perature was maintained below 35°. After the addition was completed the solution was acidified with 30% sulfuric acid to a *p*H below 4.5 and extracted with ethyl ether.[25] The ether extracts were washed with water to neutrality and then dried over anhydrous sodium sulfate. The solvent was distilled *in vacuo*. The residue was recrystallized from hexane (petroleum grade); m.p. 37.5–38.5°. The sodium salt was prepared by dissolving the acid in ethanol and neutralizing the solution with alcoholic sodium hydroxide. On cooling, the sodium salt crystallized and was filtered off and dried.

IV. Other N-Acylamino Acids.—a. The other monoaminomonocarboxylic acids (Table II) were acylated by the same method as the sarcosine derivatives except that *p*-aminobenzoic acid was acylated by the method of Ford.[26] b. The dicarboxylic amino acids (Table II) were acylated by the procedure described for the preparation of N-lauroylaspartic acid.

Preparation of N-Lauroylaspartic Acid.—Aspartic acid, 26 g. (0.2 mole) was suspended in 100 ml. of dry ethyl acetate. Lauroyl chloride, 21.8 g. (0.1 mole) was added and the mixture refluxed for 18 hours. Unreacted amino acid was filtered off and the solvent removed by distillation *in vacuo*. The residue was dissolved in hot hexane and allowed to crystallize; yield 10 g., m.p. 112.5–114.0°; anhydride analysis[27] agreed with that for N-lauroylaspartic anhydride. The anhydride was converted to the acid by dissolving in pyridine and adding 5% aqueous NaOH to a *p*H of 9. The solution was acidified with aqueous hydrochloric acid and extracted with ethyl acetate. This solution was washed with water until the washings were neutral, dried over anhydrous sodium sulfate and the solvent stripped *in vacuo*. Sodium salts were prepared as in IIIa.

Acknowledgment.—We would like to thank Drs. R. B. Wearn, A. I. Gebhart and P. Weiss for their active interest and helpful discussions relating to this work. The analytical data were obtained by the Analytical Division of the Research & Development Department of the Colgate–Palmolive Co.

(25) Colgate–Palmolive, British Patent 704,585.

(26) G. M. Ford, *Iowa State College, J. Sci.*, **12**, 121 (1937).

(27) D. M. Smith and W. M. D. Bryant, THIS JOURNAL, **58**, 2452 (1936).

JERSEY CITY, N. J.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

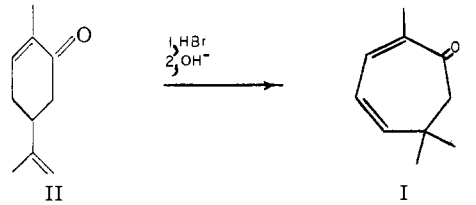
Formation of Carene [Bicyclo(4.1.0)heptene] Derivatives from Eucarvone[1,2]

BY E. J. COREY AND H. J. BURKE

RECEIVED JULY 25, 1955

A number of substitution reactions of eucarvone (1) have been shown to yield bicyclic products in the bicyclo[4.1.0]heptene series. These reactions are described together with chemical and physical data which prove the assigned structures.

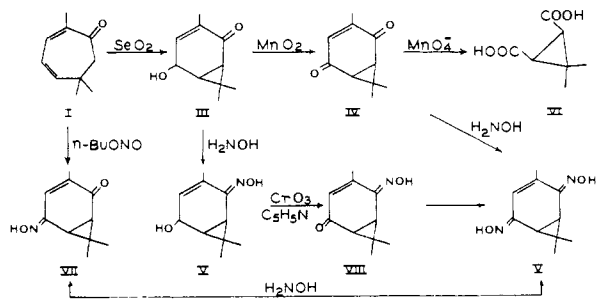
The terpenoid eucarvone (I), which was first prepared by Baeyer[3] in 1894 from the naturally occurring carvone (II), has been the subject of only desultory chemical study, despite its ready availability. As a consequence, the chemistry of eucarvone, apart from the degradative studies leading to the establishment of structure, has remained ambiguous and in certain areas completely unknown. This fact, together with the interesting possibilities inherent in this unusual seven-membered cyclic dienone system, has prompted the investigation which is reported in part in the present article.



II I

We first turned our attention to a study of certain substitution reactions of eucarvone aimed at replacement of the hydrogens of the α-methylene group.

Oxidation of eucarvone, $C_{10}H_{14}O$, by excess selenium dioxide in absolute ethanol at reflux produced a colorless solid, $C_{10}H_{14}O_2$, m.p. 85–86°, (38% yield) whose properties indicated it to be a hydroxy ketone rather than the expected 1,2-diketone. Eventually, the hydroxy ketone was shown to be a bicyclo[4.1.0]heptene derivative of structure III (Fig. 1) and, as will become apparent later, this oxidation became a point of more than passing interest both on its own account and in connection with other transformations of eucarvone.



I III IV VI VII V VIII V

FIG. 1.

