2,4-tricarboethoxy-3-ketobicyclo[2.1.0]pentane (1). This compound could be hydrolyzed and decarboxylated to varying degrees with acid and base to yield a series of acids including a monobasic acid which they characterized as 5,5-dimethyl-3-ketobicyclopentane-1-carboxylic acid (2). Degradation of this acid with nitric acid yielded α,α-dimethylsuccinic acid and α-keto-β,β-dimethylglutaric acid. Treatment with sodium amalgam yielded a monocyclic keto-acid, rather than the expected bicyclic hydroxy-acid.

In 1919, doubt was cast upon this structure assignment by N. J. Toivonen (2). He reported that the dehydration of 1-hydroxy-2,2-dimethylcyclopentan-4-one-1-carboxylic acid yielded a product which was identical with the keto-acid assigned structure 2 by Perkin and Thorpe. He argued that the reactions of this compound and its method of synthesis made the structure 4-keto-5,5-dimethylcyclopentene-1-carboxylic acid (3) much more likely correct. This report spurred

further investigations into the chemistry of this series of compounds.



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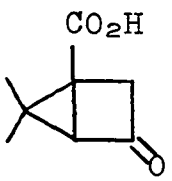

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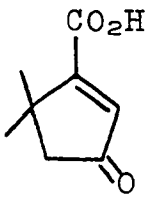

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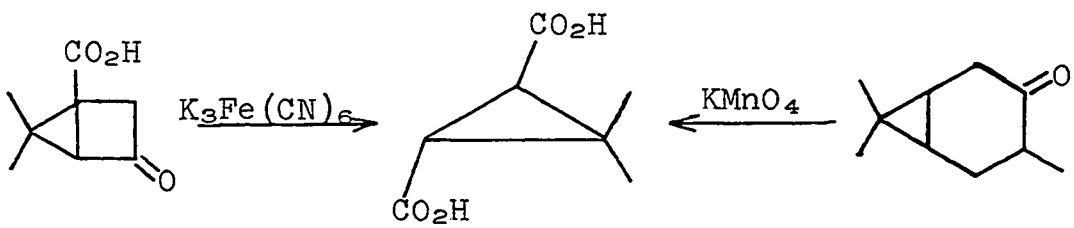
In 1920, Farmer and Ingold published in support of the bicyclic structure, mainly on the basis of one very interesting degradation reaction (3). They reported that the oxidation of Perkin and Thorpe's monobasic acid with potassium ferricyanide yielded trans-caronic acid, identical to that obtained by the oxidation of carone with potassium permanganate. They concluded from this reaction that the acid must contain a cyclopropane ring, and that therefore, 2 must be the correct

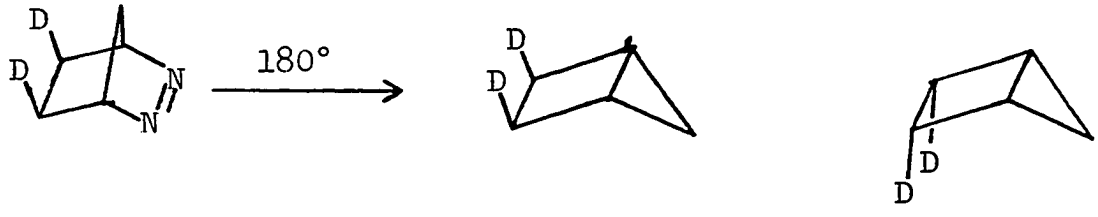


structure. They further proposed that Toivonen must have accomplished a transannular dehydration to obtain 2.

The strangely ambivalent chemistry of these compounds led to a series of papers concerning their true structures (4, 5, 6, 7, 8, 9, 10, 11, 12), including suggestions that structures 2 and 3 were valence tautomers and could thus give rise to

reactions characteristic of both (6, 10). Although research in this area continued until 1948, the true structures were never unambiguously assigned (12). However, in view of current knowledge of the chemistry of compounds containing the bicyclopentane ring structure, and the ease of formation of the compounds in question, the cyclopentene structure is currently thought to be correct.

The first authentic synthesis of bicyclopentane was carried out by Criegee in 1957 (13). Pyrolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene (4) produced a 94% yield of bicyclo-[2.1.0]pentane (5). This decomposition has been shown to be unimolecular and first order by rate studies (14, 15). Studies of the stereochemistry of the decomposition have led to disagreement as to whether there is a free diradical intermediate in the reaction. Roth and Martin have studied the pyrolysis of 4 labeled with exo-deuterium atoms at the 5 and 6 positions, and found that the reaction proceeds primarily with inversion about C-1 and C-4. They have interpreted this to exclude an intermediate diradical on the grounds that it



3 : 1

would produce a 50:50 mixture of endo- and exo-labeled product (16). Allred and Smith have studied the pyrolysis of endo- (6) and exo- (7) 5-methoxy-2,3-diazabicyclo[2.2.1]hept-2-ene and have rejected Roth and Martin's proposal of a

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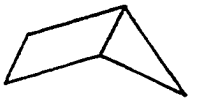

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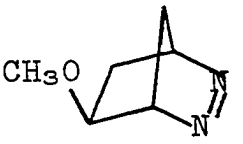

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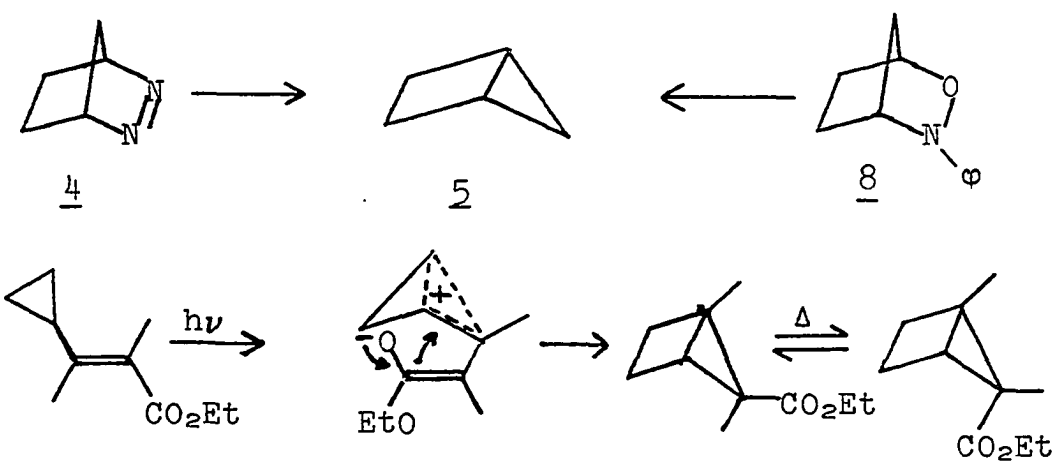
concerted mechanism (17). They argued that the inversion comes from recoil due to the energy of the broken C-N bonds, which leads to a pyramidal diradical. They maintain that the exo-methoxyl group in 7 should lead to more inversion and the endo-group in 6 to less inversion, due to steric interaction with the C-7 hydrogen. However, they observe just the opposite result. Extended Hückel calculations also predict that a concerted mechanism such as that proposed by Roth and Martin would not favor inversion (18).

The photolytic decomposition of 4 has also been studied (16, 19, 20). In the gas phase, photolysis with a Pyrex filter yields cyclopentene and 5, with an increase in pressure favoring 5 (19). In solution or as a solid, photolysis yields only 5 (16). Attempts to trap a possible diradical intermediate with NO have failed, indicating that

any such intermediate must have a lifetime of $<10^{-10}$ sec (20).

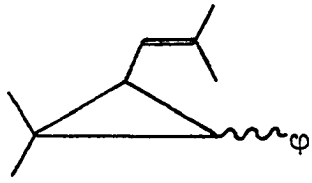
Following Criegee's original synthesis, a number of other procedures for preparing bicyclopentanes were published; however, they shared the characteristic of being valid for a very limited range of substitution. Chesick (21) prepared 2-methylbicyclopentane (cis- and trans-) by the copper catalyzed decomposition of diazomethane in the presence of 3-methylcyclobutene. Wiberg prepared 5-hydroxymethyl-bicyclopentane by the copper-catalyzed addition of ethyl diazoacetate to cyclobutene, followed by lithium aluminum hydride reduction (22). The pyrolysis of N-phenyl-2-aza-3-oxabicyclo[2.2.1]heptane (8) at 225° produced 5 in 70% yield (23), but suffered from the same lack of versatility as Criegee's synthesis.



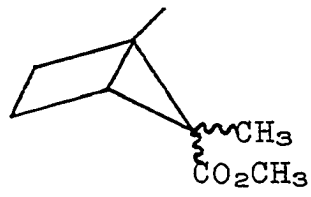
The application of photochemistry to synthesis of bicyclopentanes resulted in a number of new compounds containing

this ring structure. While studying the photochemistry of some cyclopropylacrylic esters, Jorgenson found that irradiation of ethyl 2-methyl-3-cyclopropyl-2-butenoate yielded, among other products, endo- (8a) and exo- (8b) 1,5-dimethyl-5-carboethoxybicyclopentane. The author proposed a mechanism involving a dipolar photochemical cyclopropylcarbinyl rearrangement (24).

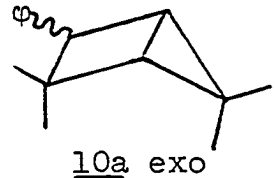
A similar photochemical synthesis of a bicyclopentane was reported by Hammond and Kristinsson (25). The irradiation of cis- (9a) and trans- (9b) 2-(2',2'-dimethylvinyl)-1-phenylcyclopropane yielded, in 50% yield, exo- (10a) and endo- (10b) 3-phenyl-2,2,5,5-tetramethylbicyclo[2.1.0]pentane, in a ratio of 2.2:1. Despite the great similarity between this reaction and that reported by Jorgenson, the authors made no mention of a cyclopropylcarbinyl type rearrangement.



9a cis
9b trans



8a endo
8b exo

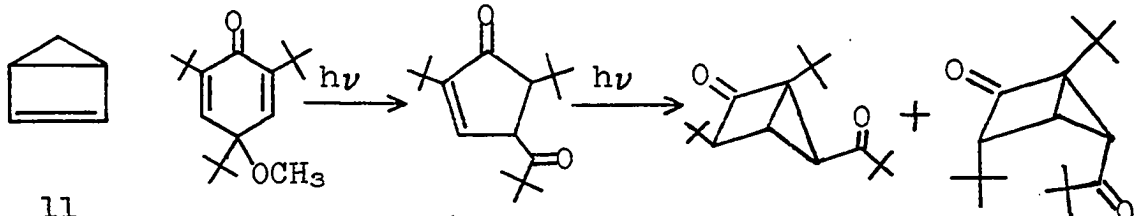


10a exo
10b endo

Perhaps the most interesting photochemical synthesis of a [2.1.0] system was that by Van Tamelen, Braumann, and Ellis (26), who reported the first synthesis of bicyclo[2.1.0]-pent-2-ene (11). Irradiation of a 0.3 M solution of

cyclopentadiene in ethanol with a high pressure mercury arc lamp produced a 10% yield of 11, which could be isolated by low temperature gpc collection. Reduction with diimide yielded 5.

In another interesting photochemical reaction, Matsuura and Ogura have reported the isolation of a bicyclopentan-2-one (27). Prolonged irradiation of 2,4,6-tri-t-butyl-4-methoxy-2,5-cyclohexadienone (12) yielded as secondary photolysis products 1-t-butyl-exo-5-t-butyl-exo-5-pivaloylbicyclopentan-2-one (13a) and 1-t-butyl-endo-3-t-butyl-endo-5-pivaloylbicyclopentan-2-one (13b). These products were shown to be products from photolabile primary products, cis- (14a) and trans- (14b) 1,4-di-t-butyl-3-pivaloylcyclopenten-5-one.



11 12 14a = cis 14b = trans 13a 13b

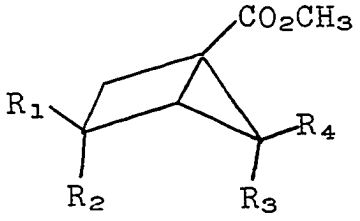
The photodimerization of cyclopropenes has provided another type of bicyclopentane, where this ring system is part of a tricyclic ring system. The irradiation of trimethyl- (28) or triphenyl- (29) cyclopropene gives rise to a 2-2 cycloaddition to form hexamethyl of hexaphenyl

tricyclo[3.1.0.$0^{2,4}$]hexane. The trans- isomer of the parent hydrocarbon has been synthesized by Allred and Hinshaw (30) by stepwise photolytic decomposition of a bis-pyrazoline in 10-15% yield. The compound is hydrogenated at atmospheric pressure to cyclohexane and methylcyclopentane, and isomerizes to 1,4-cyclohexadiene at 165°.

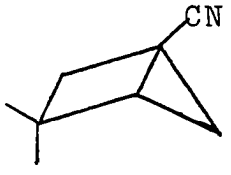
Other systems containing the [2.1.0] ring system have been synthesized (16, 17, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45) using a variety of techniques, but all these methods, as well as those mentioned previously, lack the versatility which is necessary for the specific introduction of substituents into the molecule. Thus, for several years the study of the chemistry of the bicyclopentane was rather limited in its scope.

The addition of diazoalkanes to activated carbon-carbon double bonds to form pyrazolines, and the decomposition of these pyrazolines to cyclopropanes has long been a valuable synthetic tool. However, until 1967, these methods had been applied to a very limited extent to the preparation of fused ring systems (46, 47, 48, 49). In 1967, three groups, working independently, reported the application of this technique to the synthesis of substituted bicyclopentanes (42, 50, 51). The addition of diazomethane, diazoethane, or 2-diazopropane to a cyclobutene containing an electron-withdrawing group on the double bond produced a wide variety of pyrazolines, which

could be decomposed to yield bicyclopentanes in varying yields. Compounds synthesized in this manner include 1-carbomethoxybicyclopentane (15a) (42, 50, 51), exo- (15b) and endo- (15c)-3-methyl-1-carbomethoxybicyclopentane, 3,3-dimethyl-carbomethoxybicyclopentane (15d), 3,3-exo-5-trimethyl-1-carbomethoxybicyclopentane (15e), 3,3,5,5-tetramethyl-1-carbomethoxybicyclopentane (15f), 1-cyano-3,3-dimethylbicyclopentane (16), 1-acetyl-3,3-dimethylbicyclopentane, (17) and 1-benzoyl-3,3-dimethylbicyclopentane (18) (50).



15a, $R_1=R_2=R_3=R_4=H$
15b, $R_1=CH_3$, $R_2=R_3=R_4=H$
15c, $R_2=CH_3$, $R_1=R_3=R_4=H$
15d, $R_1=R_2=CH_3$, $R_3=R_4=H$
15e, $R_1=R_2=R_4=CH_3$, $R_3=H$
15f, $R_1=R_2=R_3=CH_3$, $R_4=H$
15g, $R_1=R_2=R_3=R_4=CH_3$



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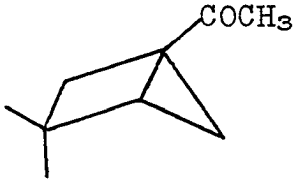

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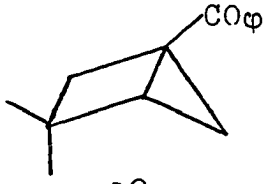

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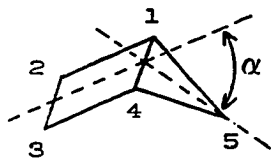
This method has also been used by Frank-Neumann (52) to prepare 5,5-dimethylbicyclo[2.1.0]pentanes, substituted with carbomethoxy groups at C-1 and C-4, or with chlorines at C-2 and C-3. He found that when dichloropyrazoline was irradiated in ether or acetone, he obtained some polymeric material which was difficult to separate from the bicyclic product, but the use of benzophenone as a sensitizer in ether led to a 97% yield of the bicyclopentane. This method of synthesis allows, either directly or indirectly, the introduction of a large variety of substituents at C-1, which had been the most difficult problem to this time, as well as a variety of substituents at any other position in the ring system. Coupled with the existing syntheses, a wide enough variety of compounds could now be prepared to thoroughly study the chemistry of the ring system.

Chemistry of Bicyclopentanes

The chemistry of bicyclopentane is dominated almost exclusively by the reactivity of the central 1 - 4 bond. Bohn and Tai have done electron diffraction work on bicyclopentane and obtained the parameters shown in Figure 1 (53).



$C_1-C_2 = 1.561 \pm 0.021$ A

$C_1-C_5 = 1.506 \pm 0.021$ A

$C_1-C_4 = 1.47 \pm 0.05$ A

$\alpha = 46.9 \pm 7.2°$

Figure 1. Electron diffraction data for bicyclo[2.1.0]pentane.

The bond length of the central bond is the most notable thing about the molecule, as it is considerably shorter than any other bond in the molecule, indicating a certain amount of double-bond character. The figure of 1.47A can be compared to the bond lengths of 1.524A measured for cyclopropane (54) and 1.56A for cyclobutane (55). The heat of hydrogenation of bicyclopentane to cyclopentane has been measured to be 55.1 kcal/mole, from which a strain energy of 47.4 kcal/mole has been calculated for the central bond (56). In comparison, heat of hydrogenation data for 1,3-dimethylbicyclo[1.1.0]-butane yield a calculated strain energy of only 41.3 kcal/mole for the central bond of that molecule (57). The large amount of strain in 5, and the resulting very high heat of

combustion has led the United States to consider its use as a rocket fuel (58).

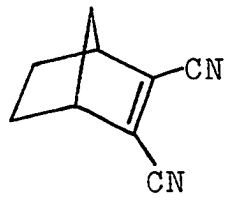
The double bond character of the central bond in 5 is reflected in the chemistry of the system. Criegee reported that 5 is easily hydrogenated to cyclopentane at atmospheric pressure; that it reacts readily with iodine; and that it slowly decolorizes a permanganate solution (13). Lalonde has studied the addition of halogens to bicyclopentane (59). Chlorine adds to the molecule at -20 to -40°C in the dark to yield a mixture of dichlorocyclopentanes. The major product is trans-1,2-dichlorocyclopentane, but both cis- and trans-1,3-dichlorocyclopentane were observed in less than 10% yield. Bromine also added readily. Lalonde proposed initial addition of Cl+ to the central bond to form a bridged 1,3 halonium ion, which could either give products directly or rearrange to a 1,2 halonium ion, leading to the 1,2 dihalocyclopentanes.

This bond reacts readily with a large number of electrophilic reagents. Criegee noted that bicyclopentane added HBr under very mild conditions to give cyclopentyl bromide (13). Lalonde and Forney studied the addition of acetic acid to various bicyclo[n.1.0]alkanes in the presence of a strong acid, but only bicyclopentane would add acetic acid to give cyclopentyl acetate in the absence of a stronger acid (60). Oxidizing reagents such as lead tetraacetate, mercuric acetate, or thallium triacetate react readily with

bicyclopentane to yield ring-opened products—3-hydroxycyclopentylmercury acetate from mercuric acetate (61) and trans-1,3-cyclopentanediol diacetate from either lead tetraacetate or thallium triacetate (62).

More recently, the addition of electrophilic olefins and acetylenes to bicyclopentane has been observed. In 1965, Gassman and Mansfield reported the addition of dicyanoacetylene to bicyclopentane at room temperature to yield 2,3-dicyanobicyclo[2.2.1]hept-2-ene (19) and cyclopent-2-enylidenesuccinonitrile (20). Under the same conditions, bicyclo[3.1.0]hexane did not react (63). It was later found that other acetylenes would react in a similar manner, including dimethylacetylene dicarboxylate and ethyl propiolate (64, 65). A kinetic study of the reaction showed very little change in the rate in going from benzene as a solvent to acetonitrile, and no change in the product ratios (65). These results are consistent with a stepwise mechanism involving the formation of diradical intermediates. The involvement of zwitterionic intermediates should cause a rate change on the order of 10^3 to 10^6 in going from benzene to acetonitrile, while a concerted multicenter reaction would require a different transition state for each product, and such a solvent change should then cause a difference in the product ratio. The diradical mechanism was confirmed in the study of the addition of fumaronitrile and maleonitrile to 5. Both olefins yielded a mixture of exo-exo- (21), exo-endo- (22), and endo-endo- (23)

1,2-dicyanobicyclo[2.2.1]heptanes, as well as cyclopentylidenesuccinonitrile (24) and cyclopent-2-enylsuccinonitrile (25) (66). Since mixtures of 21, 22, and 23 were found in the reaction of 6 with both fumaronitrile and maleonitrile, the reaction must proceed via a mechanism which allows rotation about the central bond of the two isomeric nitriles, ruling out a concerted mechanism.



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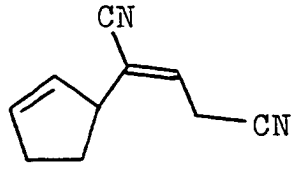

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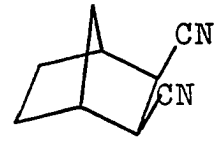

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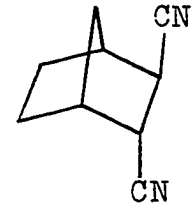

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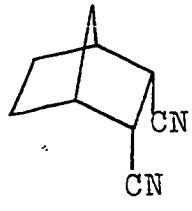

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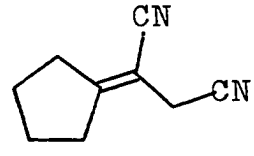

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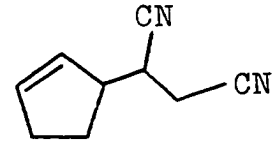

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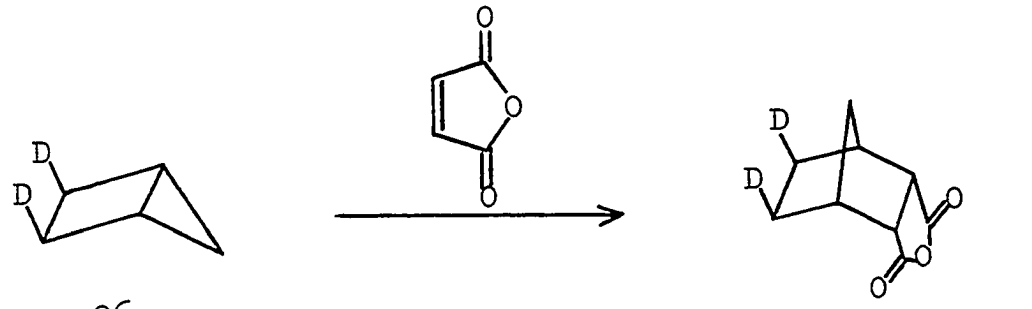
The stereochemistry of these addition reactions have been studied by Gassman, Mansfield, and Murphy by using as substrate exo-exo-2,3-dideuteriobicyclopentane (26) prepared by reducing bicyclopentene with dideuteriodiimide (66). The addition of maleic anhydride to 26 was found to give, within the limits of nmr detection, exclusively exo-deuteriums in the

adduct. These results require the attack of the maleic anhydride from the endo side of 26. This apparently involves initial overlap of the electron-deficient carbon-carbon double bond with the backside of the 1 - 4 orbital. Similar results have been obtained by Pomerantz and co-workers in their study of the reaction of labeled bicyclo[1.1.0]butane with benzyne (67). As would be expected for this mechanism, no attack occurred if the endo side of the molecule was bridged, preventing the approach of the benzyne molecule.



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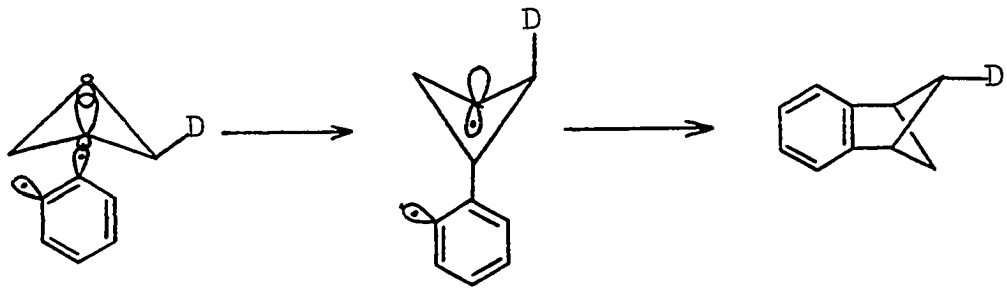
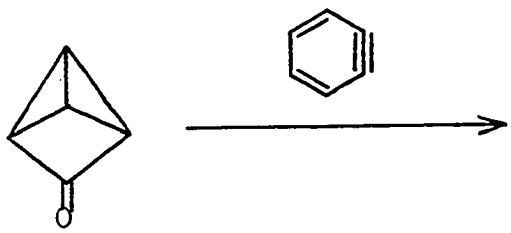




The thermal behavior of bicyclopentane and some derivatives has been studied by several workers (21, 68, 69, 70, 71, 72, 73). At low temperatures (<250°), the primary reaction is isomerization about the central bridge bond (21, 68). Chesick (21) has studied the cis-trans isomerization of 2-methylbicyclopentane for which he measured a mean activation energy of 38.9 kcal/mole. Since this was nearly 20 kcal higher than the predicted value, he interpreted this to mean that the strain of the molecule was not released in the transition state, and that if a diradical intermediate was involved, it was not a planar specie.

At higher temperatures, pyrolysis of bicyclopentanes yields cyclopentenes and 1,4 pentadienes. In the pyrolysis of 5, the reaction was found to be unimolecular and homogeneous over a wide pressure and temperature range, yielding cyclopentene (69) and ca. 0.4% 1,4-pentadiene (70). The activation energy for cyclopentene formation was found to be 45.6 kcal/mole, and that for pentadiene formation, 52.3 kcal/mole. This has been interpreted to be consistent with (70) or inconsistent with (69) a diradical intermediate, depending upon the author's estimation of other energies involved. The intermediacy of such a diradical or at least its conformation, is still being debated.

The isomerization of 5 to cyclopentene involves a hydrogen migration which is most likely a 1,2 migration from C-5.

Jorgenson has looked at the high temperature pyrolysis of 8a and 8b, which have no hydrogens on C-5, forcing them to seek other modes of rearrangement (71). The resulting products are best explained by a 1,3 hydrogen migration and a 1,2 carboethoxy migration, as shown in Figure 2 below. An ester group migration has been invoked by Matsuura and Ogura to explain the photochemical formation of 13 (72), but such a thermal rearrangement is unprecedented in the chemical literature.

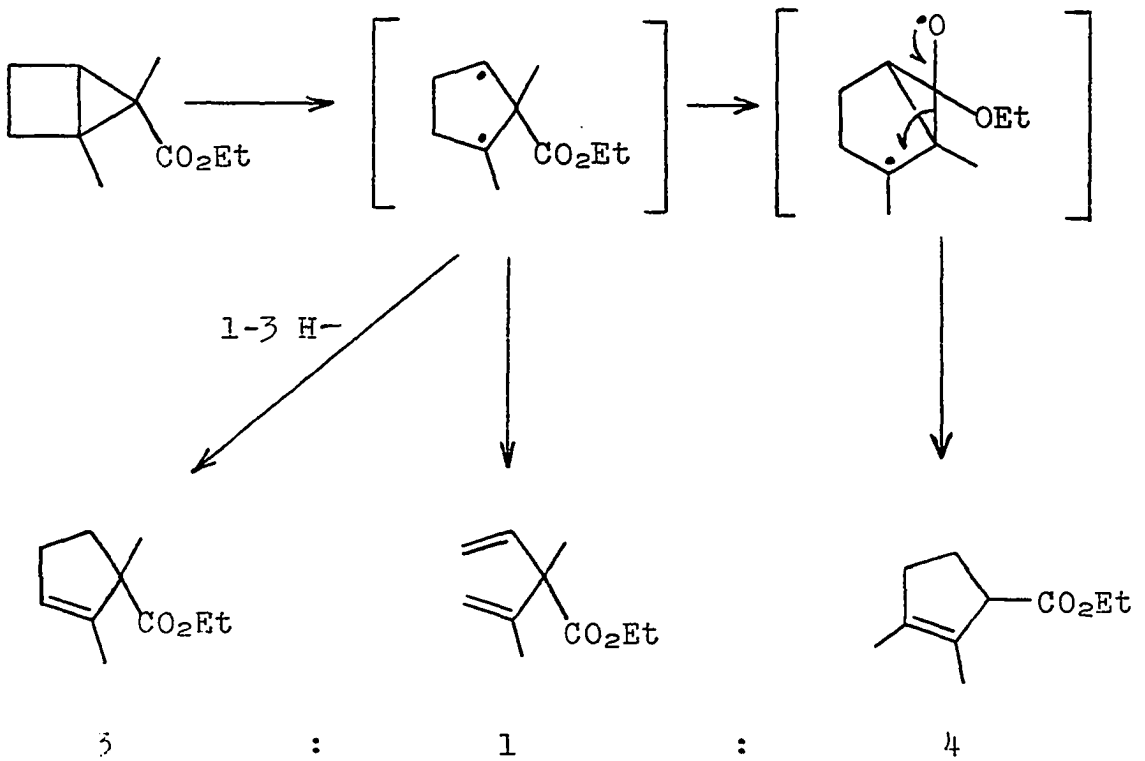


Figure 2. The thermal isomerization of 1,5-dimethyl-5-carboethoxybicyclopentane.

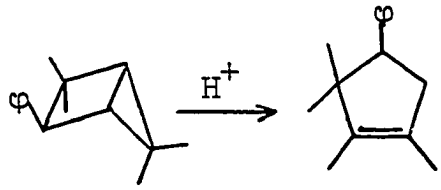
The incorporation of substituents onto the bicyclopentane nucleus often has an effect in modifying the chemistry of the system. The hydrogenation of 8 using platinum catalyst is very slow, and does not occur at all with palladium (24). Hydrogenation of 15d required the use of Pt/acetic acid at 500 lb pressure (50). Bicyclopentanones 13a and 13b were reported to be indifferent to hydrogenation with palladium catalyst (27). Compound 10a also resists hydrogenation with palladium, platinum, or Raney nickel catalysts; however, the more strained isomer 10b is hydrogenated smoothly at atmospheric pressure in the presence of palladium on charcoal (25). Jorgenson has studied the stereochemistry of the hydrogenation of 8a and 8b, and concluded from the stereochemistry of the products that hydrogenation occurs from the exo side of the molecule (73), a fact which would help to explain the great difference in reactivity between 10a and 10b. The exo-3-phenyl group would provide considerable hinderance to the approach of the catalyst, as well as causing much less strain than the endo-phenyl in 10b.

Reaction of the bicyclopentane nucleus with acid can also be modified by the introduction of certain substituents. The introduction of an electron-withdrawing group at C-1 reduces the nucleophilicity of the central bond as shown by the fact that 15d does not react with acetic acid under conditions which lead to the formation of cyclopentyl acetate from 5.

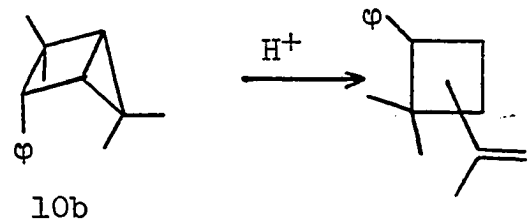
Substituents at other positions in the molecule may alter reactivity by increasing strain, as in the case of 10b, or by simply blocking the normal mode of reaction, as in the isomerization of 8. This behavior is most noticeable in the cases of 10a and b and 13a and b. Pyrolysis of 10b proceeds smoothly at 250° to yield a single product, while the anti isomer, 10a required a temperature of 290°, yielding four products at that temperature. Treatment of 10a with acid produced one product which was characterized as 1,2,3,3-tetramethyl-4-phenylcyclopentene. Isomer 10b yielded only a trace of this compound, the major product being an isopropenylcyclobutane resulting from the opening of one of the external cyclopropane bonds. This behavior is unprecedented in hydrocarbon bicyclopentanes. Treatment of 13b with acid or base also results in cleavage of a bond external to the four-membered ring, but this behavior is undoubtedly due to participation of the C-5 pivaloyl group. Pyrolysis of either 13a or 13b results in opening of the five-membered ring as well as breaking of the central bond to yield 2 isomeric lactones.

Because of the interest in the possibly non-classical cyclopropylcarbinyl cation, and the expected effect of the bicyclopentane ring strain upon its reactions, a number of derivatives of bicyclopentane alcohols have been studied with respect to solvolytic reactivity.

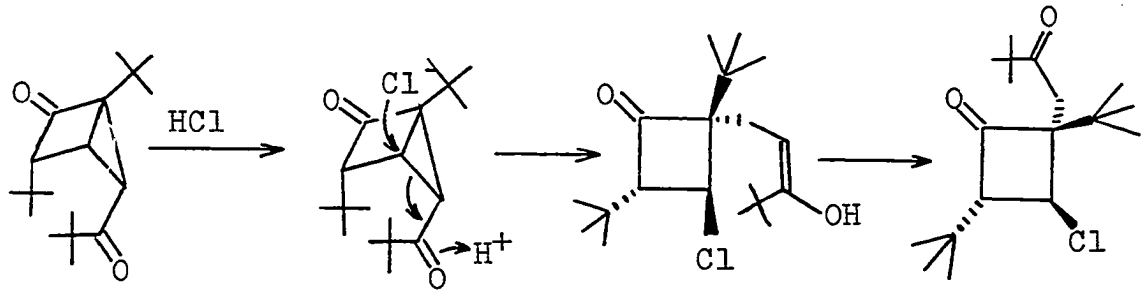
Wiberg and Ashe have studied the solvolysis of endo- (27a)

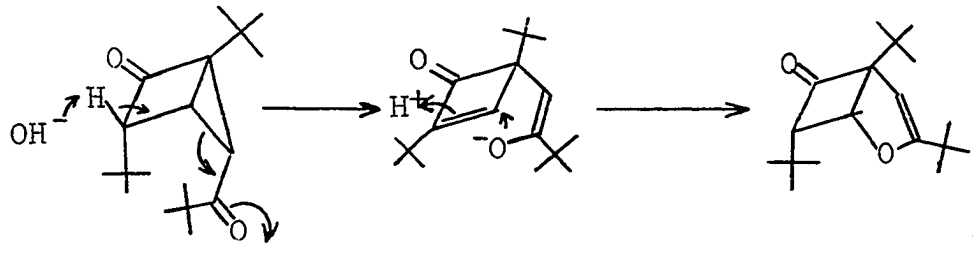


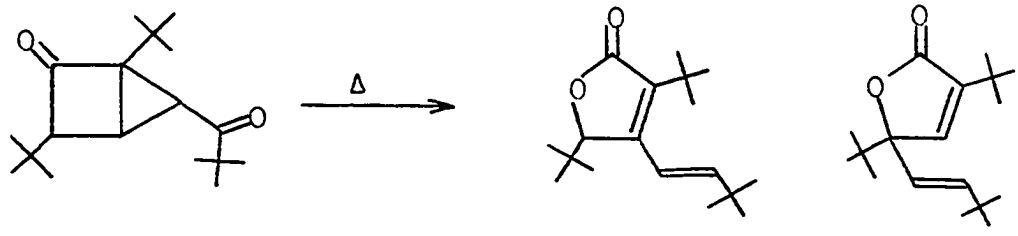
10a



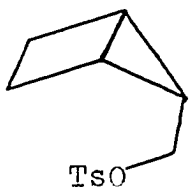
10b



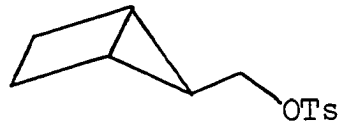




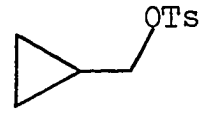
and exo- (27b) bicyclopentane-5-methyl tosylate in ethanol and in acetic acid (23, 74). They found the rate of acetolysis of these compounds nearly identical to the rate observed for the solvolysis of cyclopropylcarbinyl tosylate (28) (k_{28} = 1.0 x 10^{-4} sec^{-1}; k_{27a} = 1.17 x 10^{-4} sec^{-1}; k_{27b} = 1.35 x 10^{-4} sec^{-1}; all at 17° C). This rate is actually an order of magnitude slower than the corresponding bicyclo[3.1.0]hexane-6-methyl tosylates. The major product from acetolysis was the unrearranged acetate, along with small amounts of 2-vinyl cyclobutyl acetate and tosylate, and vinyl cyclopropylmethyl acetate.



