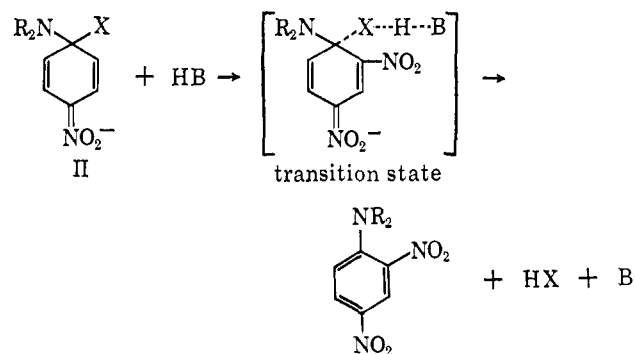


to leaving group characteristics, the curvilinear form of plots such as Figures 1, 4, and 6, the demonstration of general base catalysis, the sameness of the intercepts of inversion plots (*cf.* Figure 8) concerning catalysis by hydroxide ion and by piperidine, and the variation of solvent isotope effect with base concentration. Inasmuch as no conceivable alternative mechanism can accommodate these and other observations recorded in earlier papers, the evidence for this mechanism is compelling.

The Mechanism of Base Catalysis. We have not discussed the question of how a base catalyzes transformation of intermediate I into products. However, this question has been discussed in previous publications.^{5,6,15,38} Of several alternative mechanisms which are formally compatible with the observed kinetics, we favor one which itself comprises two steps. In the first step, intermediate I reacts reversibly with base B, losing a proton to it and forming intermediate II as well as the conjugate acid of the base. In the second and rate-limiting step, the conjugate acid (HB) of the

(38) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960), footnote 26.

base electrophilically assists separation of leaving group X from intermediate II. If this mechanism prevails, each k_3^B of eq. 2 represents the product $k'_B K'_B$, where K'_B is the equilibrium constant for reaction of I with base B to form II and HB, and k'_B is the rate coefficient for HB-catalyzed expulsion of leaving group X from II.



Acknowledgment. We thank Drs. H. Zollinger and R. H. Garst for their friendly interest in this work, and for discussions.

Photochemical Synthesis and Reactions of Carvonecamphor¹

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Contribution from the Department of Chemistry, Cornell University, Ithaca, New York. Received July 30, 1965

The cyclization of carvone (1) to carvonecamphor (2) can be conveniently carried out using a black-light source. Continued irradiation of the carvonecamphor in alcohol or aqueous dioxane results in a photolytic cleavage, giving an ester (3 or 5) or the corresponding acid (4). Photolyses of α,α -dideuteriocarvonecamphor (11) and of carvonecamphor in dioxane-deuterium oxide support the mechanism established by Quinkert for other saturated ketone photolyses, a mechanism involving intramolecular hydrogen transfer in an intermediate diradical. When 2 is irradiated in benzene-*t*-butylamine containing oxygen, the expected unsaturated acid (19) and a rearranged unsaturated acid (20) are produced, accompanied by the ketene-derived amide (7). Catalytic reduction of the methyl ester of 19 gives 3 as a minor product, along with its C-5 epimer (22); chemical reduction gives chiefly 3, correlating the two types of photolysis products. The contrast between the solution photolysis of carvonecamphor and of camphor is rationalized by considering steric requirements.

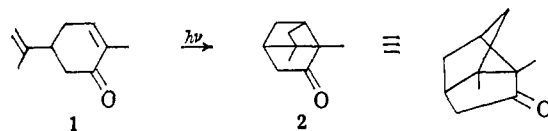
Introduction

The intermolecular photochemical addition of olefins to α,β -unsaturated ketones has recently been shown to be a synthetic reaction of considerable usefulness.³

(1) The partial support of this work by a research grant (NSF-G22541) from the National Science Foundation is acknowledged with pleasure.

(2) National Science Foundation Cooperative Graduate Fellow, 1962-1965.

However, the analogous intramolecular photochemical cycloaddition between an isolated double bond and the double bond of an α,β -unsaturated ketone has been effected only in the case of the well-known cyclization of carvone (1) to carvonecamphor (2).^{4,5} If this type



of intramolecular reaction were a general one, it would provide a convenient means of synthesizing various bi- and tricyclic small-ring molecules. As a preliminary to investigating such cycloadditions, we sought to maximize the yield of carvonecamphor, and to simplify its method of preparation. In the course of this investigation, a previously undescribed photolytic cleavage of carvonecamphor was discovered and investigated in detail.

Discussion

Carvonecamphor was characterized in 1957 by Büchi and Goldman,⁵ who prepared it in 9% yield by irradiation of carvone in sunlight for 6 months, essentially the procedure of Ciamician and Silber.⁴ Artifi-

(3) See, for example: (a) P. E. Eaton, *J. Am. Chem. Soc.*, **84**, 2454 (1962); (b) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *ibid.*, **86**, 5570 (1964).

(4) G. Ciamician and P. Silber, *Chem. Ber.*, **41**, 1928 (1908).

(5) G. Büchi and I. M. Goldman, *J. Am. Chem. Soc.*, **79**, 4741 (1957).

cial light sources seem not to have been employed, and our first objective was to develop a less leisurely technique which would be independent of sunlight.

We found that carvonecamphor is readily produced from carvone by irradiation through a Pyrex filter, either with a high-pressure mercury-vapor lamp or with black-light fluorescent lamps. When the progress of the reaction was followed by gas-liquid chromatography, however, it was observed that the concentration of carvonecamphor increased to a maximum and then declined, while simultaneously a new, slightly less volatile product was formed.

Table I shows this behavior in detail for a black-light irradiation of 400 mg. of carvone in absolute ethanol. The table indicates that carvonecamphor is photolyzed at about the same rate as it is formed. The photolysis product is an ester whose composition corresponds to the addition of the elements of ethanol to carvonecamphor; it is shown in the sequel to have structure 5.

Table I. Irradiation of Carvone in Various Solvents

Solvent	Days irradiated	Mole % of carvone	Mole % of carvonecamphor	Mole % of photolysis prod.
Absolute ethanol	1	87	13	...
Absolute ethanol	2	62	32	6
Absolute ethanol	3	32	44	24
Absolute ethanol	4	...	44	56
Absolute ethanol	5	...	27	73
Absolute ethanol	6	...	12	88
Absolute ethanol	7	...	3	97
Ethanol, 95%	3	20	46	34
Absolute methanol	3	25	46	29
Absolute ethanol	3	32	44	24
Dimethylformamide	3	74	13	13
Acetonitrile	3	88	12	...
Benzene	3	95	5	...
Ethyl ether	3	96	4	...
Cyclohexane	3	98	2	...

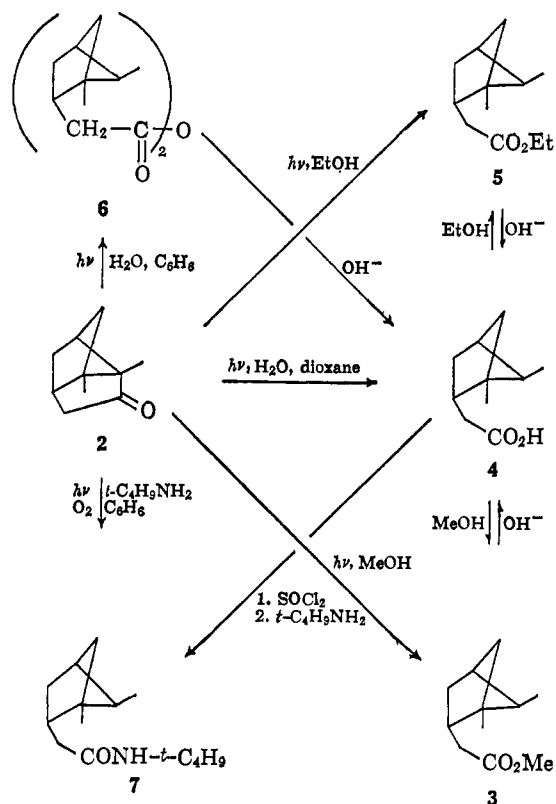
Table I also indicates that the rate of cyclization of carvone increases greatly as the polarity of the solvent increases. Accordingly, in order to avoid inconveniently long reaction times, all subsequent experiments with carvone were conducted in methanol, ethanol, or aqueous dioxane.

Experimentation with various solvents and with the two available light sources suggested that a convenient method for the preparation of carvonecamphor would be black-light irradiation of carvone in 95% ethanol. By this procedure, 17 g. of carvonecamphor (35% yield) could be obtained from 50 g. of carvone after irradiation for 23 days.

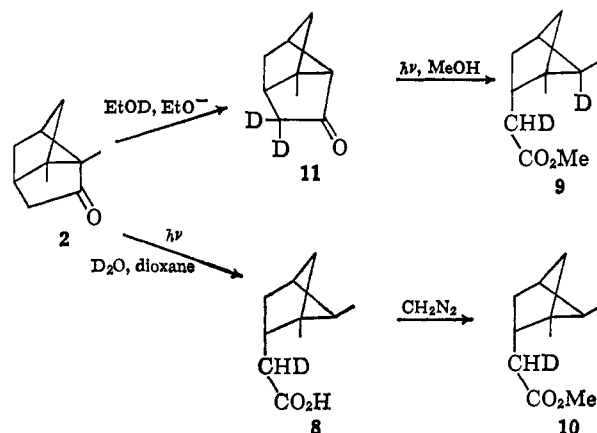
During these irradiation experiments, it was noted that the intermediate concentration of carvonecamphor was always much greater when the black lights were used than when the high-pressure mercury-vapor lamp was used. Emission of the black lights is maximal around 355 m μ , and practically nil below 320 m μ , whereas 50% of the energy at 310 m μ would be transmitted by the Pyrex filter used for the continuous spectrum of the high-pressure mercury-vapor lamp. These observations confirm the expectation that the cyclization of carvone is effected by light of wave length longer

than that required for the photolysis of carvonecamphor.