The presence of a hydroxyl group in the oxidation product is indicated by absorption peaks at 3610 and 3408 cm.$^{-1}$ in the infrared and the formation of *p*-nitrobenzoate and phenylurethan derivatives. The ultraviolet spectrum provides evidence for a structure containing an α,β-monounsaturated ketone function (λ_{max} 239 mμ, log ϵ 4.05) and rules out a dienone system as in eucarvone (λ_{max} 302 mμ, log ϵ 3.82) as well as non-conjugated systems. In agreement, the hydroxy ketone manifests conjugated carbonyl absorption in the infrared at 1659, 1641 cm.$^{-1}$ and forms an α,β-unsaturated oxime (λ_{max} 237 mμ, log ϵ 4.15). Catalytic reduction of the unsaturated hydroxy ketone with palladium–Darco catalyst resulted in the uptake of only one equivalent of hydrogen with the production of a saturated ketone (carbonyl absorption at 1700

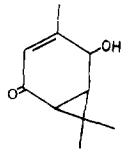
(1) Previous communication on this subject, THIS JOURNAL, **76**, 5257 (1954).

(2) Taken from the Ph.D. dissertation of H. J. Burke.

(3) A. Baeyer, *Ber.*, **27**, 810 (1894).

cm.$^{-1}$), which provides evidence for a *bicyclic* structure with only one ethylenic linkage.

The secondary nature of the hydroxyl function and the presence of a three-membered ring, as in III, were proved in the following way. Oxidation of the hydroxy ketone with manganese dioxide in carbon tetrachloride yielded an unsaturated, yellow diketone, $C_{10}H_{12}O_2$, m.p. 93–94°, (IV) which could be converted to a dioxime V. The diketone absorbed only one equivalent of hydrogen with a palladium catalyst yielding a saturated diketone (carbonyl absorption 1700 cm.$^{-1}$) and showed ultraviolet absorption (λ_{max} 240 mμ, log ϵ 3.92) consistent with structure IV. Finally, permanganate oxidation of the diketone IV produced the known *cis*-caronic acid (VI) which, together with the preceding data, constitutes proof for structure III or the alternative formulation (IIIa) in which the positions of the hydroxyl and carbonyl groups are reversed. The latter possibility, which is not at all unreasonable, was ruled out by the evidence cited below.



IIIa

Eucarvone gave no indication of forming a sodium salt with sodium hydride or sodium amide in ether or benzene, even at reflux. In dioxane, however, eucarvone and sodium amide begin to react at 50° with formation of the sodio derivative of eucarvone and evolution of ammonia. Nitrosation of the sodio derivative with *n*-butyl nitrite affords an oximino ketone, m.p. 153–154°, $C_{10}H_{13}O_2N$,[4] which must possess the bicyclic structure VII since upon treatment with hydroxylamine, it is converted to a dioxime V identical with that prepared from the bicyclic diketone IV and hydroxylamine. The oximino ketone could also be prepared directly from eucarvone and *n*-butyl nitrite in the presence of sodium ethoxide and, in fact, this procedure seems to afford a higher yield (72%).

The oximino ketone VII could be utilized to locate the hydroxyl and carbonyl functions in the selenium dioxide oxidation product in the following way. Reaction of the hydroxy ketone from the selenium dioxide oxidation with hydroxylamine produces a hydroxy oxime, as mentioned above, and this by mild oxidation with chromium trioxide–pyridine complex yields an oximino ketone (VIII), $C_{10}H_{15}O_2N$, m.p. 168–169°, position isomeric with the oximino ketone VII, m.p. 153–154°. The oximino ketones VII and VIII were shown to be position isomers rather than stereoisomers by conversion to the same dioxime V. Thus, the selenium dioxide oxidation product must have structure III and not IIIa.

The acylation of sodioeucarvone with various acid chlorides (Fig. 2) resulted in the formation of enol esters which exhibit enol ester carbonyl, but

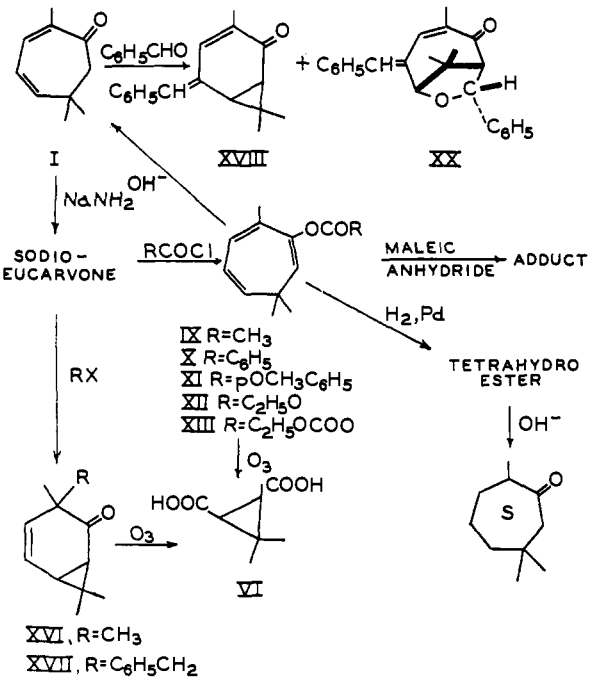
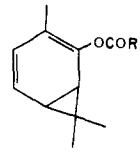