27a



27b



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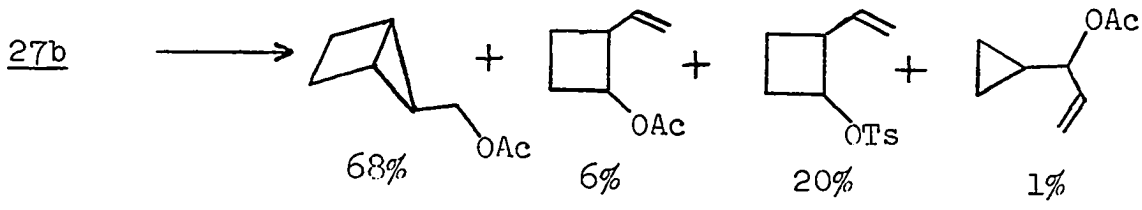
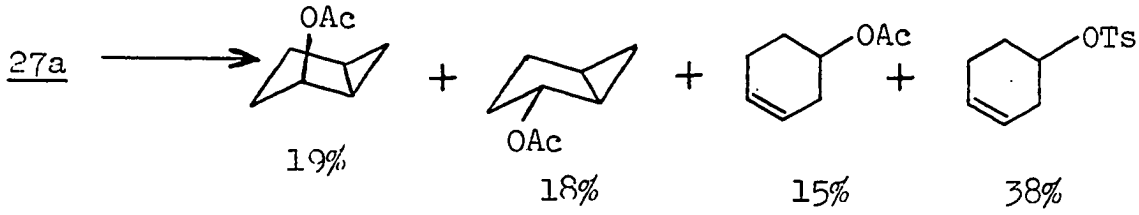
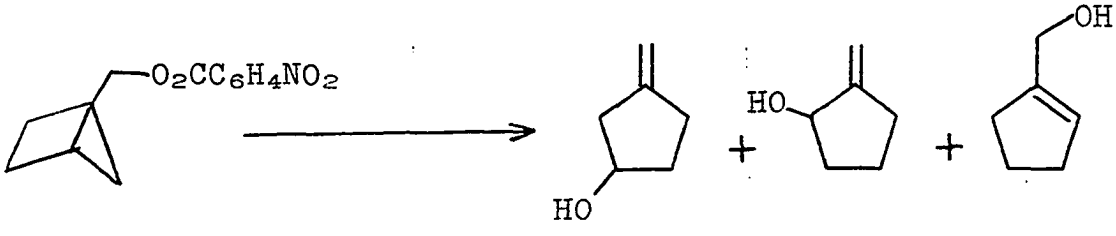




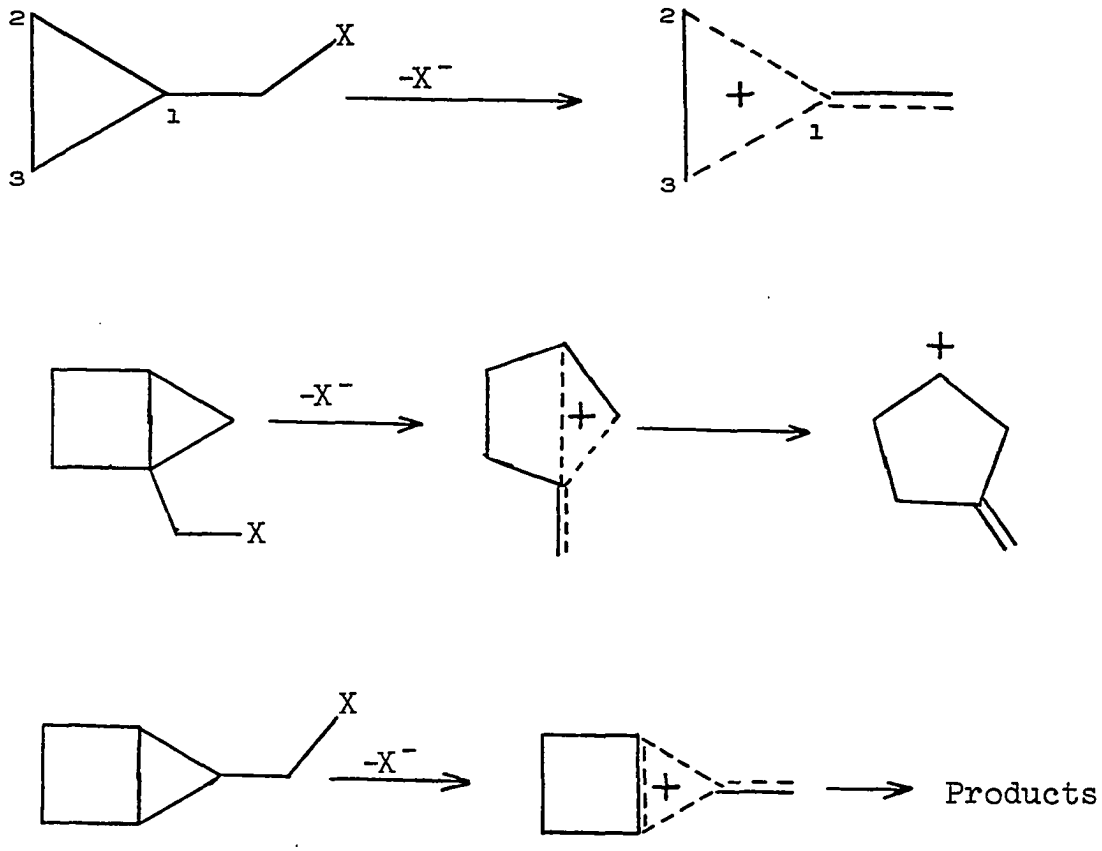
The endo- isomer 27a gave an entirely different product mixture, consisting of cis- and trans-2-acetoxybicyclo[3.1.0]hexane and cyclohexen-4-ol acetate and tosylate. The lack of norcaranyl derivatives from 27b is explained on the basis of geometry, in that such a rearrangement would yield a trans-fused ring system. In both 27a and 27b, the initially formed ion seems to be structurally similar to the corresponding reactant.

The isomeric 1-methyl compound has been studied by Dauben and Wiseman (75). Bicyclopentane-1-methyl p-nitrobenzoate (29) was prepared by the lithium aluminum hydride reduction of 15a, followed by esterification with p-nitrobenzoyl chloride. Attempts to make the tosyl ester yielded only rearranged product. Solvolysis of 29 in 60% aqueous acetone yielded 3-methylenecyclopentanol (96%), 2-methylenecyclopentanol (3%), and a trace of 1-hydroxymethylcyclopentene. The rate of solvolysis was found to be 400,000 times as fast as the rate for the corresponding cyclopropylcarbinyl p-nitrobenzoate, and more than 700 times as fast as bicyclo[3.1.0]hexane-1-methyl p-nitrobenzoate.



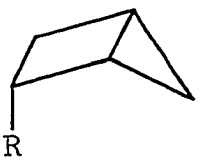
The results of these two studies are consistent with the reactivity predictions calculated for the cyclopropylcarbinyl cation by Wiberg using the CNDO method (76). These calculations predict an increase in the 2 - 3 bond order and a decrease in the 1 - 2 bond order in going to the cyclopropylcarbinyl cation. In the solvolysis of 29, this would result in a decrease in bond order and concomitant lengthening of the central bond of the ring system. Thus, the strain energy released by the lengthening and eventual rupture of this bond is available to promote ionization, resulting in a very high rate of solvolysis. However, in 27a or 27b, these calculations predict an increase in bond order of the central bond, leading to a shortening of this bond, increasing strain. Not only is the strain energy not available for ionization, but ionization actually increases the strain in the system. The slight increase in rate seen over cyclopropylcarbinyl tosylate (28), is easily explained in terms of normal 2,3-dialkyl substitution (77), which normally increases the rate by a factor of approximately 100.

The solvolysis of a third bicyclopentane derivative has been studied by Wiberg and co-workers (78). They prepared endo- (30a) and exo- (30c) bicyclopentan-2-ol acetate by the copper catalyzed decomposition of diazomethane in the presence of cyclobuten-3-ol acetate. The isomers were separated by preparative vpc and identified by nmr decoupling and



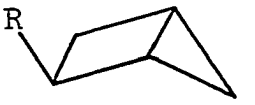
computer simulation of the spectrum of the endo- isomer. The 3,5-dinitrobenzoate ester of the exo- isomer (30d) was solvolyzed in 80% aqueous acetone, yielding cyclopenten-4-ol as the product, and a rate constant (at 110°) of 5.4×10^{-5} sec^{-1}. The enthalpy of activation was found to be 28.4 kcal/mole. The endo- isomer (30b) was much more reactive, giving a rate constant of 1.5×10^{-2} sec^{-1} at 25° in 80% aqueous dioxane, and cyclopenten-4-ol as the product. The enthalpy

of activation was found to be only 16.9 kcal/mole. Since the product in each case is the same, there are no thermodynamic factors involved. The adjusted rate difference between the isomers of 10^7:1 and the $\Delta(\Delta H)$ of 12 kcal/mole indicate that relief of strain must have occurred to a large extent in the formation of the activated complex for 30b, but not for 30d.



30a, R = acetate

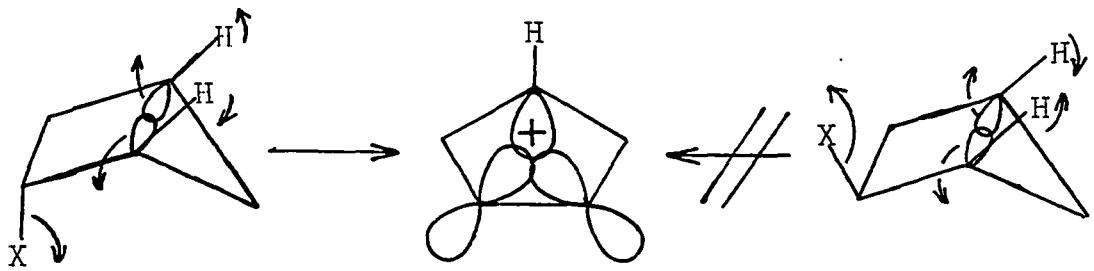
30b, R = 3,5-dinitrobenzoate



30c, R = acetate

30d, R = 3,5-dinitrobenzoate

Wiberg's CNDO calculations (76) have suggested that the activated complex for cyclobutyl solvolysis is stabilized to some extent by cross-ring interactions; a suggestion which has also been made by DePuy (79). Participation of the 1-4 bond of bicyclopentane in the solvolysis of 30b would result in the rotation of the bridgehead hydrogens away from each other, relieving part of the strain of the system. On the other hand, such participation in the solvolysis of 30d would cause the rotation of the two bridgehead hydrogens toward each other, leading to an increase in strain. These calculations therefore predict acceleration by relief of strain in the endo- case, but not in the exo- case, and are in excellent agreement with the experimental results. It is interesting

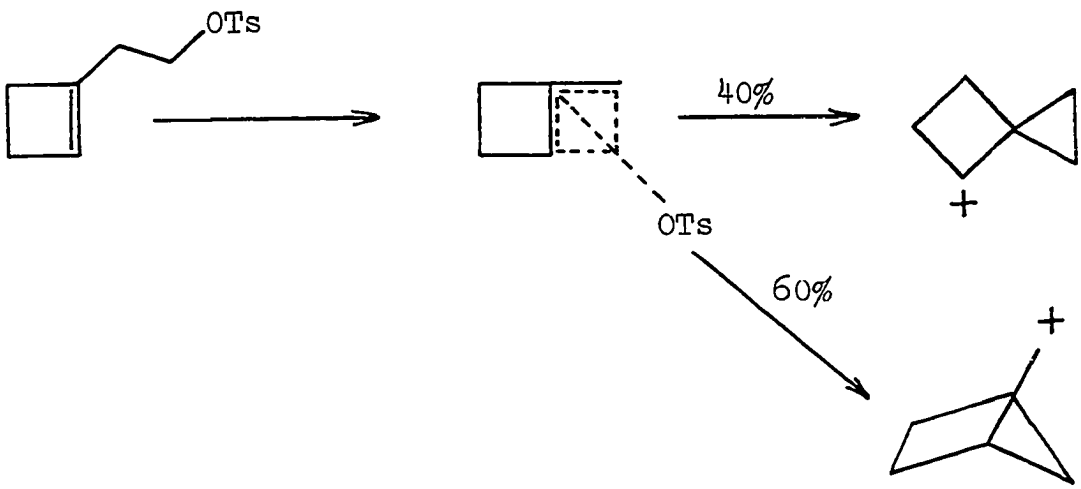


to note that this is a case where the 1-2 bond of the cyclopropylcarbinyl cation participates in the ionization, whereas in the solvolysis of 27a and 27b, it apparently did not participate; however, in this case, it is also the 1-4 bond of the bicyclopentane ring system, and therefore releases much more strain than would be released by 1-2 participation in 27.

Recently, interest in a bicyclopentane ion has been generated by the suggestion that it may be an intermediate in the rearrangement of the spiropentyl cation (80, 81). The deamination of spiropentylamine yields 1-vinylcyclopropanol, 2-methylenecyclobutanol, and 3-methylenecyclobutanol. Applequist and Fanta suggested that the products could be explained by the intermediacy of a 1-bicyclopentyl cation, or by a delocalized "bicyclobutonium" type bicyclopentyl cation (80). Konzelman and Conley prefer to invoke only classical intermediates, proposing the intermediacy of the 1-bicyclopentyl cation and the bicyclobutylcarbinyl cation to explain the methylenecyclobutanols formed (81).

Additional information concerning the nature of the intermediates in the spiropentyl cation rearrangements could be gained by examining the chemistry of the 1-bicyclopentyl cation and the bicyclobutylcarbinyl cation. Generation of the bicyclobutylcarbinyl cation would undoubtedly result in the formation of a 3-methylenecyclobutyl derivative, (82) analogously to the results from the 1-bicyclopentylcarbinyl cation (50, 75). If the reaction schemes proposed by these workers are correct, the 1-bicyclopentyl cation would be expected to yield 2-methylenecyclobutanol.

The bicyclo[2.1.0]pentane-1-methyl cation has also been implicated as an intermediate in a rearrangement reaction. Wiberg and Hiatt (83) have studied the solvolysis of 2(Δ^1-cyclobutenyl) ethyl tosylate and obtained among the products 3-methylenecyclopentanol, 2-methylenecyclopentanol, 1-hydroxymethylcyclopentene, and 1-methylcyclopenten-4-ol. Since these four products are also produced in the solvolysis of bicyclo[2.1.0]pentane-1-methyl cation. Results from a deuterium labeling experiment show that this ion could not arise directly from either the bicyclo[2.2.0]hexyl-1 cation or the spiro[2.3]hexyl-4 cation. The distribution of deuterium in the products could be explained by 60% of the reactant going directly to the bicyclopentane-1-methyl cation, and 40% going through the spiro[2.3]hexyl-1 cation.

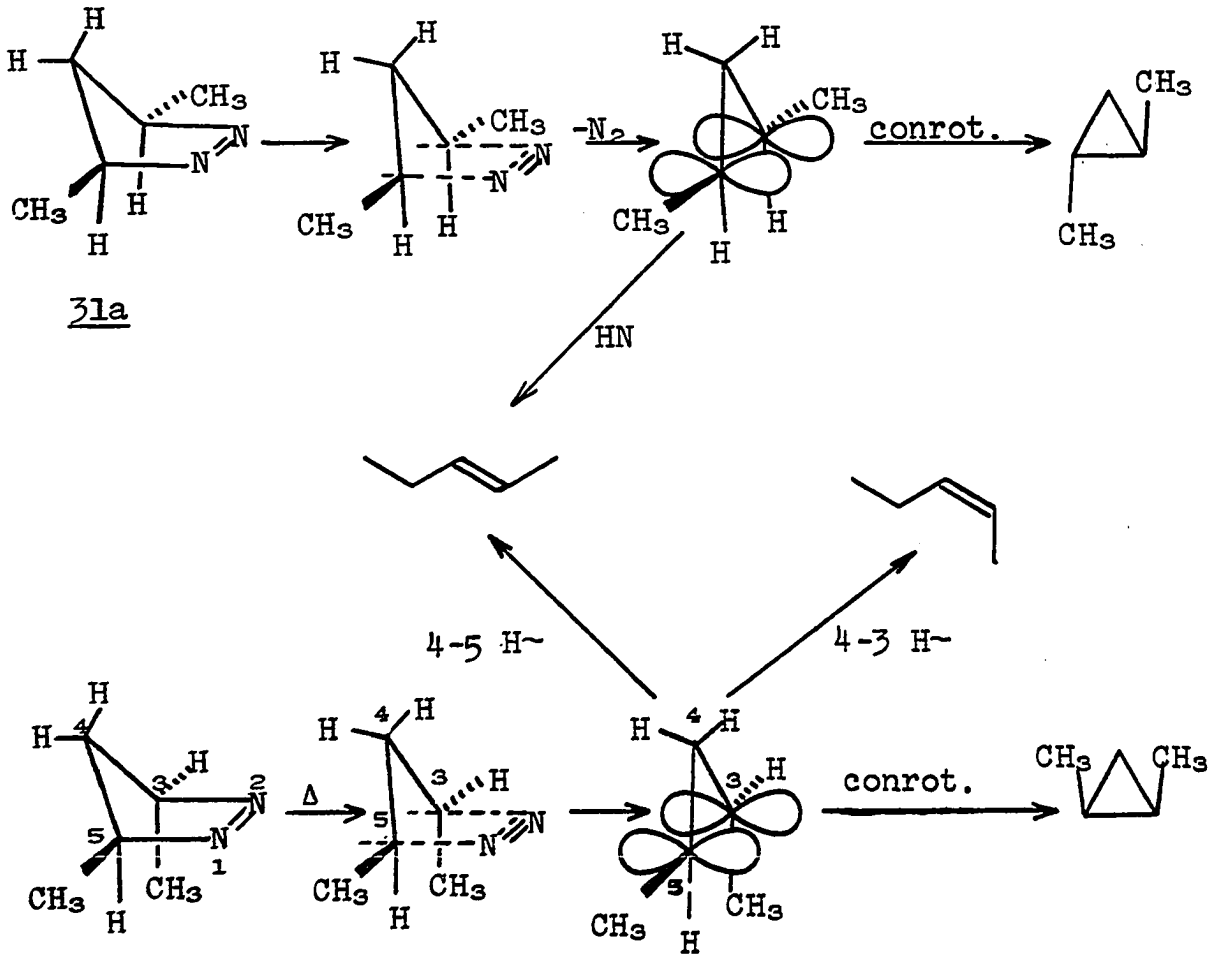

OTs
40%
OTs
60%
+
+

Pyrazoline Decompositions

In addition to the work cited on pages 2 and 3, considerable interest has been shown in determination of the mechanism of pyrazoline decompositions (84, 85, 86, 87, 88, 89, 90, 91, 92). Crawford has studied the gas-phase pyrolysis of a number of methyl-substituted pyrazolines, including some with deuterium labeling (15, 84, 85, 86, 87). Kinetic studies have shown that the decompositions are first-order to 95% completion, and that both carbon-nitrogen bonds are being broken in the transition state. The observed k_h/k_d of 1.07 ± 0.03 in the decomposition of 4-d labeled pyrazoline indicates that the rate determining step has remained unchanged, but the introduction of this deuterium atom changed the product ratio rather markedly, giving an isotope effect of 1.80 in the product determining step. This condition requires an intermediate, which Crawford believes is a trimethylene diradical (15). The magnitude of this effect was found to be consistent with the formation of both products (cyclopropanes and olefins) from the same intermediate, but not consistent with the presence of more than one intermediate.

The studies of methyl-substituted pyrazolines show a steady decrease in activation energy as methyl groups are introduced on the carbon atoms bonded to nitrogen (85), indicating that both C-N bonds are being broken in the transition state, which would require that the intermediate be nitrogen-

free. Introduction of one methyl group at C-4 had a negligible effect upon the decomposition rate, but the introduction of a second methyl group at C-4 slowed the rate by a factor of over 100 (85). Product studies in the decomposition of cis- (32a) and trans- (32b) 3,5-dimethylpyrazoline have given the following results: 31a gives a 66:33 ratio of trans- to cis-1,2-dimethylcyclopropane and exclusively trans-2-pentene, while 31b gives a 26:74 ratio of trans- to cis- cyclopropane and approximately a 1:1 ratio of cis- and trans- 2-pentene (85). Crawford has proposed a mechanism for the decomposition which is consistent with all these observations (see Figure 3) (84, 85). The stereochemical results are explained in terms of a "πu" cyclopropane intermediate, which retains the stereochemistry of the original pyrazoline, and which closes predominantly via a conrotatory mode. In 31a, this would result in the predominant formation of trans-1,2-dimethylcyclopropane, and migration of a hydrogen from the central carbon to either radical center would form trans-2-pentene. In 31b, conrotatory closing of the intermediate diradical would yield the cis-cyclopropane, and migration of a hydrogen from the central carbon would result in either cis- or trans-2-pentene, depending to which radical center it migrated. In the 4-methylpyrazoline, the methyl group can attain a conformation trans- to the leaving nitrogens, thus not hindering nitrogen loss. However, when two methyls are present at C-4, one must be cis- to the leaving nitrogens, resulting in steric



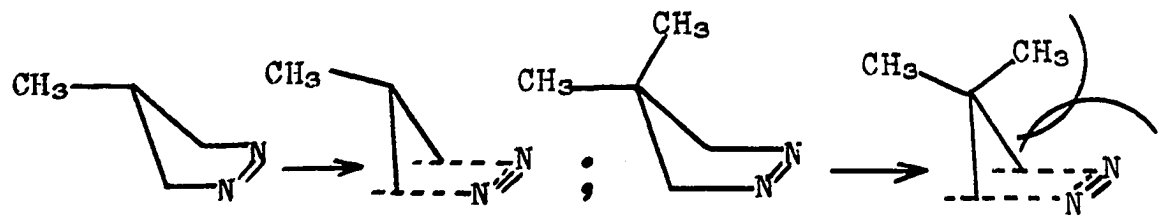


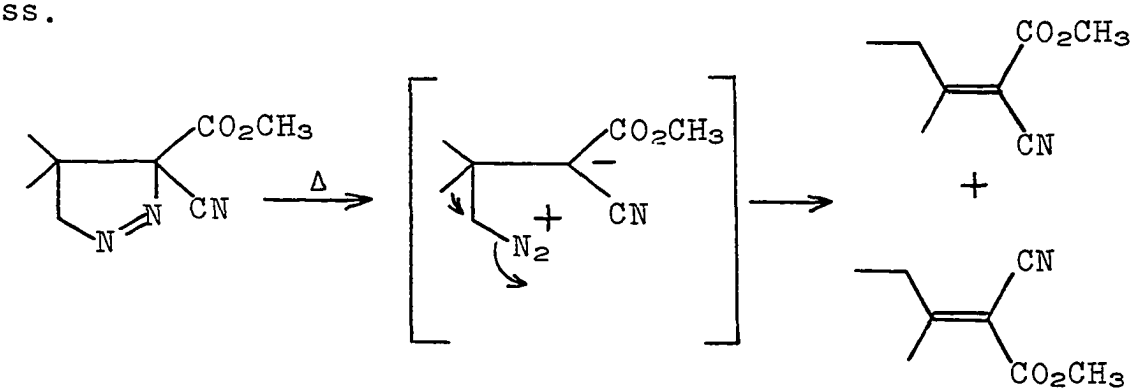
Figure 3. Proposed mechanism of pyrazoline decomposition.

compression of the transition state, and hindering the loss of nitrogen (85).

The "πu" cyclopropane intermediate has received theoretical support from Hoffmann in the form of extended HMO calculations which are in agreement with this type of intermediate, and predict conrotatory closing for it (18). To test the symmetry arguments involved, Crawford prepared and pyrolyzed cis- and trans-4-deuterio-3-methylpyrazoline (86). The results obtained were entirely consistent with the proposed intermediate. If the four carbon atoms in the molecule were in the same plane in the intermediate, as predicted, the following results would be expected, and were observed: (a) a 50:50 ratio of cis- and trans-2-deuteriomethylcyclopropane; (b) assuming a k_h/k_d ratio of 2.0 in the product determining step, the product ratio should be 94.9% methylcyclopropane, 1.4% cis-2-butene, 0.9% trans-2-butene, and 2.8% 1-butene (observed ratio: 93.3 ± 0.6, 1.9 ± 0.2, 1.16 ± 0.12, 3.7 ± 0.3); (c) each olefin should exhibit the same k_h/k_d ratio irrespective of which isomer was the initial source, since the same planar intermediate would be produced from both isomers.

Crawford's work on alkyl pyrazolines appears to be fairly definitive, but apparently does not extend to pyrazolines substituted with an electron-withdrawing group at C-3. McGreer has studied the pyrolysis of a number of these compounds (88, 89, 90), which appear to decompose through a polar

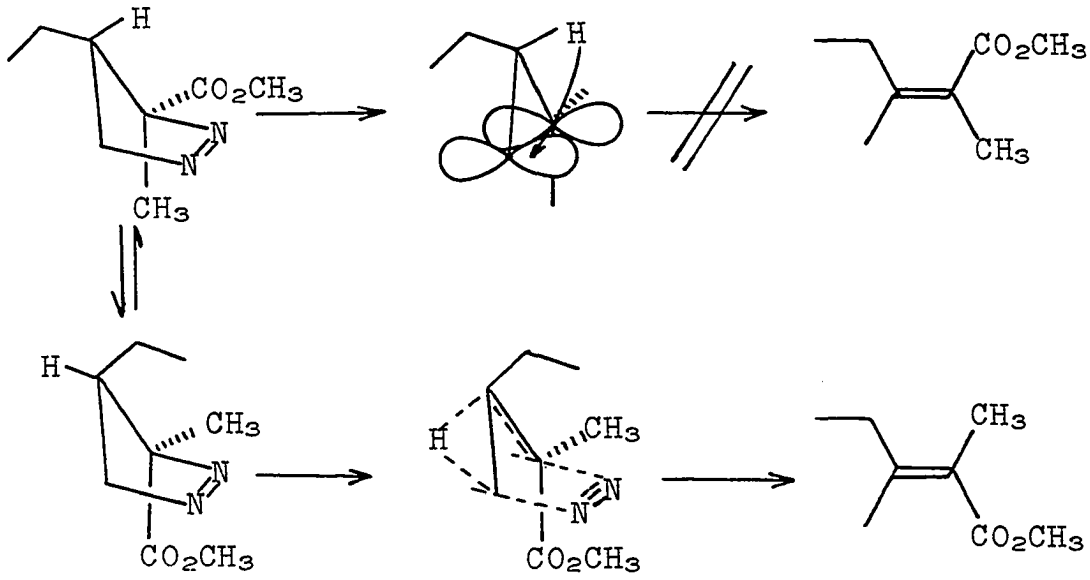
intermediate. The pyrolysis of 4,4-dimethyl-3-carbomethoxy-3-cyano-1-pyrazoline proceeds to give a cyclopropane, and olefins which can only be formed by a methyl migration (88). The decomposition was carried out in a number of solvents of varying polarities, and a definite solvent effect was noted. The solvent effect did not correlate well with those observed in other known polar reactions, but McGreer proposed a dipolar intermediate, with an alkyl migration concerted with nitrogen loss.



In the decomposition of 3-acetyl-3,5-dimethylpyrazoline, one of the products is a dihydrofuran, resulting from ring closure to oxygen rather than to carbon (90). McGreer explains this product in terms of a dipolar intermediate with the negative charge delocalized onto oxygen.

McGreer has also obtained some evidence that olefin formation in this series of pyrazolines may result from a concerted reaction (89). The decomposition of cis- and trans-3-carbomethoxy-3-methyl-4-ethylpyrazoline gives olefins of the opposite stereochemistry as would be expected from a

"πu" cyclopropane intermediate. However, concerted migration of the hydrogen from a position trans- to the departing nitrogens would give the observed stereochemistry In order for



this to happen, the C-4 ethyl group must be in the pseudoaxial conformation, resulting in steric compression of the transition state, so that there must be a large preference for concerted hydrogen migration to overcome this handicap. It is somewhat strange that McGreer prefers to write a mechanism involving simultaneous breaking of both C-N bonds in this olefin forming reaction, but a stepwise loss of nitrogen, allowing rotation about the 3-4 bond, would not explain the stereochemical results obtained.

The implication that two different mechanisms may be operative, depending upon the presence or absence of an electron-withdrawing group at C-3 appears to be in accord with

results obtained by Seltzer (93) in the study of acyclic azo compound decompositions. He found deuterium isotope effects which indicate that symmetrically substituted azo compounds break both C-N bonds in the transition state, while asymmetrical compounds decompose via a stepwise mechanism, breaking one C-N bond at a time.

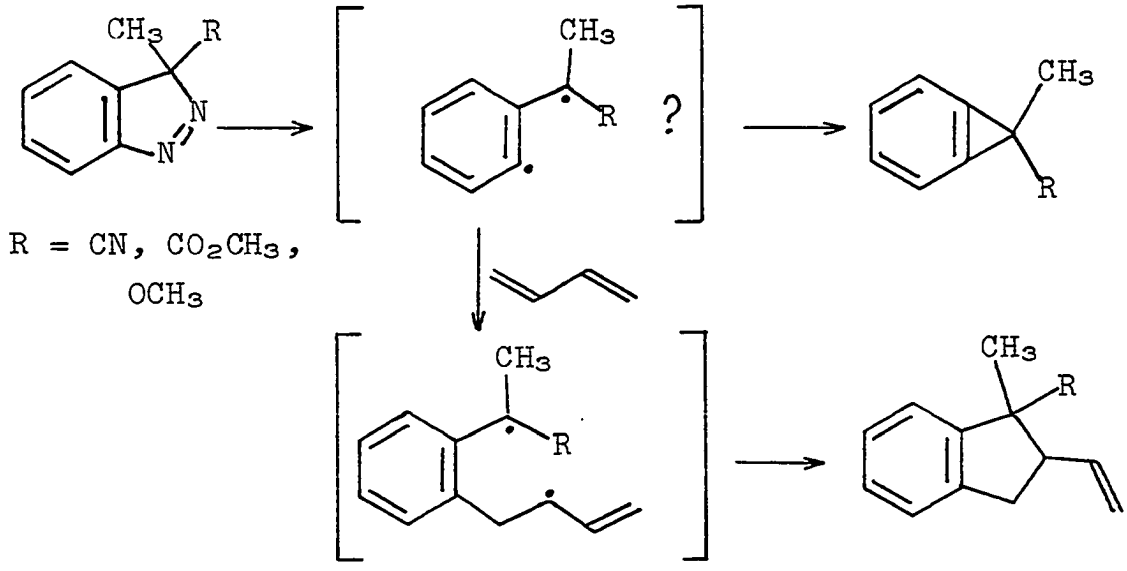
The photolytic decomposition of pyrazolines has been studied much less than the thermal decomposition. The photolysis of azo compounds has long been used as a method of generating radicals (94), so it is perhaps reasonable to expect that photolytic pyrazoline decompositions might also involve a radical mechanism. Bartlett and Engel (95) have studied the sensitized irradiation of 4 and of azo-2-methyl-2-propane (33) using several different sensitizers. They found

$$(CH_3)_3C—N=N—C(CH_3)_3$$

33

that aromatic ketones which undergo rapid intersystem crossing did not sensitize (33) toward decomposition, although they did decompose 4. Several sensitizers did lead to the sensitized decomposition of 33. However, they believe that singlet sensitization is involved in these cases. Since sensitizers which must involve a triplet are not effective towards (33), they proposed that the triplet of (33) is not unstable towards decomposition, while the triplet of 4 is, perhaps as a result of its rigid structure, which rules out geometric changes.

Closs and co-workers have studied the low temperature irradiation of several 3H-indazoles in an esr cavity and obtained spectra which could be unambiguously assigned to a triplet molecule (96). Upon warming, the signal faded, and benzocyclopropenes were among the products. Irradiation of these indazoles in the presence of butadiene yielded vinylindanes, strongly indicating the intermediacy of a diradical. Simple olefins were insufficient to yield trapping products.



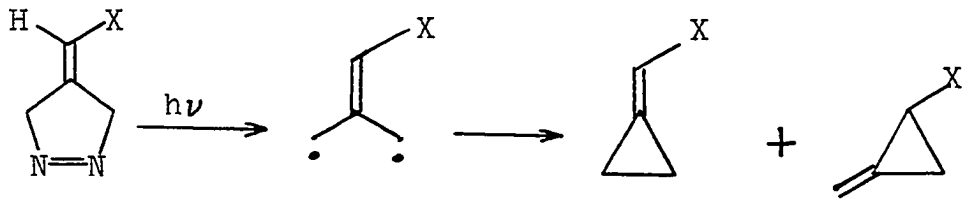
Van Auken and Rinehart have studied the photochemical decomposition of cis- and trans-3,4-dimethyl-3-carbomethoxypyrazolines in a variety of solvents (91). The cyclopropane formation was found to be essentially stereospecific. No solvent effect was noted on the kinetics of the reaction or on the product distribution. They proposed a concerted mechanism to explain their results, with a different transition

state for cyclopropane formation and olefin formation.

McGreer has also examined the photolytic decomposition of pyrazolines (88). Irradiation of cis- and trans-3,5-dimethyl-3-carbomethoxypyrazolines yielded more cyclopropane products than did pyrolysis, with less stereoselectivity in both cyclopropanes and olefins. He suggested that an excited state molecule should be no more likely to decompose than a ground state molecule, and that the products probably arose from a regenerated ground state molecule with excess vibrational energy, which would decompose via the same pathway as the thermally excited molecule.

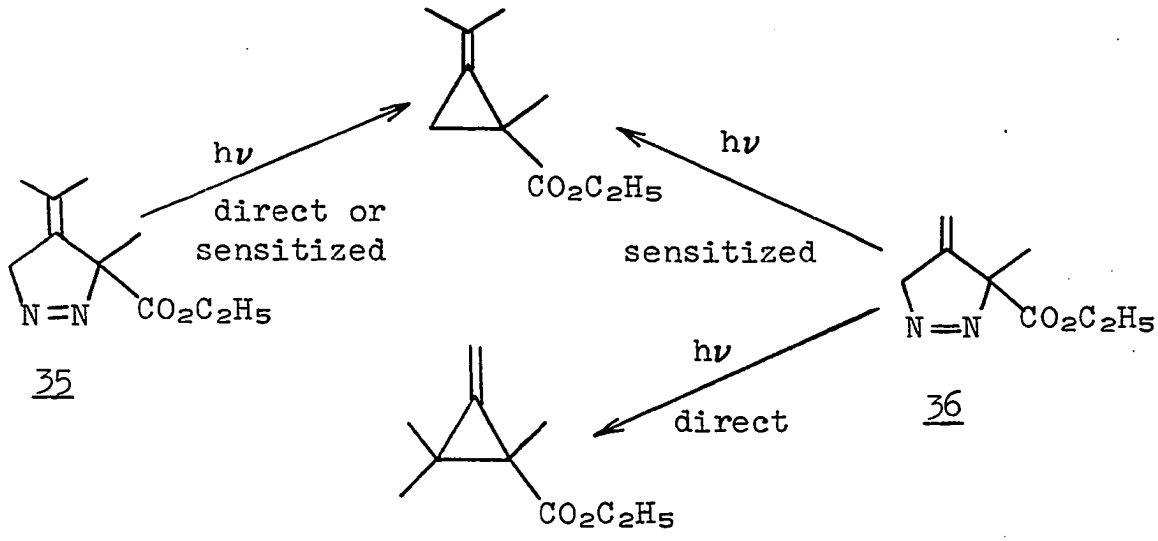
The photolysis of pyrazolines has been used by Dowd (97) and by Andrews and Day (98) to prepare the trimethylenemethane intermediate. Day irradiated 4-methylene-1-pyrazoline (34, X = H) at -185° in an esr cavity, and observed a triplet spectrum which was stable for up to one month, as long as the low temperature was maintained. Upon warming to -150°, the signal disappeared irreversibly. Day and Andrews irradiated pyrazolines 35, X = Cl and 35, X = $O_2C-C_2H_5$, both directly and in the presence of benzophenone. Under direct irradiation they could detect no esr signal, and the predominant product was the result of direct closure between the termini previously bonded to nitrogen (75% for 35b, 64% for 35c). The addition of benzophenone markedly changed the product mixture, giving a much higher proportion of "rearranged" product (ring

closure resulting in X being on the cyclopropane ring). Ring closure is not random, however, in that the proportion of rearranged product is somewhat too high.