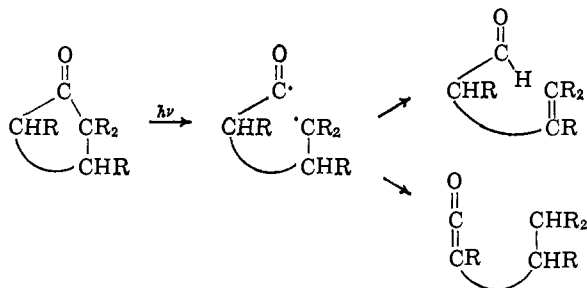
For the preparation of the photolysis product, the high-pressure mercury-vapor lamp is ideal, producing 70% yields of the methyl and ethyl esters direct from carvone within a few days. Irradiation of carvone in ethanol or methanol produces the esters, and, in dioxane-water, the corresponding acid. Irradiation of carvonecamphor in benzene containing water produces the acid anhydride, and, in benzene containing *t*-butylamine (and oxygen), the *t*-butylamide (accompanied by the unsaturated acids described below). These derivatives have been interconverted as shown below.



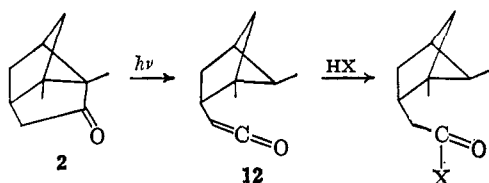
Irradiation of carvonecamphor in dioxane-deuterium oxide results in the introduction of one deuterium atom α to the carboxyl group, as will be proved later. Irradiation of α, α -dideuteriocarvonecamphor in methanol results in a product with one deuterium atom α to the methoxycarbonyl group, and one deuterium atom at C-5.



The photochemical conversion of cycloalkanones to a mixture of an unsaturated aldehyde and a saturated carboxylic acid derivative has long been known as a result of the classical studies by Ciamician,⁶ and is now a well-understood reaction as a result of the recent work of Quinkert.^{7,8} In this reaction, cyclic ketones undergo homolytic cleavage of the bond between the carbonyl group and the adjacent more substituted carbon atom, followed by intramolecular transfer of a hydrogen atom to one of the two resultant radical sites, forming either an unsaturated aldehyde or a saturated ketene. In reactive solvents, the ketene



normally reacts further to give the expected acid derivatives. That carvonecamphor follows the latter course, leading to the production of structures 3 through 9 from reaction of the ketene (12) with the solvent, is proved as follows.



The molecular formulas of the photolysis products are established by elemental analytical data, n.m.r. spectra, and mass spectra. The infrared and n.m.r. spectra show that the products can contain neither double bonds nor three-membered rings.

The mass spectra of the methyl ester 3 and the deuterated methyl ester 10 exhibit parent peaks of m/e 182 and 183. The peaks of these two compounds between m/e 25 and 120 are essentially identical. Above 120, they are identical, except that every peak in the spectrum of 3 occurs at one higher mass number in the spectrum of 10. The peaks above 120 would all be expected to arise from fragmentation of the methoxycarbonyl group plus other parts of the molecule. That all peaks of lower mass number are the same in the two spectra implies that the deuterium atom is located on the carbon α to the carbonyl and is part of a methylene group in a side chain that is easily lost. The base peak, 108, corresponds to loss of a methoxycarbonylmethyl group, plus a proton.

The n.m.r. spectrum of 10 compared to that of 3 confirms the absence of one proton in the τ 7.4 to 7.9

(6) (a) G. Ciamician and P. Silber, *Chem. Ber.*, **36**, 1582 (1903); (b) *ibid.*, **40**, 2415 (1907); (c) *ibid.*, **41**, 1071 (1908); (d) *ibid.*, **41**, 1928 (1908); (e) *ibid.*, **43**, 1340 (1910).

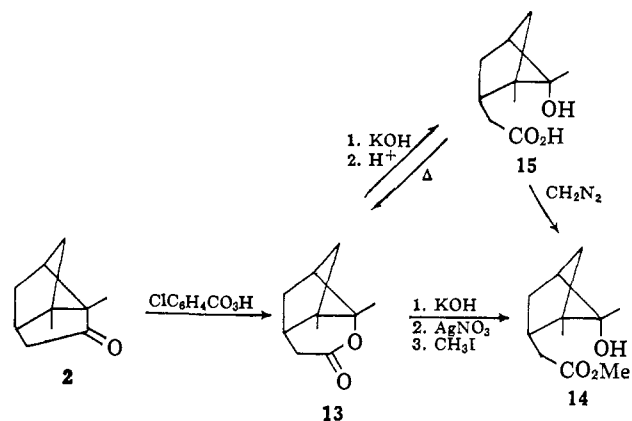
(7) G. Quinkert, *Angew. Chem.*, **77**, 229 (1965).

(8) O. L. Chapman, "Advances in Photochemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1963, p. 366 ff.

region, attributable to the protons α to the methoxycarbonyl group. Thus the presence of a CH_2COX group is established.

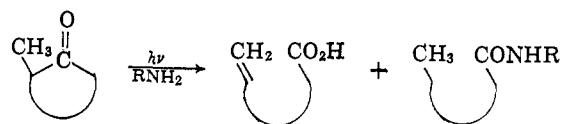
The n.m.r. spectra of the interconvertible photolysis products 3, 5, and 7 show a methyl singlet at τ 9.09 \pm 0.01 and a methyl doublet centered at 8.96 \pm 0.01 ($J = 6$ c.p.s.). Hence, one of the quaternary methyl groups of carvonecamphor has been converted into a secondary methyl group. Formulas 3 through 9 are the only ones which can be derived without unlikely structural change and which fit the above data.

A hydroxylated analog (14) of structures 3 through 9 was prepared from carvonecamphor, as shown below. In the n.m.r. spectrum of 14, the methyl groups appear



as singlets at τ 9.01 and 8.69, the latter ascribable to the methyl group at C-5, α to the oxygen atom. If the hydroxyl group of 14 were replaced by a hydrogen atom, the methyl peaks would be shifted upfield, and if only one peak appeared above 9.01, it would have to be due to the bridgehead methyl group, and the lower field peak would be split into a doublet with $J \cong 6$ c.p.s. This kind of spectrum is exactly that observed for the photolysis products.

To verify that structures 3 through 9 are in fact correct,⁹ we conducted a photolysis of carvonecamphor in the presence of oxygen, following the procedure of Quinkert.^{10,11} Carvonecamphor was irradiated with a high-pressure mercury-vapor lamp in a benzene solution containing *t*-butylamine and oxygen. By this procedure, Quinkert has cleaved several ketones to unsaturated acids as shown below. Yields of the

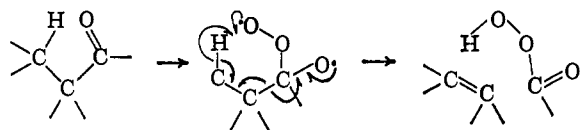


unsaturated acids were of the order of 15%, accompanied by larger amounts of the ketene-derived saturated amides. Quinkert postulates that the reaction proceeds *via* a hydroxy-hydroperoxy diradical.^{10,11}

(9) A synthesis of the photolysis products was begun by attempting to prepare the xanthate of 15 (which might either undergo a Chugaev reaction or rearrange to the dithiolcarbonate) by following a procedure which was successful for 1,6,6-trimethylbicyclo[2.1.1]hexan-2 α -ol-*exo*-5-carboxylic acid, as described by J. C. Shelton, Ph.D. Thesis, Cornell University, 1964, and by attempting to displace the carboxyl group of the lactone 13 with mercaptide ion. All these attempts were unsuccessful.

(10) G. Quinkert and H. G. Heine, *Tetrahedron Letters*, 1659 (1963).

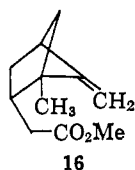
(11) G. Quinkert, B. Wegemund, F. Homburg, and G. Cimbolek, *Chem. Ber.*, **97**, 958 (1964).



The photolysis of carvonecamphor in the presence of oxygen proceeds to give the expected saturated amide **7** (94% yield) and (contrary to expectation) an acid fraction which was converted into a mixture of two methyl esters by treatment with diazomethane. Gas-liquid chromatography of this mixture gave two isomeric esters, $C_{11}H_{16}O_2$, the first in an over-all yield of 1.5%, and the second in 3.7%.

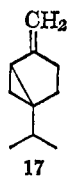
A similar experiment in the absence of oxygen proved that the two acids do not arise from oxidation of unsaturated aldehydes which might have been produced in small yields.

The first ester isolated by gas-liquid chromatography has absorption in the infrared at 3.26, 5.91, and 11.52 μ , corresponding to a terminal methylene group. The abnormally short wave length 5.91- μ band, in conjunction with the 11.5- μ band, is characteristic of a methylenecyclobutane.¹² The spectrum of this ester resembles very closely that of *exo*-5-chloro-6-methylenecyclo[2.1.1]hexane (5.90 μ)¹³ and of 6-methylene-1,5,5-trimethylbicyclo[2.1.1]hexane (3.29, 5.96, and 11.56 μ).¹⁴ The first ester is therefore assigned structure **16**.