FIG. 2.

no ketone carbonyl in the infrared. Thus, the enol acetate (IX), benzoate (X), anisate (XI) and ethoxyformate (XII) were prepared together with the enol monoethylpyrocarbonate (XIII), which was encountered as a by-product of the enol ethoxyformate synthesis. These esters, which are all liquids at room temperature with the exception of the anisate, m.p. 72.7–73.7°, have been assigned monocyclic structures rather than bicyclic structures of type XIV on the basis of physical evidence which is discussed in a separate paper.[5] The mono- and



bicyclic structures for the enol esters are valence tautomers which are interconvertible by a shift of electrons and a change in bond angles and distances. Hence, an equilibrium between the two, if not rapid at room temperature, should be attained simply by heating. Since several of the esters were found to be stable to prolonged heating at 100°, it is apparent that the monocyclic structures are more stable than the bicyclo structures.

The chemical reactions of the enol esters are especially interesting because they yield conflicting evidence with regard to structure, perhaps as a result of the possibility of valence tautomerism. Thus, ozonolysis of the enol acetate, benzoate and anisate resulted in the production of *cis*-caronic acid (VI) in yields of *ca.* 50% indicating a bicyclic structure. However, catalytic reduction of the enol anisate with a palladium–Darco catalyst gave a tetrahydro enol acetate which is converted to tetra-

(4) This compound has been prepared independently by Dr. H. L. Dryden, Jr., at Northwestern University.

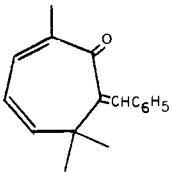
(5) E. J. Corey, H. J. Burke and W. A. Remers, THIS JOURNAL, **77**, 4941 (1955).

hydroeucarvone by gentle alkaline hydrolysis. Basic hydrolysis of the original enol esters affords eucarvone. The enol esters form maleic anhydride adducts readily.

Treatment of sodio eucarvone with methyl iodide or benzyl chloride resulted in formation, respectively, of Δ^2-4-methylcaren-5-one (XVI) and Δ^2-4-benzylcaren-5-one (XVII), both liquids. The bicyclic structures XVI and XVII follow from the observations that the infrared and ultraviolet spectra exhibit unsaturated but unconjugated ketone absorption and ozonolysis of the benzyl derivative, followed by oxidative decomposition with hydrogen peroxide, resulted in the formation of *cis*-caronic acid. Both compounds give a strong tetranitromethane test indicative of non-conjugated carbon–carbon unsaturation and both absorb one equivalent of hydrogen with palladium catalyst to form saturated ketones.

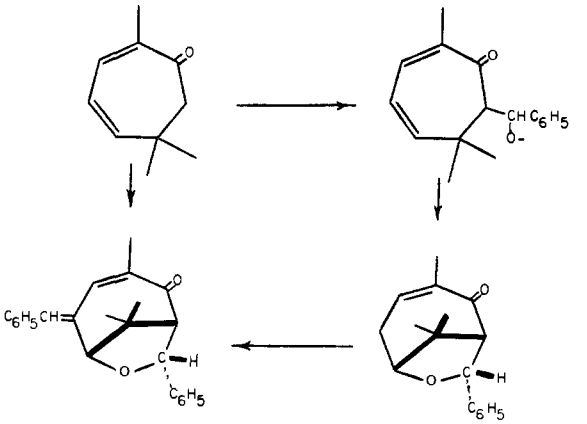
The reaction of eucarvone with benzaldehyde in the presence of sodium ethoxide leads to two products as reported by Wallach in 1899,[6] a monobenzylidene derivative, m.p. 113–114°, and a substance, m.p. 194–195°, which possesses the formula $C_{24}H_{24}O_2$ corresponding to the elements of the monobenzylidene derivative plus benzaldehyde.

Ozonolysis of the monobenzylidene derivative affords *cis*-caronic acid demonstrating that this substance has the bicyclic structure XVIII instead of the monocyclic structure XIX. The ultraviolet spectrum of the benzylidene derivative, λ_{max} 248, 334 mμ, log ϵ 4.07, 4.31, does not allow a decision to be made between XVIII and XIX, but is in



close agreement with that expected for XVIII.[7] The infrared spectrum of the benzylidene derivative manifests the expected conjugated carbonyl absorption at 1650 cm.$^{-1}$ and also a moderately strong, sharp band at 998 cm.$^{-1}$, which is also prominent in the spectra of most of the other bicyclo(4.1.0)-heptane derivatives reported herein including the hydroxy ketone III (1010 cm.$^{-1}$), the diketone IV (1004 cm.$^{-1}$) and the oximino ketones VII and VIII (1001 cm.$^{-1}$), and which is apparently due to the cyclopropane ring.[8]

The second product of the benzaldehyde condensation of formula $C_{24}H_{24}O_2$ apparently lacks the cyclopropane ring since it affords no caronic acid upon oxidation. The infrared spectrum indicates the absence of a hydroxyl group and the presence of a single conjugated carbonyl group (band at 1670 cm.$^{-1}$) and possibly of an ether function (strong band at 1060 cm.$^{-1}$). The ultraviolet absorption is quite similar to that of cinnamylidene acetone and the monobenzylidene derivative XVIII. The only structure which appears consistent with these facts is XX which might be formed by the route shown.