34a, X = H
34b, X = Cl
34c, X = $O_2C-C_2H_5$

In similar work, Sanjiki, Kato, and Ohta (99) have studied the direct and sensitized irradiations of 3-carboethoxy-3-methyl-4-isopropylidene-1-pyrazoline (35) and 3-carboethoxy-3,5,5-trimethyl-4-methylene-1-pyrazoline (36). They found that under direct irradiation, the major products were 1-carboethoxy-1-methyl-2-isopropylidenecyclopropane and 1-carboethoxy-1,3,3-trimethyl-2-methylenecyclopropane, respectively, as a result of direct ring closure, but upon sensitized irradiation, both pyrazolines produced primarily the more stable 2-isopropylidene isomer. These results would indicate that sensitized irradiation leads to a much longer time lapse between loss of nitrogen and ring closure than occurs in the direct irradiation, allowing formation of the most stable product.



Very recently, Crawford and co-workers in 100 have studied the sensitized and unsensitized irradiations of some methyl pyrazolines. They have reported that the ground state of the trimethylene diradical intermediate should be a triplet. They found that when the irradiation was sensitized with benzophenone, the production of olefins dropped to nearly zero. This was explained by saying that a triplet should not produce olefins directly, and that by the time spin inversion occurred, the intermediate should be completely collisionally stabilized, lacking energy to undergo a hydrogen migration.

RESULTS AND DISCUSSION

Syntheses of 1-Substituted Bicyclo[2.1.0]pentanes

Since Criegee first reported the synthesis of the parent bicyclo[2.1.0]pentane ring system in 1957, several substituted bicyclopentanes have been reported in the chemical literature. However, until 1967, the only 1-substituted compounds reported were 1-methyl (24, 31) and 1-isopropylbicyclo[2.1.0]-pentanes (34). Since substituents at C-1 might be expected to have a significant effect upon the reactivity of the central bond in the molecule, and since the preparation of reactive intermediates at the bridgehead required bridgehead substituted precursors, it was decided to attempt the synthesis of a 1-carbomethoxybicyclo[2.1.0]pentane. The ester function was chosen because it could ultimately provide a wide variety of functional groups at C-1 through simple chemical transformations. The ready availability of 3,3-dimethyl cyclobutene carboxylic acid (36a) from inexpensive precursors (101) and the much higher degree of stability of this compound as compared to the parent acid (102) made it the substrate of choice. In addition, the wide chemical shift difference between an exo- and an endo-methyl group on the cyclobutane ring of the bicyclopentane ring system (21) promised to provide a simple diagnostic handle for identifying the ring system by nmr.

Several possible routes from the cyclobutene to the

bicyclo[2.1.0]pentane system were envisioned. Chesick had prepared the 2-methyl derivative by carbene addition to the double bond of 3-methylcyclobutene. This procedure was tried several times under varying conditions, using 1-carbomethoxy-3,3-dimethylcyclobutene (36b) as a substrate and generating methylene by the cuprous chloride catalyzed decomposition of diazomethane, but the desired bicyclopentane was not produced. The Simmons-Smith reaction has been reported to yield 9% trans-1-carbomethoxy-2-methylcyclopropane from trans-methyl crotonate (96); however, this technique also failed to yield any bicyclic ester. It is now reasonably well known that both of these reactions proceed only poorly with electron-deficient olefins.

Since the Simmons-Smith reaction is reported to proceed in better yields on allylic alcohols (103), it was decided to attempt this reaction on 1-hydroxymethyl-3,3-dimethylcyclobutene. The first attempt to synthesize this compound involved simple reduction of ester 36b with lithium aluminum hydride. The allylic alcohol was produced, but it was contaminated with non-negligible amounts of the saturated alcohol formed by conjugate reduction of the double bond by lithium aluminum hydride. This type of reduction is normally observed only in the reduction of cinnamates or similar compounds (104), but the high degree of strain in the cyclobutene ring would make this bond more reactive than

most olefins. The presence of the saturated isomer presented a difficult separation problem, and another route was sought. Since reduction to the alcohol in the presence of the double bond caused problems, it was decided to try to introduce the double bond after the reduction. Accordingly, 1-carbomethoxy-2-(N,N-dimethylamino)-3,3-dimethylcyclobutane was prepared by the method of Brannock, et al. (101) and reduced to the amino-alcohol. This compound was converted to the amine oxide with peracetic acid. Attempted pyrolysis of the amine oxide yielded none of the desired olefin.

Brown and Weissman have reported that acid chlorides can be reduced to alcohols with lithium aluminum tri-t-butoxy hydride, a much milder reagent than lithium aluminum hydride (105). The reduction of cinnamaldehyde to cinnamyl alcohol with no accompanying reduction of the double bond indicated that this reagent might reduce the acid chloride of 36a to the desired alcohol without reducing the double bond in the cyclobutene ring. Accordingly, when the acid chloride was prepared and the reduction carried out, the desired allylic alcohol uncontaminated by any saturated alcohol was isolated.

The Simmons-Smith reaction was attempted several times on the 1-hydroxymethyl-3,3-dimethylcyclobutene prepared above, but it never produced any significant amounts of the desired bicyclic alcohol. An alternative method of producing the iodomethyl zinc iodide utilizing zinc iodide and diazomethane,

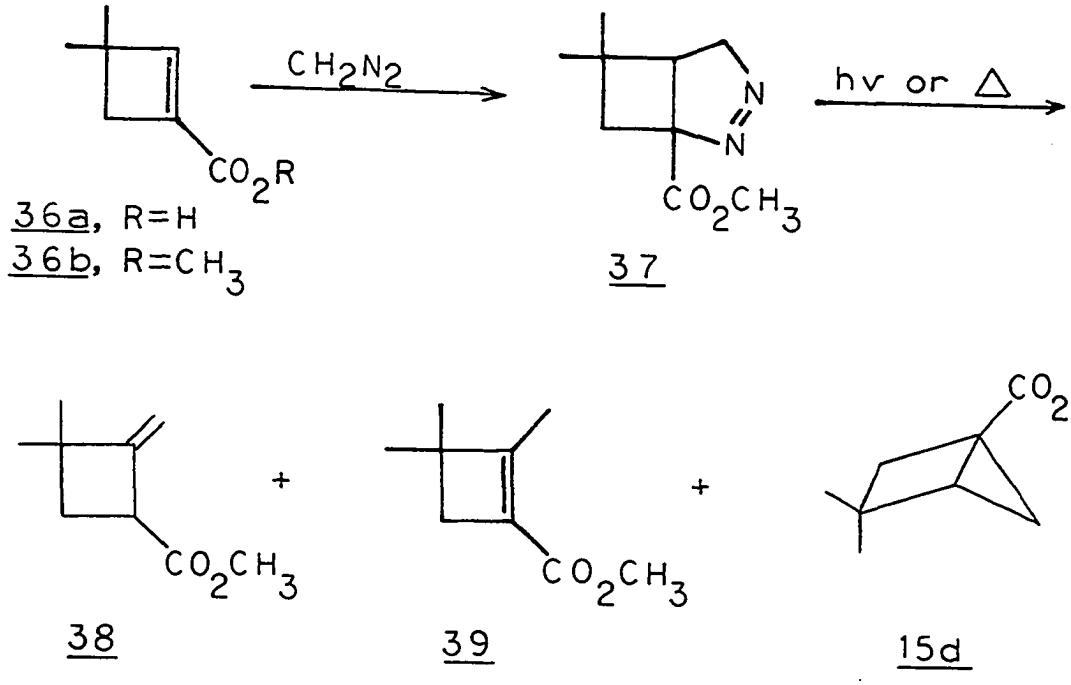
as described by Wittig and Schwarzenbach (106), also produced no significant amount of the bicyclic alcohol.

Since the alcohol function would be expected to have considerably less deactivating effect upon the cyclobutene double bond than the ester function of 36b, it was thought that perhaps the alcohol would be more prone to add methylene (from the copper-catalyzed decomposition of diazomethane) than was 36b. Accordingly, the reaction was carried out, but with no appreciable formation of bicyclic alcohol. The nmr spectrum of the product showed that some change had occurred, but, although the product was not identified, it appeared that the reaction had occurred at the hydroxyl group rather than the double bond. In an attempt to circumvent this undesired reaction, the acetate ester of the alcohol was prepared and allowed to react both with diazomethane in the presence of cuprous chloride and ethyl diazoacetate in the presence of cuprous chloride. Neither reaction appeared to produce any bicyclic product. That the catalyst was effective was shown by the production of norcarane and 6-carboethoxybicyclo[4.1.0]-heptane from the reaction of diazomethane and ethyl diazoacetate with cyclohexene. The effectiveness of the zinc-copper couple used in the Simmons-Smith reactions was tested by carrying out this reaction on cyclopentene-1-methanol, and in fact 1-hydroxymethylbicyclo[3.1.0]hexane was produced.

One last attempt was made to generate the bicyclopentane nucleus via a methylene transfer reagent. Corey has reported

the use of dimethylsulfoxonium methylide as a methylene transfer reagent to form cyclopropyl ketones from α,β-unsaturated ketones (107). Thus, the cyclobutene carboxylic acid 36a was converted to the methyl ketone by treatment with methyllithium and treated with dimethylsulfoxonium methylide according to Corey's procedure. The starting material did undergo reaction, but the nmr spectrum of the product still showed an olefinic proton resonance, which appeared at higher field than that in the starting ketone. There was no indication of any resonance due to a bicyclic ketone.

A third method of preparing cyclopropanes involves the thermal or photochemical loss of nitrogen from pyrazolines. Treatment of (36a) with an excess of ethereal diazomethane yielded 1-carbomethoxy-2,3-diaza-6,6-dimethylbicyclo[3.2.0]-hept-2-ene (37) in 93% yield. Pyrolysis of 37 in the gas phase at 280° yielded a mixture of five products, three of which accounted for >90% of the mixture. The three major components were present in a ratio of 5:8:7 by vpc retention time. They were separated by vpc and nmr, IR, and mass spectra recorded. The component with the shortest vpc retention time exhibited a carbonyl band in the IR spectrum at 1740 cm^{-1}, and bands at 1670 cm^{-1} and 890 cm^{-1}, indicative of a terminal methylene group. The mass spectral molecular weight was 154, 28 mass units greater than 36a. The nmr spectrum shown in Figure 4, a multiplet with geminal and allylic coupling centered at 4.84δ, indicative of a terminal methylene



group; the AB portion of an ABX centered at 2.04δ; a four proton resonance at 3.64δ (the OCH_3 singlet and the X of the ABX); and a perturbed six proton singlet at 1.18δ. All spectral data indicate a structure of 1-carbomethoxy-2-methylene-3,3-dimethylcyclobutane (38) for this compound. The second compound eluted also had a mass spectral molecular weight of 154, but the IR spectrum indicated a conjugated ester, showing bands at 1720 cm^{-1} for the carbonyl and 1665 cm^{-1} for the double bond. The nmr spectrum, shown in Figure 5, showed two singlets, one of three protons at 3.66δ and one of six protons at 1.26δ, as well as a two proton quarter at 2.28δ (J = 2.0 cps) and a three proton triplet at 1.85δ (J = 2.0 cps). On the basis of these

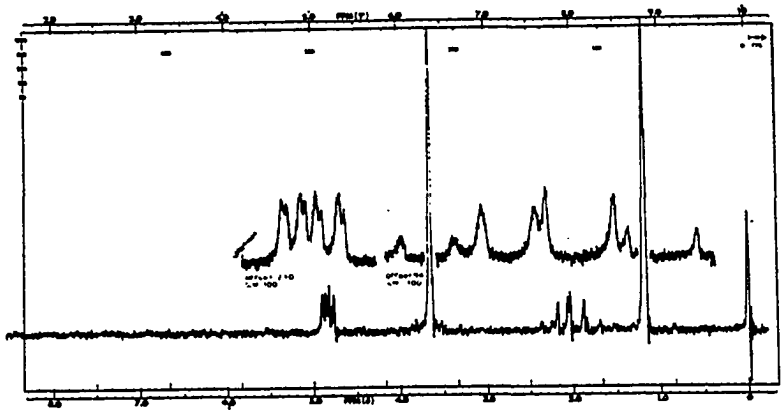


Figure 4. 60 Mc nmr spectrum of 1-carbomethoxy-2-methylene-3,3-dimethylcyclobutane.

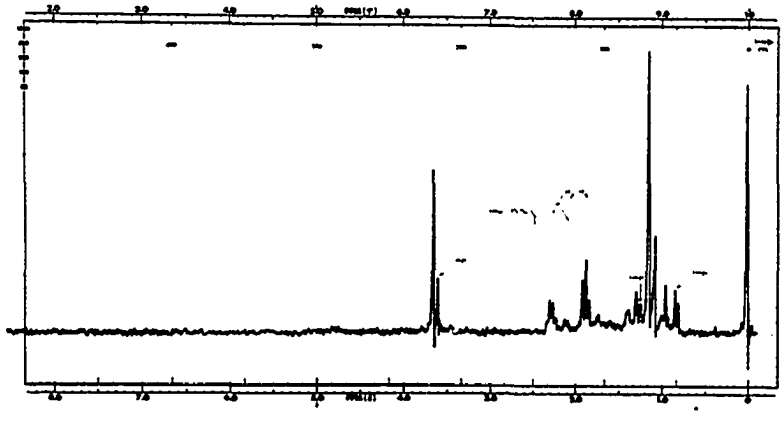


Figure 5. 60 Mc nmr spectrum of 1-carbomethoxy-2,3,3-trimethylcyclobutene.

spectral data, the compound was assigned the structure of 1-carbomethoxy-2,3,3-trimethylcyclobutene (39). The component with the longest retention time appeared from spectral data to be the desired bicyclic ester. The IR carbonyl stretching frequency was 1720 cm^{-1}, although there was no double bond absorption seen. The mass spectral molecular weight was 154, while the base peak in the spectrum appeared at m/e 95. The nmr spectrum, shown in Figure 6 exhibited the two different resonances expected for the non-equivalent geminal methyl groups, with a separation of 0.45 ppm. No resonances due to olefinic protons were seen in the spectrum. Final proof of the structure was obtained by hydrogenation of the compound at room temperature using PtO_2 in acetic acid at 500 psi, which resulted in a slow uptake of hydrogen to produce 1-carbomethoxy-3,3-dimethylcyclopentane. This hydrogenation product was found to be identical by nmr and mass spectral comparisons with an authentic sample prepared by a Favorskii reaction using 4,4-dimethylcyclohexanone. The two minor components in the mixture were not identified, but some unassigned resonances in the olefinic region of the nmr spectrum of the reaction mixture indicate that they were olefinic in nature.

Irradiation of 37 in inert solvents led to a similar mixture of products, except that the bicyclic ester 15d was the major product, and 1-carbomethoxy-3,3-dimethylcyclobutene (36b) was present as a minor product (from loss of CH_2N_2 from 37). In benzene, the ratio of the three major products was

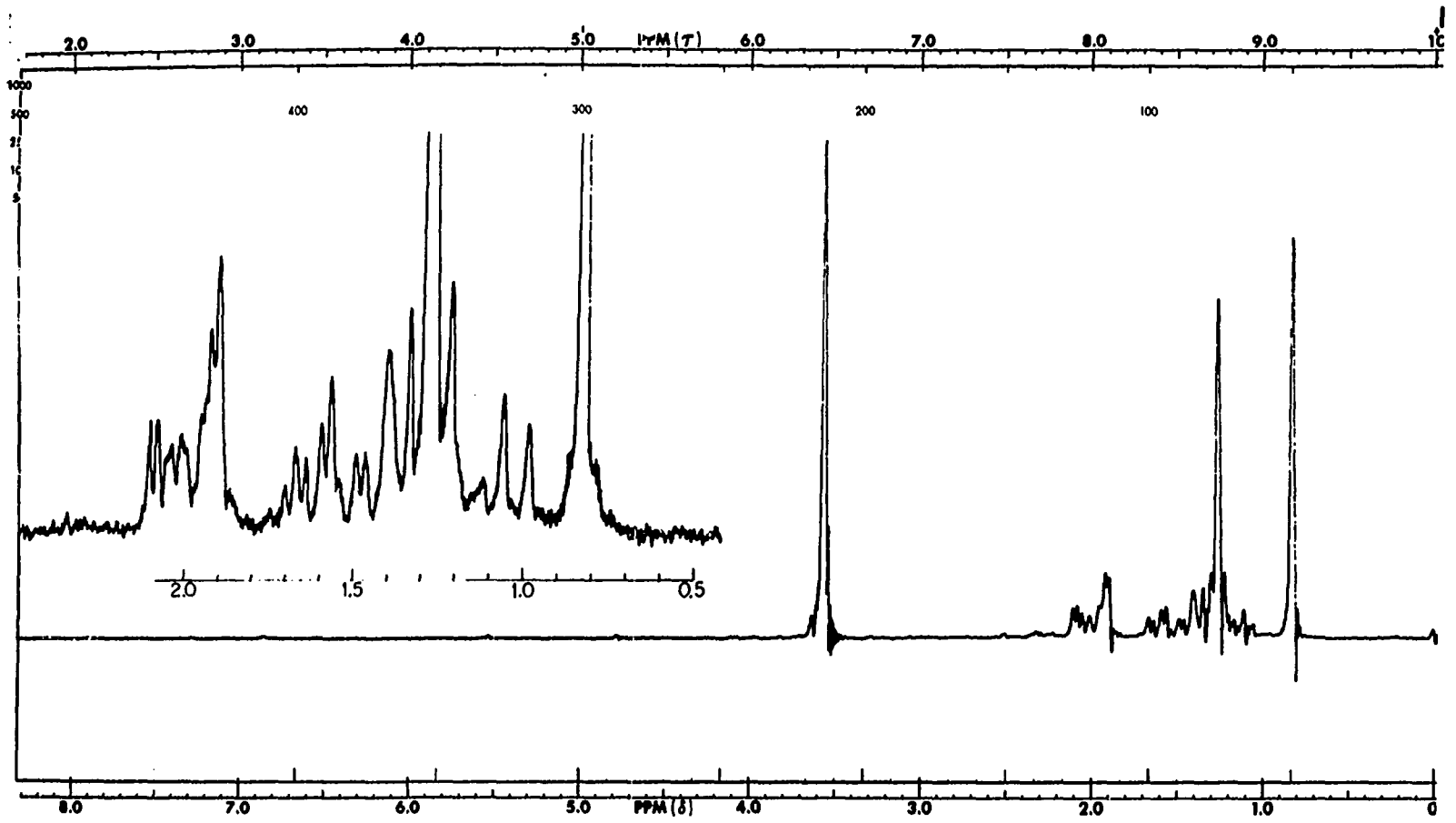


Figure 6. 60 Mc nmr spectrum of 1-carbomethoxy-3,3-dimethylbicyclo[2.1.0]pentane.

8:3:9.

When the irradiation was carried out in acetone, a non-inert solvent, the amount of volatile material decreased sharply, and the olefinic products were no longer present. The bicyclic ester accounted for nearly 90% of the volatile material, although the overall yield was less than 40%.

Photochemical reactions between acetone and cyclobutene are known, so the absence of the olefinic isomeric esters was not entirely surprising. Srinivasan (108) has studied the photochemical addition of acetone to cyclobutene, obtaining cyclobutyl acetone as a product when 3130Å light was used, with dimerization and oxetane formation being predominant when 2537Å light was used. In order to determine the fate of the olefinic esters from the pyrazoline decomposition, ester 36b was irradiated in acetone for four hours. Two major and two minor products were formed, along with a considerable amount of less volatile material. The two major products were collected by vpc and their spectra recorded. The first eluted product had a mass spectral molecular weight of 142, with fragment ions present for the loss of 15, 31, and 59 mass units, all characteristic for a methyl ester. The IR spectrum exhibited a carbonyl band at 1740 cm^{-1}, with no double bond absorption present. The nmr spectrum confirmed the presence of the methyl ester group, exhibiting a three proton singlet at 3.58δ, two-three proton singlets at 1.10δ and 1.15δ, a four proton multiplet centered at 1.95δ, and a one proton

multiplet centered at 3.0δ. That this compound was 1-carbomethoxy-3,3-dimethylcyclobutane was confirmed by hydrogenation of 36b to a compound which was identical in all respects with the above reaction product.

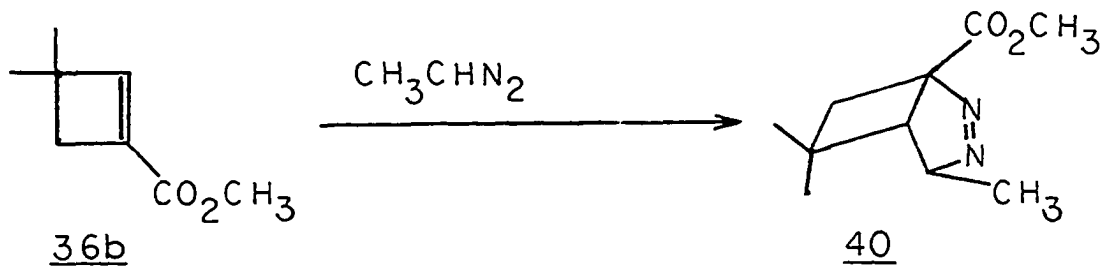
The compound with the longer vpc retention time had an extremely simple nmr spectrum, which consisted of two singlets at 2.11δ and 2.37δ, in a ratio of 3:2. The IR spectrum had a carbonyl band at 1720 cm^{-1}, a rather weak C-H absorption at 2900 cm^{-1}, and bands at 1360 and 1400-1420 cm^{-1}, corresponding to $COCH_3$ and CH_2CO, respectively. The mass spectrum was rather definitive, showing a molecule ion at m/e 114 with major fragment ions at m/e 99 (M-15), 71 (M-43), 57 (M-57), and 43 (base peak). The spectral data clearly define the compound as 2,5-hexanedione.

Srinivasan has proposed a free-radical chain mechanism to explain the formation of cyclobutylacetone during the photolysis of cyclobutene in acetone, and although a chain mechanism for the formation of the reduced products in the present study would be rather difficult to envision, a radical mechanism involving the simultaneous or nearly simultaneous abstraction of two hydrogen atoms from two acetone molecules by an excited ester molecule with subsequent combination of the acetone radicals seems likely. Other possible radical combinations could account for the less volatile products and the two minor volatile products. That this process accounted for the lack of

olefinic products during the photolytic pyrazoline decomposition in acetone solvent was shown by the identification by vpc retention times of cis- and trans-1-carbomethoxy-2,3,3-trimethylcyclobutane and 2,5-hexanedione among the photolysis products.

Although the bicyclic ester 15d was the only major product from the irradiation of 37 in acetone, the yield was not high and further purification was very difficult; therefore, yet another procedure was sought. Irradiation of 37 in benzene in the presence of benzophenone, followed by distillation of the crude photolysis mixture yielded 70% of the theoretical amount of volatile material which vpc analysis showed to be >93% 15d. Results of the various pyrazoline decompositions are summarized in Table 1.

Diazoethane also added smoothly to 36b to form a single product which was assigned the structure 1-carbomethoxy-2,3-diaza-4,6,6-trimethylbicyclo[3.2.0]hept-2-ene (40). Although two geometric isomers are possible, i.e., with the C-4 methyl group either in the endo- or exo-position, the nmr spectrum of



36b 40

Table 1. Thermal and photochemical decompositions of 37[a]

Solvent	Decomposition mode		Products 15d	38	39	36b
Benzene	Pyrolysis column		31%	22%	38%	---
Benzene	hν	1.	33%	27%	15%	6%[b]
		2.	40%	36%	8%	6%[b]
Acetone	hν		29%	---	---	---
Benzene	hν ($Ph_2C=O$)[c]	1.	67%	2%	1.5%	---
		2.	68%	4%	---	---

[a]All irradiations were carried out for four hours. Numbers are per cent of theoretical yield, as determined by nmr integration.

[b]Corrected for a small amount present in the starting pyrazoline.

[c]Olefinic products are not photochemically stable in the presence of benzophenone.

the crude pyrazoline indicated the presence of only one isomer, most likely the exo-isomer. This assignment was confirmed by examination of the coupling constant between the C-4 and C-5 protons. The observed coupling constant of 1.5 cps would indicate a dihedral angle of 60 to 120° between the two protons according to the Karplus relationship (109). Examination of models shows that neither the endo- nor the exo- C-4 hydrogen would give a dihedral angle of 60° with the C-5

hydrogen, but that the angle between the endo-4 proton and the C-5 proton would be about 120°, which is consistent with the observed coupling. The exo-proton has a dihedral angle of approximately 0° with the C-5 proton, and should thus give a coupling of ca. 9 cycles. Therefore, the proton at C-4 is in the endo-position and the methyl group is exo.

Irradiation of 40 in the presence of benzophenone yielded three products, in a 10:1:1 ratio. All three were collected by vpc for spectral data. The major product and one minor product had nearly identical IR, nmr, and mass spectra, all of which were similar to the spectra of bicyclic ester 15d, so these compounds were assigned bicyclic structures isomeric at C-5. The nmr spectra of these compounds are shown in Figures 7 and 8. The remaining minor product showed no olefinic resonances in its nmr spectrum, but appeared to be monocyclic, and was tentatively identified as 1-carbomethoxy-2-ethyl-3,3-dimethylcyclobutene.

Irradiation of 40 in the absence of benzophenone yielded a much more complex product mixture, at least five products. One major product had a vpc retention time which corresponded to the monocyclic product from the sensitized reaction. The nmr spectrum of a vpc separated and collected sample was also identical with that of the monocyclic product from the sensitized reaction. A second major product was found to be identical to the major bicyclic product from the sensitized reaction by vpc retention time and nmr spectral comparisons.

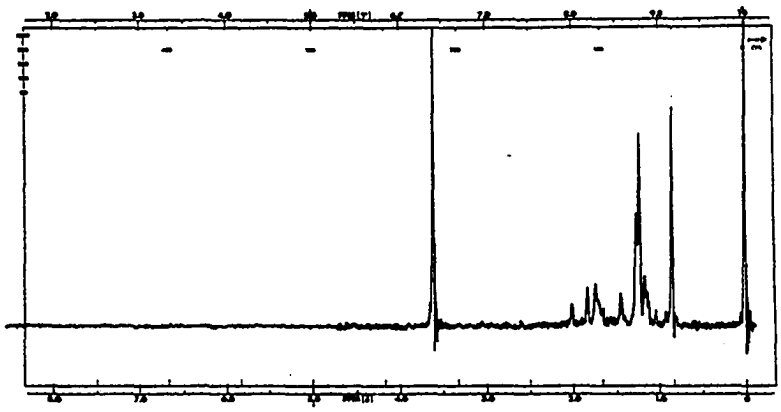


Figure 7. 60 Mc nmr spectrum of 1-carbomethoxy-exo-5-methyl-3,3-dimethylbicyclopentane (15e).

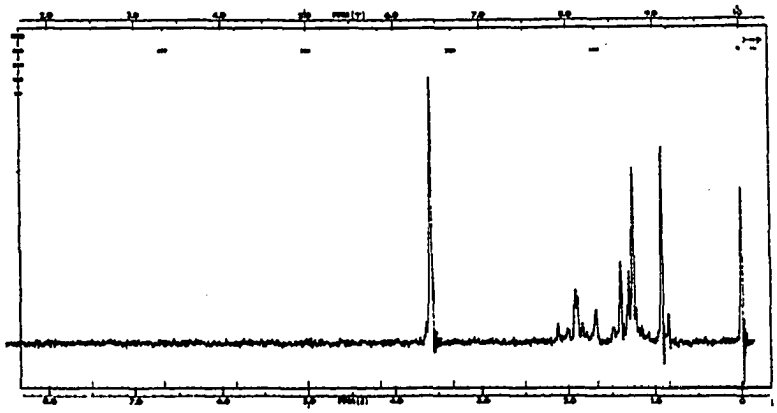


Figure 8. 60 Mc nmr spectrum of 1-carbomethoxy-endo-5-methyl-3,3-dimethylbicyclopentane (15f).

None of the minor bicyclic isomer from the sensitized reaction was detected in the unsensitized photolysis reaction mixture.

The addition of other diazo compounds to 36b were also successfully accomplished. 2-Diazopropane added smoothly during a six hour period to form a mixture of pyrazolines resulting from both normal β-addition and the reverse α-addition. Photolysis of the mixture of pyrazolines in the presence of benzophenone yielded 1-carbomethoxy-3,3,5,5-tetramethylbicyclopentane (15g) in 76% yield. The nmr spectrum of this compound will be discussed later in this section, while its mass spectrum will be discussed in a later section on mass spectra. Phenyldiazomethane added smoothly (β-addition) to yield exo-4-phenyl-1-carbomethoxy-2,3-diaza-6,6-dimethylbicyclo[3.2.0]hept-2-ene, and diphenyldiazomethane underwent α-addition (110) to form 2,3-diaza-4,4-diphenyl-5-carbomethoxy-7,7-dimethylbicyclo[3.2.0]-hept-2-ene. An attempt to add diazofluorene, however, was abandoned after one year had passed with no apparent addition.

Other cyclobutene compounds also added diazomethane. Addition to 1-carbomethoxycyclobutene and to 1-carbomethoxy-3-methylcyclobutene followed by photolysis yielded 1-carbomethoxybicyclopentane (15a) and endo-(15c) and exo-(15b)-3-methyl-1-carbomethoxybicyclopentane, respectively, the latter two in a 1:3.3 ratio. The assignment of stereochemistry in this case was based upon the chemical shift of the methyl doublet in the nmr spectrum. The major component exhibited a

doublet at 1.2δ, while the minor product showed the doublet at 0.81δ, indicating shielding by the cyclopropane ring.

Electron-withdrawing groups other than the ester function were also effective in promoting the addition of diazomethane to cyclobutenes. Diazomethane added smoothly to 1-cyano-3,3-dimethylcyclobutene, and irradiation in the presence of benzophenone yielded the bicyclic nitrile 16 in 75% yield. The nmr spectrum of this compound, shown in Figure 9, appeared to be less complex than that of the corresponding ester. Although the full analysis of such a 5-spin system is beyond the range of the author's knowledge and ability at this time, and indeed even fraught with considerable difficulty for the experienced nmr spectroscopist, the interesting patterns present in this spectrum entice one to speculate about possible interpretations. Bearing in mind that the following discussion is speculation, and no more, a possible interpretation follows.

The broadened singlet at 1.6δ and the slightly split peak at 1.8δ are reminiscent of the pattern seen in the pyrazolines and assigned to the cyclobutane ring methylene. These two protons should show a basic AB pattern, with perhaps some cis-transannular coupling to the bridgehead methine proton. If this were the case, the cluster of doublets between 2.0 and 2.3δ, each showing the same splitting as the peak at 1.8δ must be due to the methine proton, plus the wing peak of the modified AB pattern of the ring methylene. The high-field wing peak would

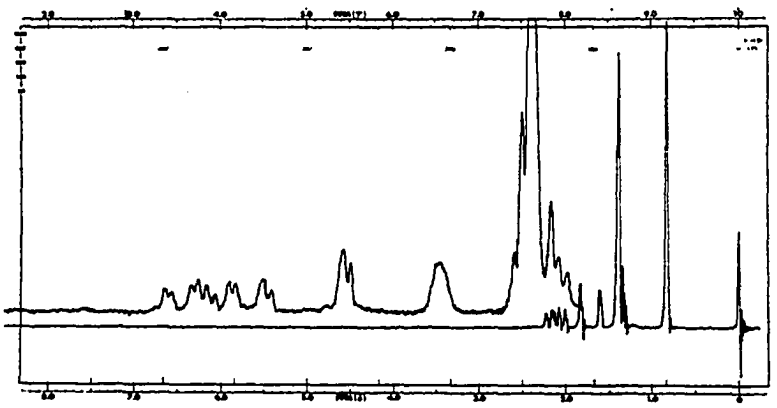


Figure 9. 60 Mc nmr spectrum of 1-cyano-3,3-dimethylbicyclo-[2.1.0]pentane (16).

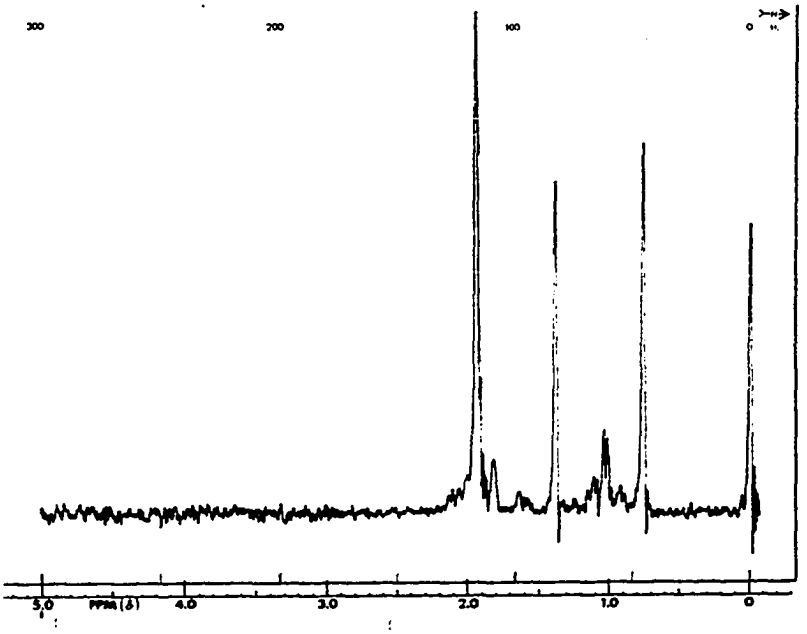


Figure 10. 60 Mc nmr spectrum of 1-acetoxy-3,3-dimethylbicyclo-[2.1.0]pentane (see p.86).

be buried under the exo-3-methyl proton resonance and the C-5 protons. The bridgehead proton, in addition to the small (>1 cps) cis-transannular splitting, should be split by ca. 7 cycles by the exo-5 proton and a smaller amount (ca. 2-3 cps) by the endo-5 proton. Numbering the cluster of doublets 1 through 5 from low to high field, one sees that the separation between 3 and 5 is approximately 7 cycles, while the separation between 1 and 2 is about three cycles. This would leave 4 as the wing peak of the AB pattern of the ring methylene. This spacing of the wing peaks would indeed place the high-field wing peak under the resonances in the 1.3-1.5 area. Although the remaining resonances are obscured by the C-3 methyl group, the C-5 protons should then appear as the AB portion of an ABM or ABX.

Examination of the integral in an expansion of this spectrum is in basic agreement with this interpretation. Basing the integral on the high-field methyl singlet as three protons, the area between 1.3 and 1.5δ integrates as 5.2 protons, the peaks at 1.6 and 1.8δ total 1.5 protons, and the set of doublets at the low-field end of the spectrum total 1.25 protons. The excess quarter-proton from the set of doublets plus the excess two tenths-proton from the obscured area, when added to the 1.5 protons of the center area yields two full protons for the ring methylene. Such detailed interpretations of nmr spectra of other derivatives will not be

offered in this thesis, although such interpretations can be made.

The conjugated ketone function was also found to be effective in promoting addition of diazomethane to cyclobutenes. The addition of diazomethane to 1-acetyl-3,3-dimethylcyclobutene and subsequent irradiation in acetone yielded 1-acetyl-3,3-dimethylbicyclopentane (17) in 25% yield. Photodecomposition of this pyrazoline was also attempted in the presence of benzophenone, however, no appreciable amount of the bicyclic compound was formed.