The n.m.r. spectrum of **16** shows only one methyl group attached to carbon, as a singlet at τ 8.88. Two one-proton singlets at τ 5.61 and 5.72 may be assigned to the terminal methylene group. A one-proton multiplet at τ 7.26 is significant in appearing at such low field. It is ascribable to the allylic bridgehead hydrogen, which appears at τ 7.15 in bicyclo[2.1.1]hexan-5-one.¹⁵

The second ester has strong absorption in the infrared at 6.07 and 11.55 μ and in the carbon-hydrogen region at 3000, 3026, 3067, and 3080 cm^{-1} . These absorptions closely resemble those of sabinene (**17**),



which shows terminal methylenic absorptions at 6.04 and 11.56 μ due to the terminal methylene,¹⁶ and at 2990, 3031, and 3069 cm^{-1} characteristic of the cyclopropane moiety.^{17a,b} The 3080- cm^{-1} absorption

(12) D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956).

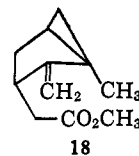
(13) J. Meinwald, C. B. Jensen, A. Lewis, and C. Swithenbank, *J. Org. Chem.*, **29**, 3469 (1964).

(14) J. Meinwald, A. Lewis, and P. Gassman, *J. Am. Chem. Soc.*, **84**, 977 (1962).

(15) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *ibid.*, **84**, 1594 (1962).

(16) V. Herout, *Chem. Listy*, **46**, 438 (1952).

is typical of terminal methylene groups. On the basis of this evidence, taken along with considerations presented below, the second ester is assigned structure **18**.



The n.m.r. spectrum of **18** shows two cyclopropane protons at about τ 9.3, only one methyl group attached to carbon (a singlet at 8.76), and a pair of one-proton doublets ($J = 2$ c.p.s.) at 5.29 and 5.40, due to the terminal methylene group. The ultraviolet absorption spectrum of **18** ($\lambda_{max}^{cyclohexane}$ 200 $m\mu$ (ϵ 11,300)) is typical of a conjugated, exomethylene cyclopropane chromophore in both its wave length and intensity.^{17c}

The acid **19** obtained from hydrolysis of the first ester (**16**) is converted by treatment with acid under mild conditions to a new acid (**20**), which, upon esterification with diazomethane, yields the second ester (**18**). This facile conversion of a bicyclo[2.1.1]hexane into a bicyclo[3.1.0]hexane is to be expected by analogy with the rearrangement of the lactone **13** to the lactone **21** described by Büchi and Goldman.⁵

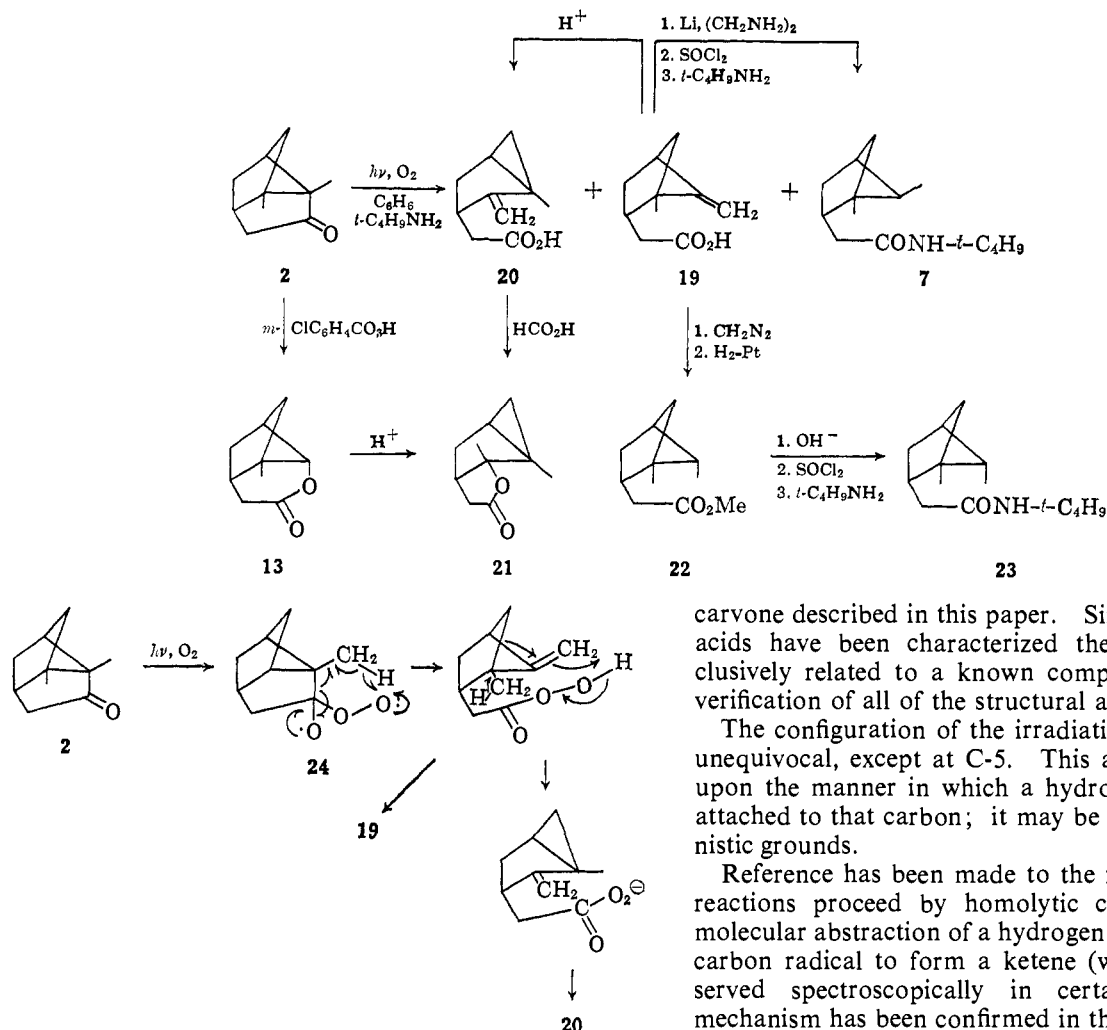
Under conditions slightly more harsh than those employed in the work-up of the photolysis mixture, however, the potassium salt of **19** is converted completely to the first ester (**16**), and none of the rearranged second ester (**18**) is formed. Therefore, acid **20** must be formed directly during the photochemical reaction, and cannot be an artifact produced in the subsequent work-up.

Nevertheless, it is still possible to assume that the photochemical reaction proceeds through the postulated hydroxy-hydroperoxy diradical (**24**) with the initial formation of the peracid corresponding to **19**. For this assumption to be tenable, a rearrangement of the peracid corresponding to **19** would have to take place immediately following its formation, before the conformation of the molecule had changed appreciably. In the conformation of the molecule immediately following the abstraction of the hydrogen atom by the hydroperoxy radical, the new acid is in the ideal position to return to the methylene carbon the proton which it had just abstracted as a hydrogen atom. Thus, although the acid **19** does not rearrange spontaneously in dilute solution, the major part of the corresponding peracid appears to rearrange at the moment of its formation.

When a solution of **20** in formic acid is allowed to stand for several hours, it is converted (72% yield) to the corresponding lactone **21**, prepared independently⁵ by Baeyer-Villiger oxidation of carvonecamphor, followed by rearrangement. A mixture melting point was undepressed.

Once the esters **16** and **18** had been characterized and converted one into another and into a known compound, experiments in catalytic hydrogenation were conducted to convert **16** to the saturated products of

(17) (a) G. V. Pigulevskii and A. I. Konokotina, *Zh. Obshch. Khim.*, **31**, 2410 (1961); (b) M. Horák, J. Šmejkal, and J. Farkaš, *Collection Czech. Chem. Commun.*, **28**, 2280 (1963); (c) we are indebted to Professor W. G. Dauben for this spectral measurement, as well as for the comparison with a number of model compounds.



carvonecamphor photolysis, **3** and **7**. All catalytic hydrogenations resulted in two products, a small amount of an ester with g.l.p.c. retention time coincident with that of **3**, and a larger amount of an ester of shorter retention time. The latter ester was converted to the corresponding *t*-butylamide, which melted 20° higher than **7**. The new ester and amide were found to be isomers of **3** and **7**, according to elemental analytical data; they give n.m.r. spectra with a methyl singlet at τ 8.93 and a methyl doublet at 9.18 ($J = 6.5$ c.p.s.); their infrared spectra were extremely similar to those of **3** and **7**. On this basis, they are considered to be the C-5 epimers, **22** and **23**.

Since catalytic hydrogenation produces preferentially the unsought stereochemistry, a chemical reduction was sought which would favor the desired product (**3**). When **19** is reduced using lithium in ethylenediamine,¹⁸ the ratio of **3** to **22** in the product, as determined by g.l.p.c. analysis after treatment with diazomethane, was about 7:2, and the infrared spectrum of the mixture was indistinguishable from that of **3**. The mixture was converted into the corresponding *t*-butylamide, which was recrystallized until a mixture melting point with authentic **7** was undepressed.

The conversion of the unsaturated ester **16** to the saturated products of photolysis **3** and **7** establishes the interrelationship of all the photoderivatives of

carvone described in this paper. Since the unsaturated acids have been characterized themselves, and conclusively related to a known compound, it completes verification of all of the structural assignments.

The configuration of the irradiation products is also unequivocal, except at C-5. This assignment depends upon the manner in which a hydrogen atom becomes attached to that carbon; it may be decided on mechanistic grounds.

Reference has been made to the fact that analogous reactions proceed by homolytic cleavage and intramolecular abstraction of a hydrogen atom by the hydrocarbon radical to form a ketene (which has been observed spectroscopically in certain cases).¹⁹ This mechanism has been confirmed in the present case.