In accord with structure XX for the benzyloxybenzal derivative and in agreement with the sequence presented above is the fact that the benzyloxybenzal compound is not formed from the preformed monobenzylidene derivative XVIII by treatment with benzaldehyde and base under conditions which suffice for its formation from eucarvone.

In view of the ready formation from eucarvone of the bicyclic products described above, several attempts were made to prepare the bicyclic isomer of eucarvone having the bicyclo(4.1.0) heptane skeletion, XXI. Lapworth and Clarke[9] had previously attempted to prepare this substance by elimination of hydrogen cyanide from the cyanodehydrocarone (XXII), but were able to isolate only eu-

carvone itself. We have attempted to prepare XXI by neutralization of sodioeucarvone and by hydrolysis of the enol ethoxyformate XII. In each case, however, eucarvone was the only isolable product.[10] These experiments would seem to indicate that the bicyclic isomer XXI does not result from the protonation of eucarvone anion or that it is rapidly converted to eucarvone even under mild conditions.

The relative stability of the bicyclic hydroxy ketone III[11] provides some indication that it may be possible to isolate the bicyclic isomer of eucarvone XXI. It must be recognized, however, that the

(6) O. Wallach and H. Lohr, *Ann.*, **305**, 237 (1899).

(7) The ultraviolet absorption for structure XVIII may be estimated from that reported for cinnamylidene acetone [A. L. Wilds, *et al.*, THIS JOURNAL, **69**, 1985 (1947)], λ_{max} 234, 319 mμ, log ϵ 3.83, 4.56, plus a small positive increment for the bathochromic effect of the cyclopropyl group. While it is difficult to predict accurately the absorption for structure XIX, the data of H. S. French and L. W. Inskip [*ibid.*, **71**, 3702 (1949)] indicate that it ought to absorb in the region 300 to 350 mμ.

(8) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., p. 27.

(9) A. Lapworth and R. W. L. Clarke, *J. Chem. Soc.*, 11 (1910).

(10) Another attempt to prepare the bicyclic isomer XXI from carvone hydrobromide in the presence of silver ion yielded only carvone by 1,2-elimination of hydrogen bromide.

(11) The hydroxy ketone can be recrystallized and sublimed without change. Although it is decomposed gradually by acids or bases it survives exposure for short periods of time.

stability of III may, at least in part, be a function of its stereochemistry. With regard to this latter point, no decisive information is available at the present time. Several observations are at hand, however, which may be pertinent. The hydroxyl function of III is readily acylated and may be regarded as unhindered. The oxidation of the hydroxy ketone is considerably more difficult than would be expected for a γ-hydroxy-α,β-unsaturated ketone. The hydroxyl group is not oxidized by cupric sulfate–pyridine at reflux or by Fehling solution. Perhaps even more significant is the fact that the oxidation of III to the diketone with active manganese dioxide[12] is unusually slow requiring about 40 hours at 25° for good conversion.

The foregoing reactions illustrate the rather striking tendency of eucarvone to form carene (bicyclo(4.1.0)heptene) derivatives in reactions which are the type commonly considered to proceed by way of enols or enolate ions. In the examples cited attachment of the new group has occurred in all mechanistically probable positions with formation *in every case* of bicyclic products. Only during the formation of the benzoxybenzylidene derivative XX from eucarvone has attack been observed at the α-methylene carbon, which, *a priori*, might have been considered the predominating site substitution.

It is likely that there are other reactions of eucarvone which proceed to give bicyclic products. However, it is all the more interesting that this phenomenon need not be restricted to the eucarvone system, but can probably be generalized, within certain bounds, to similar unsaturated cyclic structures of various ring sizes. The following paper on this subject presents evidence on the course of the ring-bridging reactions of eucarvone.

Experimental[13]

Eucarvone (I).—Two hundred grams (1.33 moles) of freshly distilled carvone was added to a solution of 296 g. (3.66 moles) of hydrogen bromide in glacial acetic acid at 6–11°. The rate of addition was determined by the effectiveness of the cooling and stirring; with a good paddle-type stirrer and a cooling bath at −30°, 15–30 minutes were required. The faster the addition was made, the better.

The cooling bath was removed and stirring was continued for 15 minutes. The resulting dark solution was poured into 2 l. of water, the lower layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, then with saturated potassium bicarbonate solution until basic to litmus, and finally with water until neutral. The ether solution was dried roughly over sodium sulfate, then dropped into a well-stirred and cooled solution of 145 g. of potassium hydroxide in 550 ml. of methanol.