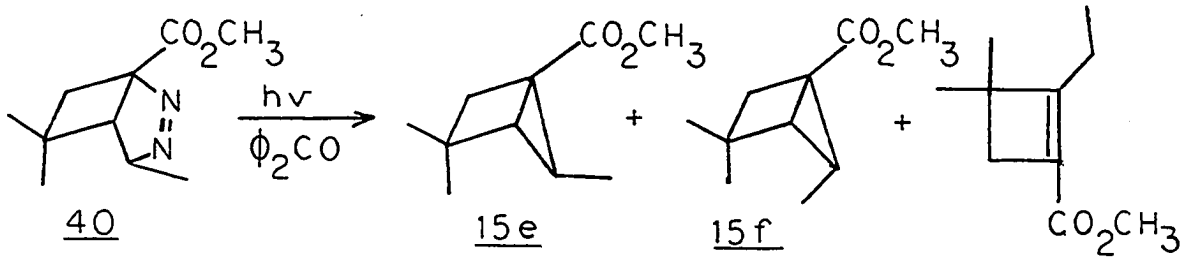
Although diazocompounds appear to add smoothly to double bonds substituted with an electron withdrawing group, attempts to add diazomethane to cyclobutenyl acetate and 1-phenylcyclobutene over a several day period showed no signs of yielding pyrazolines, indicating that the electron-withdrawing group at C-1 is a necessity for reaction at a reasonable rate. Diazocompounds have been successfully added to olefins which do not contain an activating group, but the reactions are generally quite slow, or require a catalyst (111). For instance, ethylene adds diazomethane very slowly at 0° as does styrene, but stilbene and triphenylethylene will not react with diazomethane (111). Addition of diazomethane to a few strained double bonds has been reported. Wiberg and deMeijere (112) have reported the addition of diazomethane to trans-cyclooct-1-en-3-ol, to the trans double bonds of cis-trans-1,3-cyclooctadiene and cis-trans-1,5-cyclooctadiene, while

Russian workers have reported the addition of diazomethane to norbornene (113).

Assignment of the stereochemistry at C-5 in the bicyclo-[2.1.0]pentane ring system is usually based on the chemical shift of the proton or proton-containing substituent (16, 114), with the endo-substituent appearing at higher field due to the shielding effect of the cyclobutane ring bonds (16). As an example, Jorgenson (68) assigned the stereochemistry of esters 8a and 8b on the basis of the chemical shift of the C-5 methyl group: the isomer with the methyl signal at higher field was assigned the structure 8a, with the methyl group in the endo-position. The introduction of a carbonyl-containing function at C-1, however, complicates this interpretative method considerably. Examination of molecular models suggests that rotation about the C-1-carbonyl carbon bond will be somewhat hindered, and that the two preferred conformations for the carbonyl function will place the exo- C-5 substituent in the shielding region of the carbonyl and the endo-substituent, although further removed, in the deshielding region. Since the anisotropic effect of a carbonyl group would be expected to be larger than the effect of the cyclobutane sigma bond anistropy, it might be expected that the exo- C-5 substituent should appear at higher field in such a compound.

Assignment of the structures of the exo- (15e) and endo- (15f) isomers of 1-carbomethoxy-3,3,5-trimethylbicyclo[2.1.0]-pentane on the basis of chemical intuition agrees with this

premise. The single bicyclic product from the direct irradiation of 40 shows the C-5 methyl doublet at 1.21δ, while the minor bicyclic isomer from the sensitized irradiation exhibits a C-5 methyl doublet at 1.35δ. The direct irradiation, proceeding through a singlet diradical, should result in ring closure being faster than rotation about the 4-5 bond to give the exo- isomer from the exo- pyrazoline. If irradiation in



40 15e 15f

the presence of benzophenone does generate a longer-lived triplet intermediate as suggested by Crawford in 100 rotation about the 4-5 bond could be faster than spin inversion and subsequent ring closure, but the steric hinderance provided by the endo- C-3 methyl group should preclude the formation of large amounts of the endo- C-5 methyl isomer. It is unreasonable to assign the endo- configuration to the major product of this reaction. Accordingly, the major product from the sensitized irradiation was assigned structure (15e) and the minor bicyclic product structure (15f).

Although spin-decoupling experiments on these two esters and/or nuclear Overhauser effect experiments on the tetramethyl ester could be of considerable help in assigning the relative shifts of the exo- and endo- C-5 methyl groups, in the absence

of these experiments, solvent effects on the chemical shifts of these groups could provide some information. The close proximity of the exo-5 methyl group to the carbonyl as compared to the remaining methyl groups would indicate that the effect of a solvent which coordinated with the carbonyl should be greater on it. Bhacca and Williams (115) have studied the effect of solvent upon the C-18 and C-19 methyls in several keto-steroids and have found that with the solvent change from deuteriochloroform to benzene, the more remote methyl group suffered less upfield shift than the closer methyl group. In one case, that of 5α-androstan-11-one, the C-19 methyl group was shifted downfield while the C-18 methyl group was shifted upfield. In a rigid system such as steroids, these results can be explained by examining the probable geometry of the collision complex. In a system in which the geometry of the carbonyl is more mobile, the direction of the shift caused by an aromatic solvent would not be easily predicted, but the effect of such a solvent on the exo-5 methyl group in 15e or 15g should be different and/or greater than on the remaining methyls.

The spectrum of the tetramethyl ester 15g was recorded in carbon tetrachloride, pyridine, and benzene. The spectrum in carbon tetrachloride was deceptively simple in appearance, consisting of six apparent singlets at 3.59, 1.85, 1.68, 1.41, 1.21 and 0.91δ, in a 3:2:1:3:6:3 ratio. On first examination, it appears that one C-5 methyl and one C-3 methyl are superimposed at 1.21δ, and that the ring methylene protons are

fortuitously equivalent, although broadening of the peak could indicate some small coupling beyond the resolution range of the spectrometer.

When the solvent was changed to benzene, the spectrum appeared somewhat more complex. The broadened singlet of the ring methylene now appeared to be an AB pattern, centered at 1.93. Three of the aliphatic methyl groups and the ester methyl group had been shifted upfield by 5 to 8 cycles, while the fourth had been shifted downfield by 4 cycles, and the bridgehead methine proton at 1.68δ had not shifted. There now appeared a six proton singlet at 1.29δ, apparently due to superimposition of the two C-5 methyl groups, since the spacing of the two high-field methyl resonances remained constant and was consistent with the spacing between the geminal C-3 methyls in many other esters of this series.

Changing the solvent to pyridine finally separated the four aliphatic methyl groups. Three were shifted upfield by 3.5-4.0 cycles, while the fourth was shifted downfield by 4 cycles, and the OCH_3 resonance was shifted downfield by 2.5 cycles. The two proton resonance thought to be the ring methylene was an unresolved multiplet showing fine splitting of 1 cycle centered at 1.95δ (-6 cps), while the one proton resonance still appeared as a singlet at 1.75δ (-3.5 cps).

In the carbon tetrachloride spectrum of 15g, the assignment of the position of the two C-3 methyl groups is straight-

forward. The singlet at highest field is due to the endo-3 methyl. By analogy with esters 15b-e, the exo-3 methyl should appear 20-25 cycles downfield. This would identify it as one of the two superimposed methyl proton resonances at 1.21δ. Of the remaining methyl proton resonances, the higher field one of the two shows the abnormal effect of solvent, indicating that it is the exo-5 methyl.

The spectrum of 15e was also recorded in benzene to remove any ambiguity as to which methyl groups were on C-3 and which were on C-5. This compound shows the effect quite clearly: the two methyl singlets were shifted upfield by 9.5-12 cycles, as was the ester methyl, while the distorted doublet of the C-5 methyl was shifted downfield by 2.5 cycles.

Although more definitive data could still be obtained by the use of more sophisticated nmr techniques, it is felt by the author that the data thus far accumulated puts these structural assignments on reasonably solid ground.

The syntheses of two other interesting compounds were considered and some work done toward the synthesis of one of these. With the successful synthesis of 1-substituted bicyclopentanes, a logical extension of the synthetic procedure would be to prepare compounds substituted at both bridgehead carbons. One interesting precursor, 1,2-dicyanocyclobutene, was formerly available from Standard Oil Company of Ohio, who holds a patent for a commercial synthesis (116), but several inquiries as to its availability failed to get a positive response. This

compound could undoubtedly be prepared in the laboratory, and should be a worthwhile compound to prepare for study.

Another possibly interesting disubstituted compound would be the diester. One attempt to prepare the precursor to this compound was unsuccessful, but other methods are available (117, 118, 119, 120, 121). A quantity of 2,3-dicarbomethoxy-4,4-dimethylcyclobutene was prepared by the method of Brannock, et al., (101) but several attempts to isomerize the double bond to a position between the two ester functions were unsuccessful.

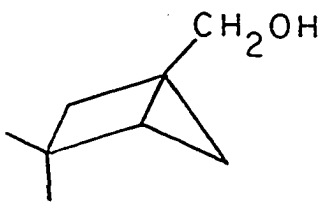
Chemical Conversions of Bridgehead Functional Groups

The chemical reactivity of the parent compound in the bicyclopentane series is dominated almost exclusively by the reactivity of the central bond. Although the reactivity of this bond must always be kept in mind, it is possible to carry out chemical transformations on the functional groups of substituted bicyclopentanes. The esters 15a-g seem to be considerably less reactive toward electrophilic reagents, and are reasonably stable thermally. Reaction of ester 15d with lithium aluminum hydride proceeds smoothly to give a compound in which the bicyclic ring is intact, if an acid work-up is avoided. The nmr spectrum of the reduction product, shown in Figure 11, shows the characteristic resonances of the bicyclic ring system, but replacing the OCH_3 singlet in the spectrum of the ester is an AB pattern centered at 3.5δ and a broad hump at 2.2δ which was washed out upon shaking with D_2O. The spectrum confirms that straightforward reduction of the ester to the bridgehead carbinyl alcohol, 1-hydroxymethyl-3,3-dimethylbicyclopentane (41), has occurred. The alcohol, as expected, is very acid sensitive, as shown by the fact that exposure to a trace of mineral acid for one hour results in almost complete destruction of the bicyclic ring system. The product of this reaction with acid was shown by nmr and IR spectral data to be 2,2-dimethyl-4-methylenecyclopentanol. An attempt to prepare the tosyl ester of the bicyclic alcohol

resulted in isolation of only rearranged material.

Treatment of 15d with 2.5 equivalents of methyllithium in refluxing ether for four hours yielded a tertiary alcohol, 1-(2-propane-2-ol)bicyclo[2.1.0]pentane (42) which was even more acid sensitive than 41. An attempt to remove a trace of remaining ester by chromatography on a silica gel column resulted in rearrangement with rupture of the central bond. The fact that some ester remained unreacted after treatment with excess methyllithium for four hours is indicative of the steric hindrance provided by the tertiary center adjacent to the carbonyl function.

The nmr spectrum of the tertiary alcohol (42) shows that the bicyclic ring is intact, since the three proton singlets due to the two methyl groups remain separated by at least 0.25 ppm with very little change in the underlying multiplets. The only marked change is the substitution of two three-proton singlets at 1.15 and 1.21δ for the one three-proton singlet in the ester region.



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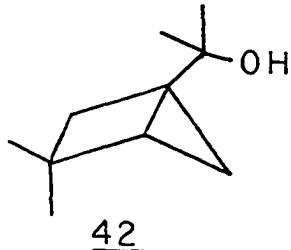

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If mild conditions are used, these esters can undergo other characteristic reactions without destruction of the bicyclic

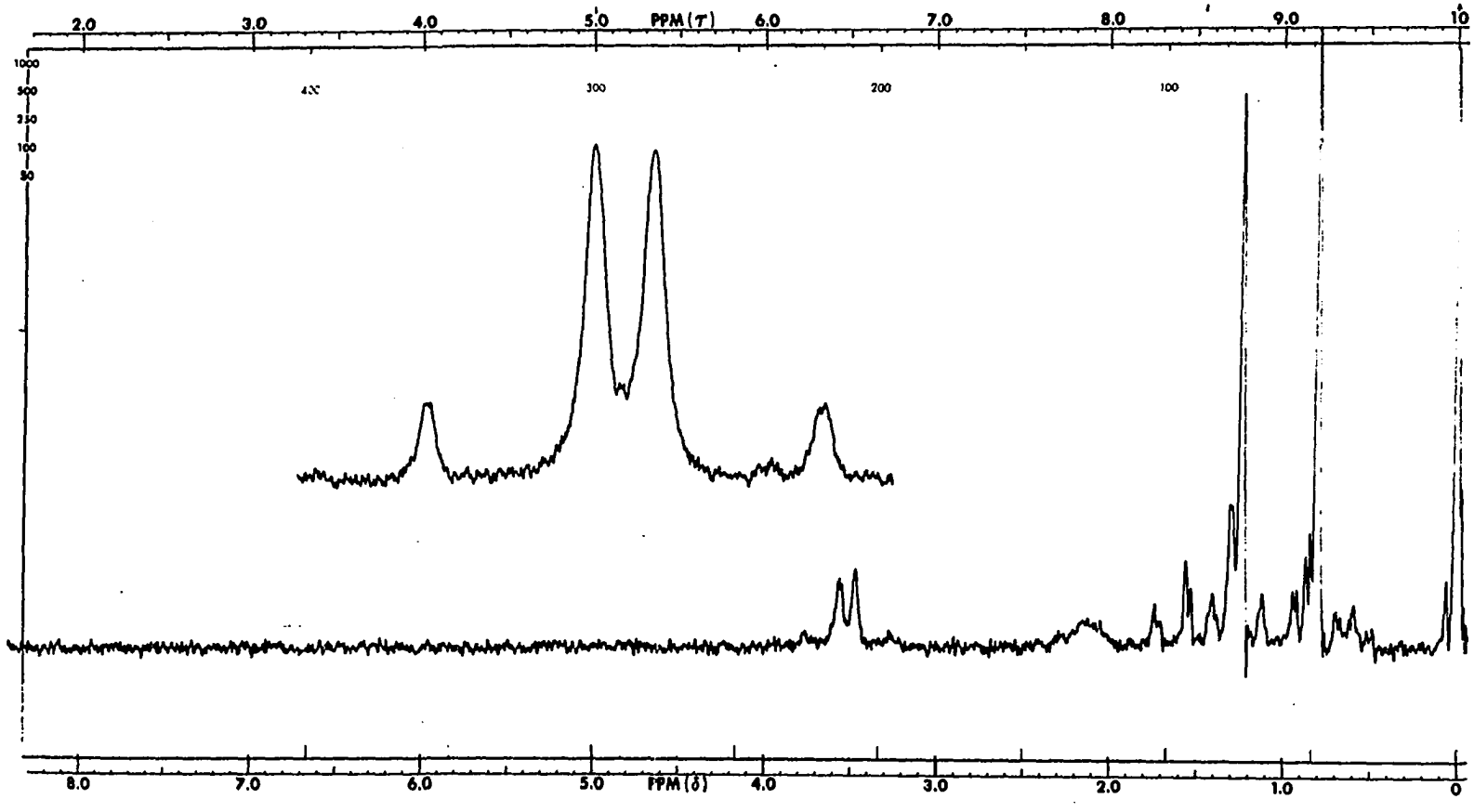


Figure 11. 60 Mc nmr spectrum of 1-hydroxymethyl-3,3-dimethylbicyclo[2.1.0]-pentane (41).

nucleus. Saponification of 15d with dilute base at 50° for 24 hours yielded the bridgehead acid, but attempted acid hydrolysis destroyed the ring system, as did refluxing in concentrated base. Treatment of 15d with hydrazine hydrate at room temperature for 16 hours gave a nearly quantitative yield of the acid hydrazide. Attempts to prepare the acid chloride from the carboxylic acid however, met with less success. Saponification of 15d, followed by treatment of the acid with thionyl chloride yielded only ring-opened material, apparently by addition of hydrogen chloride to the central bond as indicated by ions at m/e 194, 196, and 198 in the mass spectrum of the product. In an attempt to use less acidic conditions, the potassium salt of the acid was treated with oxalyl chloride in benzene (dried). The result was that a small amount of the desired acid chloride was obtained along with a considerable amount of ring opened product. The acid chloride could be obtained in reasonable purity only if all reagents and apparatus were scrupulously dried shortly beforehand.

The problems involved in preparing and working with the acid chloride prompted a search for a milder method of converting the carboxyl group to other acid derivatives. The method of Staab (122, 123), utilizing the imidazole amide, which undergoes many of the reactions of acid chlorides, seemed particularly appropriate because of the very mild conditions employed. Treatment of the above bicyclic acid with one equivalent of 1,1′-carbonyldiimidazole at room temperature,

followed by treatment with 30% aqueous hydrogen peroxide at 0°, led to a high yield of the diacyl peroxide. This method of converting these bicyclic acids to other carboxyl derivatives is apparently subject only to the limitations of imidazole amide reactions as outlined by Staab in his review article (122).

Although 1-acetyl-3,3-dimethylbicyclopentane, 16, was available from decomposition of the ketone-pyrazoline, the yield was rather seriously limited by the necessity of irradiating in acetone. It was found that the overall yield could be significantly improved by converting the acid function to the ketone after the bicyclic nucleus was formed. Treatment of the bridgehead carboxylic acid with methyllithium generated the ketone in 60% yield. Reaction of the acid with phenyllithium also produced a ketone, 1-benzoyl-3,3-dimethylbicyclopentane (18), although it was not obtained in pure form.

Since reduction of the bridgehead ester function to the alcohol with lithium aluminum hydride proceeded without difficulty, it was thought that perhaps a reductive method of preparing the bridgehead aldehyde might be successful. This compound was of interest as a precursor to the bicyclopentyl carbene. There are a number of methods in the literature for converting various carboxylic acid derivatives to aldehydes (105, 124, 125, 126, 127, 128, 129, 130, 131). Reduction of nitriles to aldehydes by a number of reagents, such as lithium aluminum hydride (124), lithium triethoxy aluminum hydride

(125), and diisobutyl aluminum hydride (126) have been described in the chemical literature. Reduction of phenyl esters and acid chlorides to aldehydes by lithium tri-t-butoxy aluminum hydride has been reported by Brown and co-workers (105, 130). Due to the difficulty of preparing and handling the acid chloride needed in the latter reaction, either for direct reduction or for preparation of the phenyl ester, several attempts were made to reduce the bridgehead nitrile. Reaction with lithium aluminum hydride, lithium triethoxy aluminum hydride, and diisobutyl aluminum hydride under the prescribed conditions led to no reduction, while more forcing conditions led to complete reduction to the amine. Possibly the steric hindrance provided by the adjacent tertiary center prevents reaction under the normally mild conditions required for aldehyde formation, while the more forcing conditions necessary to promote any reaction are sufficiently strong to further reduce the aldehyde precursor if it had been formed.

With the failure of reductive methods of aldehyde synthesis, two oxidative procedures were attempted. Young and Trahanovsky (132) have reported the oxidation of cyclopropylmethanol to cyclopropane carboxaldehyde with ceric ammonium nitrate. Although this reagent is quite acidic in aqueous solution, it was hoped that in acetonitrile, the oxidation of the bridgehead alcohol could be carried out before rearrangement of the ring system. Accordingly, the reaction was carried out in acetonitrile, but only olefinic products were isolated. A second

procedure involving the oxidation of chlorocarbonate esters with DMSO was attempted (155). Treatment of the bridgehead carbinyl alcohol with phosgene in the presence of triethylamine yielded the chlorocarbonate ester, which was then treated with DMSO. The crude isolated product showed a very weak resonance in the aldehyde region of the nmr spectrum, but the rest of the spectrum indicated extensive rearrangement of the ring system. A resonance at 4.75δ indicated the presence of olefinic protons, and ten separate peaks were present in the methyl region.

Reactions Involving 1-4 Bond Cleavage

Since chemical reactions of parent bicyclo[2.1.0]pentene nearly always involve the breakage of the 1-4 bond, it was of interest to examine briefly some of these reactions with substituted bicyclopentanes.

Lalonde and Forney have studied the addition of acetic acid to a number of bicyclo[n.1.0]alkanes, and found that only the bicyclopentane ring system would react with acetic acid in the absence of a stronger acid such as p-toluenesulfonic acid (60). Since in this reaction the bicyclopentane is reacting as a nucleophile, the presence of an electron-withdrawing group on the bridgehead should reduce the electron density in the central bond, thus reducing its reactivity toward electrophilic reagents. Treatment of 1-carbomethoxy-3,3-dimethylbicyclopentane (15d) with acetic acid containing a trace of p-toluenesulfonic acid at room temperature for 52 hours resulted in no reaction, as did treatment at 50° for 36 hours. Treatment at reflux in acetic acid for seven hours was sufficient to destroy the ring system and given a complex product mixture. Since Lalonde reported that treatment of bicyclopentane with acetic acid-toluenesulfonic acid at 47° for 24 hours yielded only cyclopentyl acetate, it would seem that the ester function does markedly reduce the reactivity of the 1-4 bond with electrophilic reagents.

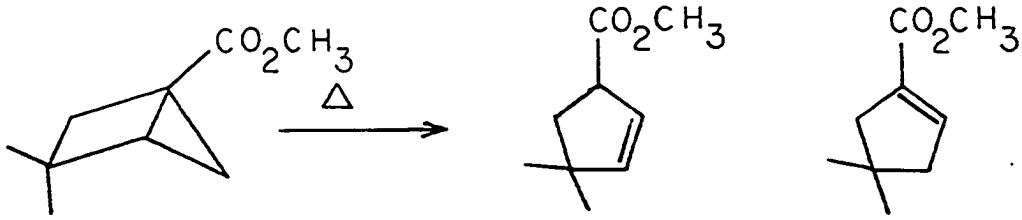
With the failure of acetic acid to react with 15d under

mild conditions, a stronger acid was used. Criegee reported that treatment of bicyclopentane with HBr yielded cyclopentyl bromide very rapidly under mild conditions (13). Treatment of 15d with 48% HBr for 36 hours at 0° yielded a product which showed ions in its mass spectrum at m/e 232 and 234. Although the HBr adduct should have molecule ions at m/e 234 and m/e 236, the presence of ions in this region indicates bromine incorporation in some form.

Since the pyrolysis of bicyclopentane to cyclopentene presumably proceeds via a radical mechanism, the presence of an electron-withdrawing or electron donating group at C-1 should have less of an effect on this reaction, although the lower electron density in the bond might make it more easily ruptured. In order to determine the effect, if any, of an electron withdrawing group at C-1, the pyrolysis of 15d was studied under a variety of conditions.

The first method used involved passing the ester, as a solution in benzene, through a vertical Pyrex column 30 cm long and packed with glass helices. The temperature was varied from 220° to 550°, while the nitrogen flow rate was kept as constant as possible, in the vicinity of 40 ml/min. Products were trapped in a Dry Ice-acetone bath. It was found that no pyrolysis took place when the column was at 220°, while partial pyrolysis occurred at 300° to give a mixture of starting material and product esters. At 350° complete pyrolysis occurred during the short residence time to give a 50:50

mixture of product esters. The products were separated by vpc and spectral data recorded. The material with the shorter retention time on the vpc column (Carbowax) showed three singlets of three protons each in its nmr spectrum, at 1.05, 1.12, and 3.62δ, as well as multiplets at 1.8-2.1, 3.3-3.7, and 5.35-5.7δ in a ratio of 2:1:2. The carbonyl frequency of 1740 cm^{-1} in the IR spectrum indicated a non-conjugated ester, as did the position and integral of the olefinic proton resonance in the nmr. The mass spectral molecular weight was 154. The compound was assigned the structure of 1-carbomethoxy-4,4-dimethylcyclopent-2-ene. The second compound showed a singlet at 1.12δ in its nmr spectrum for the geminal methyl groups, a four proton multiplet at 2.2-2.5δ, an $-OCH_3$ singlet at 3.67δ, and a one proton resonance, a broadened singlet, at 6.55δ. This data, accompanied by a mass spectral molecular weight of 154 and an IR carbonyl frequency of 1720 cm^{-1} identified the compound as the conjugated isomer, 1-carbomethoxy-4,4-dimethylcyclopent-1-ene.



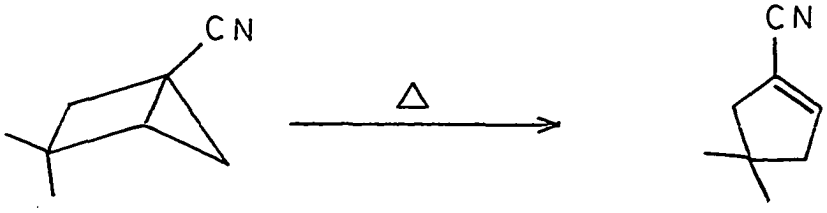
When the column temperature was raised to 550°, the product ratio was no longer 50:50, but rather the conjugated ester

predominated to the extent of 2:1. A control experiment indicated that the non-conjugated ester was not appreciably isomerized to the conjugated isomer under these conditions.

Since the residence time in the column pyrolysis was very dependent upon flow rate of nitrogen, and since this was not easily controlled, the pyrolysis was also carried out in a sealed tube in an electric oven. Upon heating at 360° for 2.07 hours, 15d gave a mixture of 36.5% non-conjugated ester and 63.5% conjugated ester. During the same period, pure samples of each product ester were also subjected to oven pyrolysis, resulting in no change in the conjugated isomer and the production of 8.6% conjugated ester from the non-conjugated isomer. Pyrolysis of 15d for 2 hours at 235° yielded about 60% reaction, with the conjugated ester predominant. Although accurate measurements could not be made due to peak overlap on the vpc, this result indicates a half-life of less than two hours at 235°, as compared to a half-life of 193 hours for the parent hydrocarbon at 223° (70). The high activation energy for the reaction to form cyclopentene (45.6 Kcal/mole) makes this reaction very temperature dependent. The first order rate constant for the reaction at 276° as measured by Steel and co-workers in 20 provides a calculated half-life of 1.83 hr--comparable to that of ester 15d at 235°. Calculation of the rate constant for bicyclopentane pyrolysis at 235° using the Arrhenius equation yields

a figure of 2.45×10^{-6}, or a half-life of 78.5 hours.

Pyrolysis of the bridgehead nitrile 16 yielded more interesting results. Upon heating at 242° in a sealed tube for two hours, only one product was formed, and less than 10% starting material was recovered. The nmr spectrum of the pyrolysate exhibited a one proton multiplet centered at 6.4δ, a four proton multiplet at 2.3δ, and a six proton singlet at 1.11δ. This, combined with the presence of a nitrile band in the IR spectrum at 2225 cm^{-1}, indicative of a conjugated nitrile, seemed to indicate that the product was 1-cyano-4,4-dimethylcyclopentene. The fact that less than 10% of starting material remained after two hours would indicate that



this time period constituted at least three half-lives, assuming first order kinetics. Again using the Arrhenius equation, the calculated half-life of the parent hydrocarbon at 242° would be 45 hours.

Considering the unrefined nature of the rate data obtained in these experiments, the rate difference between the ester and the nitrile may certainly be insignificant, but the difference between the parent system and either the ester

or the nitrile is large enough to be considered real and significant. A difference this large would seem to indicate a definite effect upon the strength of the 1-4 bond by a substituent on that bond.

A second effect which might be occurring is steric acceleration due to the endo-methyl group at C-3. An examination of molecular models shows considerable steric crowding in this compound which could lead to acceleration of 1-4 bond breakage; however, if the intermediate is a non-planar diradical as proposed by Chesick, the presence of the second methyl group at C-3 should make this effect less important.

The fact that the bicyclic ester yields a mixture of the two possible products, in ratios varying from 1:1 to 3:1 in favor of the conjugated isomer, while pyrolysis of the nitrile yields only the conjugated product is in keeping with the results of Huang (134) in his studies of substituent effects on radical stability. In the radical addition of butanal to a series of β,β-dimethylacryates, including mesityl oxide, β,β-dimethylacrylonitrile, and ethyl β,β-dimethylacrylate, β-addition (formation of the new carbon-carbon bond at the β position producing a free radical at the α position) predominated to the extent of 10:1 in the ketone and 3:1 in the ester, but he found no α addition to the nitrile. These results are interpreted to mean that the ability of the nitrile function to stabilize an α radical center is greater than or

perhaps roughly equal to that of the ketone, and greater than that of the ester. In the pyrolysis of substituted bicyclopentanes, the hydrogen atom at C-5 apparently migrates preferentially to the less stable radical center, with the degree of preference dependent upon the difference in stability. Thus, the product ratio will depend upon the radical stabilizing ability of the substituent, while the rate of pyrolysis seems to be more dependent upon the electron-withdrawing capability of the substituent.

Hydrogenation is another reaction in which the central bond is broken, and in which the presence of a substituent at C-1 seems to have an effect on the rate. Criegee reported that the parent hydrocarbon is easily hydrogenated to cyclopentane using palladium catalyst at atmospheric pressure (13). Ester 15d, on the other hand, was inert to these conditions, requiring the use of platinum in acetic acid at 500 lbs pressure to effect slow hydrogenation. It might be expected that the more electron-poor bond in the ester would not be adsorbed on the surface of the catalyst as easily as the parent compound; however, it is likely that the largest effect is due to steric hindrance provided by the exo- C-3 methyl group and the bridgehead ester group to the approach of the catalyst (73).

Treatment of 1-hydroxymethylbicyclopentanes with acid also results in breakage of the 1-4 bond of the molecule. When 1-hydroxymethyl-3,3-dimethylbicyclopentane was heated at 40°

in the presence of a trace of mineral acid for 30 minutes, the bicyclic nucleus was almost completely rearranged. The nmr and IR spectra of the product indicated the presence of an exocyclic methylene function in the molecule (nmr; multiplet at 4.8δ: IR; bands at 1655 and 878 cm^{-1}). The product was identified as 4-methylene-2,2-dimethylcyclopentanol (50).

This ring opening raises an interesting question with respect to stereochemistry. If ring opening to a free cation occurs, no preferred stereochemistry should be observed; however, if attack of the nucleophile is concerted with cleavage of the 1-4 bond, a predominance of either retention or inversion about C-4 might be observed. Approach of the nucleophile from the exo- side of the molecule should then lead to retention of configuration at C-4, while attack from the endo- side would result in inversion about C-4. Although approach from the exo- side seems more likely, reactions of bicyclopentanes with electron-deficient multiple bonds have been shown to result from endo- attack (63, 64, 65, 66, 135) with resulting inversion at the bridgehead carbon.

Although the stereochemistry of the reaction could not be observed in the case of 41, the introduction of a methyl group at C-5 would provide the required tag for observing the stereochemistry of the reaction. With the methyl group in the exo- position, opening with retention at C-4 would result in the two protons at C-4 and C-5 being cis- in the product. (Although these protons are trans- with respect to the

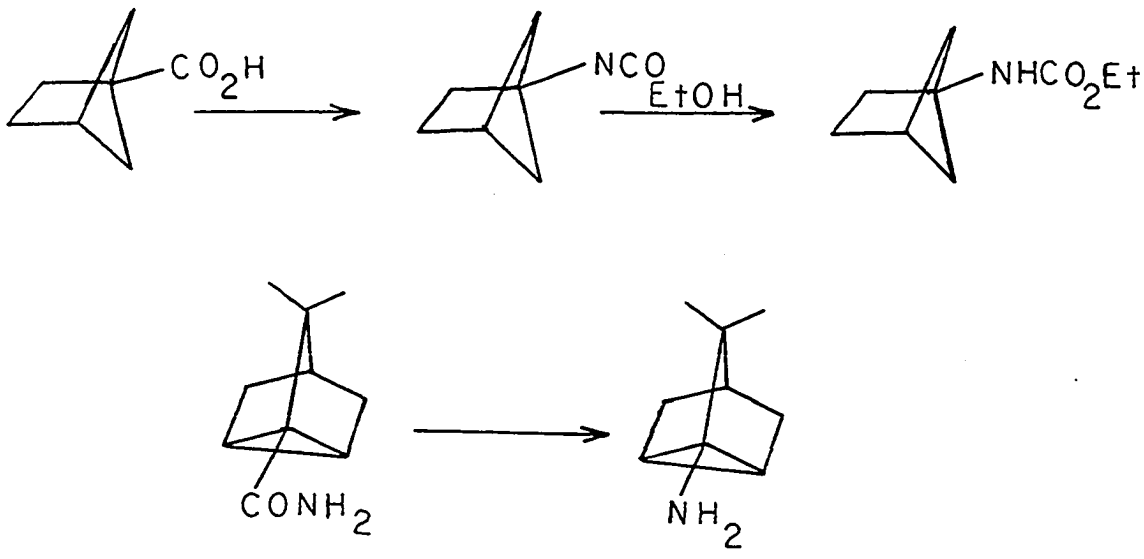
cyclopropane ring, they are cis- with respect to the cyclopentane ring). Likewise, inversion about C-4 would yield a trans- geometry between the C-4 and C-5 protons.

The availability of ester 15f, containing an exo- methyl group made such an experiment seem quite straightforward. Reduction of 15f to the alcohol by lithium aluminum hydride was accomplished, although with some difficulty. A 40% excess of hydride was used and the reaction heated at reflux in ether for 45 minutes, but only partial reduction occurred. The reaction was repeated but even after 90 minutes at reflux reduction was incomplete, indicative of the severe steric hindrance about the ester function in this molecule. Since esters 15a-g have been shown to be reasonably stable toward acid treatment, the presence of some unreduced ester would not be expected to complicate the reaction, so the reduction mixture was treated with a trace of mineral acid for one hour at 50° in aqueous dioxane. The resulting material was chromatographed on Silica Gel to remove the ester and dioxane. A minty-smelling oil was obtained whose nmr spectrum showed the expected methyl proton resonances (two singlets at 0.89 and 1.02δ, one doublet at 1.12δ and the exocyclic methylene olefinic proton resonances (4.8 ppm). The proton on the hydroxyl-bearing carbon appeared as a doublet at 3.15δ with a separation between the peaks of 9 cycles, consistent with a cis- arrangement with the proton causing the splitting, but not with a trans- arrangement. Unfortunately, the recovery of

alcoholic material in the reaction was less than 50%, so this result cannot be viewed as definitive. Loss of the trans- isomer could have occurred at some point in the work-up, making these data worthless. It would not be expected, however, that the reactivity or behavior on Silica Gel of the trans- isomer would be enough different from the cis- isomer to result in selective loss or destruction of it, so these data are suggestive that retention of stereochemistry at C-4 has occurred.

Reactions Involving Migration of the Bicyclopentane Nucleus

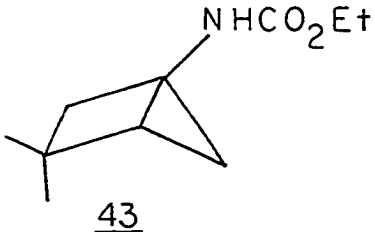
Many examples of rearrangements involving the migration of a bridgehead carbon to an electron deficient center have been reported in the literature, including examples of fused small ring systems (136). Wiberg has reported that bicyclo-[2.1.1]hexane-1-carboxylic acid undergoes a Schmidt rearrangement to give the bridgehead urethane (137), and as long ago as 1921, Lipp and Padberg (138) reported the synthesis of 1-aminotricyclene by way of a Hoffmann rearrangement from tricyclene-1-carboxamide. However, no examples of rearrangements



of this type involving the bridgehead position of a bicyclopentane have been reported to date. Accordingly, the Curtius rearrangement and the Baeyer-Villiger oxidation were attempted on this system, with success.