The photolysis of a cycloalkanone to give a saturated acid has not previously been carried out in a deuterium-containing solvent. As has been shown above, when the photolysis of ordinary carvonecamphor takes place in a solvent the only active hydrogen of which is deuterium, one deuterium atom is incorporated α to the carbonyl group. Several mechanisms might be imagined which would leave the methylene group intact, but the only reasonable mechanism in which one hydrogen atom would be replaced by a deuterium atom would involve the formation of a ketene. The ketene then would react with any solvent containing active hydrogen, to form the appropriate acid derivative.

The manner in which the ketene is formed must involve abstraction of a methylene hydrogen, either intra- or intermolecularly, by the radical at C-5, since in the last-mentioned experiment only deuterium atoms are otherwise available. This mode of abstraction was confirmed by preparation and photolysis of α,α -dideuteriocarvonecamphor (**11**) in methanol solution. The product (**9**) contains only deuterium at C-5, as shown by the appearance in the n.m.r. spectrum of a methyl singlet which replaces the methyl doublet of **3**. The second deuterium atom was retained, as expected, α to the methoxycarbonyl group. Recently, Quinkert has carried out a similar experiment involving migration of a deuterium atom,¹⁹ and our results are in good accord with his.

(18) E. J. Corey and E. W. Cantrall, *J. Am. Chem. Soc.*, **81**, 1745 (1959).

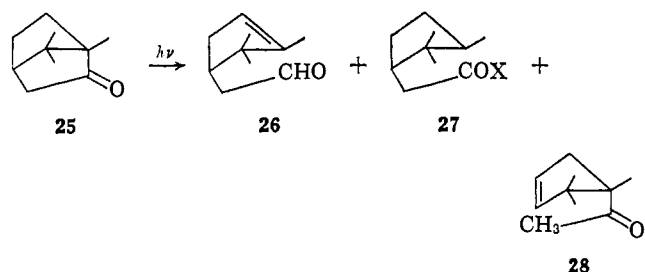
(19) G. Quinkert, E. Blanke, and F. Homburg, *Chem. Ber.*, **97**, 1799 (1964).

The reaction has been assumed to be intramolecular, which is entirely reasonable, especially considering the small concentrations employed in some of these experiments. The intramolecular nature of the reaction is substantiated by the fact that even in a solution saturated with oxygen, the photolysis occurs to give the crude ketene-derived product in 94% yield, whereas reaction of the hydrocarbon radical with oxygen would be expected to be orders of magnitude more rapid than bimolecular reaction with another carvonecamphor molecule.²⁰

Since the radical at C-5 must abstract the hydrogen atom intramolecularly, this hydrogen atom must be *endo* in the product. It follows that C-5 epimers (**22** and **23**) produced by catalytic reduction must be *endo* methyl compounds. This argument completes the assignment of structure and configuration to all new compounds in this paper.

It appears from these results that the *endo* side of these 2-substituted bicyclo[2.1.1]hexanes is the more hindered. A further consequence is that, just as hydrogen atoms in an *endo* position on the one carbon bridge of a bicyclo[2.1.1]hexane appear at higher field in the n.m.r. spectrum than those in an *exo* position, other things being equal,²¹ in like manner a methyl group in an *endo* position appears at higher field than one in an *exo* position. Thus, in the n.m.r. spectra of the *endo* methyl compounds (**22** and **23**), the methyl doublet is centered at τ 9.18, whereas it appears at 8.96 for the *exo* methyl compounds (**3**, **5**, and **7**).

In concluding it is interesting to note that the diradical arising from photolysis of camphor (**25**) abstracts a hydrogen atom to give predominantly the unsaturated aldehyde **26**, and only 1% or less of the ketene derivative **27**,²² whereas the diradical from carvonecamphor abstracts hydrogen in the opposite sense to give only the ketene, with no detectable amount of unsaturated aldehyde.

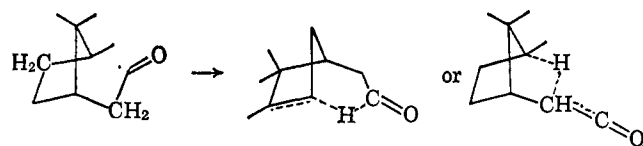


This behavior is easily explained by considering steric effects in the transition states leading to the possible products. Quinkert²² has already suggested this sort of argument to explain the behavior of camphor. In camphor, the six-membered ring (or bicyclo[3.2.1]octyl type) transition state leading to the formation of the unsaturated aldehyde is evidently highly favored over the strained five-membered ring (or bicyclo[2.2.1]heptyl type) transition state leading to the ketene.

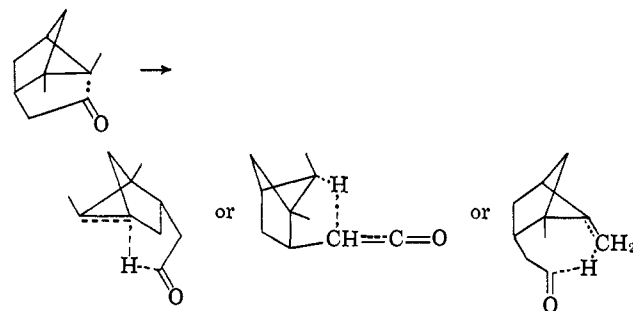
(20) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 169, 170.

(21) (a) J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769 (1961); (b) R. Srinivasan, *ibid.*, **83**, 4923 (1961).

(22) G. Quinkert, B. Wegemund, and E. Blanke, *Tetrahedron Letters*, 221 (1962).



In the case of carvonecamphor, however, the hydrogen atom involved in the former transition state is drawn away from the carbonyl, and has become a bridgehead hydrogen atom, the abstraction of which would lead to a product violating Bredt's rule. The



only other hydrogen atom on a carbon atom adjacent to the radical is one of those in the C-5 methyl group. Evidently, either the seven-membered ring transition state which could form after the methyl group had moved to an *endo* position is unfavorable, or else the methyl group has no time to epimerize before the reaction leading to ketene is complete. The analog of the bicyclo[2.2.1]heptyl transition state, leading to a ketene, is the only one through which the photolysis of carvonecamphor progresses.²³

In summary, these studies on the photochemistry of carvone have resulted not only in a convenient laboratory technique for the preparation of carvonecamphor, but also in additional support for the Quinkert mechanisms for the anaerobic and oxidative photolyses of non-conjugated ketones. Finally, they have made a group of polysubstituted bicyclo[2.1.1]hexanes readily available in a single experimental step, starting from carvone.

Experimental Section

Melting points were taken in capillaries and are corrected. Microanalyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark. Infrared spectral data reported in microns were obtained with a Perkin-Elmer Infracord, and those reported in cm^{-1} with a Perkin-Elmer Model 337 grating spectrophotometer. Ultraviolet spectra were obtained with a Model 14 Cary recording spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer, and taken in carbon tetrachloride solution with an internal

(23) A more surprising aspect of the comparative behavior of camphor and carvonecamphor is that camphor is reported^{23, 24} to give upon irradiation in several solvents a methyl ketone assigned structure **28** for which no analogy can be found, and which is produced in yields comparable to those of the normal unsaturated aldehyde **26**. Yet carvonecamphor is converted, in high yields, only to the expected ketene derivatives. It has already been pointed out that the reaction path leading to unsaturated aldehyde becomes impossible for carvonecamphor, but there is no such obvious reason why carvonecamphor should not produce a methyl ketone analogous to **28**. Whatever the reason for this difference in behavior, the results with carvonecamphor are readily understood, while the photochemistry of camphor remains in part aberrant, and merits further attention.

(24) R. Srinivasan, *J. Am. Chem. Soc.*, **81**, 2604 (1959).

standard of tetramethylsilane unless otherwise noted. Mass spectra were obtained through the courtesy of Dr. A. F. Thomas, Firmenich & Cie, Geneva, Switzerland. Gas-liquid partition chromatography (g.l.p.c.) was conducted using either an Aerograph Hy-Fi Model 600, an Aerograph Model 660, or, for preparative work, a Beckman GC-2 gas chromatograph. Columns employed in the Aerographs were 5 ft. \times $\frac{1}{8}$ in. and contained either 5% SE30 silicone rubber gum on 60-80 mesh acid-washed Chromosorb W, or 20% Carbowax 20 M on 80-100 mesh Chromosorb P. The column used in the Beckmann chromatograph was 10 ft. \times $\frac{3}{8}$ in., packed with 15% SE30 silicone rubber gum on 60-80 mesh acid-washed Chromosorb W.

Except where noted, organic liquids from liquid-liquid partition separations were dried by swirling over anhydrous potassium carbonate, unless the solute was an acid, in which case the solution was dried over anhydrous magnesium sulfate. Solutions were evaporated by means of a rotary evaporator, and the residues were always kept under vacuum for a time before weighing.

Solvents used in photolysis were obtained as follows: anhydrous methyl alcohol, AR, benzene, AR, and anhydrous ether, AR, from Mallinckrodt; cyclohexane, b.p. 80-81°, Spectroquality dioxane, and Spectroquality acetonitrile from Matheson Coleman and Bell; dimethylformamide, Certified Reagent, from Fisher; and absolute and 95% ethanol from U. S. Industrial Chemicals. Solvents were used directly without further purification.

The (+)-carvone used was obtained from K & K Laboratories, and was redistilled twice. It showed b.p. 114-115° (20 mm.), n_D^{20} 1.4994, $[\alpha]_{5461}^{20} +70.9^\circ$ (c 0.96, 95% ethanol) (lit.²⁵ n_D^{20} 1.4990, $[\alpha]_{5461}^{20} +73.2^\circ$). The (-)-carvone was obtained from Fluka and was used directly. All formulas drawn are those corresponding to (+)-carvone.