After completion of the addition the resulting stirred suspension was refluxed for 15 minutes and poured onto ice–sulfuric acid to precipitate the eucarvone. The yellow oil was separated and the aqueous layer was extracted with ether. The ether solution was washed with saturated potassium bicarbonate solution and transferred to a steam distillation apparatus along with 20 g. of barium carbonate. After the ether had distilled, *ca.* 9 l. of distillate was collected, saturated with salt and extracted with ether. The combined extracts were dried over sodium sulfate, concentrated *in vacuo* to a yellow oil, and fractionated in a spinning band column of approximately 25 plates to yield a total of 146.5 g. (73%) of eucarvone, b.p. 82.5–84° (8 mm.), $n^{21}D$ 1.5080.

Δ^3-2-Hydroxycaren-5-one (III).—To a refluxing solution of 7.50 g. (0.068 mole) of selenium dioxide in 60 ml. of absolute ethanol, 10.03 g. (0.069 mole) of eucarvone was added. The theoretical amount of selenium (2.64 g.) had precipitated after 19.5 hours of refluxing.

The red solution was filtered, diluted to 100 ml. with alcohol, saturated with hydrogen sulfide to precipitate excess selenium dioxide and filtered through a bed of Filter-Cel. Excess hydrogen sulfide escaped during the vacuum filtration, and residual selenium was removed by stirring for several hours with precipitated silver.

The resulting red-orange solution was thoroughly extracted with low- and with high-boiling petroleum ether, and the combined extracts concentrated at room temperature in a slow current of air. Heavy crystals formed, from which the supernatant liquid was poured off at intervals. The crystals were washed with *n*-pentane, the wash added to the mother liquor and evaporation resumed. After several crops only oil precipitated, at which point the mother liquor was added to the original alcohol solution, the solvents were removed *in vacuo*, and the oil saved for further workup.

The crude crystals of hydroxyeucarvone were sublimed at 75–80° (0.1 mm.), then recrystallized from methylene chloride–*n*-pentane to yield 2.93 g. (26%) of white crystals, m.p. 84–86°, plus 1.36 g. (12%) of less pure product, m.p. 83–85°. Hydroxyeucarvone is readily soluble in polar organic solvents and aqueous base and fairly soluble in petroleum ether and water. An analytical sample melted at 85–86°; λ_{max} 229 mμ (log ϵ 4.05), ν_{max} 3610, 3408, 1659, 1641, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.00; H, 8.46.

The following derivatives of hydroxyeucarvone were obtained.

Phenylurethan: best crystallized from carbon tetrachloride; m.p. 155–156°; λ_{max} 236 mμ (log ϵ 4.40); ν_{max} 3420, 3310, 1742, 1670, 1001 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.85; H, 6.78; N, 4.98.

***p*-Nitrobenzoate:** tan crystals, m.p. 155.8–157.8° (CCl_4). The mild conditions recommended by Mills[14] were required; ν_{max} 1728, 1672, 1653, 1021, 1003 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{18}NO_5$: C, 64.54; H, 5.74; N, 4.43. Found: C, 64.76; H, 5.65; N, 4.39.

Oxime: white crystals, m.p. 171.5–173.5° with browning, when put into a bath preheated to 170° with the temperature increasing 1° per minute. This compound is heat sensitive, and is best recrystallized by dissolving it in ether, adding carbon tetrachloride, and removing the ether *in vacuo*; λ_{max} 237 mμ (log ϵ 4.15); ν_{max} 3250, 1604, 1015, 1004 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.29; H, 8.54; N, 7.92.

The residual oils from several batches of hydroxyeucarvone were combined and fractionated, yielding eucarvone, small amounts of carvacrol, a few per cent. of Δ^3-caren-2,5-dione (see below), b.p. 68° (1.5 mm.), and large amounts of a viscous orange oil, b.p. 141° (1.5 mm.), ν_{max} 3420, 1605, 1250, 1018 cm.$^{-1}$, not further investigated.

Δ^3-Caren-2,5-dione (IV).—A suspension of 6.00 g. of active manganese dioxide[12] in a solution of 1.00 g. (0.0061 mole) of the hydroxy ketone III in 60 ml. of carbon tetrachloride was stirred at room temperature for 50 hours. The manganese dioxide was filtered off and washed with methylene chloride, and the combined filtrates concentrated to dryness *in vacuo*, leaving 814 mg. (82%) of moderately volatile yellow crystals, m.p. 87–96.8°. Two recrystallizations from methanol–water followed by a sublimation *in vacuo* yielded 614 mg. (62%) of pure diketone, m.p. 93–94°, not improved by further treatment. The methanol solution is best diluted with water slowly so that massive crystals form, since this gives a purer product; λ_{max} 240 mμ (log ϵ 3.92); ν_{max} 1670, 1628, 1009 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.19; H, 7.25.