Treatment of the hydrazide of 3,3-dimethylbicyclopentane-1-carboxylic acid with nitrous acid at 0° yielded the acyl azide, which could be isolated and investigated spectrally (typical bicyclopentane nmr patterns, IR bands at 2125 and 1690 cm^{-1}). Pyrolysis of this azide in benzene (much slower rate of decomposition than pivaloyl azide) yielded a red oil which exhibited a typical bicyclic nmr spectrum and a strong band in the IR spectrum at 2250 cm^{-1}. This material was not stable at room temperature and slowly polymerized to a brown tar. When the acyl azide was pyrolized in the presence of ethanol, the reaction proceeded smoothly to yield N-(3,3-dimethylbicyclopentane) ethyl carbamate (43), as characterized by nmr and mass spectral data. The nmr spectrum exhibited the typical non-equivalent methyl resonances associated with the bicyclopentane nucleus with a separation even greater than in the ester (0.65 ppm, as compared to 0.4 in 15d), and an ethyl triplet and quartet at 1.2 and 4.05, respectively. Moss (139) has published the chemical shifts of the N-ethyl protons in a number of urethanes, all of which were quite consistent with the shifts observed in this compound. The mass spectrum of 43 confirmed the carbamate structure. A weak molecule ion was present at m/e 183, while the base peak at m/e 124 corresponded to the typical loss of CO_2 and $CH_3\cdot$ from ethyl carbamates (140), and a large fragment ion at m/e 95, corresponding to C-1–N cleavage.

The effect of an electron-donating group at C-1, albeit a weak one, has the effect of increasing the reactivity of the 1-4 bond toward electrophilic reagents. It was found that 43, in the presence of water, apparently added water across the 1-4 bond with loss of ethyl carbamate to yield 3,3-dimethylcyclopentanone. When a sample of 43 was left in the freezer for two days in solution in absolute ethanol, partial rearrangement occurred to yield 3,3-dimethylcyclopentanone. Whether this was due to reaction with ethanol, or with traces of water in the ethanol is not known. All attempts to purify a sample of 43 for analysis resulted in appreciable hydrolysis to the ketone. Attempts to hydrolyze the carbamate to the free amine resulted in complete hydrolysis to the ketone.



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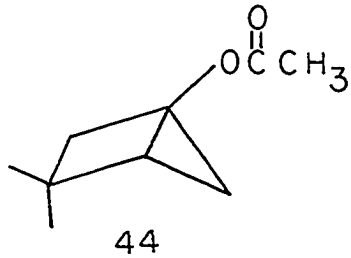

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The bridgehead methyl ketone 17 was chosen as the substrate for the Baeyer-Villiger oxidation. Treatment of the ketone with a buffered solution of peracetic acid for eight hours in methylene chloride yielded a mixture of 1-acetoxy-13,3-dimethylbicyclopentane (44) and the isomeric bridgehead methyl

ester 15d, in a ratio of 10:1. The nmr spectrum of 44 is shown in Figure 10, p. 58 , while the mass spectrum will be discussed in a later section. The Baeyer-Villiger reaction has been the subject of a number of studies concerning the migratory aptitude of various groups (141), the results of which show a trend of $3° > 2° > \emptyset > 1° > CH_3$, and correlate with the ability of the migrating group to stabilize a positive charge. The difference in migratory aptitudes between t-butyl and methyl was found to be approximately 4×10^3 (142). Methyl cyclopropyl ketone was found not to react with perbenzoic acid (143), but Emmons and Lucas (144) found that trifluoroperacetic acid would convert it to cyclopropyl acetate in 55% yield. The reaction was examined later by Sauers and Ubersax (145) who found that the oxidation also yielded carbomethoxypropane in an acetate: carboxylate ratio of 95:5, which would make the cyclopropyl group comparable to a primary substituent in its migratory ability. The 10:1 ratio observed in the oxidation of 1-acetyl-3,3-dimethylbicyclopentane is reasonably in line with the ratio observed from methyl cyclopropyl ketone, but indicative of a bit more reluctance to support a partial positive charge. In view of the strain induced by any move toward planarity at C-1, this reluctance is to be expected.

The bridgehead acetate seemed less sensitive to moisture than did the carbamate 43, but was not indefinitely stable even in a refrigerator. The decomposition product was not examined.

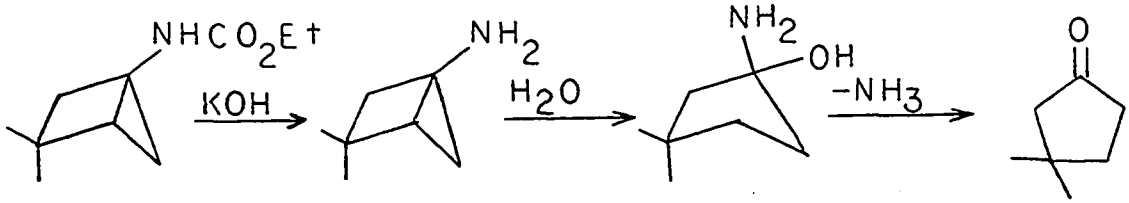
Reactive Intermediates at The Bridgehead Carbon

Since the 1-bicyclo[2.1.0]pentyl cation has been proposed as an intermediate in the rearrangement of the spiropentyl cation (80, 81), it was of interest to generate this cation. An analysis of products could cast doubt on the intermediacy of the 1-bicyclopentyl cation if the products were not the same as those observed from the spiropentyl cation.

Three procedures were considered as methods of generating the 1-bicyclopentyl cation from available bicyclic compounds. They were: 1) deoxidation of the bridgehead alcohol, potentially available from the bridgehead acetate 44; 2) deamination of the bridgehead amine, potentially available from the bridgehead carbamate 43; and 3) anodic oxidation of the bridgehead carboxylate anion. Deoxidation could be discarded immediately in view of the structure of the needed alcohol. Nickon has reported the isolation of a strained "homoenol", 1-nortricyclanol (146), but under basic conditions, the alkoxide or "homoenolate" ion underwent irreversible rearrangement in the presence of a proton source to norbornanone. Since the reaction conditions for the deoxidation reaction are strongly basic, and since rearrangement of 3,3-dimethylbicyclo[2.1.0]pentan-1-ol to 3,3-dimethylcyclopentanone releases considerably more strain energy than the rearrangement of nortricyclanol (approximately 25 kcal/mole more using Turner's (147) estimates of the strain energy of nortricyclene,

norbornane, and bicyclopentane), the alkoxide ion might well rearrange much faster than deoxidation could occur. In view of the relief of strain available in this rearrangement, isolation of the alcohol in the first place would be a very doubtful proposition.

Isolation of 3,3-dimethyl-1-aminobicyclo[2.1.0]pentane also seemed somewhat improbable in view of the previously discussed reactivity of the carbamate (see p. 86). Reactions of the central bond in bicyclo[2.1.0]pentane are generally as a nucleophile, and adding an electron donating group at C-1 should increase the nucleophilicity of this bond. Attempts to hydrolyze 43 to the amine confirmed this fear, yielding only monocyclic products. In a typical attempt, the carbamate was stirred at room temperature for 48 hours in a 20% aqueous potassium hydroxide solution. The only product isolated was 3,3-dimethylcyclopentanone, in 50% yield. A mechanism explaining this product can be written, involving the addition of water to the 1-4 bond of the intermediate amine, with subsequent loss of ammonia.



Anodic oxidation of carboxylic acids (Kolbe electrolysis) normally produces hydrocarbons through formation and coupling of free radicals (148, 149, 150). In certain cases, however, products more easily explained in terms of a cationic intermediate are obtained (151, 152). In 1960, Corey and co-workers showed that cationic intermediates could be involved in anodic oxidations (153) and in 1964, Koehl found that the use of a carbon anode rather than the usual platinum electrode led almost exclusively to cation-type products (154). Skell and co-workers have studied the anodic oxidation of certain carboxylates under chronopotentiometric conditions and have proposed a two-step oxidative pathway involving the intermediacy of an adsorbed carboxylate radical, which loses CO_2 to form an adsorbed alkyl radical, which undergoes further oxidation to an alkyl cation (155). In recent years, the method has been used extensively to study carbonium ion reactions (156, 157, 158).

The anodic oxidation of 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxylic acid was carried out using a carbon anode and an aqueous medium containing one equivalent of potassium hydroxide to convert the acid to the carboxylate anion. The anion was extremely resistant to oxidation, requiring 100 volts to form products at an appreciable rate. In a typical experiment, electrolysis of 2.6 grams of acid at 100 volts (2 amps) for four hours yielded 0.35 grams of neutral products, while 1.75

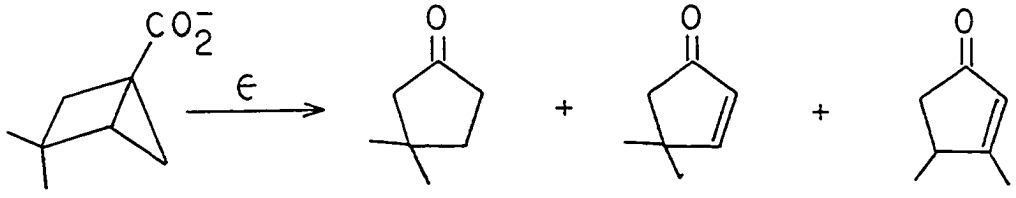
grams of acid were recovered unchanged.

Analysis of the neutral products from the electrolysis by vpc showed the presence of three components, A, B, and C, in a ratio of 0.4:1:1.02, in order of retention time. The products were separated by vpc and spectral data collected. All three had carbonyl absorptions in their IR spectra; B and C showed a conjugated double bond absorption, while A appeared to be saturated. The mass spectra of B and C showed molecule ions at m/e 110, with base peaks at m/e 67 and 95, respectively, with the base peak at m/e 56.

The nmr spectrum of A showed a six proton singlet at 1.11δ, a two proton singlet at 2.05δ, and an A_2B_2 pattern centered at 2.05δ. A was therefore assigned the structure 3,3-dimethylcyclopentanone (45). The spectrum of B was quite simple, showing a six proton singlet at 1.21δ, a two proton singlet at 2.15δ, and an olefinic AB pattern centered at 6.65δ, J_{AB} = 5.5 cycles, δ_{AB} = 94.1 cycles. The presence of the olefinic AB pattern rather than the saturated A_2B_2 pattern as found in the spectrum of the previous ketone indicated the compound was 5,5-dimethylcyclopenten-3-one (46). The remaining compound had a more complex nmr spectrum which contained a three proton doublet at 1.2δ, a three proton singlet, with possible allylic coupling, at 2.09δ, a one proton multiplet at 5.8δ (ca. 1 cycle splitting), and multiplets totaling three protons spread from 1.3 to 3.0δ. The high field methyl doublet would indicate

a methyl group adjacent to a methine proton, while the slightly split resonance at 2.1δ would indicate the presence of an olefinic methyl experiencing allylic coupling with the olefinic proton at 5.8δ. The position of the olefinic proton resonance is characteristic for a proton α to the ketone function. The spectral data for this compound then indicated a structure of 1,5-dimethylcyclopenten-3-one (47).

In view of the rather forcing conditions necessary to effect the oxidation of the carboxylate anion, and since it has long been known that secondary alcohols can be electrolytically oxidized to ketones (159), the isolation of ketones from the reaction mixture was not entirely surprising, although the usual products under milder conditions are alcohols. The



45 46 47

production of a saturated ketone can also be rationalized under such conditions. Electrolytic hydrogenations of unsaturated compounds have been reported in both acidic and basic media, although the reaction does not occur with ease (159). It has been reported that in basic medium, benzoic acid can be reduced

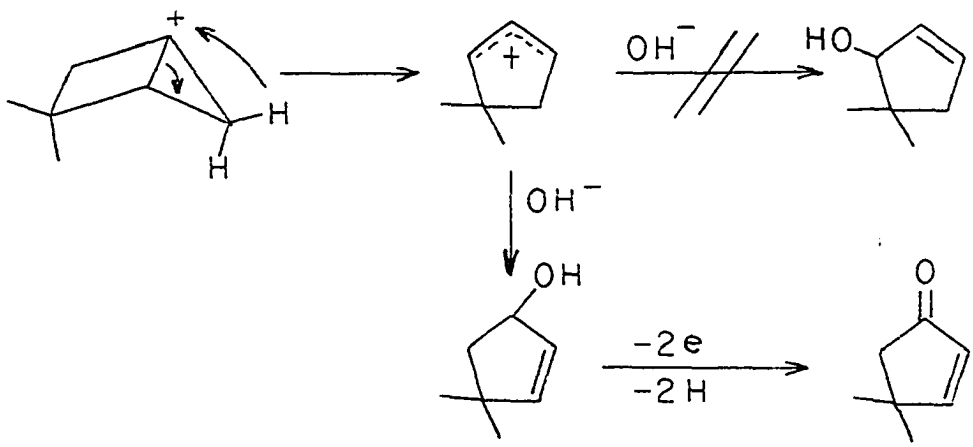
at a high overpotential electrode to cyclohexene-3-carboxylic acid (160).

In order to determine whether the ketonic products actually arise via oxidation of 3,3-dimethylcyclopenten-3-ol, this alcohol was synthesized and subjected to the electrolysis conditions. Analysis by vpc and nmr integration showed that the reaction was less than 50% complete, but that all three ketonic products were present, in a ratio of 0.27:1:1.6. The presence of ketones 45 and 46 was not surprising, but the formation of 47 from the geminal dimethyl alcohol indicates that the process is somewhat more involved than a simple oxidation reaction. It does, however, remove the necessity of postulating it as a primary oxidation product.

The formation of a cyclopentene skeleton from rearrangement of the 1-bicyclopentyl cation rather than the methylenecyclobutane skeleton observed in the rearrangement of the spiropentyl cation demonstrates that the former is probably not an intermediate in the rearrangement of the latter. The formation of the cyclopentene ring from the bicyclopentyl cation can be rationalized in terms of a 1,2 hydride shift from C-5 to C-1, either immediately preceding or concerted with the rupture of the 1-4 bond. Although the rupture of an external cyclopropane bond to yield a methylenecyclobutane would not involve a hydride shift, and thus should proceed more easily, the release of strain energy would be considerably less. This release of strain energy is very important in

the reactions of bicyclopentanes, so much so that only two examples have been reported in which an external bond is broken rather than the internal bond (25, 27). If the hydride shift is concerted with the breaking of this bond, the recovery of the strain energy of the system would provide more than enough driving force for the hydride migration.

This rearrangement leads to an allylic cation which, with the methyl groups serving as a positional label, could lead to two products. One of the positions of possible nucleophilic attack, however, is a neopentyl position and no product resulting from attack at that position is seen.

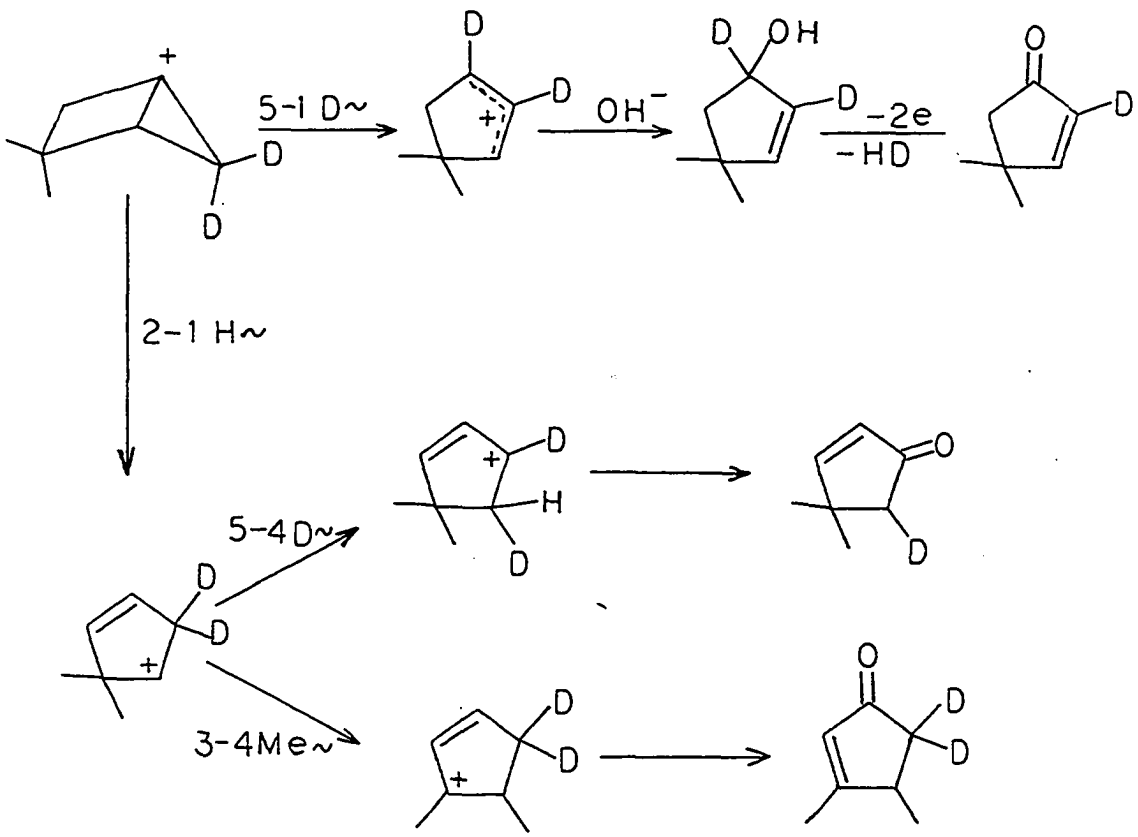


A second, similar mechanism can be drawn to explain the products observed. Migration of a hydrogen from C-2 rather than C-5 followed by ring opening and a second hydride shift from C-5 to C-1 would generate the same allylic cation. Although this mechanism requires two hydride shifts rather than one, the release of strain should provide all the energy

necessary. This mechanism has an advantage in that it allows an easy explanation for the formation of the vicinal dimethylcyclopentenone 47. If, rather than undergoing a hydride shift after ring expansion, the unconjugated ion undergoes a methyl migration, an allylic ion with vicinal methyl groups is formed. This ion could then react with water to form an alcohol which could be oxidized directly to 47 (see Figure 10).

The introduction of an isotopic label at C-2 or C-5 should allow one to distinguish between these two possible mechanisms, and the use of deuterated diazomethane (161) would allow the introduction of a label at C-5 without difficulty. The deuterium distribution from each pathway is shown in Figure 10. Migration of a hydrogen (deuterium) from C-5 would result in the retention of one deuterium in the molecule at the olefinic alpha position, while migration of a C-2 hydrogen would result in the retention of one deuterium, at the saturated alpha position. Unfortunately, the fact that the products are ketones rather than alcohols makes this procedure useless since both positions in which the label might be located in the products are labile to reaction conditions. In a test experiment, a sample of 5,5-dimethylcyclopenten-3-one was treated with D_2O under the reaction conditions which resulted in the exchange of all three alpha protons.

Examination of the possible mechanistic pathways showed that labeling the C-2 position would give retention of one



deuterium at the β-olefinic position if a hydrogen from C-2 migrates, and no deuterium retention if a hydrogen from C-5 migrates. However, introduction of a label at C-2 would not be straightforward.

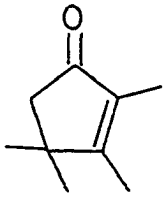
The oxidation of 1-carbomethoxy-3,3,5,5-tetramethylbicyclopentane was examined in the hope that the product from this reaction would give some insight into the mechanism, although blocking of the C-5 position could force the rearrangement to proceed through a different pathway if the C-5 position were involved. The oxidation proceeded with considerable difficulty;

the disappearance of acid was quite slow, and the formation of neutral products occurred in very low yield. From 1.5 g of acid, 80 mg of crude reaction product was obtained. Analysis by vpc showed the presence of two products with only slightly different retention times. They were collected together, and spectral data obtained on the mixture, which then amounted to only a few milligrams. The 100 Mc nmr spectrum showed no resonances below 2.5δ, with a large singlet at 1.17δ. The spectrum reflected the fact that the sample was a mixture, in that quite a number of less intense peaks were present. The mass spectrum of the mixture was somewhat more revealing. The more intense peaks in the spectrum occurred at m/e 138, 123, 103, 95, 70, 69, 67, 59, and 55. The behavior of the ion at m/e 138 at low electron energy indicated that it was a molecule ion. Since the expected product of the reaction was a tetramethyl cyclopentenone (MW = 138) possible fragmentation modes of such a compound were examined. By analogy with the dimethylcyclopentenones formed from the dimethyl acid, such a compound would be expected to show a large loss of methyl (m/e 123), a smaller loss of CO (m/e 110, present but not intense), and loss of both functions (m/e 95).

Examination of the IR spectrum of the mixture also indicated the presence of a ketone (or ketones). In the carbonyl and carbon-carbon double bond stretching region were five bands at 1760, 1720, 1700 (strongest), 1645, and 1623 cm^{-1}.

The strongest band in the carbonyl region at 1700, along with the band at 1645 cm^{-1}, suggested that an α,β-unsaturated ketone was the major product.

Of all the possible isomers of tetramethyl-2-cyclopentenones, only three have no olefinic protons: 1,2,5,5-tetramethylcyclopenten-3-one (48), 1,2,4,4-tetramethyl cyclopenten-3-one (49), and 1,2,4,5-tetramethyl cyclopenten-3-one (50). Of these, only one could be accounted for reasonably in terms of the mechanisms discussed. Migration of a C-5 methyl group to C-1, with ring opening and attack by solvent would yield 49.



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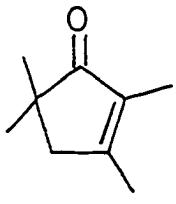

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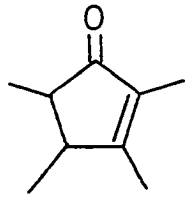


50

Since the nmr spectrum, with its large singlet indicating equivalent geminal (or at least unsplit) methyls seemed to rule out the 1,2,4,5-tetramethyl isomer, it was decided to synthesize the two other isomers for comparison. Since the 1,2,5,5-tetramethyl isomer 48 was readily available by the method of Conia and Leriverend (162), it was prepared first, although it was not expected to match the reaction product. The nmr spectrum consisted of four singlets, at 1.27, 1.60, 1.90, and

2.12δ, in a ratio of 6:3:3:2. Although it was much less complex than the electrolysis product mixture, a direct comparison showed that there were peaks in the spectrum of the mixture corresponding to each peak in the spectrum of 48. A direct comparison of IR and nmr spectra also gave no conclusive evidence against 48 as the possible electrolysis product. Although intensities varied slightly, all peaks and absorptions in the spectra of 48 were present in the electrolysis product mixture. The intensity differences could not be counted as too important because of the fact that the electrolysis product was a mixture. Finally, comparison of vpc retention times showed a remarkable similarity. On a Carbowax column, adjusted so that the retention times were about fifteen minutes, the difference in retention times was only a few seconds. The fact that one was being injected neat while the other was a dilute solution could account for the small difference. In fact, when both were then injected as dilute solutions, the difference in retention times diminished to insignificance.

Synthesis of 49 was much less straightforward. Alkylation of 1,2,4-trimethylcyclopenten-3-one, prepared from 2-butyl methacrylate in the same manner as 48 did not yield 49, although the actual structure of the product was not determined. The procedure of Bardhan and Adhya (163) for the preparation of the saturated tetramethyl ketone was attempted, both as presented and with certain modifications, but the low yields

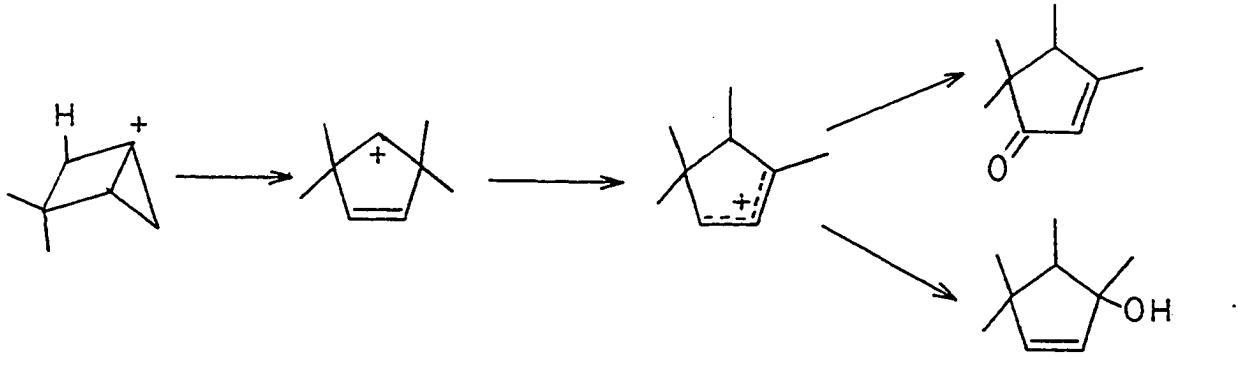
in the first two steps made it an impractical method. This precursor was finally prepared as a component of a mixture by reducing isophorone to the alcohol, oxidizing it with nitric acid to a mixture of adipic acids, followed by esterification, Dieckmann cyclization, alkylation with methyl iodide, and decarboxylation. Bromination of this ketone mixture with NBS, and dehydrobromination with triethylamine yielded 49 as one component of a mixture, and separation was carried out by preparative vpc.

The method of separation suggested that 49 was not one of the electrolysis products, since the vpc retention time was quite different from that of the electrolysis mixture. The nmr spectrum was similar to that of 48, but with slightly different chemical shifts and the two olefinic methyls and the ring methylene showed considerably more long-range coupling. Comparison of this spectrum with that of the electrolysis product mixture also indicated that this compound was not one of the products. The chemical shift position of the ring methylene in 49 did not match any resonance in the spectrum of the electrolysis products.

IR, UV, and mass spectra were recorded on 49, all of which were consistent with the assigned structure. The IR spectrum showed bands at 1700 and 1655 cm^{-1}, while the UV spectrum showed a λ_{max} at 235 mμ with an extinction coefficient of 10,000. The mass spectrum exhibited a molecule ion at m/e 138, the base

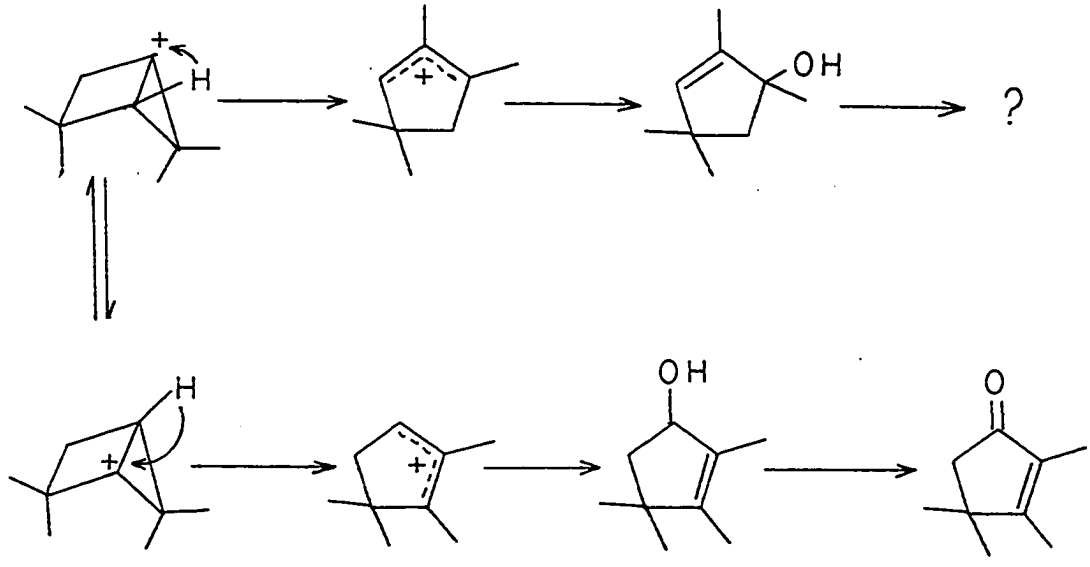
peak at m/e 123, and other major fragments at m/e 109, 95, 94, 93, 91, 81, 79, 77, 67, 57, and 55.

With the failure of 49 to match the electrolysis products, and the apparent match with 48, it was apparent that neither of the two mechanisms discussed for the dimethyl acid oxidation would explain the products from the tetramethyl acid oxidation. The presence of the vicinal methyl groups in the electrolysis product demands a methyl migration at some stage in the reaction, the straightforward 5-1 methyl migration is ruled out by the position of the methyl groups in the product. The fact that the four methyl groups are apparently on three adjacent carbon atoms means that the methyl which migrates must move to the carbon which was originally the unsubstituted bridgehead carbon. A positive charge at this position could be brought about by a 2-1 hydrogen migration, followed by ring opening to give a symmetrical unconjugated ion. Migration of a methyl group would then give a conjugated ion with proper methyl substitution, but the site of hydroxylation of the cation system makes explanation of the observed product very difficult.



Attack of solvent at the neopentyl end of the system (not seen in the oxidation of the dimethyl acid) would eventually yield a ketone with an olefinic hydrogen, while attack at the opposite end would produce a tertiary alcohol with two olefinic protons which could not give a ketone.

A second process for putting a charge in the proper position involves an unlikely 4-1 hydrogen migration, from one bridgehead to the other. Just why this might occur is unknown, but perhaps the hydrogen equilibrates rapidly between the bridgehead positions before ring opening occurs. Migration of the methyl group from C-5 to C-4 would then give an



allylic ion which could easily give the observed product. Presumably 5-1 migration could also occur, but in this system, the only secondary center in the allylic ion is a neopentyl position,

possibly too sterically hindered for solvent attack. Attack at the opposite end of the allylic ion would give a tertiary alcohol, which could not give rise to a ketone, and might then be oxidized to fragments too volatile to be retained in the reaction flask. It is interesting to note that migration of a C-5 hydrogen to either bridgehead position in the oxidation of the dimethyl acid would give the same set of products.

In summary, it is not possible from the available data to determine the mechanism for formation of the cyclopentenones formed in these oxidation reactions. From the poor yield in the oxidation of the tetramethyl acid, it is apparent that blocking the 5 position hinders the reaction considerably, and that this rearrangement quite probably proceeds via a different mechanism than for the dimethyl acid. Generation of the cation in another manner, in which the product alcohols are stable, allowing the use of deuterium labeling would provide much valuable information concerning these possible mechanisms. In view of the fact that other 1-4 bond-breaking reactions in these compounds which require the migration of a hydrogen usually involve the C-5 hydrogens, (as in pyrolysis), that mode of reaction seems more likely than the alternative which requires two hydrogen migrations.

Since the electrolytic oxidation of carboxylate anions involves a radical species at least transiently, it was necessary to examine the behavior of the bridgehead radical of bicyclopentane to determine whether or not the oxidation

products could possibly arise from the radical as an intermediate rather than the carbonium ion. This was expected to be highly unlikely, since radical rearrangements involving hydrogen or alkyl migrations are virtually unknown (141), but the great driving force toward ring expansion in bicyclopentanes might possibly provide an example of a radical rearrangement.

The most consistent method of generating the radical would be to use the normal Kolbe electrolysis: oxidation at platinum electrodes. When this oxidation was attempted, however, no neutral products were isolated. After carrying out the electrolysis for 10 hours at 100 volts, 60% of the starting acid was recovered, with apparently no production of neutral products.

With the failure to obtain meaningful results from the Kolbe electrolysis, it was necessary to find some other method of generating this radical. Since the behavior of radicals is essentially independent of their mode of formation or reaction media (with certain exceptions (141)), this should not affect the behavior of the radical to a very large extent. It was hoped that pyrolysis of the nitrite ester of the tertiary alcohol 41 would lead to β-cleavage of the alkoxy radical to yield acetone and the bridgehead radical, but the only observed product was the starting alcohol 41. The difficulty in preparing the acid chloride of 3,3-dimethylbicyclopentane-1-carboxylic acid made its use in preparing radical precursors such as the t-butyl perester very unattractive. However, the

procedure of Staab (122, 123) for preparing peresters and peroxides from acids via the imidazole amide provided a convenient and very mild synthesis of the required precursor. Treatment of the bridgehead acid with 1,1'-carbonyldiimidazole and aqueous hydrogen peroxide as described earlier yielded the diacyl peroxide. Pyrolysis of the peroxide was carried out in cumene in a sealed tube at 90° for 16 hours. Analysis of the product solution by vpc showed the presence of four components besides cumene. Comparison with a sample of the cumene used as solvent in the reaction showed that one of these was due to an impurity in the solvent. Other comparisons identified two more components as diethyl ether (presumably from rinsing the tube and insufficient drying before pyrolysis) and tetrahydrofuran (solvent for the preparation of the diacyl peroxide). The remaining component did not match any common laboratory solvent, and was collected for spectral analysis. The nmr spectrum was complicated by the presence of cumene, apparently due to tailing of the peak during collecting and an insufficiently long period of time between injections, but the major feature of the spectrum was the presence of two methyl singlets separated by 0.5 ppm at 0.77 and 1.28δ. The mass spectrum was also complicated by the cumene, but the region from m/e 90 to 100 was free of cumene ions and showed the presence of ions at m/e 96 and 95, which could correspond to the M^+ and M-1 ions of 2,2-dimethylbicyclopentane.

In order to allow the radical more time to rearrange before being trapped by solvent, the pyrolysis was carried out in perfluorobenzene. The nmr spectrum of the crude pyrolysate showed considerable aliphatic hash with no distinguishing features, but there was no indication of olefinic proton resonances. The solution was distilled at atmospheric pressure to separate the volatile material and solvent from the non-volatile tars. Although the sample was very dilute, the nmr spectrum showed the same major feature as did the spectrum from the pyrolysis in cumene: two singlets in the methyl region at 0.73 and 1.25δ.

Photolysis of the diacyl peroxide in cumene using a high pressure mercury arc lamp and pyrex apparatus yielded a somewhat more complex reaction mixture. The product from the pyrolysis was present, as was a new product with approximately twice the retention time of the pyrolysis product. The two were collected together and submitted for a mass spectral analysis. Definite ions were present at m/e 96 and 95. The 96 peak increased in intensity with respect to the 95 ion at low electron energy which indicated that it was a molecular ion. Also present in the spectrum ionized with 16 ev electrons was a very small peak at m/e 190, possibly due to some hydrocarbon dimer.

These three separate experiments perhaps do not conclusively prove that the bridgehead radical yields only 2,2-dimethylbicyclopentane as the product, but this would be the expected

behavior of an alkyl radical. The fact that in no case was any detectable amount of olefin formed, however, demonstrates that the radical plays no major part in the production of the products found in the electrolysis experiments.

In conjunction with these experiments dealing with reactive intermediates at the bridgehead position of the bicyclopentane ring system, the anion should be an interesting species to examine. Since the acidity of cyclopropyl hydrogens is known to be reasonably high (164), and since the incorporation of the cyclopropane ring into a fused ring system is known to increase this acidity (165, 166), it might be expected that an anion at the bridgehead position in bicyclopentane would be reasonably stable as compared to most hydrocarbon anions. Gassman has reported that treatment of bicyclopentane with amylsodium for several days, followed by carbonation yielded a mixture of the 1- and 5-carboxylic acids (42). Although the bridgehead position should be the most acidic, the 5-carboxylic acid predominated.

It has long been known that non-enolizable ketones can be cleaved by strong base to yield a carboxylic acid and a hydrocarbon fragment (167). This Haller-Bauer reaction was originally thought not to involve a carbanion, since water was necessary for the reaction to proceed (168). Although the normal base used in this reaction is sodium amide, Gassman has recently reported that potassium t-butoxide will cleave non-enolizable ketones and has studied the mechanism of the

reaction (169). He showed that a carbanion is involved, and that cleavage is in the direction which gives the most stable carbanion.

Since 1-benzoyl-3,3-dimethylbicyclopentane was available by reaction of phenyllithium with the bridgehead carboxylic acid, it was thought that the cleavage of this non-enolizable ketone might provide some interesting data concerning the relative stability of the bicyclopentane anion *vs* the phenyl anion. Since the estimated pK_a's of a cyclopropyl hydrogen and the hydrogen on an sp^2 carbon are 39 and 36.5, respectively, (170) based on the amount of s-character of the carbon-hydrogen bond, it might be expected that the acidities of bicyclopentane and benzene should be even closer, with bicyclopentane perhaps more acidic.