Photochemical reactions were carried out in one of two ways. Reference to the use of a Hanovia lamp indicates that the solution irradiated was contained in a foot-long, vertical Pyrex vessel in the center of which was a water-cooled immersion well made of either quartz or Pyrex, containing a 550-w. Hanovia high-pressure quartz mercury-vapor lamp, number 673A-36. Reference to the use of black lights indicates that the solution was contained in a Pyrex vessel suspended in the center of a metal cylinder lined with eight F15T8/BL Sylvania black-light lamps. All photochemical reactions, except for those involving oxygen, were carried out at room temperature after bubbling nitrogen vigorously through the solution for 1 hr., and then either allowing nitrogen to bubble slowly through the reaction mixture during irradiation, or sealing the vessel.

Irradiation of Carvone (1) in Various Solvents. One-half per cent solutions of (+)-carvone in several different solvents were irradiated with the black lights for varying lengths of time, then analyzed by g.l.p.c. (Carbowax, 150°). (See Table I.) In all cases, the peaks observed of retention time greater than 3.0 min. were among those due to carvone ($T_r = 12.6$ min.), carvonecamphor ($T_r = 6.1$ min.), the ethyl ester 5 ($T_r = 7.9$ min.), the methyl ester 3 ($T_r = 6.7$ min.),

(25) Y. R. Naves and P. Bachmann, *Helv. Chim. Acta*, 29, 61 (1946).

and an unassigned peak²⁶ ($T_r = 7.9$ min.) appearing when dimethylformamide was the solvent.

Table I shows the relative mole percentages of these compounds as determined by measuring the g.l.p.c. peak areas and multiplying each area by a correction factor obtained from g.l.p.c. analysis of a known solution of carvonecamphor, the ethyl ester 5, and carvone.

The benzene solution after irradiation for 3 days was evaporated, and the infrared spectrum of the residue was identical with that of the starting material, carvone, except for several weak peaks which are all characteristic of carvonecamphor. This result and the results from the preparation of the esters 3 and 5 indicate that the relative mole percentages in the table are close to the absolute mole percentages of carvone and all compounds derived from it.

The solution in 95% ethanol was worked up by distillation of the ethanol, followed by water-ether extraction, and the product was subjected to small-scale preparative g.l.p.c. on the Aerograph 660 (Carbowax, 153°). The compounds collected were identified by their infrared spectra. The first was carvonecamphor, m.p. 96-101° (lit.⁵ m.p. 101-104°), the second, the ethyl ester 5, and the third, the starting material, carvone.

Carvonecamphor (2). A solution of 50.0 g. of (-)-carvone in 2500 ml. of 95% ethanol in a 3-l. round-bottom Pyrex flask was irradiated with the black lights with continuous stirring for 23 days, at which time g.l.p.c. analysis showed the solution to be composed of carvonecamphor, ester 5, and carvone in the ratio 5:1:1. The solution was brought to pH 7 with a few milliliters of aqueous ammonia, 100 ml. of benzene was added, and the solvent was removed by distillation through a Podbielniak column at reduced pressure. The residue was distilled at 13 mm. to give as fraction 1 (b.p. 88-92°), 21.4 g. of a slush which was nearly pure carvonecamphor as indicated by g.l.p.c. analysis, and as fraction 2 (b.p. 92-95°), 8.4 g. of a liquid mixture of roughly equal amounts of carvonecamphor, ester, and carvone.

Fraction 2 was dissolved in a solution of 1 g. of potassium hydroxide in 5 ml. of water and 20 ml. of ethanol, and heated under reflux for 1 hr. The solution was found to be neutral. Another gram of potassium hydroxide was added and heating was continued for 3 hr. The product was recovered by ether extraction and placed in a 1-l. flask with 100 ml. of water. Saturated potassium permanganate solution was added in small portions, with periodic addition of Dry Ice chips to keep the solution neutral, until 133 ml. had been added and the color persisted for several minutes. The mixture was steam distilled to give 1.74 g. of nearly pure carvonecamphor. This product was combined with fraction 1, and the saponification and oxidation steps were repeated. The product from steam distillation was sublimed at 100° (10 mm.) to give 17.3 g. (35%) of carvonecamphor, m.p. 99-103°; the infrared spectrum was identical with that reported by Büchi and Goldman⁵; and its n.m.r. spectrum (τ -

(26) This peak is not due to the N,N-dimethylamide of the acid 6, for that amide was synthesized from 6, and has $T_r = 50$ min. The dimethylformamide is reported by Fisher to contain less than 0.01% of ethanol, which is not quite enough to produce a peak of the size observed.

scale) showed singlets at 8.99 and 8.95 (3 protons each), singlets at 8.52 and 8.65 (the area from 8.5 to 8.9 = 2 protons), and multiple peaks between 7.5 and 8.3 (6 protons).

A semicarbazone, m.p. 231–233° dec., was prepared in the usual manner. Carvonecamphor was regenerated from the semicarbazone by steam distillation from water containing phthalic anhydride, but the carvonecamphor so obtained was contaminated with side products.

1-exo-5-Dimethyl-syn-2-ethoxycarbonylmethylbicyclo[2.1.1]hexane (5). A solution of 2.50 g. of (+)-carvone in 500 ml. of absolute ethanol was irradiated for 7 days with the Hanovia lamp in a Pyrex well. The solution was concentrated by distillation; water and ether were added to the residue. The ether layer was washed with sodium bicarbonate solution and with water, dried, and evaporated. Steam distillation of the residue gave 2.4 g. (73%) of fairly pure 5. A small portion was purified by g.l.p.c. (Carbowax, 124°), followed by a short-path distillation: n_{D}^{25} 1.4559; $\lambda_{\max}^{\text{CCI}_4}$ 5.76 (s), 6.78 (m), 6.87 (s), 6.91 (s), 7.06 (w), 7.25 (s), 7.38 (w), 7.59 (m), 7.72 (s), 8.45 (s), and 9.66 (s) μ ; n.m.r. spectrum (τ), a quadruplet centered at 6.03 (2 protons, $J = 7$ c.p.s.), and a complex pattern between 7.5 and 9.5 (with a total area 10.1 times that of the quadruplet), including peaks at 8.66, 8.78, 8.91, 9.02, and 9.09 (1.0, 1.7, 2.7, 1.4, and 2.7 protons) which are interpreted as a triplet centered at 8.78 (3 protons, $J = 7$ c.p.s.), a skew doublet centered at 8.97 (3 protons, $J = 7$ c.p.s.) and a singlet at 9.09 (3 protons).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; OEt, 22.95. Found: C, 73.80; H, 10.24; OEt, 20.54.

Hydrolysis of the Ethyl Ester 5. A mixture of 622 mg. of 5 and 20 ml. of 5% sodium hydroxide solution was heated under reflux with vigorous stirring for 3.5 hr. The resulting homogeneous solution was extracted with ether, acidified, and extracted again with ether. The second ether extract was washed, dried, and evaporated to yield 529 mg. of a pale yellow oil. Short-path distillation at 120° (8 mm.) gave 480 mg. (89%) of the colorless acid 4: n_{D}^{25} 1.4691; $\lambda_{\max}^{\text{neat}}$ 3.5 (m, broad), 5.88 (s), 6.90 (m), 7.09 (s), 7.25 (m), 7.70 (s), 8.19 (m), 8.30 (w), 8.54 (w), 8.77 (w), 9.27 (w), 9.96 (w), and 10.6 (m, broad) μ ; n.m.r. spectrum (pure liquid 4) (τ), a singlet at -2.40 (1 proton), a singlet at 9.04 (3 protons), a doublet centered at 8.93 (3 protons, $J = 7$ c.p.s.), and a series of peaks stretching from 7.3 to 9.0 (9 other protons).

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.56.

syn-2-Carboxymethyl-1-exo-5-dimethylbicyclo[2.1.1]hexane (4) Directly from Photolysis. A solution of 5.00 g. of (+)-carvone in 1150 ml. of 30% dioxane in water was irradiated for 80 hr. with the Hanovia lamp in a Pyrex well, with two interruptions to clean polymer from the inner part of the apparatus. Concentrated sodium bicarbonate solution was added until litmus changed to blue, and then 5 g. of sodium bicarbonate, 500 ml. of water, and 500 ml. of ether were added. A large amount of polymer was insoluble in either phase. The aqueous layer was extracted thoroughly with ether to remove neutral material, acidified with sulfuric acid, and extracted with three 150-ml. portions of ether. The combined ether extract was washed with water,

dried over magnesium sulfate and Norit, and evaporated to give 2.24 g. (40%) of a colorless acid with an infrared spectrum similar to pure 4, but slightly contaminated as evidenced by small additional peaks.

Esterification of the Acid 4. A solution of 94 mg. of 4 in 15 ml. of absolute ethanol and 4 ml. of benzene was distilled until 3 ml. was collected. Then 10 mg. of *p*-toluenesulfonic acid was added and the solution was heated under reflux for 12 hr. in a micro Soxhlet apparatus containing a thimble full of anhydrous magnesium sulfate. Most of the ethanol was removed by distillation, and ether was added. The resultant solution was washed with water, dried, and evaporated to give 87 mg. (71%) of the ester 5, with an infrared spectrum superimposable on that of 5 obtained by irradiation of 1 in ethanol.