The dioxime (V) of the diketone forms readily under standard conditions. The melting point is easily raised to

(12) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(13) Microanalyses by Mr. J. Nemeth and associates.

(14) J. A. Mills, *J. Chem. Soc.*, 2332 (1951).

184–186° dec., but to improve it further repeated recrystallization from methanol–water alternating with ethyl acetate–chloroform are necessary. An analytical sample showed m.p. 185–186° dec., λ_{max} 278 mμ (log ε 4.43); ν_{max} 3180–3250, 1625, 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.62; H, 7.00; N, 14.28.

Oxidation of Δ^3-Caren-2,5-dione (IV).—A solution of 1.50 g. (0.0092 mole) of diketoeucarvone, 1.70 g. (0.137 mole) of potassium permanganate, 16.70 g. (0.140 mole) of magnesium sulfate and 75 ml. of acetone in 150 ml. of water was allowed to stand with occasional stirring for 175 hours at room temperature. The suspension was filtered, the residue washed with acetone and with water, and the filtrate decolorized with sodium bisulfite. The filtrate was concentrated *in vacuo* until salts began to precipitate. It was then extracted continuously with ether for 36 hours.

The extract was concentrated to dryness *in vacuo* and the yellow crystals extractively recrystallized with chloroform in a Soxhlet extractor. The slightly discolored crystals were filtered off, sublimed at 130° (0.3 mm.) and recrystallized from water. The crude material weighed 546 mg., m.p. 168–171°. Further recrystallization from water raised the melting point to 175.5–176.5° (reported[15] for *cis*-caronic acid 174–175°). The acid was converted to its anhydride by refluxing with acetyl chloride, and the anhydride alcoholized to the monomethyl ester, m.p. 107–109° (reported[15] m.p. 108–110°); ν_{max} 3180, 1725, 1685, 988 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.22; H, 6.57.

Δ^3-Caren-2,5-dione-2-oxime (VII).—To a cold solution of 0.77 g. (0.034 mole) of sodium in 33 ml. of absolute ethanol was added 3.43 g. (0.033 mole) of *n*-butyl nitrite. Five grams (0.033 mole) of eucarvone was then added with cooling. The temperature was held below 25° for 10 minutes; the solution was then allowed to stand at room temperature for 2 days. It was then concentrated *in vacuo* to *ca.* 15 ml., diluted with 50 ml. of water, extracted with three 25-ml. portions of ether, cooled to 15° and acidified with hydrochloric acid until no more precipitate formed. The product was extracted with three 25-ml. portions of ether and the extract washed with saturated salt solution until neutral to litmus. The extract was dried over sodium sulfate and concentrated to a red-brown residue, which was sublimed to light yellow crystals. These were precipitated from boiling methylene chloride with *n*-hexane to yield 4.24 g. (72%) of light tan crystals, m.p. 152.5–153.8°. Further recrystallization and sublimation of a portion produced white crystals, m.p. 153–154°; ν_{max} 3580, 1648, 1590, 1023, 1001 cm.$^{-1}$; λ_{max} 222, 295 mμ (log ε 3.92, 4.00). Treatment of the oximino ketone VII with hydroxylamine solution resulted in formation of the dioxime V, identical with authentic material according to melting point, mixture melting point and infrared spectrum.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.31; N, 7.82. Found: C, 67.12; H, 7.30; N, 7.78.

An alternative route to the oximino ketone utilizes the sodium salt of eucarvone.

To the sodioeucarvone solution from 3.08 g. (0.077 mole) of sodium amide and 8.85 g. (0.059 mole) of eucarvone was added with stirring at 15–20° a solution of 8.25 g. (0.080 mole) of *n*-butyl nitrite in 25 ml. of absolute dioxane. The red-brown sodioeucarvone solution turned blue-green during the addition. Stirring was continued one-half hour at room temperature, then the cooling bath was replaced and the solution cautiously made slightly acid with glacial acetic acid. It was then filtered and the solvent removed *in vacuo*.

The residue was diluted with 300 ml. of water and extracted with ether. The extract was washed with 5% sodium bicarbonate solution, water, saturated salt solution and dried over sodium sulfate. It was then concentrated to a red oil which crystallized when triturated with low-boiling petroleum ether. A chloroform solution was passed through a column of active Florisil which removed the brown impurities. The resulting yellow solution was concentrated to dryness and the residue recrystallized from boiling methylene chloride with *n*-hexane, yielding 1.32 g. (12%) of light tan crystals, m.p. 150–153°. A mixture of this with the oximino ketone prepared by the first method melted at 152–153.5°.