Cleavage of 1-benzoyl-3,3-dimethylbicyclopentane was carried out in DMSO using potassium *t*-butoxide according to the procedure of Gassman. When the reaction was worked up, and the carboxylic acid fragment isolated, it was found to be entirely benzoic acid, with no trace of the bicyclopentane acid. This would indicate that the bicyclopentane anion is more stable than the phenyl anion. Attempts to determine the fate of the bicyclic portion of the ketone were unsuccessful.

Mass Spectra of Bicyclo[2.1.0]pentanes

Djerassi and co-workers in 140 have recently studied the mass spectral behavior of bornylamine and N,N-dimethylbornylamine, in which they found that the bicyclic hydrocarbon skeleton exerted an abnormally powerful fragmentation-directing ability, to the extent that the fragmentation pattern did not differ extensively from that of camphor and that the base peak was the bicyclic hydrocarbon ion. In the bicyclopentane series, this also seems to be true, as most of the compounds examined show a base peak corresponding to the hydrocarbon nucleus, and the fragmentation patterns of most of the compounds are similar.

A number of 1-carbomethoxy substituted bicyclopentanes with varying degrees of methyl substitution at C-3 and C-5 have been examined. The simplest compound, the parent bridgehead ester with no methyl substituents (15a), showed a base peak at m/e 67 ($C_5H_7^+$), corresponding to the bicyclopentyl (or cyclopentenyl) cation, with other fragment ions at m/e 66, 65, and 41. A metastable is seen for the transition m/e 67 → m/e 65. With the introduction of a methyl group at C-3 either exo- or endo- 15b or 15c, the base peak is shifted by 14 mass units to m/e 81. Ions at m/e 80 and 79 are also present, with a metastable for the loss of two hydrogen atoms or a hydrogen molecule from the m/e 81 ion, followed in this case by another metastable loss of two units to m/e 77. Other major fragments are observed at m/e 59, 53, 41, and 39.

The addition of two methyl groups at C-3 causes no marked change in the fragmentation modes. The base peak is again shifted by 14 mass units, to m/e 95, with a metastable loss of two hydrogens to 93, again followed by another metastable loss of two hydrogens to 91. Major fragment ions occur at m/e 139, 123, 79, 67, 55, 43, and 41, with metastables seen for the transitions 154 → 139, 154 → 95, 123 → 95, and 95 → 67.

With the introduction of methyl groups at C-5 a change in the base peak in the spectrum occurs. Ester 15e gives a base peak of m/e 93, corresponding to loss of 16 mass units in addition to the carbomethoxy group. The spectrum of the endo-isomer 15f was very similar, also showing the base peak at m/e 93. Both compounds formed fragment ions at m/e 109 with intensities of 50-55% due to cleavage of the carbomethoxy group. Both also showed metastable transitions from m/e 153 to m/e 93 and m/e 121 to m/e 93, as well as from m/e 93 to m/e 91. However, when the spectra were obtained using 16 ev electrons, an interesting difference appeared. Ester 15d (exo-C-5 methyl) exhibited the base peak at m/e 93, as in the 70 ev spectrum, with an intense fragment ion at 153 (80% of the base peak), corresponding to loss of a methyl radical from the molecule ion. In the spectrum of 15f, the ion at m/e 153 became the base peak at 16 ev, while the ion at m/e 93 diminished to 68%.

Since esters 15a-d do not show such a pronounced loss of

a carbon atom (as a methyl group) from the bicyclic skeleton, one might speculate that the methyl group at C-5 provides this extra loss in compound 15e and 15f. This loss of a methyl radical from the molecule ion to form the ion at m/e 153 is followed by the metastable loss of 60 mass units (methyl formate?) to form the ion at m/e 93. If one assumes that this extra loss of a methyl radical does come from the C-5 position, the low-energy mass spectral behavior leads to some interesting speculation. Woodward-Hoffman rules (171) predict that cyclopropyl cation ring opening should be a disrotatory process, and further, that groups cis to the leaving group should rotate inward, while groups trans to the leaving group should rotate outward. These predictions have been experimentally supported by DePuy's work with cyclopropanols, (79) and by the work of several other investigators (172, 173, 174, 175, 176). If the methyl radical at C-5 is viewed as the leaving group from the radical cation, an endo- methyl group should lead to a concerted ring opening to a planar, conjugated allyl cation. If the methyl group is in the exo- position, however, concerted ring opening would lead to a hopelessly strained trans-trans- allyl cation. DePuy and other workers have shown that exo- substituents in fused cyclopropanes of this type are quite resistant to ionization in solution (172, 173, 174, 175, 176). Since concerted ring opening could not occur in this case, the loss of the methyl radical from the exo- isomer

should be less favorable. Similar mass spectral behavior has been noted by Baird and Reese in their work with endo- and exo- 6-chlorobicyclo[3.1.0]hexanes. The endo- isomer, which should and does rearrange readily according to Woodward-Hoffman rules, exhibits a base peak at m/e 79, due to the loss of H_2Cl from the molecular ion and the spectrum as a whole is nearly identical to that of 3-chlorocyclohexane. The exo- isomer shows the base peak at m/e 67, due to the loss of CH_2Cl. It may be, however, that in this case thermal rearrangement is occurring in the mass spectrometer prior to ionization. Also, no low energy electron impact data were obtained.

The introduction of a second methyl group at C-5 causes no unexpected changes. The base peak is shifted to m/e 107, an increase of 14 mass units. Ions with an intensity of >30% of the base peak occur at m/e 167 (M-15), 150, 123 ($M-CO_2CH_3$), 81, 79, 76, 73, 55, 43, and 41. No significant differences were noted when the spectrum was recorded at 16 ev. The ions above m/e 107 were more intense than in the 70 ev spectrum, while those below m/e 107 were less intense. Using 12 ev electrons, the molecule ion was the base peak, and only five other ions had an intensity of 20%: m/e 167, 154, 150, 123, and 107.

Reduction of the ester function at C-1 to an alcohol causes little change in the spectrum below m/e 95, which remains the base peak. Metastable transitions from m/e 95 to 93 and 93 to

91 are present, as noted in the ester. The intensity of the base peak is less as compared to the other peaks in the spectrum, but all major peaks present in the spectrum of the ester (below m/e 95) are present. Reduction of the ester with lithium aluminum deuteride rather than hydride caused little change in the mass spectrum of the resulting alcohol. The molecule ion was shifted two mass units to m/e 128, as was the peak due to loss of methyl (121 → 123). The ions due to loss of water showed that part of the loss was due to loss of HOD, since the M-19 ion was larger with respect to the M-18 than in the unlabeled compound. No changes were seen in the spectrum below m/e 95, as would be expected, since cleavage of the C-1 substituent has removed all of the label.

The introduction of more powerful fragmentation-directing substituents at C-1 has the effect of changing the base peak, but generally the fragmentation pattern of the bicyclic ring is not markedly affected. The spectrum 1-acetyl-3,3-dimethylbicyclo[2.1.0]pentane (17) shows the expected base peak due to retention of the charge on the CH_3CO fragment when cleavage occurs, but the m/e 95 peak is moderately intense (64%), and becomes the base peak at 16 ev. The ions at m/e 93 and 91 are less intense than in the spectrum of the ester or the alcohol, but both are present, and the metastable peaks for the transitions are also present, as is the ion at m/e 67 and the metastable for its formation from the m/e 95 ion.

The bridgehead carbamate 43 also exhibits a base peak due to a process other than cleavage of the C-1 functionality, but the peak at m/e 95 is very intense (92%). The base peak in the spectrum arises from a typical ethyl carbamate rearrangement (140), i.e., loss of a methyl radical and CO_2 to yield an ion at m/e 124.

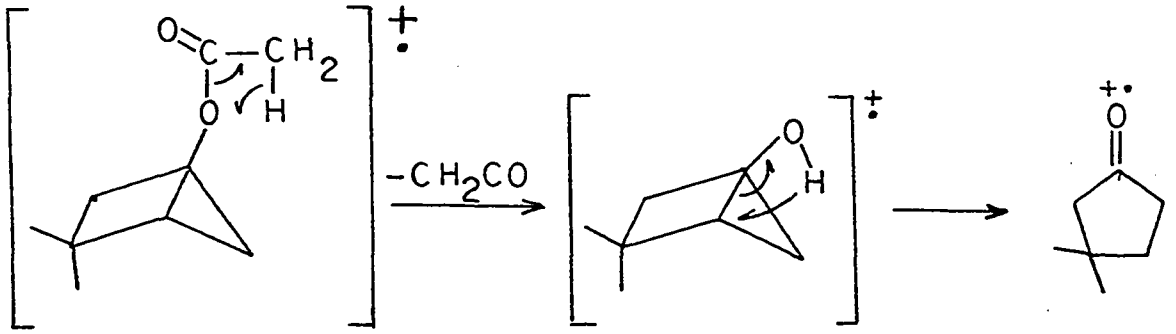
The 1-cyano compound (17) is an exception to the general fragmentation pattern discussed thus far. The base peak at m/e 120 arises from the loss of 1 hydrogen from a moderately intense molecule ion (35%) at 121. The ion at m/e 95 is of very low intensity, only 1.1% of the base peak, although 93 and 91 are both present, with a metastable for 93 → 91. Other intense ions in the spectrum appear at m/e 107 and 79. Metastable ions are present for the transitions 106 → 79 (-HCN) and 94 → 79 ($-CH_3\cdot$).

The lack of α-cleavage in this aliphatic nitrile is consistent with the behavior of other aliphatic nitriles which have been studied, some in considerable detail (140). In general, these compounds show very weak molecule ions, with more pronounced M + 1 (pressure dependent) and M-1 peaks. The usual mode of decomposition involves loss of a hydrogen atom or an alkyl fragment from the molecule ion to give an even electron ion, occasionally accompanied by loss of HCN. In general, loss of HCN is not an important process in these compounds.

The bicyclic nitrile does deviate in some respects from

the general pattern reported by McLafferty (177) for aliphatic nitriles. The intensity of the molecule ion is very high (35% of the base peak) as compared to the usually minute molecule ion of these compounds, and the occurrence of the base peak at M-1 in a nitrile without an α-hydrogen is unusual.

The bridgehead acetate also deviates from the general fragmentation pattern, but in a manner that is easily rationalized. The base peak at m/e 43 (CH_3CO^+) is by far the most intense ion in the spectrum, with the second most intense ion at m/e 97 amounting to only 7.5%. A comparatively intense ion is seen at m/e 112, corresponding to the loss of ketene from the molecule ion. From this point on, the spectrum resembles that of 3,3-dimethylcyclopentanone more than it does any of the previously examined bicyclic compounds. Loss of ketene with transfer of a hydrogen from the acetyl group to the remaining oxygen atom, followed by homoketonization would yield the molecule ion of the cyclopentanone.



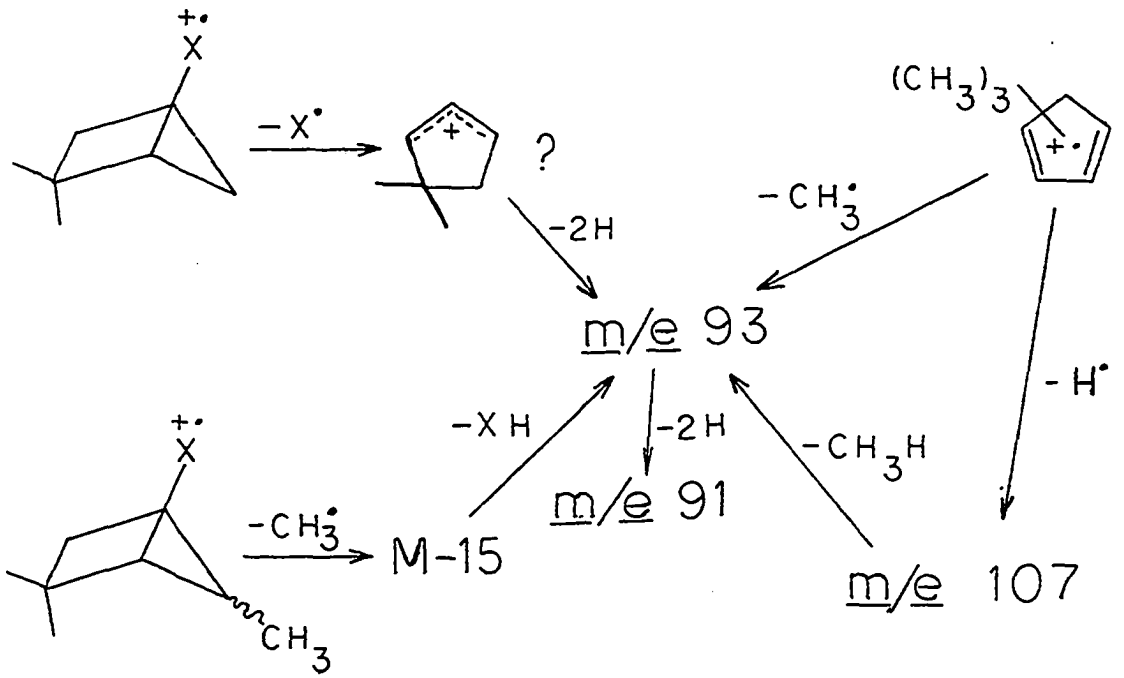
With the exceptions noted above, the mass spectral behavior of these bicyclic compounds is strikingly similar to the

behavior of methylated cyclopentadienes (140). Trimethylcyclopentadiene undergoes the loss of a methyl radical as a main process to form an ion at m/e 93, which then suffers either the loss of two hydrogens to m/e 91 or the loss of methane to m/e 77. A second process begins with the loss of one hydrogen (m/e 107), followed by the loss of methane to produce m/e 93, ethylene to produce m/e 79, or two hydrogens to form m/e 105, followed by acetylene loss to produce m/e 79. The m/e 79 ion can lose two hydrogens to form m/e 77 followed by another loss of acetylene to form m/e 51, or alternatively lose ethylene to form m/e 51 directly. Although the structures of these ions are not known, it is doubtful that they are cyclopentadienyl cations. There is some evidence that they are substituted benzenium ions, but open chain species cannot be ruled out.

The mass spectrum of 1,2,5,5-tetramethylcyclopenten-3-one is also very similar. The molecule ion at m/e 138 shows consecutive metastable losses of 15, 28, 2, and 2 mass units to give rise to ions at m/e 123, 95, 93, and 91. There is also a metastable loss of 28 (presumably ethylene) from the m/e 95 ion to give an ion at 67. As with previously discussed compounds, peaks are also present at m/e 83, 81, 79, 77, 55, 53, 43, and 41.

In view of the similarity between these spectra, it is likely that one pathway of decomposition of these bicyclic

compounds involves cleavage of the C-1 substituent to yield a cyclic allylic ion, which then loses two hydrogens to give the same ion that is derived from the methylated cyclopentadienes.



The ions at m/e 79 and lower weights are generally more intense with respect to the m/e 93 ion in the bicyclic compounds than in the trimethylcyclopentadiene due to the fact that they are also formed in a second pathway involving initial loss of a methyl radical, followed by the loss of XH to give an m/e 79 ion.

SUGGESTIONS FOR FURTHER RESEARCH

The study of the chemistry of the bicyclopentane ring system was hampered for several years by the unavailability of a large variety of substituted compounds. However, recent advances in the synthesis of substituted bicyclopentanes, including this work, have largely removed this barrier to the study of the ring system. A number of interesting possibilities have been touched on in the course of this work.

The synthetic procedure itself should be examined more thoroughly. Although the bridgehead ester function can be converted into a wide variety of functional groups, the addition of diazo compounds to other olefins shoul be examined more closely. The fact that diazomethane can be reacted with other strained carbon-carbon double bonds (112, 113) would seem to indicate that the presence of an electron-withdrawing group at C-1 is not an absolute necessity. Diazomethane should form a pyrazoline from such compounds as phenylcyclobutene, halocyclobutenes, and cyclobutenyl acetate. The reaction of diazoalkanes with cyclobutene double bonds should be more rapid than with unstrained bonds, raising the possibility of selectively reacting the intermal bond of methylenecyclobutene without reaction at the external bond Ozonolysis of the resulting methylenebicyclopentane could provide a route to a bicyclopentanone.

In addition to establishing the scope of the cyclo

addition of diazoalkanes to cyclobutenes, the full utility of benzophenone sensitization of pyrazoline decomposition should be examined. Although it raises the yield significantly in the cases of the bridgehead-substituted esters and nitriles, the presence of benzophenone appears to be detrimental in the case of the methyl ketone.

Although the literature does not report many syntheses of phenylcyclobutenes (178, 179, 180), the decomposition of the tosylhydrazones of various substituted phenyl cyclopropyl ketones should make available a number of substituted phenyl cyclobutenes. Alternatively, addition of phenyl Grignards to cyclobutanone, followed by dehydration (180) should supply more such compounds. Successful conversion of these compounds to bicyclopentanes would provide compounds for a study of the effect of substituents on the rate of pyrolysis of 1-substituted bicyclopentanes. Insight into this effect could also be gained by studying the kinetics of the pyrolysis of bridgehead esters, nitriles, and other bridgehead substituted compounds. The effect of two bridgehead substituents could be examined by pyrolyzing 1,4-dicarbomethoxy and 1,4-dicyanobicyclopentanes. Although one attempt at the synthesis of 1,2-dicarbomethoxy-3,3-dimethylcyclobutene was unsuccessful in this work, other syntheses of this and other 1,2-dicarbomethoxy compounds have been reported in the literature (117, 118, 119, 120, 121). A synthesis of the dicyano compound has

been patented by Standard Oil Company of Ohio (116), and although attempts to obtain a sample of this compound from them were unsuccessful, the compound presumably could be prepared in the laboratory by this or an alternate procedure.

It would also be informative to study the pyrolysis of endo- and exo-3-methyl-1-carbomethoxybicyclopentane. If steric crowding by the C-3 methyl group is exerting an influence on the rate of pyrolysis of 1-carbomethoxy-3,3-dimethylbicyclopentane, it should be clearly reflected in the rate difference between these two isomers.

The preparation of a number of halogenated bicyclopentanes should be possible using these methods, and should provide a number of interesting compounds. Bartlett (181) has reported the synthesis of 2-chloro-3,3-difluorocyclobutene-1-carboxylic acid. The chlorine group should be removable via trialkyltin hydride reduction, and subsequent reaction with diazomethane and photolysis should yield the 3,3-difluorobicyclopentane ester. A comparison of the chemistry of this compound with the chemistry of the non-halogenated compound should be interesting: for example, the acid-catalyzed rearrangement of the carbinyl alcohol containing the 3,3-difluoro group, if it followed the route of the non-fluorinated compound, would generate a cation α to the geminal difluoro group. The powerful electron-withdrawing effect of the fluorines might force the rearrangement to proceed in a different manner.

Although the nmr spectra of five-spin systems can be very complex and difficult to interpret, the nmr spectra of these compounds appear intriguing. By examining the nmr spectra of more highly substituted compounds first, one might be able to gain information which would simplify the interpretation of the more complex systems. Specifically, the spectrum of 1-cyano-3,3-exo-5-trimethyl bicyclopentane should be examined, as should that of 1-cyano-3,3,5,5-tetramethylbicyclopentane. The introduction of fluorine substituents on the cyclobutane ring might well make the proton spectrum too complex for analysis, but examination of the fluorine spectrum could provide valuable information concerning long-range splitting in the bicyclopentane ring system.

The hydrolysis of geminal difluorides to ketones by strong acid is a well known reaction (182). Whether the bicyclic nucleus of 1-carbomethoxy-3,3-difluorobicyclopentane could withstand such treatment is perhaps doubtful, but if the compound were in hand from other studies, this should be worth an attempt as a preparation of a bicyclopentanone.

Although an attempt to isomerize 2,3-dicarbomethoxy-4,4-dimethylcyclobutene to the 1,2-dicarbomethoxy isomer failed, the 2,3-dicarboxylate could be of interest itself. Reaction with diazomethane and photolysis should lead to a mixture of cis- and trans-1,2-dicarbomethoxybicyclopentanes, which could be separated by formation of the anhydride from the cis- compound. If selective reduction of the carboxyl function at

C-2 could be achieved, the generation of a 2-carbinyl cation should provide some interesting chemistry.

Since the use of easily placed isotopic labels in the electrolytic oxidation of the bridgehead carboxylic acid cannot provide any useful information due to further oxidation of products and subsequent exchange of the label, the generation of the bridgehead cation by another procedure would be most attractive. Although the isolation of a bridgehead alcohol seems impossible, it might be feasible to cleave 1-acetyl-3,3-dimethylbicyclopentane to the alkoxide ion, and, by immediate treatment with phosgene convert it to a chlorocarbonate ester. Treatment of this compound with silver ion should cause the loss of carbon dioxide and formation of the bridgehead cation in a non-oxidative process which would lead to retention of the label in the molecule.

If another method of generating the cation cannot be found, conditions for the electrolysis might be found such that the first formed product would not be an alcohol, but a specie which would be stable to further oxidation. A trapping experiment using a very good nucleophile might give such an alternative product.

Although the results obtained in this study indicate that the 1-bicyclopentyl cation is not involved in the rearrangement of the spiropentyl cation, the different methods used to generate the cations in these two experiments do not allow a definite direct comparison. It is conceivable that the 1-bicyclopentyl

cation generated by electrolysis of the acid is more energetic than the spiropentyl cation generated by deamination, and that the bicyclopentyl ion could rearrange through a methylene-cyclobutyl cation, undergoing ring expansion to a vinyl cation and then isomerizing to the 3-cyclopentenyl cation. In order to make a definite comparison, the electrolysis of spiropentane-carboxylic acid should be carried out. This compound has been prepared as a precursor to spiropentylamine in both deamination studies cited earlier (80, 81). Similarly, it would be informative to examine the behavior of the 2-methylene cyclobutyl cation generated by electrolysis. The requisite 2-methylene-cyclobutane carboxylic acid should be available by suitable transformations on t-butyl-2-hydroxymethylcyclobutane-1-carboxylate, as prepared by Gassman and Mansfield (42). Acetate or xanthate pyrolysis or dehydration of the alcohol, followed by saponification of the ester with a weak base should give the desired acid. Alternatively, the lactone from which the hydroxy-ester was prepared could be hydrolyzed with anhydrous HBr, and the resulting acid dehydrobrominated with a suitable reagent such as diazabicyclo[4.3.0]non-5-ene.

The electrolysis of some homologous bicyclic acids should also be examined, and if possible, compared to the deamination of the corresponding amines. It should be possible to prepare the bridgehead amines of bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane and compare the deamination and electrol-

ysis products, and to compare the electrolysis products with those from the bicyclopentane system.

EXPERIMENTAL

General

All melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian Model A-60 spectrometer, in carbon tetrachloride solution with tetramethylsilane as an internal standard, unless otherwise specified. Chemical shifts are reported in δ units, with the number in parenthesis indicating the number of protons causing the signal. The letter immediately following the parenthesis designates the multiplicity of the signal: s, singlet; d, doublet; t, triplet; q, quartet; m, unresolved multiplet. Infrared spectra were obtained on a Perkin-Elmer 21 spectrometer, and mass spectra on an Atlas CH-4 spectrometer. All irradiations were carried out in Pyrex apparatus, unless otherwise specified, using a Hanovia type 673A 450 watt high-pressure mercury arc lamp as a light source.

1-Carbomethoxy-2,3-diaza-6,6-dimethylbicyclo[3.2.0]hept-2-ene (37)

An ether solution of 3,3-dimethylcyclobutene carboxylic acid (5.0 g, 40 mmoles) prepared by the method of Brannock, et al. (101), was treated overnight with a 4 molar excess of ethereal diazomethane at room temperature. The excess diazomethane was removed by heating the solution on a hot plate until colorless (in a fume hood). Removal of solvent under reduced pressure yielded 6.7 g of a viscous yellow oil which

was identified as the pyrazoline ester by its nmr spectrum (0.80 (3), s; 1.21 (3), s; 3.61 (3), s; 4.1-5.0 (2), AB of ABX, J_{AB} = 19 cps; 1.6-2.7 (3), including X of the ABX, m). The material appeared to be pure by nmr and so was used without further purification. The yield was 93%.

Irradiation of 37 in acetone

The pyrazoline ester 37 (3.0 g, 16.5 mmoles) was dissolved in acetone and irradiated for 4 hr, with monitoring of nitrogen evolution, which was complete at that time. The solvent was removed by a rotary evaporator, leaving a sweet-smelling yellow oil, which was distilled under reduced pressure (bp 36°C/1.4 mm), yielding 0.9 g of a colorless liquid. Analysis of this material by vpc (6 ft x 0.375 in Carbowax 20M column) showed the presence of 6 products, one of which accounted for 87% of the sample, with the other 5 peaks accounting for less than 5% each. The major product was collected for spectral and chemical analysis.

The material had a mass spectral molecular weight of 154, with major fragment ions at m/e 123 and 95. The IR spectrum exhibited a carbonyl stretching frequency of 1705 cm^{-1}, and showed no indication of unsaturation. The nmr spectrum was consistent with the expected 1-carbomethoxy-3,3-dimethylbicyclo[3.1.0]pentane (15d): 0.80 (3), s; 1.22 (3), s; 3.56 (3), s; 1.0-1.7 (3), m; 1.8-2.2 (2), m. Further proof of the structure was obtained by its chemical behavior. The material was resistant to hydrogenation at atmospheric pressure with

Pd/C catalyst, but at 500 lbs pressure, using Pt/acetic acid, one mole of hydrogen was taken up to yield 1-carbomethoxy-3,3-dimethylcyclopentane, which was identical with an authentic sample. The yield was 31%.

Since the expected olefinic isomers of 15d were not present in the product, and irradiation of cyclobutene esters in acetone was found to involve a photoreduction of these esters of the minor products were suspected to be cis- and trans- 1-carbomethoxy-2,3,3-trimethylcyclobutane and 2,5-hexanedione. Irradiation of the pyrazoline in benzene, followed by hydrogenation of the reaction products at atmospheric pressure (Pd/C catalyst) provided a mixture of 15d and the cis- and trans-cyclobutane esters. Comparison of the retention times of this mixture with that obtained from the acetone irradiation showed two small peaks with the same vpc retention times as the 2 cyclobutane esters. Comparison of the vpc retention time of 2,5-hexanedione also showed its presence in the acetone irradiation.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.099; H, 9.15. Found: C, 70.22; H, 9.01. (Spang Microanalytical Laboratories).

Irradiation of 37 in benzene

The procedure was the same as above except that the solvent was benzene rather than acetone. Distillation at reduced pressure yielded 2.31 g of colorless liquid. Vpc analysis (10 ft x 0.25 in LAC-446 column) showed components present, 2 major and 2 minor. One major component had the same vpc

retention time as 15d, prepared above, and upon vpc collection, showed an identical nmr spectrum. One minor product was identified by vpc retention time comparison as 1-carbomethoxy-3,3-dimethylcyclobutene. The 2 remaining products were collected for spectral analysis. Both had a mass spectral molecular weight of 154, indicating that they were isomeric with the bicyclic ester 15d. The one present in the larger amount showed an IR carbonyl stretching frequency of 1740 cm^{-1}, and a band at 890 cm^{-1}, characteristic of a terminal methylene. The nmr spectrum (1.18 (6), s, perturbed; 4.83 (2), d, further split by allylic coupling; 2.0 (2), AB of ABX; (4), s + X of ABX) also indicated the presence of a terminal methylene, and confirmed the structure as 1-carbomethoxy-2-methylene-3,3-dimethylcyclobutane. The less abundant isomer showed a carbonyl frequency of 1720 cm^{-1} and a C=C band at 1665 cm^{-1}, indicating a conjugated ester. The nmr spectrum (1.12 (6), s; 1.85 (3), t, J = 2.0 cps; 2.28 (2), q, J = 2.0 cps; 3.62 (3), s, showed an olefinic methyl group with long-range coupling. This product was assigned the structure 1-carbomethoxy-2,3,3-trimethylcyclobutene. The ratio of products in the order discussed above, was 1.0:0.28:0.9:0.18. The yield of bicyclic ester was 40%.

Irradiation of 37 in benzene with benzophenone

The procedure was the same as above, except that 3.0 g of benzophenone was added to the solution prior to irradiation.

Distillation of the crude product yielded 1.78 g of product, which vpc analysis (Carbowax column) and nmr integration showed to be >93% 15d. The yield was 67%.

Irradiation of 1-carbomethoxy-3,3-dimethylcyclobutene (36b) in acetone

The cyclobutene ester (5.0 g, 35.6 mmoles, prepared by esterification of the acid with diazomethane) was dissolved in 250 ml of acetone and irradiated for 4 hr. Removal of solvent through a vigreux column, followed by a crude bulb-to-bulb distillation yielded 2.0 g of distillate and considerable high-boiling residue. Vpc analysis of the distillate (6 ft x 0.25 in butanediol succinate column) showed the presence of 4 components, one of which was the starting ester. Of the remaining components, one was present in a very small amount and was not investigated. The 2 remaining products were collected for spectral characterization. The product with the shorter retention time exhibited a mass spectrum which had a molecule ion at m/e 142 and major fragment ions at m/e 87, 56, and 55; a carbonyl band at 1735 cm^{-1} in the IR spectrum; and an nmr spectrum consistent with a cyclobutane carboxylic ester (1.09, (3), s; 1.15 (3), s; 3.58 (3), s; 1.80-2.10 (4), m; 2.8-3.4 (1), 5-line pattern). The material was found to be identical to authentic sample prepared by hydrogenation of 36b. The second product had very simple spectra: MS, molecule ion at m/e 114, major fragments at 99, 71, 57, and 43; IR, ν_{CO} 1720 cm^{-1}; nmr, 2.10 (3), s, and 2.57 (2), s. On the basis of this

spectral data, the product was assigned the structure of 2,5-hexanedione. Thus, the net result of the irradiation of 36b in acetone is the transfer of one hydrogen from each of 2 molecules of acetone to the double bond of the ester, and the coupling of the 2 acetone fragments to form the 6 carbon diketone.

Pyrolysis of 37

The pyrazoline ester 37 (0.5 g, 2.75 mmoles) was dissolved in 2 ml of benzene and passed through a vertical pyrolysis column 1 ft long, packed with glass helices and heated at 280°C. The nitrogen flow rate was 45 ml/min, and the products were trapped in a liquid nitrogen-cooled collector. Vpc analysis showed the presence of 3 major products and 2 minor products. Relative amounts could not be determined because of peak overlap, but the major products had retention times corresponding to those of the major products from the photolysis in benzene. Nmr integration gave a ratio of bicyclic ester: α,β-unsaturated ester: β,γ-unsaturated ester of 5:6:3.5. The minor products were not identified, but were apparently responsible for several small olefinic proton resonances in the nmr spectrum.

1-Carbomethoxy-3,3-dimethyl-5,5-dideuteriobicyclopentane

Dideuteriodiazomethane was prepared by a modification of the procedure of Robinson and McCarty (183). An ether solution of diazomethane was prepared by the base catalyzed decomposition of 5.0 g of nitrosomethylurea. A solution of NaOD in

D_2O was prepared by the addition of 15 g of sodium to 40 ml of D_2O (the addition was carried out slowly, with cooling, under nitrogen). The two solutions were mixed together and stirred rapidly for 1 1/2 hr. The reaction was monitored by periodically esterifying a few mg of benzoic acid with the diazomethane solution and integrating the nmr spectrum. At the end of 90 min, the integral indicated that the diazomethane had incorporated 57% deuterium, either as mono- or dideuterio compound.

The deuterated diazomethane was reacted with 2.0 g of 1-carbomethoxy-3,3-dimethylcyclobutene as described earlier, and irradiated in benzene in the presence of benzophenone. The mass spectrum of the labeled ester showed 35.8% d_2, 29.8% d_1, and 34.4% d_0, for an average incorporation of 49.3%.

Diazoethane

Diazoethane was prepared from N-ethyl-N-nitrosourea. The procedure used was that of Vogel (184) for nitrosomethylurea, substituting ethylamine hydrochloride for methylamine hydrochloride in the urea synthesis.

2-Diazopropane

Diazopropane was prepared by the method of Day, et al., (185) with the exception that flash distillation was not found to be necessary if the material was used immediately. A normal experiment involved the oxidation of 30 g of acetone hydrazone with 120 g of mercuric oxide, to provide diazopropane for reaction with 10 g of 1-carbomethoxy-3,3-dimethylcyclobutene.

1-Carbomethoxybicyclo[2.1.0]pentane (15a)

Cyclobutenecarboxylic acid (3.4 g, 34.6 mmoles, prepared by the method of Campbell and Rydon (102)) was treated with a 4 molar excess of diazomethane for 22 hr at room temperature. The excess diazomethane was removed by evaporation of the ether solution on a steam bath (fume hood) until colorless. Evaporation of the remaining solvent yielded 4.2 g of crude pyrazoline. Distillation under vacuum (bp 65°/0.5 mm) yielded 1.72 g of pyrazoline, which was still not pure by nmr. The pyrazoline was dissolved in 250 ml of acetone and irradiated for 4 hr. Work-up as described earlier and distillation yielded 0.43 g of ester (bp 52°/10 mm), which was >90% pure by vpc analysis. The ester had an nmr spectrum which was identical with that reported by Gassmann (42). The yield was 31%.

1-Carbomethoxy-3-methylbicyclo[2.1.0]pentane (15b,c)

The methyl ester of 3-methylcyclobutene carboxylic acid was prepared by treatment of the acid with diazomethane (101). Distillation under reduced pressure (bp 36°/2 mm) yielded a colorless sweet-smelling liquid with a very complex nmr spectrum (1.19 (3), d; 1.9-2.3 (2), m; 2.6-3.0 (4), m; 3.64 (3), s; 6.7 (1), m). The ester (2.5 g, 20 mmoles) was treated with a 2 molar excess of diazomethane in ether to form the pyrazoline in the usual manner. The resulting exo- and endo- mixture had a complex nmr spectrum, but exhibited the expected

set of methyl doublets at 0.82δ (endo) and 1.15δ (exo), and the complex pattern from the 2 protons adjacent to the nitrogens at 4.4-4.7. Nmr integration showed that the material was reasonably pure, and methyl region indicated an exo-endo ratio of 4:1. The yield was 3.25 g, or 97%.

The pyrazoline mixture was dissolved in benzene and 3 g of benzophenone were added. The mixture was irradiated for 4 hr and worked up as described earlier. Distillation (bulb to bulb) yielded 1.68 g of colorless liquid. Vpc analysis (LAC-446 column) showed only 2 products, which were vpc collected for spectral data. The isomer with the shorter retention time had an nmr spectrum (1.0-1.4 (4), m; 1.5-2.2 (5), m; 3.58 (3), s, which had no resonances above 1.0δ, while the other isomer (0.8-1.0 (2.4), m; 1.0-2.8 (6.6), m; 3.56 (3), s, showed resonances up to 9.8δ. On the basis of the chemical shift of the methyl doublets (included in the high-field multiplet in each case) which should be shifted upfield in the endo- isomer and downfield in the exo- isomer, due to shielding effect of the cyclopropyl ring, product 1 (shortest retention time) was assigned the exo- configuration (15b) and product 2 the endo- configuration (15c). The IR spectra of the 2 isomers were very similar, as would be expected, both showing a carbonyl frequency of 1705 cm^{-1}. The mass spectra differed only in ion intensities, both showing molecule ions at m/e 140 and major fragment ions at m/e 79, 53, and 41, with the base peaks at m/e 81.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.49; H, 8.68. (Chemalytics, Inc.).

1-Carbomethoxy-3,3,5-trimethylbicyclo[2.1.0]pentane (15e)

An ether solution of 1-carbomethoxy-3,3-dimethylcyclobutene (2.5 g, 18 mmoles) was treated with a 2 molar excess of diazoethane for 2i hr at room temperature. Work-up as described earlier yielded 2.78 of a pale yellow oil. The nmr spectrum of this material (0.80 (3), s; 1.20 (3), s; 1.22 (3), d, J = 7 cps; 1.6-2.7 (3), 2q+m; 3.70 (3), s; 4.6-5.1 (1), doublet of quartets, J = 7 cps and 1.5 cps) indicated that only onf othe possible isomeric pyrazolines had been formed. The coupling between the C-4 and C-5 hydrogens of 1.5 cps was consistent with the C-5 methyl group being in the exo- position as would be expected on steric grounds. The region which had contained the AB portion of the ABX pattern in the diazomethane addition was now simply two quartets, as the C-4 proton was split by the C-4 methyl and the C-5 proton. The yield of pyrazoline was 84%.