1-exo-5-Dimethyl-syn-2-methoxycarbonylmethylbicyclo[2.1.1]hexane (3). A solution of 11.0 g. of (-)-carvone in 1100 ml. of absolute methanol was irradiated for 48 hr. with the Hanovia lamp in a Pyrex well. The solution was carefully distilled to a volume of 60 ml., and poured into a solution of 11 g. of potassium permanganate in 500 ml. of water. After several minutes, the permanganate color disappeared, and the solution was steam distilled. The distillate was extracted with ether, and the ether was washed with sodium carbonate solution, dried, and evaporated, leaving 9.13 g. (66%) of 3 as a colorless oil. This product gave a single, symmetrical peak of $T_r = 6.2$ min. upon g.l.p.c. analysis (Carbowax, 150°). A small portion was hydrolyzed, as described for the ethyl ester 5, to give 4, and 4, on treatment with diazomethane, yielded 3. Of the remaining crude 3, 8.10 g. was distilled and 7.32 g. was collected, b.p. 83–84° (7 mm.): n_{D}^{25} 1.4546; $\lambda_{\max}^{\text{neat}}$ 5.75 (s), 6.99 (m), 7.26 (m), 7.61 (m), 7.73 (m), 7.83 (m), 7.99 (m), 8.24 (w), 8.41 (s), 8.53 (s), 8.64 (s), 9.03 (w), 9.27 (w), 9.48 (w), 9.86 (m), 10.10 (w), 10.56 (w), 11.2 (w), and 11.83 (w) μ ; n.m.r. spectrum (τ), a singlet at 6.44 (3.0 protons), a singlet at 9.09 (3.0 protons), two peaks at 8.90 (2.2 protons) and 9.00 (1.4 protons) which must comprise a 3-proton doublet ($J = 6$ c.p.s.), and multiple peaks between 7.5 and 9.0 (of an area corresponding to 10.3 other protons); mass spectrum (the base peak followed by selected other fragments in order of decreasing intensity), m/e 108, 93, 41, 55, 85, 67, 122, 153, 141, 167, and 182.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.73; H, 10.21.

syn-2-Carboxymethyl-d-1-exo-5-dimethylbicyclo[2.1.1]hexane (8). A solution of 462 mg. of carvonecamphor in 400 ml. of dioxane and 20 ml. of deuterium oxide was irradiated for 3 days with the Hanovia lamp in a Pyrex well. Then 1 g. of sodium bicarbonate was added, most of the liquid was distilled, and the remainder was removed using a rotary evaporator. The resulting white powder was dissolved in water, and the solution was extracted with carbon tetrachloride, then acidified to pH 3 with phosphoric acid and extracted again. The second extract was evaporated to leave 380 g. (74%) of a colorless acid with an n.m.r. spectrum substantially identical with that of pure 4 between τ 8.0 and 10.0, but differing significantly between τ 7.0 and 8.0. The integration was not sufficiently

accurate to determine unambiguously the relative numbers of protons.

1-exo-5-Dimethyl-syn-2-methoxycarbonylmethyl-d-bicyclo[2.1.1]hexane (10). Diazomethane in ether solution was added to a solution of 380 mg. of the crude deuteriated acid **8** in 8 ml. of ether, until the yellow color persisted. The solution was decolorized with a few drops of acetic acid, extracted with sodium bicarbonate solution, dried, and evaporated. The residue was distilled (b.p. 85° at 7 mm.) to yield 296 mg. (72%) of **10**, which was arbitrarily cut into four fractions, all of which had n_{D}^{23} 1.455 and identical infrared spectra: $\lambda_{\text{max}}^{\text{neat}}$ 5.75 (s), 6.96 (m), 7.23 (m), 8.02 (s), 8.35 (s), 8.63 (w), 9.80 (m), 10.05 (w), and 11.8 (w) μ ; mass spectrum (the base peak followed by selected other fragments in order of decreasing intensity), m/e 108, 93, 85, 55, 41, 67, 123, 154, 142, 168, and 183. The n.m.r. spectrum (τ) was identical with that of **3** between 8.36 (a minimum) and 10.0, very similar between 7.9 and 8.36, and grossly different between 7.4 and 7.9, principally in that the spectrum of **3** has its principal peak in this region at 7.81, while this peak is absent in the spectrum of **10**. If the methoxyl peak is taken as 3.0 protons, the region from τ 7.4 to 8.36 contains 5.6 protons in the spectrum of **10** and 7.0 protons in the spectrum of **3**.

Deuterium Exchange with Carvonecamphor. To 20 ml. of deuterioethanol under nitrogen was added 425 mg. of carvonecamphor and 1.0 g. of potassium *t*-butoxide. The solution was maintained at reflux under nitrogen for 72 hr. After cooling, it was poured into a mixture of water and benzene, and the benzene was washed three times with water, dried, and evaporated to give 404 mg. of α,α -dideuteriocarvonecamphor (**11**). The n.m.r. spectrum of **11** showed the same two protons between τ 8.5 and 8.9 and the same two methyl groups as carvonecamphor shows, but the peaks between τ 7.5 and 8.5 had an area corresponding to 4.05 protons, if the area between τ 8.9 and 9.1 (the methyl groups) was taken as 6.0 protons. The major peak (7.92) below τ 8.5 in the spectrum of carvonecamphor was reduced to several small peaks in the spectrum of α,α -dideuteriocarvonecamphor.

1-exo-5-Dimethyl-syn-2-methoxycarbonylmethyl-d-bicyclo[2.1.1]hexane-5-d (9). A solution of 178 mg. of α,α -dideuteriocarvonecamphor (**11**) in 80 ml. of methanol was irradiated with the black lights for 12 days, whereupon g.l.p.c. analysis showed the reaction to have been 95% complete. The solution was evaporated to a small volume, and carbon tetrachloride was added. The resultant solution was washed with water, dried, and evaporated. The residue was distilled by short-path distillation at 85° (7 mm.) to give 139 mg. (65%) of **9**, which has an n.m.r. spectrum identical with that of the monodeuterated ester **10**, except that the methyl doublet centered at τ 8.95 is absent and is replaced by a methyl singlet at 8.95. A few very small contaminating peaks in the methyl region were also apparent.

The Lactones 13 and 21. The lactone **13** was prepared using a modification of the method of Büchi and Goldman.⁵ A solution of 1.12 g. (0.0075 mole) of carvonecamphor and 2.03 g. (0.010 mole) of 85% *m*-chloroperbenzoic acid in 35 ml. of dry benzene was stored in the dark for 5 days. Then 50 ml. of ether

was added and the solution was washed with solutions of sodium carbonate, water, ferrous ammonium sulfate and oxalic acid, water, sodium carbonate, and finally water. After drying, the solution was evaporated to give 1.25 g. (101%) of a yellow oil whose infrared spectrum was substantially identical with that reported by Büchi and Goldman⁵ for **13**. The spectrum lacked the characteristic peaks of carvonecamphor, and showed only a slight inflection on the side of the carbonyl peak representing the peak at 5.63 μ due to the rearranged lactone **21**, which had in the past always been a troublesome contaminant in **13**.

Upon treatment for 12 hr. at room temperature with dilute aqueous sulfuric acid, the lactone **13** was converted into the rearranged lactone **21**, m.p. 45–61°. It was recrystallized from hexane giving pure **21**, m.p. 65–66° (lit.⁵ m.p. 64–65°); the infrared spectrum was identical with that reported by Büchi and Goldman⁵; the n.m.r. spectrum (τ) showed significant peaks, singlets at 8.66 and 8.77 (3 protons each), and a series of progressively larger peaks at 9.28, 9.39, 9.48, 9.57, 9.63, and 9.70 (total of 2 protons).

1-exo-5-Dimethyl-endo-5-hydroxy-syn-2-methoxycarbonylmethylbicyclo[2.1.1]hexane (14). A solution of 464 mg. of potassium hydroxide (a 10% excess) in 10 ml. of 95% ethanol was prepared, and about three-quarters of it was added to 1.25 g. of the crude lactone **13**. After 5 min. of heating on a steam bath, the mixture became neutral, and the remaining potassium hydroxide solution was added and heated for another hour. Then 100 ml. of ethanol was added, followed by a solution of 1.5 g. of silver nitrate in 75 ml. of ethanol. The precipitate was filtered and washed with ethanol and ether, dried in air, and powdered. Only 55 mg. of organic material was recovered from the filtrate.

The powdered silver salt was added to 10 ml. of stirred methyl iodide, in a flask equipped with a reflux condenser. The mixture was stirred for 3 days, then filtered and evaporated to give 686 mg. (46%) of a yellow oil, crude **14**: $\lambda_{\text{max}}^{\text{neat}}$ 2.85 (m), 5.79 (s), 6.95 (m), 7.24 (m), 7.56 (w), 7.76 (w), 8.08 (m), 8.61 (s), 9.31 (w), 9.46 (w), 9.82 (w), 10.03 (w), 10.38 (w), and 10.75 (w) μ ; n.m.r. spectrum (τ) significant peaks, singlets at 6.39, 8.69, and 9.01 (3 protons each), and at 6.53 (1 proton).

When the crude hydroxy ester **14** was distilled at 75° (0.5 mm.), it was converted back to the lactone **13**. On silicone and on Carbowax g.l.p.c. columns, it gave only one major peak, with retention time equal to that of the lactone. It was also converted into lactone, plus smaller amounts of rearranged lactone and other products, during chromatography over neutral alumina (activity I).

An attempt was made to prepare **14** by hydrolyzing the lactone in aqueous base and adding methyl sulfate, but a mixture of side products was produced.

syn-2-Carboxymethyl-1-exo-5-dimethyl-endo-5-hydroxybicyclo[2.1.1]hexane (15). A solution of 1.70 g. of the lactone **13** and 595 mg. of potassium hydroxide (a 10% excess) in 20 ml. of absolute ethanol was allowed to stand overnight at room temperature; then Dry Ice chips were added and the solution was evaporated. The moist residue was treated with benzene and filtered. Upon evaporation of the filtrate, 1.95 g. (83%) of a white powder was obtained. This carboxylate salt,

when dry, is insoluble in benzene, but when wet with alcohol, or when treated with benzene containing alcohol, it is readily soluble. The salt is deliquescent.