Δ^3-Caren-2,5-dione-5-oxime (VIII).—To 40 ml. of dry pyridine at 0° was added in portions 365 mg. of chromium trioxide. After the complex had formed a solution of 968 mg. of hydroxyeucarvone oxime in 6 ml. of dry pyridine was added. The solution was stored in an ice-bath for 12 hours, then kept at room temperature for an additional 12 hours. The pyridine was removed *in vacuo* and 25 ml. of water was added. The resulting solution was extracted with methylene chloride and the extract washed with 10 ml. of saturated salt solution. This was dried over magnesium sulfate and concentrated *in vacuo*. Recrystallization of the residue was best accomplished by dissolving it in chloroform and boiling off the chloroform while replacing it with carbon tetrachloride. When the solution was heated a red oil formed, apparently as a result of decomposition of unreacted starting material. It was found best simply to boil the material in carbon tetrachloride for an hour or two to complete the decomposition, after which further recrystallizations were more successful.

Alternate recrystallizations from chloroform–carbon tetrachloride and methanol–water resulted in white crystals, yield not noted but only fair, m.p. 167.5–168.5°. An analytical sample was sublimed and showed m.p. 168–169°; λ_{max} 223, 287 mμ (log ε 3.91, 4.10); ν_{max} 3620, 3300, 1650, 1600, 1017 cm.$^{-1}$. Treatment with hydroxylamine solution resulted in formation of the dioxime V, identity with authentic material established by mixture melting point and comparison of infrared spectra.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.00; H, 7.31; N, 7.82. Found: C, 67.01; H, 7.48; N, 8.03.

Sodioeucarvone.—A suspension of finely powdered sodium amide (25–80% excess) in 125 cc. of refluxing purified dioxane was treated, all at once, with eucarvone in 25 cc. of dioxane under nitrogen with stirring. The evolution of ammonia was swift at the start. The progress of the reaction was followed by titration of the ammonia evolved, and the refluxing was discontinued when ammonia evolution had substantially ceased (1–3 hours). The conditions for addition of further reactants are specified under the name of the product obtained.

The usual workup procedure was to remove the solvents at water-pump vacuum and room temperature. The residue was then extracted with 9:1 ether–methylene chloride. The extract was washed with saturated salt solution until neutral and dried over sodium sulfate. The solvents were removed *in vacuo* and the residue fractionally distilled or crystallized.

Eucarvone Enol Acetate.—To the sodioeucarvone prepared from 11.40 g. (0.076 mole) of eucarvone and 5.12 g. (0.131 mole) of sodium amide was added a solution of 10.30 g. (0.131 mole) of acetyl chloride in 50 ml. of absolute ether, the temperature being kept at 12–14°. The resulting suspension was stirred one-half hour with continued cooling, then worked up as above. Fractionation of the resulting red oil gave a main fraction boiling at 73–100° (4.2 mm.). Refractionation yielded 11.81 g. (81%), b.p. 64–66° (0.95 mm.), $n^{20}D$ 1.4950. An analytical sample had b.p. 92.5° (5 mm.), $n^{20}D$ 1.4942; λ_{max} 273, 207 mμ (log ε 3.42, 4.09); ν_{max} 1762, 1685, 1649, 1020 cm.$^{-1}$

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.10; H, 8.42.

Refractionation of the forerun of the first fractionation yielded *ca.* 1 g. of colorless liquid, b.p. 41–42° (4.5 mm.), $n^{20}D$ 1.4263, ν_{max} 1752, 1662, 1645, 1240, 1210, 1012 cm.$^{-1}$. This compound was not examined further.

Anal. Calcd. for $C_4H_6O_2$: C, 55.80; H, 7.02. $C_8H_{14}O_4$: C, 55.15; H, 8.10. $C_4H_8O_2$: C, 54.53; H, 9.15. Found: C, 55.47; H, 8.01.

Ozonolysis of Eucarvone Enol Acetate (IX).—A solution of 1.00 g. (0.0052 mole) of eucarvone enol acetate in 50 ml. of ethyl acetate was ozonized at −80°. The solution was hydrolyzed by adding it to hot 30% hydrogen peroxide dropwise. The ethyl acetate was evaporated in a stream of air, the remaining solution made basic with sodium carbonate, extracted with ether, acidified with hydrochloric acid and extracted thoroughly with ether. The extract was dried over magnesium sulfate and concentrated to dryness. Recrystallization from ether–carbon tetrachloride, benzene and ether–*n*-pentane gave 0.224 g. (37%) of *cis*-caronic

(15) W. H. Perkin and J. F. Thorpe, *J. Chem. Soc.*, **75**, 48 (1903).

acid, m.p. 172–174°, no depression upon admixture with authentic material, infrared spectrum identical with that of an authentic sample.

Eucarvone Enol Anisate.—To the stirred solution of sodioeucarvone from 13.73 g. (0.092 mole) of eucarvone and 4.88 g. (0.125 mole) of sodium amide was added a solution of 21.3 g. (0.125 mole) of anisoyl chloride in 100 ml. of absolute ether, the temperature being kept at 10–15°. Stirring was continued for 15 minutes while the solution was allowed to warm up. It was then worked up as above. Recrystallization of the residue from ether at −80° gave 14.05 g. (54%) of white ester, m.p. 72.7–73.7°; λ_{max} 259 mμ (log ε 4.23), with strong end absorption at *ca.* 205 mμ; ν_{max} 1732, 1641, 1257, 1011 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.02; H, 7.09. Found: C, 75.81; H, 7.02.