Irradiation of the pyrazoline (2.7 g) in acetone for 4 hr yielded 2.5 g of a yellow oil. Bulb to bulb distillation yielded 0.75 g of a colorless liquid which had an nmr very similar to that of the 3,3-dimethyl compound 15d. The nmr spectrum of a vpc collected sample showed that the clean doublet of the C-4 methyl seen in the pyrazoline was not present, but a distorted doublet was present at 1.21δ. The IR spectrum

showed a carbonyl band at 1715 cm^{-1} and the mass spectrum showed a molecule ion at m/e 168.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.42. Found: C, 71.76; H, 9.55. (Chemalytics, Inc.).

When the irradiation was carried out in benzene in the presence of benzophenone, the same major product was produced, however vpc analysis (Carbowax column) showed a different set of minor products. Where the irradiation in acetone showed minor products analogous to those observed in the irradiation of 37 in acetone, irradiation in the presence of benzophenone produced one major and two minor products, neither of which was present in the acetone product mixture. Both minor products were collected for spectral analysis. One exhibited an nmr spectrum which showed it to be a monocyclic system with no olefinic protons, and was tentatively identified as 1-carbomethoxy-2-ethyl-3,3-dimethylcyclobutene. The other had an nmr spectrum very similar to that of the major product (0.91 (3), s; 1.27 (3), s; 1.34 (3), d; 1.0-1.5 (1), m; 1.6-2.2 (4), m; 3.58 (3), s), and the mass spectrum was also nearly identical at 70 ev. The strong similarities between the two compounds led to the assignment of a bicyclopentane structure with the C-5 methyl group in the endo-position for the minor product (15f).

Irradiation of 2g of pyrazoline yielded 1.07 g of distilled product, with a product ratio of 10:1:1. The yield

was 52%.

Irradiation in benzene in the absence of benzophenone yielded a more complex product mixture, in which the bicyclic ester was not the most abundant product. The most abundant product had a vpc retention time and an nmr spectrum identical with that of the monocyclic product from the sensitized irradiation, while the second most abundant product was identified by vpc retention time and spectral comparison as 15e. The remaining four minor products were not identified.

1-Carbomethoxy-3,3,5,5-tetramethylbicyclo[2.1.0]pentane (15g)

An ether solution of 2-diazopropane (generated from 30 g of acetone hydrazone) was added to a flask containing 10 g of 36b and allowed to stand until all color had disappeared. The solvent was removed on a rotary evaporator and the pyrazoline warmed (40°) under vacuum to remove the acetone azine formed from the excess diazopropane. The material was chromatographed on Silica Gel, with benzene slowly eluting the pyrazoline (1.57 g). The nmr spectrum was very complex, showing 7 singlets in the methyl region, and a small multiplet at 5.01, where the protons adjacent to nitrogen had been seen in the pyrazolines prepared previously. This situation could arise only through α addition (110) of the diazopropane to the ester. The integral and the complexity of the spectrum suggested that β-addition had also occurred to give a mixture of pyrazolines.

The pyrazoline was dissolved in 250 ml of benzene and 1.5 g of benzophenone were added. Irradiation was carried out for 4 hr, and work-up as described earlier followed by vacuum distillation (bp 48°/0.3 mm) yielded 1.02 g of a colorless liquid. The spectral data was consistent with the bicyclic structure for the ester (nmr: 0.94 (3), s; 1.21 (6), s; 1.41 (3), s; 1.67 (1), s, broadened; 1.82 (2), s, broadened; 3.60 (3), s. IR: 1720 cm^{-1}. Mass spectrum: M^+ = m/e 182, base peak = m/e 107, major fragment ions, m/e = 167, 150, 123, and 95). The 6 proton singlet at 1.21δ was due to overlap of the exo- methyl with one of the C-5 methyl groups. Saponification of the ester yielded an acid with a very similar nmr, except that it showed 2 singlets at 1.25δ, separated by 3 cps.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 9.92 (Spang Microanalytical Laboratories).

1-Cyano-3,3-dimethylbicyclo[2.1.0]pentane (16)

The preparation of 1-cyano-3,3-dimethylcyclobutene was carried out according to the procedure of Brannock, et al. (101). Treatment with diazomethane and irradiation in the presence of benzophenone was as described previously for the esters. Distillation under vacuum yielded 4.6 g of product from 6.0 g of pyrazoline (bp = 55°/1 mm), for a yield of 75%. The nmr spectrum was somewhat simpler than those obtained from the esters, and entirely consistent with the bicyclic structure (0.81 (3), s; 1.38 (5), s+m; 1.60-2.30 (3), m). The IR

spectrum exhibited a strong nitrile absorption at 2225 cm^{-1} and a gem-dimethyl doublet at 1380 cm^{-1}. The mass spectrum showed a molecule ion at m/e 121, and a base peak at m/e 120.

Anal. Calcd for $C_8H_{11}N$; C, 79.29; H, 9.15; N, 11.56. Found: C, 79.34; H, 9.16; N, 11.57 (M-H-W Laboratories).

Reaction of 1-carbomethoxy-3,3-dimethylcyclobutene with phenyldiazomethane

Phenyldiazomethane was prepared by the thermal decomposition of the sodium salt of the tosylhydrazone according to the procedure of Closs and Moss (186). The diazo compound (4.2 g) was dissolved in ether and 2.5 g of 36b were added. The reaction was allowed to stand at room temperature overnight. The excess diazo compound was destroyed by addition of formic acid, and the solution washed with aqueous sodium bicarbonate until neutral. Drying over anhydrous $MgSO_4$ and evaporation of solvent yielded 0.8 g of solid and 5.5 g of oil. Chromatography on a Silica Gel column yielded 1.15 g of material eluted with hexane (mostly stilbene) and 4.3 g of a yellow oil. The nmr spectrum of the oil showed the presence of some aromatic material in addition to the pyrazoline.

The nmr spectrum of the pyrazoline fraction showed a one proton doublet at 5.8δ with a coupling of 2.2 cycles, and a large aromatic resonance. The remainder of the nmr was not very different from the pyrazolines previously described, showing methyl singlets at 0.91 and 1.2δ; an ester methyl

singlet at 3.71δ, and a 3 proton multiplet between 1.5 and 2.7δ. It also showed a trace of methyl singlets at slightly higher field than the pyrazoline peaks, probably due to a trace of the 2-isomer.

The excess material giving rise to the extra aromatic protons could not be removed by chromatography, and apparently interfered with the photolysis, as no nitrogen evolution was seen and no bicyclic ester obtained from the irradiation in acetone.

Reaction of 1-carbomethoxy-3,3-dimethylcyclobutene with diphenyldiazomethane

Diphenyldiazomethane was prepared by oxidation of the hydrazone of benzophenone with mercuric oxide as described by Smith and Howard in Organic Syntheses (187). The diazo compound was reacted with the cyclobutene ester as described above for phenyldiazomethane. The resulting pyrazoline was formed by α-addition to the olefin, as shown by the shift of the ester methyl group (3.0δ). The geminal methyls appeared at 0.88 and 1.2, while the cyclobutane ring methylene protons appeared as an AB with the two downfield peaks split by the cross-ring methine. Again the aromatic portion of the spectrum was too large, indicating the presence of an aromatic impurity which chromatography would not remove. Again the impurity apparently interfered with the photolysis in acetone, as no nitrogen evolution was seen.

Attempted reaction of 1-carbomethoxy-3,3-dimethylcyclobutene with 9-diazofluorene

The procedure of Nenitzescu and Solomonica in Organic Syntheses (188) was followed for the preparation of 9-diazofluorene from 9-fluorenone hydrazone. The cyclobutene ester, 36b, was added to an ether solution of the diazo compound and allowed to stand at room temperature for one year. No appreciable loss of color could be detected after this time.

1-Acetyl-3,3-dimethylcyclobutene

An ether solution of 3,3-dimethylcyclobutene carboxylic acid (2.0 g, 16.1 mmoles) was placed in a flask fitted with a reflux condenser and rubber septum and flushed with nitrogen. The flask was cooled in an ice-methanol bath, and 20 ml of 1.62 M (methyllithium in ether was slowly added via a syringe through the rubber septum. The mixture was stirred with a magnetic stirrer for 45 min. A 400 ml beaker containing 150 ml of ice water was placed on the magnetic stirrer and stirred rapidly while the reaction mixture was slowly added. The ether solution was separated and washed twice with water, once with 5% sodium hydroxide solution, then with water again until neutral. The ether solution was dried over anhydrous magnesium sulfate, filtered, and the solvent removed by a rotary evaporator, yielding 1.8 g of a pale yellow, sweet-smelling liquid. The nmr spectrum showed 4 singlets; at 1.24 (6), 2.14 (3), 2.31 (2), and 6.67δ (1). The carbonyl frequency in the IR spectrum was 1675 cm^{-1}.

Anal. (As semicarbazone) Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34. Found: C, 59.43; H, 8.27. (Chemalytics, Inc.).

1-Acetyl-3,3-dimethylbicyclo[2.1.0]pentane (17)

An ether solution of 1-acetyl-3,3-dimethylcyclobutene was treated with excess ethereal diazomethane and the resultant pyrazoline irradiated in acetone as described earlier for 15d. Distillation yielded 0.66 g of crude ketone from 1.0 g of pyrazoline. A sample of the major product was collected for spectral analysis. The carbonyl band appeared at 1680 cm^{-1} in the IR spectrum. The mass spectrum had a molecule ion at m/e 138, the base peak at m/e 43, and major fragment ions at m/e 123 and 95. The nmr spectrum exhibited three singlets, at 0.85 (3), 1.23 (3), and 1.85δ (3), and an extended multiplet from 0.9 to 2.4δ (5). The yield of bicyclic ketone was 46% by vpc (Carbowax column).

A satisfactory analysis could not be obtained for the free ketone, and no derivatives could be made because of the steric hindrance of the bicyclic nucleus, so a second unambiguous synthesis was sought.

The bicyclic ester 15d was saponified by treatment with 5% potassium hydroxide solution at room temperature for 24 hr. The nmr spectrum of the acid showed essentially no change in the aliphatic region of the spectrum, but the singlet at 3.56δ had been replaced by a one proton singlet at 10.0δ. The carboxylic acid was treated with methyllithium as described

for the synthesis of 1-acetyl-3,3-dimethylcyclobutene. Treatment of 2.0 g (14 mmoles) of acid with 28 mmoles of methyllithium in ether yielded 0.97 g of a product which had identical nmr, IR and mass spectra to that obtained from the pyrazoline irradiation. The yield was 50%.

The pyrazoline irradiation was also carried out in benzene in the presence of benzophenone, however in this case the major product was not the bicyclic ketone.

1-Acetoxy-3,3-dimethylbicyclo[2.1.0]pentane

Sodium monohydrogen phosphate (2.0 g) and 1-acetyl-3,3-dimethylbicyclopentane (0.4 g) in 4 ml of methylene chloride were placed in a 25 ml flask, and 4 ml of 40% peracetic acid in acetic acid were added. The mixture was heated at reflux for 10 hr, then poured into 50 ml of a cold 10% sodium carbonate solution. This mixture was stirred for 10 min, then the organic phase was separated, dried over anhydrous magnesium sulfate, and evaporated. The reaction mixture was analyzed by vpc (Carbowax column), which showed the presence of 2 products in a 10:1 ratio. The minor product was identified by comparison of vpc retention time and spectral data as the methyl ester 15d, which could arise from migration of the methyl group rather than the bicyclopentane ring system. The major component showed a carbonyl band at 1760 cm^{-1} in the IR spectrum, as well as an ester ether linkage band at 1220 cm^{-1}. The mass spectrum showed a molecule ion at m/e

154. The nmr spectrum exhibited three singlets (3 H each) at 0.72, 1.35, and 1.90δ; and 2 multiplets, 0.8-1.2 and 1.5-2.2δ (5).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.099; H, 9.15. Found, C, 69.76; H, 9.09. (Spang Microanalytical Laboratories).

N-(3,3-dimethylbicyclo[2.1.0]pentyl) ethylcarbamate

Hydrazine hydrate (10 g, 200 mmoles) and 1-carbomethoxy-3,3-dimethylbicyclopentane (2.8 g, 20 mmole) were stirred together at room temperature for 24 hr. The mixture was extracted with 25 ml of carbon tetrachloride, and the carbon tetrachloride layer dried over anhydrous magnesium sulafe. Evaporation of the solvent yielded 2.25 g of hydrazide as a viscous white oil. The nmr spectrum showed that the bicyclic ring system was intact and that no ester remained. The N-H protons were seen as a large broad peak centered at 4.6δ.

The hydrazide was dissolved in dilute hydrochloric acid (3 ml of 37% HCl in 50 ml water) and cooled to -10° in an ice-acetone bath. Ether (50 ml) was added, followed by a solution of 1.25 g of sodium nitrite in 3 ml of water. The addition was slow, so that the temperature of the reaction mixture never rose above 10°. The reaction mixture was stirred for 10 min, then the organic phase was separated, the aqueous phase extracted with 50 ml of ether, and the 2 ether solutions combined. This material was washed with 25 ml of saturated sodium bicarbonate solution, 25 ml of water, and then dried

over anhydrous magnesium sulfate. Absolute ethanol (50 ml) was added, and the solvent distilled off through a vigreux column. When the volumn had been reduced to 20 ml, the remaining solvent was removed by a rotary evaporator yielding a mixture of a pale yellow oil and white crystals. Filtration using a minimum amount of ether separated the two materials. The oil had an nmr spectrum which showed the presence of the bicyclopentane ring system, as well as an ethyl ester triplet and quartet (1.21 and 4.05δ, respectively), and a broad 1H resonance at 5.8δ. The methyl singlets of the bicyclic ring system were separated by 0.65 ppm (0.74 and 1.35δ). The mass spectrum confirmed the structure as the bridgehead carbamate. A weak molecule ion at m/e 183 showed a loss of 59 mass units to the base peak at m/e 124, corresponding to the typical (140) loss of CO_2 and $CH_3\cdot$ in ethyl carbamates. Intense fragment ions were also seen at m/e 95 and 81. The yield was 1.6 g, 60%. Attempts to prepare an analytical sample of this material repeatedly resulted in hydrolysis to ethyl carbamate and 3,3-dimethylcyclopentane.

1-Carboethoxybicyclo[3.1.0]hexane

Cyclopentene-1-carboxylic acid was prepared by the method of Maitte (189) and esterified by heating with ethanol in the presence of a trace of sulfuric acid. The resulting 1-carboethoxycyclopentene (1.0 g, 7.15 mmoles) was treated with excess ethereal diazomethane for 18 hr. Evaporation of solvent and excess diazomethane on a steam bath yielded 1.2 g

of a mobile yellow oil. The nmr spectrum of the material showed no olefinic protons, and a complex pattern from 4.1 to 4.9 indicated the presence of the desired pyrazoline.

The pyrazoline was irradiated in acetone for 3.5 hr (N_2 evolution ceased) and the solvent was then removed, yielding a yellow liquid with a quite sweet odor. Distillation (bp = 73°/18 mm) yielded 0.46 g of colorless liquid (3.0 mmoles), 46% yield). The nmr spectrum (0.7 (1), t; 1.2 (4), t+m; 1.4-2.6 (7), m; 4.01 (2), q) showed evidence of a cyclopropyl resonance at 0.7 and was generally consistent with the bicyclohexane structure. The IR spectrum exhibited a carbonyl band at 1720 cm^{-1}, while the mass spectrum showed a molecule ion at m/e 154 and a base peak at m/e 81, corresponding to the bicyclic hydrocarbon ion. Despite the unremarkable boiling point, the material was quite volatile and care was needed in handling to avoid loss by evaporation.

A purified sample was sent to Chemalytics, Inc., for a carbon-hydrogen analysis, but it was reported that the sample evaporated after opening the sample, but before the analysis could be carried out. In order to prove the structure, the ester was reduced with lithium aluminum hydride to an alcohol which had an nmr spectrum identical with an authentic sample prepared by the method of Clossen and Kwiatkowski (190).

1-Hydroxymethylbicyclo[3.1.0]hexane

Lithium aluminum hydride (45 mg, 1.18 mmoles) was dissolved in 20 ml of dry ether in a 100 ml 3-necked flask

(flame-dried) which was fitted with a nitrogen inlet, a reflux condenser, and an addition funnel (all flame-dried). The flask was flushed with nitrogen, and 300 mg (1.95 mmoles) of 1-carboethoxybicyclo[3.1.0]hexane in 20 ml of ether were slowly added to the flask. The reaction was heated at reflux for 30 min, then cooled and quenched by the dropwise addition of ice water. The ether layer was separated and dried over anhydrous magnesium sulfate, then evaporated, yielding 185 mg of a white oil. The nmr spectrum was identical with that of an authentic sample prepared by the method of Clossen and Kwiatkowski (190). The yield was 85%.

1-Hydroxymethyl-3,3-dimethylbicyclo[2.1.0]pentane (41)

Lithium aluminum hydride (27 mg, 0.70 mmoles) was dissolved in dry ether in a flame-dried flask fitted with a reflux condenser and dropping funnel. The flask was flushed with nitrogen, and a solution of 200 mg of 15d (1.3 mmoles) in 5 ml of dry ether) was slowly added through the dropping funnel. When the addition was complete, the reaction mixture was heated at reflux for 30 min, the ice water was slowly added to quench the remaining hydride. The ether layer was separated and dried over anhydrous magnesium sulfate, then evaporated, leaving 155 mg of a white oil. The nmr spectrum showed two methyl singlets (0.80 and 1.22δ), a high field multiplet (0.45-0.75δ) due to the cyclopropane methylene, a broad singlet (2.1δ) which washed out upon addition of D_2O, an AB

pattern centered at 3.51δ (J = 12 cps) which was assigned to the hydroxymethylene protons, and an extended multiplet from 0.8 to 1.8δ. The IR spectrum had a broad OH band at 3350 cm^{-1} and no carbonyl absorption. The mass spectral molecular weight was 126, with major fragment ions at m/e 111, 108, 95 and 93.

1-Dideuteriohydroxymethyl-3,3-dimethylbicyclo[2.1.0]pentane

The labeled compound was prepared as above, using lithium aluminum deuteride as the reducing agent rather than hydride. The mass spectral molecular weight was 128, with major fragment ions at m/e 113, 110, 95, and 93.

1-(2-Propane-2-ol)-3,3-dimethylbicyclo[2.1.0]pentane

An ether solution of 0.75 g of 15d (4.9 mmoles) was placed in a flask fitted with a reflux condenser and a rubber septum. The flask was flushed with nitrogen and 15 mmoles of methyllithium (8 ml of a 1.4 molar ether solution) introduced through a syringe. The reaction was stirred at reflux for 4 hr, then quenched by the slow addition of 4 ml of water. The organic layer was separated, and the aqueous layer extracted once with ether. The 2 ether portions were combined and dried over anhydrous magnesium sulfate. Evaporation of solvent yielded 0.5 g of a white oil which was very unstable to acid. An attempt to chromatograph a portion of it on Silica Gel led to complete rearrangement. The nmr spectrum of the oil was consistent with expected structure, showing the following

resonances: 0.80 (3), s; 1.04 (3), s; 1.15 (3), s; 1.21 (3), s; 0.60-0.90 (1), m; 1.0-2.2 (4), m; and 1.90 (1), broad singlet. Due to the instability of the compound, no attempts were made to further purify or characterize it, and it was used immediately.

1-(2-Nitrito-2-propane)-3,3-dimethylbicyclo[2.1.0]pentane

The title nitrite ester was prepared immediately before use from the above alcohol and nitrosyl chloride (191). The alcohol (0.5 g, 3.2 mmoles) was dissolved in carbon disulfide (3 ml) and pyridine (0.5 g, 6.5 mmoles) was added. The reaction flask was cooled in a Dry Ice-acetone bath and nitrosyl chloride (0.22 g, 3.2 mmoles) was added as slowly as possible with stirring. A white precipitate of pyridine hydrochloride formed immediately. The mixture was maintained at -78° and stirred for 30 min, then filtered. The nmr spectrum was recorded in the reaction solvent, and showed that the bicyclic ring system was intact. The spectrum was very similar to that of the alcohol, showing four methyl singlets (0.80, 1.10, 1.41, and 1.46δ) and no resonances below 2.2δ. The two carbinyl methyl resonances were shifted downfield by 0.2 ppm.

The material was found to be stable at room temperature for several hours; however, when stored in the refrigerator for several weeks, it decomposed even at that temperature.

3,3-Dimethylbicyclopentane-1-carboxylic acid

The acid was prepared by saponification of the ester 15d.

Five g of ester were dissolved in 50 ml of dioxane and treated with 50 ml of 10% KOH for 24 hr at room temperature. The reaction mixture was extracted several times with ether to remove most of the dioxane, then the solution was acidified with 10% HCl and the acid extracted into ether. The remaining dioxane was removed by pumping on the acid for several hours with a vacuum pump. The yield was 4.0 g, 88%. The nmr of the acid showed that the bicyclic nucleus was still intact, and that the ester methyl resonance had been replaced by a one proton resonance at 11.5δ.

3,3-Dimethylbicyclo[2.1.0]pentane-1-carbonyl chloride

The potassium salt of 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxylic acid (1.0 g) dispersed in 20 ml dry benzene was placed in a 100 ml 3-necked round bottom flask. The flask was fitted with a reflux condenser, a dropping funnel, and a calcium chloride drying tube (all flame dried). The dispersion was stirred in an ice bath with a magnetic stirrer while 0.75 g oxalyl chloride in 2 ml of dry benzene were added over a 15 min period, then allowed to warm up to room temperature. Carbon dioxide evolution was observed. The flask was heated slowly to reflux temperature for 30 min. Filtration, followed by evaporation of solvent and distillation yielded 0.47 g of acid chloride (bp 65°/25 mm). The nmr spectrum exhibited the usual resonances of the bicyclic nucleus, with no acid or ester absorptions. The yield was 53%.

t-Butyl perester of 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxylic acid

The acid chloride of 3,3-dimethylbicyclopentane-1-carboxlic acid (0.8 g) was dissolved in 10 ml of pentane and 5 ml of ether and added dropwise to a mixture of 0.6 g of t-butyl hydroperoxide and 0.5 g of pyridine at -25°. The mixture was stirred for an additional 20 min at -20°, then placed in the freezer overnight. The material was then filtered to remove the pyridine hydrochloride, washed with cold water, followed by three portions each of cold 10% sulfuric acid, cold 10% potassium hydroxide, and cold water. Drying over anhydrous magnesium sulfate followed by evaporation of solvent yielded 1.0 g of a colorless liquid with a slightly pungent odor. The nmr spectrum exhibited the usual resonances of the bicyclic nucleus, as well as a large singlet at 1.25δ. The IR spectrum showed a carbonyl absorption at 1755 cm^{-1} and a band at 855 cm^{-1}.

The material was not pure, but would not crystallize in the freezer, and no further purification was attempted. The crude yield was 93%.

Reaction of 1-carbomethoxy-3,3-dimethylbicyclopentane with acetic acid

The bicyclic ester 15d (200 mg) was dissolved in 2 ml of acetic acid containing 1 drop of concentrated sulfuric acid and 5 drops of water and stirred at room temperature for 24 hr. An nmr spectrum of the crude reaction mixture indicated

no change had occurred, so the reaction was continued for an additional 28 hr, at which time the nmr spectrum still indicated no change.

A second attempt to react acetic acid with the ester was also unsuccessful. The ester (0.5 g) was dissolved in 25 ml of acetic acid and enough p-toluenesulfonic acid added to make the solution 0.07 M in toluenesulfonic acid. The reaction was heated and stirred at 50° for 4 hr. An aliquot was removed and esterified with diazomethane and washed with aqueous sodium bicarbonate, yielding only starting material and methyl p-toluenesulfonate. The recovery of starting material was 75%.

The remaining material was heated for 36 hr at 50° and then allowed to stand for two days at room temperature. The previously described work-up yielded an 87% recovery of starting material.

When the ester (0.3 g) was heated at reflux in acetic acid (100 ml) containing 0.15 g of p-toluenesulfonic acid for 7 hr, the starting material was destroyed. The reaction was washed with aqueous sodium bicarbonate until neutral, extracted into ether, dried, and the solvent evaporated. The resulting brown oil was analyzed by vpc, which showed 16 peaks. The recovery of material was 180 mg. The mass spectrum showed an ion at m/e 154, but no peak corresponding to acetic acid addition (m/e 214).

Reaction of 1-carbomethoxy-3,3-dimethylbicyclopentane with hydrobromic acid

Ten mg of 15d were placed in a 5 ml flask and 1.5 ml of ether was added. The solution was cooled to 0° and 3 drops of 48% HBr was added. The reaction was stirred for 3 days at 0°, neutralized with a small amount of solid sodium bicarbonate, and a few crystals of sodium sulfate added to dry the solution. The solids were then filtered and the solution submitted for a mass spectrum. The spectrum did not show the expected ions at m/e 234 and 236, but rather showed ions at m/e 232 and 234. The relative intensities indicated the presence of one bromine atom. Although the structure was not the expected bromo-ester formed by addition of HBr to the 1-4 bond, bromine was incorporated in some form.

Hydrogenation of 3,3-dimethyl-1-carbomethoxybicyclo[2.1.0]-pentane

A solution of 1.0 g of 15d in 250 ml of acetic acid was placed in a stainless steel bomb with 0.1 g of PtO_2 catalyst. The hydrogen pressure was maintained at 500 lb for 8 hr at room temperature. The products were separated by alternate extractions with water and ether. The ether layer was washed with aqueous sodium bicarbonate until neutral, then dried over anhydrous magnesium sulfate. Vpc analysis (Carbowax column) indicated 2 components in a 4:1 ratio. The mass spectrum of the mixture exhibited molecule ions at m/e 154 (starting material was the major component) and m/e 156. The minor

component was collected by vpc and the spectrum of the collected sample was identical to that of an authentic sample of 1-carbomethoxy-3,3-dimethylcyclopentane.

The acid-catalyzed rearrangement of 1-hydroxymethyl-3,3-dimethylbicyclopentane (41)

A solution of 0.58 g of 41 in 5 ml of dioxane was treated with 1 drop of concentrated sulfuric acid in 5 ml of water at 40° for 30 min. The solution was then added to 25 ml of ether, which was washed with aqueous sodium bicarbonate, then dried and the solvent evaporated. The resulting yellow oil gave an nmr spectrum which indicated that some starting material remained, but the primary component was a rearranged product. A sample of the product was collected by vpc for spectral analysis. The nmr spectrum (0.9 (6), s; 2.0-2.7 (5), m; 3.65 (1), t; 4.8 (2), pentuplet) showed the characteristic olefinic pentuplet of a methylenecyclopentane (192), and a singlet for the geminal methyls, indicating collapse of the bicyclic ring. That the methyl groups were a singlet was somewhat surprising, since the anticipated structure of the product, 4-methylene-2,2-dimethylcyclopentanol, would have a hydroxy group on the adjacent carbon, cis to one methyl and trans to the other, but an authentic sample of 2,2-dimethylcyclopentanol prepared by the procedure of Wilcox and Mesirov (193) also exhibited a singlet for the two methyl groups. The IR spectrum was consistent with the assigned structure,

showing absorptions for OH (3340), C=C (1655), and exocyclic C=C (878 cm^{-1}). The mass spectral molecular weight was 126. On the basis of these data, the product was identified as 4-methylene-2,2-dimethylcyclopentanol.

The acid-catalyzed rearrangement of 1-hydroxymethyl-3,3,5-trimethylbicyclopentane

A solution of 160 mg of the trimethyl bicyclic alcohol in 2 ml of dioxane was treated with 2 ml of water containing 2 drops of concentrated sulfuric acid for 1 hr at 50°. The bicyclic alcohol was contaminated by a small amount of ester which remained unreduced, indicative of the severe steric hindrance in the vicinty of the carbony. The nmr spectrum of the rearranged alcohol was complicated by the presence of this ester, as well as by remaining dioxane, so the material was chromatographed on a Silica Gel column to remove these components. The resulting minty-smelling oil showed an nmr spectrum indicative of a structure analogous to the rearranged alcohol from the above experiment: 2 singlets, each 3H, at 0.89 and 1.02δ; a 3 proton doublet (J = 6.5 cps) centered at 1.15δ; a one proton multiplet at 1.6δ; a broad multiplet centered at 2.5δ, integrating to 3 protons; a doublet or two singlets separated by 9 cycles, centered at 3.5δ, (1H); and an olefinic multiplet of 2 protons at 4.8δ. The proton on the carbon bearing the hydroxyl group should give a resonance in the vicinty of 3-3.5, with a coupling dependent upon whether

is cis or trans to the adjacent methine proton. A cis arrangement would give a dihedral angle of ca. 0°, and a coupling of approximately 9 cycles, while a trans arrangement would give an angle of about 120°, and a coupling of 1-3 cycles. The alcohol was therefore assigned the structure cis-2-methyl-3-methylene-5,5-dimethylcyclopentanol.

The product recovery from the chromatography was rather poor (<40%), so a definitive statement concerning the stereochemistry of ring opening would be on poor evidence, but it suggests that the ring opening does occur stereospecifically, giving the cis geometry in the product.

Static pyrolysis of 1-carbomethoxy-3,3-dimethylbicyclo[2.1.0]-pentane (15d)

The bicyclic ester 15d (45 mg, 0.29 mmoles) was degassed and sealed into a pyrex test tube under vacuum, then heated at 360° for 2 hr. The product mixture was analyzed by vpc (Carbowax column) which showed the presence of two products in a ratio of 36.5 to 63.5. Samples of each were collected for spectral data. The product with the shorter retention time showed a carbonyl band in the IR spectrum at 1740 cm^{-1}, a mass spectral molecular weight of 154, and an nmr spectrum (1.05 (3), s; 1.12 (3), s; 3.62 (3), s; 1.8-2.1 (2), m; 3.3-3.7 (1), m; 5.3-5.7 (2), m) showing non-equivalent methyl groups and a 2 proton olefinic resonance. The spectra suggest the structure 1-carbomethoxy-4,4-dimethyl-2-cyclopentene. The second product

exhibited a carbonyl frequency of 1720 cm^{-1} and a mass spectral molecular weight of 154, suggesting the conjugated cyclopentene isomer. The nmr spectrum (1.12 (6), s; 2.2-2.5 (4), m; 3.67 (3), s; 6.55 (1), m) was consistent with this assignment. Hydrogenation (atmospheric pressure, Pd/C catalyst) of the product mixture yielded only one product, which was identified as 1-carbomethoxy-3,3-dimethylcyclopentane by comparison with an authentic sample and with the product from the hydrogenation of 15d.

A pure (vpc collected) sample of each pyrolysis product was degassed and sealed in a tube and pyrolyzed at 360° for 2 hr to determine its stability under the pyrolysis conditions. Vpc analysis showed that the conjugated ester underwent no change, and that the unconjugated ester produced a mixture of 91.5% unconjugated ester and 8.5% conjugated ester.

The pyrolysis of 15d was repeated at 234° for 2 hr. Decomposition was incomplete under these conditions after 2 hr, giving a mixture of starting material and the two product esters in a ratio of 1:0.5:1.12. Thus, the reaction was 61% complete, yielding 71% conjugated ester and 29% non-conjugated ester.

Column pyrolysis of 1-carbomethoxy-3,3-dimethylbicyclopentane

The pyrolysis apparatus consisted of a vertical pyrex column 1 ft long, packed with glass helices and fitted with a heating jacket and an iron-constantan thermocouple for monitoring the internal temperature. The column was flushed with

prepurified nitrogen for 15 min before pyrolyses were carried out, at a flow rate of 40 ml/min, as closely as it could be controlled. Products were trapped in a Dry Ice-acetone bath. Samples were introduced via a syringe through a rubber septum at the top of the column. Samples consisted of 200 mg of ester 15d in 2 ml of benzene. Analysis was carried out by vpc (Carbowax column).

When the pyrolysis was carried out at a column temperature of 220°, vpc analysis showed only starting material. When the column was heated to 354°, vpc analysis showed the presence of no starting ester, and the 2 isomeric cyclopentene esters were present in about equal amounts (measurement of the peak areas by planimeter showed almost exactly a 50:50 mixture). The pyrolysis was re-run at 348°, with the same results. The product ratio remained within 1% of 50:50.

When the pyrolysis was carried out at 550°, the product ratio shifted to 63% conjugated ester in the mixture. Pyrolysis of the 50:50 mixture from the previous run at 550° showed no change in ratio, indicating that no thermal isomerization was occurring after the products were formed.

Static pyrolysis of 1-cyano-3,3-dimethylbicyclopentane (16)

The bicyclic nitrile 16 (200 mg) was degassed and sealed in a tube, then heated at 242° for 2 hr in an electric oven. Vpc analysis showed the presence of only one component, with a retention time slightly shorter than the bicyclic nitrile. A mixed sample showed two definite peaks. The product was

collected by vpc and identified by spectral features as 2-cyano-5,5-dimethylcyclopentene.

Electrolysis apparatus

All anodic oxidations were carried out using a copper-carbon electrode pair with the carbon electrode used as the anode. The electrodes measured 65 x 20 x 6 mm, and were separated 7 mm by the use of a polyethylene washer. The reactions were carried out in a 1l 3-necked flask, fitted with a reflux condenser and a nitrogen inlet (gas dispersion tube) on the outside necks, and the electrode assembly inserted through the center neck (35/45 joint). The assembly was sealed by a 34/45 inner joint through which two platinum wires had been sealed. The power was provided by a D. C. power source (rectifier) with a range of 0-120 volts and 0-6 amps. The voltage was controlled by a variac between the power source and an A. C. outlet.

The heat generated by the electrolysis was sufficient to keep the reaction at a vigorous reflux. Materials swept out of the reaction flask were trapped in a Dry Ice-isopropanol bath. The reaction mixture was stirred continuously with a magnetic stirrer.

Electrolysis of 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxylic acid

The carboxylic acid was prepared by saponification of 15d (5% KOH-dioxane at room temperature for 24 hr). The acid (2.64 g, 18.8 mmoles) was added to 500 ml of distilled water in

which 1 g of KOH had been dissolved, and the entire solution placed in the electrolysis flask and electrolyzed for 5 hr. The solution was quite black by that time, apparently due to carbon particles from the anode, since it showed considerable wear. The solution was extracted with 3 100 ml portions of ether, the extracts combined, dried over anhydrous magnesium sulfate, and evaporated, yielding 0.35 g of a yellow-brown oil. Analysis by vpc (LAC-446 column) showed 3 products with retention times of 4.2 min, 5.5 min, and 13.5 min, in a ratio of 0.41:1:1.02. All 3 products were collected by vpc for spectral analysis. The product with the shortest retention time was identified from its spectral data as 3,3-dimethylcyclopentanone (mol weight (mass spec) 112: nmr; 1.11 (6), s; 1.5-2.5 (6), m), and was found to be identical to an authentic sample. The second product had a mass spectral molecular weight of 110, and an nmr which consisted of 2 singlets (1.21 (6) and 2.11 (2)) and an AB pattern ($\delta/J = 16$, $\delta_{AM} = 94.1$ cps; $J = 5.5$, $\delta_A = 5.85$, $\delta_M = 7.42$). These data suggested the structure 5,5-dimethylcyclopenten-3-one, and the sample was found to be identical to an authentic sample. The remaining product also exhibited a mass spectral molecule ion at m/e 110, and was tentatively identified by its nmr spectrum (1.21 (3), d, J = 7 cps; 2.07 (3), d, J = 1 cps; 1.6-2.9 (3), m; 5.76 (1), q, J = 1 cps) as 1,5-dimethylcyclopenten-3-one. The structure was verified by comparison with an authentic sample.