When an aqueous solution of the potassium salt is acidified with phosphoric acid and extracted with ether, and the ether is evaporated, a solid acid is obtained which can be recrystallized rapidly from a mixture of carbon tetrachloride and hexane to give colorless crystals of the hydroxy acid **15**: m.p. 114.5–115°; $\lambda_{\text{max}}^{\text{KBr}}$ 3.00 (m), 3.78 (w), 5.84 (s), 6.87 (w), 7.09 (w), 7.22 (w), 7.57 (s), 7.78 (m), 8.08 (m), 8.33 (m), 8.68 (m), 9.44 (w), 9.66 (w), 9.95 (w), 10.41 (w), 10.82 (m), and 13.46 (w) μ , with no peaks in the region 3000 to 3100 cm^{-1} ; n.m.r. spectrum of a saturated solution in deuteriochloroform, singlets at τ 8.96 and 8.64 as the only readily discernible peaks; n.m.r. spectrum in a solution of one equivalent of potassium carbonate in deuterium oxide (with τ -values relative to an external standard of tetramethylsilane in carbon tetrachloride), singlets at 8.90 and 8.59 (3 protons apiece) and multiple peaks between 7.2 and 9.2 (9 other protons).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_3$: C, 65.19; H, 8.75. Found: C, 65.16; H, 8.70.

When the hydroxy acid **15** is gently heated, as during recrystallization, it is slowly converted into the lactone **13**. On melting, it is transformed to the lactone. When dissolved in formic acid and kept at room temperature for 45 min., it is converted to the rearranged lactone (**21**), m.p. 48–62.5°. Upon treatment with ethereal diazomethane, it is quantitatively converted to the methyl ester **14**.

syn-2-(N-Butylcarbamoylmethyl)-1-exo-5-dimethylbicyclo[2.1.1]hexane (7). A solution of 10.26 g. of carvonecamphor and 30 ml. of *t*-butylamine in 1050 ml. of benzene was irradiated for 3 hr. with the Hanovia lamp in a quartz well, with vigorous bubbling of oxygen through the solution.^{10,11} The solution was extracted with 100 ml. of a 5% solution of sodium bicarbonate, dried, and evaporated to leave 13.1 g. (94%) of a brown solid, m.p. 70–111°, which by its infrared spectrum was almost entirely **7**. The crude **7** was recrystallized twice from ethanol–water to give 4.37 g. of white, crystalline **7**: m.p. 130.5–131°; $\lambda_{\text{max}}^{\text{CCl}_4}$ 2.91 and 3.00 μ (the latter disappearing upon dilution), 5.96 (s), 6.69 (s), 6.90 (s), 7.19 (m), 7.24 (m), 7.34 (m), 7.71 (m), 7.81 (w), 8.20 (m), 8.42 (m), 8.58 (w), 8.80 (w), 9.28 (w), 9.56 (w), and 10.6 (w) μ ; n.m.r. spectrum (τ), a broad singlet at 6.22 (1 proton), a singlet at 8.70 (9 protons), a singlet at 9.10 (3 protons), a doublet with peaks at 8.92 and 9.02 (total of 3 protons), and multiple peaks between 7.5 and 9.0 (9 other protons).

Anal. Calcd. for $\text{C}_{14}\text{H}_{25}\text{NO}$: C, 75.28; H, 11.28. Found: C, 75.18; H, 11.34.

syn-2-Methoxycarbonylmethyl-1-methyl-5-methylenebicyclo[2.1.1]hexane (16) and 3 α -Methoxycarbonylmethyl-1 α -methyl-2-methylenebicyclo[3.1.0]hexane (18). The aqueous bicarbonate solution obtained during the isolation of **7** described above was washed twice with methylene chloride. Then 200 ml. of methylene chloride was added and the mixture was cooled in an ice bath and stirred rapidly. A solution of 20 g. of potassium dihydrogen phosphate and 3 ml. of phosphoric acid in 75 ml. of water was added, and then dilute phosphoric acid was added to pH 4. The mix-

ture was immediately poured into a separatory funnel, and the methylene chloride layer was drained directly into a solution of an excess of diazomethane in ether. The excess diazomethane was destroyed with acetic acid, and the ethereal solution was washed with sodium carbonate solution, dried, and evaporated. The residue was distilled to give 524 mg. of fraction 1 (b.p. 60–70° at 2.5 mm.), 634 mg. of fraction 2 (b.p. 70–80° at 2.5 mm.), and 245 mg. of fraction 3 (b.p. 70–85° at 1 mm.). Upon g.l.p.c. analysis (silicone, 126°), fraction 1 was found to consist of approximately equal amounts of the terminal methylene compounds **16** and **18** ($T_r = 2.5$ and 3.5 min.). Fraction 2 was found to consist almost wholly of the same two compounds, in the ratio 1:4, and fraction 3 to consist predominantly of compounds of longer retention time than **18**. Combined fractions 1 and 2 (representing a 9.6% yield) were separated by preparative g.l.p.c. (15% silicone, 132°). A total of 184 mg. (1.5%) of **16** was collected, between 26 and 35 min., and 445 mg. (3.7%) of **18**, between 45 and 59 min.

The infrared spectrum showed $\lambda_{\text{max}}^{\text{CCl}_4}$ 3.26 (w), 5.74 (s), 5.91 (m), 6.96, 7.30, 7.65, 7.81, 8.02, 8.36, 8.59, 8.78, 9.80, 10.04, and 11.52 (s) μ ; n.m.r. spectrum (τ), singlets at 8.88 (3 protons), 6.40 (3 protons), 5.72 (1 proton), and 5.61 (1 proton), a multiplet at 7.26 (1 proton), and multiple peaks between 7.5 and 9.0 (7 other protons).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.24; H, 9.09.

The infrared spectrum showed $\lambda_{\text{max}}^{\text{CCl}_4}$ 5.75 (s), 6.07 (s), 6.98, 7.37, 7.60, 8.04, 8.40, 8.59, 9.23, 9.68, 9.84, and 11.55 (s) μ ; $\lambda_{\text{max}}^{\text{CCl}_4}$ 3000, 3026, 3067, and 3080 cm^{-1} ; $\lambda_{\text{max}}^{\text{cyclohexane}}$ 200 $\text{m}\mu$ (ϵ 11,300); $\lambda_{\text{max}}^{\text{ethanol}}$ 200 $\text{m}\mu$ (ϵ 10,500)^{17c}; n.m.r. spectrum (τ), a complex multiplet at 9.3 (2 protons), a singlet at 8.76 (3 protons), a singlet at 6.40 (3 protons), a doublet at 5.40 (1 proton, $J = 2$ c.p.s.), a doublet at 5.29 (1 proton, $J = 2$ c.p.s.), and multiple peaks between 7.5 and 9.0 (6 other protons).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_2$: C, 73.30; H, 8.95. Found: C, 73.24; H, 9.12.

Hydrolysis and Re-esterification of the Unsaturated Ester 16. A solution of 0.5 mg. of **16** and 10 mg. of potassium hydroxide in 1 ml. of 95% ethanol was heated under reflux on a steam bath for 1 hr., and then the solvent was evaporated.

The residue was washed with methylene chloride. Then 1 ml. of water and 1 ml. of methylene chloride were added and the mixture was cooled in an ice bath and stirred vigorously, acidified to pH 2 with dilute phosphoric acid, and allowed to stand for 5 min. The methylene chloride layer was removed and added to diazomethane in ether. A g.l.p.c. analysis showed that only pure **16** was present in the ethereal solution with no trace of any compound of similar retention time.

In another experiment, **16** was hydrolyzed as above; then to the cooled ethanol were added 5 ml. of water and 5 ml. of methylene chloride and the mixture was shaken. The methylene chloride was removed, ether was added, and the aqueous solution was acidified to pH 2 with dilute phosphoric acid at room temperature. Samples of ether were periodically removed, treated with diazomethane, and analyzed by g.l.p.c. (silicone, 126°). A sample removed immediately

after acidification gave rise to three peaks, $T_r = 2.0$, 2.5, and 3.5 min., in the ratio 1:16:3. An injection of the solution mixed with pure **16** confirmed the fact that **16** comes at 2.5 min., and a similar mixed injection showed that the 3.5-min. peak was coincident with that due to **18**. The 2.0-min. peak was not assigned. A sample removed after the ether solution had been in contact with the acid for 25 min. showed that **16** had almost entirely disappeared, producing roughly equal amounts of the other two compounds.

Reaction of 16 in Acid. To 0.5 mg. of **16** in 1 ml. of ether were added, over a period of time, increasing amounts of formic and then of phosphoric acid, until a change was observed on g.l.p.c. analysis. After 0.3 ml. of phosphoric acid had been added and the solution had stood for 1.5 hr. after that addition, g.l.p.c. analysis (silicone, 140°) showed four peaks, $T_r = 1.8$, 2.0, 3.6, and 4.4 min., in the ratio 1:1:4:2. The second was coincident with the peak due to **16**. The peak of **18** came at 2.7 min., and was not observed at all in any of the samples taken. The 3.6-min. peak proved to be coincident with the rearranged lactone **21**. Analysis on the Carbowax column at 195° revealed, again, four peaks, $T_r = 6.1$, 10.7, 14.0, and 15.2 min., in the ratio 1:3:2:1, and a mixed injection proved the coincidence of the 10.7-min. peak with the peak of the rearranged lactone **21**.

Cyclization of the Acid 20 in Acid. One-half milligram of the ester **18** was hydrolyzed with alcoholic potassium hydroxide and acidified with phosphoric acid in the presence of ether as described for **16**. No volatile products were observed until the ether was evaporated and the residue was dissolved in formic acid. Analysis by g.l.p.c. (silicone, 126°) revealed the emergence of a single peak, $T_r = 4.8$ min., which grew to constant height after several hours, and was coincident with the peak of the rearranged lactone **21**.