The remaining aqueous phase was acidified with hydrochloric acid, then saturated with sodium chloride and extracted continuously with ether for two days, yielding 1.75 g of unreacted acid. This accounted for only 75% of the original material. The material in the cold trap accounted for another 0.2 g. Vpc analysis showed the presence of 6 products with short retention times, while the nmr spectrum showed only aliphatic resonances. None of these products were identified.

Electrolysis of 5,5-dimethylcyclopenten-3-ol

The title alcohol was prepared by lithium aluminum hydride reduction of the corresponding ketone as reported by Rouse and Tyler (194). Electrolysis of the alcohol (0.60 g, 5.35 mmoles) in 500 ml of distilled water containing 0.2 g of KOH was carried out for 4 hr at 100 volts. The mixture was cooled to room temperature and extracted with two 100 ml portions of ether, and the organic phase dried and evaporated, yielding 0.18 g of material. The nmr spectrum of the reaction mixture showed olefinic resonances corresponding to the starting alcohol, 5,5-dimethylcyclopenten-3-one, and 1,5-dimethylcyclopenten-3-one. Analysis by vpc (LAC-446 column) confirmed the presence of the two olefinic ketones, as well as the presence of the saturated 3,3-dimethylcyclopentanone, in a ratio of 0.27:1:1.62.

The aqueous layer was saturated with sodium chloride and extracted continuously for 15 hr, yielding an additional 0.15 g of material. Analysis by nmr and vpc indicated that the

material did not contain any of the starting alcohol or product ketones, and that it was probably polymeric.

5,5-Dimethylcyclopenten-3-one

The unsaturated ketone was prepared by dehydration of the acyloin of methyl-β,β-dimethylglutarate. The acyloin condensation of the disubstituted glutarate ester was carried out according to the procedure of Schräpler and Ruhlmann (193) for the condensation of the unsubstituted glutaric ester. Thus, 19 g (100 mmoles) of methyl-β,β-dimethylglutarate was treated with sodium-potassium alloy (112) in the presence of trimethylchlorosilane (70 g, 0.65 mmole) for 1 1/2 days at room temperature. Filtration and evaporation of solvent yielded the bis-trimethylsiloxycyclopentene. This material was hydrolyzed to the acyloin by heating at reflux in methanol for 8 hr.. Evaporation of solvent and distillation (bp 78°/8 mm) yielded 3 g of the acyloin (overall yield = 22%).

Dehydration of the acyloin was carried out according to the procedure of Rouse and Tyler (194), using polyphosphoric acid as the dehydrating agent, in 84% yield.

The 5,5-dimethylcyclopenten-2-one thus obtained was found to be identical in all respects with the material isolated from the anodic oxidation of 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxylic acid, mp 2,4-dinitrophenylhydrazone 163-164°C (lit 163-164° (194).

1,5-Dimethylcyclopenten-2-one

Methyl 3,4-dimethyladipate was prepared by the method of Ställberg-Stenhagen (196), with the exception that a Parr shaking apparatus was not used, as it was insufficient to thoroughly mix the copper-bronxe, pumice, and β-iodobutyric acid. Instead, the materials were thoroughly mixed as a slurry in hexane, and the hexane then distilled out of the reaction flask, leaving behind the solid reactants. The resulting 3,4-dimethyladipic acid was esterified by heating at reflux with methanol containing a few drops of sulfuric acid, and the ester was distilled under vacuum (bp 110°/3 mm, lit 114°/8 mm).

Methyl 3,4-dimethyladipate (21 g, 0.104 moles) was dissolved in 100 ml dry tetrahydrofuran (freshly distilled from sodium hydride) and added to a suspension of 16 g of sodium hydride (32 g of a 50% suspension in mineral oil) in 200 ml of tetrahydrofuran and stirred for 35 hr at room temperature, then 3 hr at reflux. The unreacted hydride was destroyed by the slow addition of a methanol-ether solution. The reaction mixture was then poured into a 1 l beaker containing 100 g of ice, acidified with 4 N hydrochloric acid, and extracted twice with 100 ml portions of methylene chloride. The organic phase was dried (anhydrous magnesium sulfate) and the solvent evaporated. Distillation (80°/0.7 mm) yielded 10.7 g of 2-carbomethoxy-3,4-dimethylcyclopentanone (63 mmoles, 61% yield).

Decarboxylation of the β-keto ester was accomplished by

adding it (6.4 g, 37.6 mmoles) to a 5% aqueous solution of sulfuric acid and heating at reflux for 4 hr. The reaction flask was cooled to room temperature and extracted twice with 50 ml portions of ether. The organic layer was dried and evaporated. Distillation of the residue (bp 60°/20 mm) yielded 2.6 g (23.2 mmoles, 61% yield) of 3,4-dimethylcyclopentanone.

The cyclic ketone (0.8 g, 7.1 mmoles) was dissolved in 10 ml of carbon tetrachloride and treated with 1.25 g (7 mmoles) by heating the mixture to reflux and initiating by irradiating with a sun lamp. The reaction was heated at reflux for 30 min, then filtered. Evaporation of the solvent yielded 1.0 g of black tar. This material was distilled, with two fractions collected. The lower boiling fraction was identified by vpc retention time as unreacted 3,4-dimethylcyclopentanone (0.2 g), while the higher boiling fraction (100°/1 mm) was identified by spectral properties as the α-bromoketone (0.8 g, 59% yield).

The bromoketone (0.8 g, 4.2 mmoles) was dissolved in dimethylsulfoxide (DMSO) (10 ml) and 0.6 g (4.7 mmoles) of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) were added. The solution was heated at 90° for 30 min, then cooled, placed in a separatory funnel with 100 ml of ether, and washed with 100 ml of saturated aqueous sodium chloride. The ether solution was dried and evaporated, then distilled (70°/30 mm). The yield

of 1,5-dimethylcyclopenten-2-one was 90 mg, or 20%. Mp 2,4-dinitrophenylhydrazone, 209-212° (lit (197) 210-212°).

The yield could likely be improved in the dehydrobromination step by using milder conditions, either DBN-DMSO at room temperature or a milder base such as quinoline or triethylamine.

3,3-Dimethylcyclopentanone

Hydrogenation of 5,5-dimethylcyclopenten-3-one (113 mg, 1.02 mmoles) was carried out in methanol at atmospheric pressure using 5% Pd/C catalyst, until one equivalent of hydrogen had been consumed. The solution was filtered to remove the catalyst, and the solvent was removed by distillation. The mass spectrum of the remaining material showed a molecule ion at m/e 112 and base peak at m/e 56. The nmr spectrum showed a singlet at 1.11 (6) and a multiplet from 1.5 to 2.5 (6). Mp semicarbazone 177-179° (lit (198) 179-180°). The yield was 97 mg (85%).

Electrolysis of 3,3,5,5-tetramethylbicyclo[2.1.0]pentane-1-carboxylic acid

The carboxylic acid was prepared by saponification of 15g, as described earlier for the saponification of 15d. The acid (1.2 g, 7.15 mmoles) was electrolyzed as previously described for 10 hr. The work-up as described earlier yielded 0.28 g of volatile material, which proved to be mostly acetone, 0.08 g of neutral material, and 0.23 g of recovered acid. Analysis

of the neutral fraction by vpc (LAC-446) showed the presence of 3 products, one very minor, and the remaining 2 poorly separated. The IR spectrum exhibited several bands in the carbonyl region. The 2 poorly separated products were collected by vpc (as one sample) and spectral data recorded. The IR spectrum had the appearance of an α,β unsaturated ketone, showing a carbonyl band at 1700 cm^{-1} and a C=C band at 1645 cm^{-1}. Other bands were present in the region, at 1720 and 1760 cm^{-1}, but were much weaker. The nmr spectrum (100 Mc, Varian HA-100) was rather cluttered, but showed no resonances in the olefinic region of the spectrum. A large singlet was present in the aliphatic region, suggesting a gem-dimethyl function. The mass spectrum was more informative, exhibiting a molecule ion at m/e 138, a base peak at m/e 123, and major fragment ions at m/e 95, 93, 91, 83, 81, 79, 77, 69, 67, 55, and 53. Comparison of these spectra with the spectra of an authentic sample of 1,2,5,5-tetramethylcyclopenten-3-one (48) revealed striking similarities, and very few differences. A comparison of vpc retention times also demonstrated that this ketone was possibly one of the electrolysis products. Comparison of spectra and vpc retention times with the isomeric 1,2,4,4-tetramethylcyclopenten-3-one (49) showed that it was not the electrolysis product.

1,2,5,5-Tetramethylcyclopenten-3-one (48)

The title ketone was prepared according to the method of Conia and Leriverend (162), by the treatment of 2-butyl-β,β-dimethylacrylate with polyphosphoric acid. Polyphosphoric acid (25 g) and the acrylate ester (3.25 g, 0.024 mole) were stirred together and heated at 100° for 1 hr. The resulting black tar was poured onto 100 g of ice and stirred until hydrolysis was complete, then the mixture extracted with three portions of ether. The combined ether extracts were washed twice with saturated sodium bicarbonate solution, once with water, and dried over anhydrous magnesium sulfate. Evaporation of solvent yielded a red-brown tar, which upon distillation yielded 1.5 g of the ketone. The nmr spectrum of the product consisted of four singlets: 1.16 (6), 1.59 (3), 1.90 (3), and 2.11 (2). The mass spectrum exhibited a molecule ion at m/e 138, with consecutive metastable losses of 15 (base peak) and 28 mass units, mp 2,4 DNP, 183-84° (lit (162) 194-95°). (It is suspected that these workers isolated the dinitrophenylhydrazine reagent).

1,2,4-Trimethylcyclopenten-3-one

Although this ketone was not one reported by Conia and Leriverend, it was prepared by their technique. Sec-t-butyl methacrylate was prepared from glacial methacrylic acid (199) and treated with polyphosphoric acid at 100° for 1.25 hr, and worked up as previously described. The compound obtained showed

a carbonyl frequency of 1710 cm^{-1} and a C=C band at 1650 cm^{-1}. The 100 Mc nmr spectrum (Varian HA-100) showed three methyl resonances, a doublet at 1.08, an 8 line pattern at 1.61, and a broadened singlet at 2.0, and a multiplet extending from 1.7 to 3.0δ (3 H). The mass spectrum showed a molecule ion at m/e 127, with fragment ions at m/e 109, 96, 95, 93, 91, 81, 79, 77, 67, and 55. Metastables were present for 124 → 109 (95.8), 95 → 93 (91), 93 → 91 (89), 81 → 79 (77.1), 124 → 96 (74.3), 96 → 81 (68.3), and 109 → 81 (60.2). Derivatives were prepared for melting points: 2,4 DNP melted with decomposition over a 10 degree range, 215 to 225, even after several recrystallizations; the semicarbazone melted with decomposition over a 5 degree range, 207 to 212. The phenylhydrazone was an oil.

1,2,4,4-Tetramethylcyclopenten-3-one (49)

Several methods were used in attempts to prepare this ketone. Alkylation of the above ketone with methyl iodide yielded a tetramethyl ketone in poor yield, but it was not the correct one, as shown by the 100 Mc nmr spectrum. The saturated ketone had been reported by Bardhan and Adhya (163), but attempts to follow their procedure resulted in extremely poor yields in the first two steps. Attempts to prepare the needed 2,2,4-trimethyladipic acid by means of a modified Wittig reaction on 4-cyano-4-methyl-2-pentanone and on ethyl 2,2-dimethyl-4-ketopentanoate were unsuccessful. The ketone was finally prepared as one component in a mixture by the procedure below.

Isophorone (25 g, 0.2 mole) was hydrogenated using a Parr apparatus and palladium-charcoal catalyst in methanol at 40 psi. The resulting ketone was reduced to the alcohol with sodium borohydride. Part of the resulting 2,2,4-trimethylcyclohexanol (11 g) was dropped slowly into an ice-cold solution of 70% nitric acid, with rapid stirring. The rate of addition was controlled so that the evolution of NO_2 fumes was moderate. The addition was complete after about one hour, at which time the reaction was warmed to room temperature, then to 50° for 30 min. The reaction mixture was then cooled and extracted with ether, which was then extracted with 20% KOH. The basic aqueous wash was then acidified with HCl and re-extracted with ether. The ether was dried and evaporated, and the resulting acid esterified with methanol and sulfuric acid. Distillation (77°/1.5 mm) yielded 8.6 g of crude dimethyl ester.

The ester thus obtained was a mixture of 2,2,4-trimethyl adipate and 3,3,5-trimethyl adipate, but no attempt was made at separation at this point. The ester mixture (8.6 g) was placed in an addition funnel and slowly added to a dispersion of 1 g of sodium in toluene, followed by 0.1 ml of absolute ethanol, all at room temperature. The mixture was then heated to 80° for 2 hr, cooled in an ice bath, and 10 g of methyl iodide added and heating resumed at 70° for an additional 12 hr. The reaction was worked up by pouring over ice and extracting with ether. The organic phase was dried and evaporated, then distilled, collecting the higher boiling fraction (75°/0.4 mm),

using a 12 in column with a heated jacket and a spiral wire core. The yield was 3.75 g of a mixture containing possibly 2 tetramethyl keto-esters and one trimethyl keto-ester, although the careful distillation should have removed a large percentage of the more volatile trimethyl ester.

Decarboxylation was carried out by heating the keto-esters at reflux in 10% KOH for 12 hr. The reaction mixture was extracted with ether, which was dried and evaporated. Analysis by vpc showed only 2 peaks present (Carbowax 20 M column). The nmr spectrum showed no ester remaining, but the aliphatic region was quite complex, as would be expected. Distillation yielded 0.9 g of product (74°/30 mm).

The ketone mixture was dissolved in CCl_4 and treated with excess N-bromosuccinimide, yielding 1.0 g of crude bromo-ketone. Dehydrobromination was achieved using triethylamine as the base in methylene chloride solution. The crude bromo-ketone mixture was dissolved in methylene chloride and slowly added to a solution of 3.5 ml of triethylamine in ethylene chloride, then stirred for 30 min at room temperature. The reaction mixture was washed with 4 N HCl, then with saturated sodium bicarbonate, dried, and the solvent evaporated. Distillation separated the olefinic ketones from any remaining bromo-ketones, and the volatile fraction was analyzed by vpc. Using a Carbowax column, 2 peaks were observed in approximately equal amounts, while a DC-550 column again showed two peaks, in a very different ratio.

This behavior indicated at least 3 components with separation of only two, but a different two on each column. Collection of the 2 peaks on the Carbowax column yielded one reasonably pure component which appeared by the nmr spectrum to be 2,4,-5,5-tetramethylcyclopenten-3-one, and a mixture which appeared to contain the desired 1,2,4,4-tetramethyl isomer. Collection using the DC-550 column gave a reasonably pure sample of this material. All spectral data were consistent with the assigned structure. Nmr: 1.02 (6), s; 1.62 (3), m, splitting = 1 cps; 1.98 (3), s, broadened; and 2.28 (2), m. IR: ν = 1700 cm^{-1}, C=C = 1655 cm^{-1}. UV: $_{max}$ = 237 m, log ϵ = 4.0. Mass spectrum: M^+ = 138, base peak = 123, major fragments at m/e 109, 95, 94, 93, 91, 81, 79, 77, 67, 55, 53, and 51.

3,3-Dimethyl-1-bicyclo[2.1.0]pentoyl peroxide

The diacyl peroxide was prepared according to the procedure of Staab (122, 123). To a solution of 1.62 g of 1,1'-carbonyldiimidazole (0.01 mole) in 10 ml of tetrahydrofuran was added 1.40 g (0.01 mole) of 3,3-dimethylbicyclopentene-1-carboxylic acid over 10 min at room temperature. After 5 min, vigorous gas evolution was noted. The solution was stirred for 50 min at room temperature, then cooled in an ice-water bath. To the cold azolide solution was added 0.53 ml of 30% hydrogen peroxide solution. The mixture was stirred at 0° for 2 hr, then poured into 25 ml of water, and extracted with methylene chloride. The extract was washed three times with salt water, dried over anhydrous magnesium sulfate, and the

solvent evaporated in vacuo, yielding a white oil, which refused to solidify or crystallize from pentane. The nmr spectrum showed only resonances associated with the bicyclopentane nucleus, while the IR spectrum showed characteristic bands at 1780 cm^{-1} and 1755 cm^{-1}. The mass spectrum showed a very weak ion at m/e 278, corresponding to the molecule ion of the peroxide, and weak fragment ions at m/e 140 and 139. Intense fragment ions were present at m/e 123 and 95. The yield was 1.08 g, 78%.

Pyrolysis of 3,3-dimethylbicyclopentoyl peroxide in cumene

One mmole of the diacyl peroxide (278 mg) was dissolved in 5 ml of redistilled cumene, placed in an ampoule with a volumn of 25 ml and degassed, then sealed under vacuum. The ampoule was then placed in an oil bath pre-heated to 90° and allowed to stand for 16 hr. The tube was cooled in a liquid nitrogen bath, opened, and the products analyzed by vpc, which showed the presence of 5 components. A comparison of retention times identified 4 of these as cumene, an impurity in the cumene used, diethyl ether, and tetrahydrofuran. The ether could have resulted from insufficient drying after the tube was rinsed with ether prior to use, while THF was the solvent used in preparing the peroxide. All products less volatile than cumene were collected together by vpc for nmr and mass spectra. The nmr spectrum showed the presence of considerable cumene, but in addition, also showed the typical methyl pattern of the bicyclic ring system: two singlets separated by 30 cycles. No

olefinic resonances were seen. The mass spectrum of the mixture was compared with the spectrum of the cumene used as the solvent, and peaks were found at m/e 96, 95, and 81 which were not present in cumene.

Pyrolysis of 3,3-dimethyl bicyclopentoyl peroxide in perfluorobenzene

In order to examine the behavior of the radical in the absence of a good hydrogen source, the pyrolysis of the diacyl peroxide was carried out as described above, but substituting perfluorobenzene for cumene as the solvent. The temperature was lowered to 70° due to the lower boiling point of perfluorobenzene. The nmr spectrum of the crude pyrolysis solution showed no olefinic protons, but the aliphatic region was so complex as to be uninterpretable. Distillation of the solvent and volatiles gave a very dilute solution of product in perfluorobenzene, and the nmr spectrum of this showed two singlets, with the same separation as those seen when the pyrolysis was carried out in cumene. The sample was too dilute to show any peaks other than cumene in the mass spectrum, and the product did not separate from solvent by vpc.

Photolysis of 3,3-dimethylbicyclopentoyl peroxide in cumene

A sample of the diacyl peroxide in cumene was sealed in an ampoule as described for the pyrolysis experiment, and irradiated for 16 hr using a 450 watt Hanovia high pressure mercury arc lamp and pyrex apparatus. Analysis of the resulting product solution by vpc showed the presence of two products, one

of which corresponded by retention time to the pyrolysis product, and a second which had a retention time approximately twice as long. These were collected and submitted for a mass spectrum, which showed ions at m/e 96, 95, and 81. The behavior of the m/e 96 ion at low electron energy showed that it was a molecule ion. A tiny peak was seen at m/e 190, possibly due to a hydrocarbon dimer; however the intensity was too small to determine whether or not it was a molecule ion.

1-Benzoyl-3,3-dimethylbicyclopentane (18)

The procedure for the preparation of the bridgehead acetyl compound 17 from the bridgehead carboxylic acid and methyllithium was followed, using phenyllithium rather than methyllithium. Treatment of 0.5 g of the acid with two equivalents (3.3 ml of 2.14 M solution) of phenyllithium yielded 285 mg of ketone, which was impure, and could not be obtained in pure form. Chromatography improved the purity, but not sufficiently for chemical analysis. The compound refused to form a carbonyl derivative, apparently due to the steric hindrance of the phenyl-t-butyl type structure. The nmr spectrum showed the typical non-equivalent methyl group resonances at 0.88 and 1.22, and a benzoyl-type resonance in the aromatic region of the spectrum. The integration showed that the impurity present had some aromatic character, as this region of the spectrum contained several extra protons.

Cleavage of 18 with potassium t-butoxide

The procedure of Gassman (169) for the cleavage of non-enolizable ketones was followed, using DMSO as a solvent and potassium t-butoxide as the base. DMSO (6 ml) was placed in a 25 ml 3-necked flask fitted with a nitrogen inlet and a drying tube. To this was added 2.0 g of potassium t-butoxide and 96 mg of water. The ketone was then added dropwise and the solution heated at 60° for 2 hr, then stirred at room temperature for 3.5 hr. The reaction was worked up by acidifying to pH 1 and extracting with two portions of ether. The ether portion was then made alkaline with KOH solution, and the acid isolated by acidifying the aqueous layer, extracting the acid into ether, drying, and evaporating the solvent. The result was 0.2 g of a brown solid. The nmr spectrum showed that the product was benzoic acid, although rather impure.

1-Hydroxymethyl-3,3-dimethylcyclobutene

Lithium aluminum tri-t-butoxy hydride (6.55 g, 25.8 mmoles) was dissolved in dry tetrahydrofuran in a flask fitted with a dropping funnel and reflux condenser. A solution of 3,3-dimethylcyclobutene carboxylic acid chloride (1.8 g, 12.5 mmoles) in 5 ml of dry tetrahydrofuran was placed in the dropping funnel. The flask was cooled in an ice bath and the acid chloride added slowly. The reaction mixture was stirred with a magnetic stirrer for 1 1/2 hr at 0°, then quenched by addition of ice water. The organic phase was separated and the

aqueous phase extracted with ether. The two organic phases were combined, dried with anhydrous magnesium sulfate, and the solvent evaporated. Distillation through a short-path apparatus yielded 0.6 g of the colorless alcohol (bp 26°/2 mm). Nmr: 1.14 (6), s; 2.15 (2), s, broadened; 3.95 (2), q, J = 1.5 cps; 4.3 (1), s, broadened; 5.90 (1), t, J = 1.5 cps. Yield = 43%.

3,3-Dimethylcyclobutene carboxylic acid chloride

Thionyl chloride (7 g) and 3,3-dimethylcyclobutene carboxylic acid (3.2 g, 39.4 mmoles) were heated at reflux for 2 hr, then distilled under reduced pressure, with the acid chloride collected at 60°/20 mm. Nmr: 1.28 (6), s; 2.48 (2), s; 7.15 (1), s. IR: $\nu_{c=o}$, 1770 cm^{-1}. Yield = 3.43 g (94%).

1-Carbomethoxy-3,3-dimethylcyclopentane

Five g of 4,4-dimethylcyclohexenone (40 mmoles, prepared by the method of Dauben, et al. (200) was hydrogenated in methanol at atmospheric pressure and room temperature, using 5% Pd/C catalyst, until 1 equivalent of hydrogen had been consumed. The cyclohexanone was isolated by filtration to remove the catalyst and evaporation of the solvent.

The 4,4-dimethylcyclohexanone obtained above was dissolved in 30 ml of carbon tetrachloride and placed in a 100 ml flask. N-bromosuccinimide (7 g, 39.2 mmoles) was added and the mixture heated to reflux. A sun lamp was used to help initiate the reaction. When the initial exothermic reaction was finished, the mixture was stirred for an additional 30 min at reflux, then filtered. Evaporation yielded 3.5 g of crude bromoketone

(45%).

The bromoketone was dissolved in 5 ml of methanol and placed in a dropping funnel. Sodium methoxide (1.1 g, 20 mmoles) was dissolved in 20 ml of methanol and placed in a flask fitted with a reflux condenser and the dropping funnel containing the bromoketone, and cooled to 0° in an ice bath. The bromoketone was slowly added to the reaction flask, with stirring. The mixture was stirred for 7 hr at room temperature, then at reflux for 30 min. After cooling back to room temperature, 30 ml of water was added, and heating was resumed for 1 hr. The reaction mixture was then extracted with three 100 ml portions of ether. The aqueous layer was acidified and extracted with 100 ml of ether. This portion of the ether extract was treated with diazomethane (generated from 6 g nitrosomethylurea) and worked up in the usual manner, yielding 0.53 g of ester (3.4 mmoles, 20% yield). The material was found to have the same retention time as the ester obtained from the hydrogenation of 15d, and a vpc collected sample had an identical nmr spectrum.

The low yield obtained in the Favorskii rearrangement was in part due to direct displacement of the bromine by methoxide, yielding 2-methoxy-4,4-dimethylcyclohexanone, which was isolated from the ether extracts of the basic reaction mixture.

Attempts to prepare 1-carbomethoxy-3,3-dimethylbicyclo[2.1.0]-pentane

A solution of 1.0 g (7.15 mmole) of 36b in 30 ml of cyclohexane was placed in a 50 ml flask fitted with a dry-ice condenser and a gas inlet tube for bubbling gas through the solution. All apparatus was free of cracks, chips, or ground glass joints. In a separate flask were placed 25 ml of a 50% KOH solution and 50 ml of decalin. This flask was linked to the gas inlet tube of the reaction flask via Tygon tubing. Anhydrous cuprous chloride (prepared according to the procedure of Fieser (201) (0.2 g) was added to the reaction flask, and N-methyl-N-nitrosourea (16 g) was added in small quantities to the generator flask and the diazomethane which was formed was bubbled through the solution in the reaction flask. After four hr, the Dry-Ice condenser was removed and the excess diazomethane allowed to evaporate. The now-black catalyst was removed by filtration and the solvent was evaporated. The mass spectrum of the remaining material showed only a very minute peak at m/e 154, while the nmr spectrum showed no indication of the expected non-equivalent methyl groups of the bicyclic ester.

The Simmons-Smith reaction was next attempted on 36b. A solution of 0.5 g of ester in 30 ml of ether was placed in an addition funnel and fitted to a 100 ml 3-necked flask. In the flask were placed 2.5 g of methylene iodide, 0.65 g of zinc-copper couple, and a crystal of iodine in 25 ml of ether. The

flask was fitted with a magnetic stirrer and reflux condenser, and the mixture heated at reflux for 30 min. The ester solution was then added and heating continued for 50 hr. Filtration of the catalyst and evaporation of solvent yielded a viscous material, the nmr spectrum of which showed no trace of the expected resonances from the bicyclic ester. Peaks attributable to ether and to the starting ester were present.

Attempted preparation of 1-acetyl-3,3-dimethylbicyclo[2.1.0]-pentane

The method of Corey and Chaykovsky (107) was used in an attempt to synthesize the title ketone. Sodium hydride (0.8 g of a 55% dispersion in mineral oil) was washed three times with dry cyclohexane to remove the mineral oil, then evacuated to remove any remaining cyclohexane. To the flask was added a solution of trimethyl sulfoxonium iodide in 25 ml of dried dimethylsulfoxide (DMSO). The mixture was stirred for 20 min under nitrogen, until hydrogen evolution ceased. A solution of 1.25 g of 1-acetyl-3,3-dimethylcyclobutene in 15 ml of dried DMSO was then added dropwise at room temperature, and stirring continued for two hr. The reaction mixture was then heated at 60° for an additional hr, then poured into cold water and the resulting mixture was extracted twice with 50 ml of ether. The ether extracts were washed with two 50 ml portions of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and evaporated. The nmr spectrum of the product showed no indication of bicyclic product or starting

ketone. Olefinic proton resonances were present in the spectrum, but at higher field than in the starting ketone, indicating that attack occurred at the carbonyl rather than at the double bond.

Attempted preparation of 1-hydroxymethyl-3,3-dimethylbicyclo-[2.1.0]pentane

Both the Simmons-Smith and the carbene addition reaction described for the cyclobutene ester were attempted on 1-hydroxymethyl-3,3-dimethylcyclobutene, without success. The Simmons-Smith reaction was carried out on 0.6 g of the alcohol, using 0.8 g of zinc-copper couple, 2.7 g of methylene iodide, and a crystal of iodine. The reaction mixture was heated at reflux for 30 hr, then filtered, washed with saturated ammonium chloride solution, dried, and evaporated. The nmr spectrum of the product showed none of the expected resonances of the bicyclic alcohol, although some of the material appeared not to be the starting alcohol. Very little reaction had occurred, however.

The carbene addition reaction was carried out as described for the cyclobutene ester, using 1.0 g of alcohol, 0.6 g of cuprous chloride and 10 g of nitrosomethylurea. Although the product was not the desired bicyclic alcohol, some reaction had taken place, as the nmr spectrum was not that of the starting material. The product was not identified.

The acetate ester of the alcohol was prepared by treatment of the alcohol with acetic anhydride and treated with

diazomethane in the presence of cuprous chloride catalyst. The nmr spectrum of the reaction mixture upon work-up showed only starting material. The reaction was carried out again, using ethyl diazoacetate rather than diazomethane as the carbene precursor. Filtration of the catalyst and evaporation of solvent yielded a mixture, which was identified by nmr as diethyl maleate, diethyl fumarate, and starting material.

Attempts to prepare 3,3-dimethylbicyclo[2.1.0]pentane-1-carboxaldehyde

A number of attempts to prepare the title aldehyde were carried out, without success. Reduction of bridgehead nitrile 16 with lithium aluminum hydride according to the procedure of Smith and Rogier (124) yielded only a minute amount of aldehyde, as shown by the presence of a small peak in the nmr spectrum at 9.65^{δ}, while the remaining material was unreacted nitrile and completely reduced amine. The procedure of Brown and Garg (125) utilizing lithium triethoxy aluminum hydride also yielded little or no aldehyde. Attempted reduction with diisobutyl aluminum hydride (126) in refluxing hexane for 3 hr, followed by stirring at room temperature for 12 hr yielded no reduction products.

Two oxidative procedures were attempted: the Cerium(IV) procedure by Young and Trahanovsky (132) for the preparation of cyclopropane carboxaldehyde from cyclopropyl carbinol, which yielded olefinic products containing no aldehyde function, and the DMSO oxidation of chlorocarbonate esters reported by Barton

(133), which yielded only a minute amount of aldehyde and much aliphatic material which showed no bicyclic ring proton resonances.

1-Phenylcyclobutene

1-Phenylcyclobutene was prepared by the method of Newman and Kaugars (178), by treatment of γ-chlorobutyrophenone with the Grignard reagent of ethylene bromide. Distillation of the crude reaction mixture (bp 60°/1 mm) yielded a mixture which showed two components by vpc analysis (SE 30 column). The nmr spectrum indicated the presence of 1-phenyl-1-butene as well as 1-phenylcyclobutene, in a ratio of 1:1. The two products could not be separated by distillation, so the mixture was allowed to stand in the presence of excess ethereal diazomethane for three days. Analysis by nmr showed no addition had occurred.

Cyclobutenyl acetate

The enol acetate of cyclobutanone was prepared by the method of Machinskaya, Smirnova, and Barkhash (202), by treatment of cyclobutanone with isopropenyl acetate. It was found, however, that separation of cyclobutenyl acetate and isopropenyl acetate by distillation as described was quite inefficient, and that good separation in fact could not be obtained. The mixture containing both enol acetates was treated with ethereal diazomethane for 20 hr and worked up in the usual manner. The nmr spectrum of the resulting yellow gel showed only cyclobutenyl acetate proton resonances, indicating that

perhaps the diazomethane had reacted preferentially with the isopropenyl acetate to give an insoluble, possibly polymeric material. A second attempt to add diazomethane to the resulting cyclobutenyl acetate gave identical results: no apparent addition.

Attempted preparation of 2,2-dicarbomethoxy-3,3-dimethylcyclobutene

The procedure of Brannock, et al. (101) for the preparation of 2,3-dicarbomethoxy-4,4-dimethylcyclobutene was followed. Attempts to isomerize this diester to the 1,2-dicarbomethoxy-3,3-dimethyl isomer were unsuccessful, however. Treatment of the diester with sodium methoxide in methanol yielded only the Michael adduct, as shown by the disappearance of the olefinic proton resonance in the nmr spectrum and the appearance of an OCH_3 resonance at 3.28δ. Heating the diester with triethylamine for 16 hr in refluxing benzene yielded no change, as did heating with sodium hydride in refluxing tetrahydrofuran for 12 hr.

Attempted preparations of 2,2,4-trimethyladipic acid

The procedure of Bardhan and Adhya (163) for the preparation of this precursor to 1,2,4,4-tetramethylcyclopenten-3-one involved a Michael addition of HCN to mesityl oxide, hydrolysis to the acid, esterification, and a Knoevenagel condensation of the resultant keto-ester with ethyl cyanoacetate. Hydrogenation and hydrolysis then yielded the diacid.

The Bardhan-Adhya procedure for the Michael addition was followed. Mesityl oxide (50 g) was dissolved in 300 ml of hot ethanol, and 65 g of potassium cyanide in 190 ml of hot water were added and heated on a steam bath for 20 min. The mixture was cooled to room temperature and 26 g of ferrous sulfate were added to form a complex with the excess cyanide, and the mixture was heated again to boiling. The ethanol was removed by distillation and the solution diluted with cold water, then extracted twice with ether. Evaporation of the ether yielded only aqueous ethanol. Continuous extraction of the aqueous solution overnight with ether yielded only aqueous ethanol. Apparently the product had been converted to the cyanohydrin, although the authors assured that these conditions would minimize cyanohydrin formation.

An alternative procedure for the Michael addition, as described by Meyer and Wolfe (203) was attempted, using dimethylformamide (DMF) as the solvent and ammonium chloride as the base. Mesityl oxide (25 g) was dissolved in 300 ml of DMF, and 37.5 g of potassium cyanide and 20 g of ammonium chloride in 200 ml of water were added. The cloudy solution was heated at reflux for 3 hr, then the solution was reduced to a volumn of 120 ml by vacuum distillation (aspirator pressure). The solution was diluted with 300 ml of cold water and extracted with methylene chloride. The orgaric phase was washed with water, dried, and the solvent evaporated, yielding 10 g of 4-cyano-4-methyl-2-pentanone (32% yield).

In an attempt to shorten the reaction sequence, the keto-nitrile was treated with the ylide of trimethyl-α-phosphono-propionate. The phosphonate ester (5.2 g) was dissolved in 5 ml of dry dimethoxyethane (DME) and placed in an addition funnel which was then fitted to a 100 ml 3-necked flask. In the flask was placed 0.93 g of a 55% dispersion of sodium hydride in mineral oil and 10 ml of dry DME. The flask was cooled in an ice bath and the phosphonate ester added dropwise. Hydrogen evolution was seen, and continued until all the ester had been added. The reaction was stirred at room temperature for 1.5 hr, then cooled again and the 4-cyano-4-methyl-2-pentanone (5 g) was added slowly. The reaction was stirred for 3 hr at 50°, quenched by addition of water, and extracted with 3 portions of ether. The organic phase was dried and the solvent was evaporated, yielding 4.2 g of a white solid. The nmr spectrum of the product showed no ester proton resonances, while the mass spectrum showed ions as high as m/e 394. No indication of the desired product was seen. The IR spectrum showed only a very weak absorption in the nitrile region, indicating that attack had occurred at the nitrile function rather than at the carbonyl group.

In an attempt to circumvent this undesired reaction, the Michael adduct was heated at reflux in concentrated hydrochloric acid for 3 hr, and the resulting keto-acid esterified by heating overnight in refluxing ethanol containing a trace of mineral acid. The resulting ester was distilled (81°/6 mm, lit (204)

97°/16 mm) and treated with the phosphonate ylide as described for the nitrile, without any production of the desired di-ester.

The next attempt involved the Knoevenagel condensation. Since malononitrile undergoes this reaction much faster than ethyl cyanoacetate, 5 g of 4-cyano-4-methyl-2-pentane and 2.6 g of malononitrile were dissolved in 50 ml of water, and 50 ml of ethanol and 0.8 g of piperidine were added. The reaction mixture was heated at 40° for 4 hr. The mixture was then poured into 10% hydrochloric acid, the ethanol removed by a rotary evaporator, and the remaining solution extracted with three portions of ether. The ether was washed with aqueous sodium bicarbonate, dried, and evaporated, leaving a black tar. Distillation removed 0.9 g of low boiling material. Crude distillation of the remaining material and recrystallization from carbon tetrachloride yielded 1.0 g of a white solid, mp 68-72°. The nmr spectrum showed three singlets in a 6:3:2 ration, and the mass spectrum exhibited a molecule ion at m/e 173, indicating that the desired addition had occurred. The yield was 14.5%. The overall yield based on mesityl oxide was 4.65%, so the procedure was abandoned.

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