The experiment was repeated using 88 mg. of **18**. After standing overnight, the formic acid solution was mixed with water and ether, and the ether layer was extracted and washed with bicarbonate solution and water, dried, and evaporated to yield 59 mg. (72%) of a slushy solid with an infrared spectrum identical with that of the rearranged lactone **21**. The material was subjected to short-path distillation at 110° (5 mm.) and recrystallized twice from hexane giving white crystals, m.p. 64.5–66°, mixture melting point with authentic **21** undepressed.

Catalytic Hydrogenation of the Unsaturated Ester 16. Several experiments were conducted in which **16** in methanol was hydrogenated at atmospheric pressure using Adams catalyst. In all cases, the starting material had completely disappeared within 2 hr., and two products appeared, as determined by g.l.p.c. analysis (silicone, 103°; starting material, $T_r = 7.6$ min.; products, $T_r = 8.8$ and 9.3 min.). However, the ratio of the product of lower retention time to that of higher retention time was not reproducible, and varied from 3:2 to about 10:1. Modifications of procedure, such as using very low hydrogen pressure or palladium on charcoal instead of platinum, all gave almost entirely the product of lower retention time.

When the hydrogenated material was injected mixed with authentic **3**, the peak of higher retention time proved to be coincident with that of **3**, on both the silicone and

Carbowax columns (Carbowax, 165°, $T_r = 4.8$ and 5.1 min.). Authentic **3** was not isomerized under the hydrogenation conditions.

When 58 mg. (0.32 mmole) of **16** was hydrogenated as described, uptake of hydrogen was rapid during the first 0.5 hr., after which it practically ceased. The compound consumed 0.28 mmole of hydrogen. The product ratio was about 4:1. The yield was 53 mg. of a liquid (crude **22**) with an infrared spectrum very similar to that of authentic **3**, but differing in the region from 7.7 to 8.7 μ : $\lambda_{\text{max}}^{\text{neat}}$ 5.76 (s), 6.98 (m), 7.27 (m), 7.57 (w), 7.72 (m), 7.79 (m), 7.95 (w), 8.41 (m), 8.63 (s), 9.00 (w), 9.27 (w), 9.42 (w), 9.85 (m), 10.02 (w), 10.21 (w), 10.53 (w), 11.2 (w), and 11.8 (w) μ ; n.m.r. spectrum (τ), a singlet at 6.39 (3 protons), a singlet at 8.93 (3 protons), a peak at 9.13 (1.9 protons), and one at 9.24 (0.8 protons) which together must correspond to a 3-proton doublet ($J = 6.5$ c.p.s.), and complex peaks between 7.5 and 9.0 (9 other protons).

Conversion of the Ester 22 to the *t*-Butylamide (23). Twenty-five milligrams of the hydrogenated methyl ester (crude **22**) was hydrolyzed as usual, giving 22 mg. of acid. To the acid was added 0.1 ml. of thionyl chloride, which was then evaporated under a stream of nitrogen. Then 1 ml. of anhydrous ether was added, followed by 0.2 ml. of *t*-butylamine. After filtration, the solution was evaporated to give 29 mg. of pale yellow crystals, m.p. 80–135°, which after two recrystallizations from hexane gave pure **23**, m.p. 149–150.5°. The infrared spectrum was identical with that of **7** except that the peaks at 7.24 and 8.58 μ were absent, and peaks at 8.04 (very w), 8.64 (very w), 9.02 (w), and 9.74 (w) μ were present; no peaks were present in the region from 2980 to 3100 cm^{-1} . The n.m.r. spectrum was identical with that of the ester **22** except for the presence of a 9-proton peak at τ 8.70, the absence of the methyl at 6.39, and a slightly different pattern of peaks in the vicinity of 8.0.

Anal. Calcd. for $\text{C}_{14}\text{H}_{25}\text{NO}$: C, 75.28; H, 11.28. Found: C, 75.48; H, 11.26.

Conversion of the Ester 3 to the Amide 7. The product (**3**) of photolysis in methanol in the absence of oxygen was converted into the corresponding *t*-butylamide by the procedure described in the last section. Recrystallization first from hexane, then from ethanol-water, gave white crystals, m.p. 129.5–131°, melting point undepressed upon admixture of the crystals with the product, **7**, obtained by photolysis of **1** in benzene and *t*-butylamine in the presence of oxygen.

Lithium-Ethylenediamine Reduction of the Unsaturated Ester 16 to 3, and Conversion to the Amide 7. Fifty-five milligrams of **16** was hydrolyzed by the procedure described which caused no isomerization. Two drops of ethylenediamine were added to the methylene chloride solution before it was evaporated. To the residue was added 5 ml. of dry dioxane and 15 ml. of freshly distilled ethylenediamine.¹⁸ Then 200 mg. of lithium metal was added and the solution was stirred overnight. The mixture was poured into water and ether, and acidified with dilute hydrochloric acid. The ethereal solution was washed with water and treated with excess diazomethane in ether. Analysis of the solution by g.l.p.c. revealed starting material and the two reduction products, in the proportions of 1:2:7, in order of increasing retention time. The

solution was evaporated to give 13 mg. of a liquid which was treated with permanganate and steam distilled as in the preparation of 3. The product was 8 mg. of a liquid with an infrared spectrum identical with that of 3.

The ester was converted to the *t*-butylamide as described for 22, and purified by chromatography over 8 g. of neutral alumina (activity I) which was eluted with hexane-chloroform(2:1). After 180 ml. had passed through the column, 6 mg. of the amide, m.p. 90–105°, was eluted. The infrared spectrum was superimposable on that of 7. The amide was sublimed and recrystallized from ethanol-water to give white needles, m.p. 127–130°, melting point undepressed upon admixture of the needles with 7 from photolysis in the presence of oxygen.

Nonoxidative Photolysis of Carvonecamphor in Benzene. A solution of 4.0 g. of carvonecamphor in 1050 ml. of benzene mixed with 10 ml. of water was stirred continuously and irradiated for 3 hr. with the Hanovia lamp in a quartz well. The solution was extracted

with sodium carbonate solution. Acidification and extraction of the aqueous solution resulted in only a trace of product. The benzene was removed by distillation at reduced pressure, leaving 4.1 g. of a syrupy residue, $\lambda_{\text{max}}^{\text{neat}}$ 5.49 and 5.73 μ . To the residue was added 0.8 ml. of bis(2-ethoxyethyl) ether (which has a boiling point nearly that anticipated for an unsaturated aldehyde, C₁₀H₁₄O), and the mixture was distilled at 63° (2 mm.). The residue was hydrolyzed to the acid 4. The distillate showed no 5.49- μ absorption. One milliliter of benzene was added to the distillate and the solution was washed thoroughly with water. The n.m.r. spectrum of the benzene solution showed the product mixture to contain a maximum of 2% of aldehyde, and no trace at all of protons in the region of τ 5.5 to 5.9, or 9.2 to 9.6. A crude 2,4-dinitrophenylhydrazone derivative was prepared, and the n.m.r. spectrum of this derivative likewise indicated the complete absence of methylenecyclobutane and cyclopropane protons.

The Diterpene Alkaloids. A Study of the Isomerization of Iso-Type Diterpene Alkaloid Salts to Normal-Type Salts

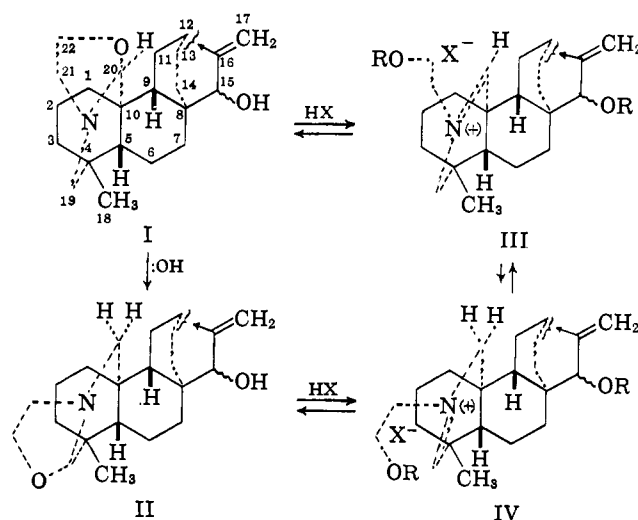
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The iso-type diterpene salts are smoothly isomerized to the normal-type salts at reflux temperature in such solvents as DMA, DMF, DEF, DMSO, phenol and high-boiling alcohols. The isomerization follows first-order kinetics and the rate is greater in the proton-donor type solvents than in the nondonor type. The effect of temperature on the rate of isomerization of isoatisine chloride in DEF, DMSO, methyl carbitol, ethyl carbitol, and 2-butoxyethanol is shown by Arrhenius plots. The energy of activation (E_a), enthalpy of activation (ΔH^\ddagger), entropy of activation (ΔS^\ddagger), and frequency factor (A) were calculated for isomerization in DEF, DMSO, methyl carbitol, and 2-butoxyethanol. A plot of $\ln k_1/T$ vs. $1/T$ demonstrates that the data for the isomerization do not show a true isokinetic relationship. Thermal isomerization of the ternary iminium salts provides a convenient, practical method of reversing the facile normal base \rightarrow isobase isomerization.

The smooth isomerization of the normal-type diterpene bases (I)¹ such as atisine, veatchine, garryfoline, and cuachichicine to the iso-type bases (II) has been accounted for in terms of the steric interaction between substituents on the tetrahedral C-20 atom of the oxazo-

lidine form and other parts of the molecule.^{1a,b,e,2-4} In the normal-type bases it can readily be demonstrated with models that serious repulsive interactions exist between the 20-H and the 13-H and 14-H, when C-20 is tetrahedral. However, in the ternary iminium salt form (III) in which C-20 is trigonal, these interactions are relieved.^{2,3,5} The isomerization may, therefore,



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