Ozonolysis of Eucarvone Enol Anisate (XI).—A solution of 3.42 g. (0.0012 mole) of eucarvone enol anisate in 50 ml. of ethyl acetate was ozonized for 21 hours. The blue-violet solution was added dropwise to a beaker containing 50 ml. of hot 30% hydrogen peroxide and the ethyl acetate evaporated in a stream of air. Sodium carbonate was added to make the solution basic, and the neutral materials were removed by ether extraction. The solution was then acidified with hydrochloric acid, cooled and the anisic acid filtered off. The filtrate was saturated with salt and extracted with ether continuously for 36 hours. The extract was concentrated to dryness and washed with 25 ml. of chloroform. Extractive recrystallization of the crystals, using chloroform in a Soxhlet extractor gave, after concentration to *ca.* 15 ml., cooling and filtration, 0.66 g. (35%) of *cis*-caronic acid, m.p. 171–173.5°, mixture m.p. 172–174° with authentic material. The infrared spectrum was identical with that of authentic material. An additional 280 mg. (15%), m.p. 171–175°, was obtained by workup of the mother liquor.

Reduction of Eucarvone Enol Anisate (XI).—2.00 g. of eucarvone enol anisate was reduced with hydrogen and 107 mg. of prereduced 5% palladium on charcoal in 40 ml. of ethanol; 2.19 equivalents of hydrogen was absorbed. The alcohol was removed under vacuum and the residue was evaporatively distilled at 105° (0.02 mm.), $n^{20}D$ 1.5339; ν_{max} 1730, 1615, 1520, 1013 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.53; H, 8.11.

Hydrolysis of Tetrahydroeucarvone Enol Anisate.—Sodium hydroxide (241 mg.) was dissolved in 5 ml. of water, 437 mg. of tetrahydroeucarvone enol anisate and 3 ml. of methanol were added, and the suspension warmed on a steam-cone until a clear solution was obtained. The solution was then allowed to stand for 3 days before dilution to 50 ml. with water and extraction with 4 × 10 ml. of methylene chloride. The extract was dried over magnesium sulfate, concentrated *in vacuo*, and a semicarbazone made from the residue. Recrystallization from methanol raised the melting point to 187–192°, not further improved. Authentic tetrahydroeucarvone semicarbazone behaved identically, and a mixture melting point of samples with the same melting range showed no depression.

Eucarvone Enol Benzoate.—To the hot solution of sodiocarvone from 16.00 g. (0.1065 mole) of eucarvone and 4.16 g. (0.1065 mole) of sodium amide was added slowly 14.68 g. (0.1065 mole) of benzoyl chloride. The suspension was refluxed for one-half hour, cooled to 15–20°, made slightly acid with glacial acetic acid, and worked up as above. Fractionation of the orange oil gave 2.20 g. of eucarvone plus a yellow oil, b.p. 155–165° (3 mm.).

Refractionation yielded 11.75 g. (43%) of a viscous, yellow oil with a eucarvone-like odor, b.p. 129–131°. An analytical fraction had b.p. 130.5° (0.6 mm.), $n^{20}D$ 1.5549; λ_{max} 204, 231, 269 mμ (log ε 4.11, 3.95, 3.49); ν_{max} 1740, 1640, 1028 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.29; H, 7.14. Found: C, 80.32; H, 7.32.

Maleic Anhydride Adduct of Eucarvone Enol Benzoate.—A solution of 5.08 g. (0.020 mole) of eucarvone enol benzoate and 2.06 g. (0.021 mole) of maleic anhydride in 10 ml. of benzene was refluxed for 4 hours, the color changing from deep yellow to orange. The benzene was replaced with carbon tetrachloride and the solution cooled. The heavy crystals which slowly formed weighed 4.58 g., m.p. 140.5–153°. The filtrate was kept at *ca.* 70° for 2 days, resulting in an additional 1.06 g. of adduct, m.p. 154.5–157°. Recrystallization of the total amount yielded 5.03 g. (72%), m.p. 155–157°. An analytical sample, recrystallized from acetone–*n*-pentane, melted at 156.5–157.5°; ν_{max} 1860, 1785, 1728, 1605, 1026, 1003 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.59; H, 5.88.

Eucarvone Enol Ethoxyformate.—To the sodioeucarvone from 50.00 g. (0.333 mole) of eucarvone and 13.10 g. (0.333 mole) of sodium amide was added at 65° a solution of 32 ml. of ethyl chloroformate in 50 ml. of absolute dioxane. The yellow suspension was allowed to cool to room temperature, then was worked up as above. Fractionation at 3 mm. gave 16.54 g. of eucarvone, b.p. 68–77°, an intermediate fraction, b.p. 98–115°, and 21.03 g. (42%) of the enol ester, b.p. 115–119°. An analytical fraction showed b.p. 97.5° (2 mm.), $n^{20}D$ 1.4881; λ_{max} 207.5, 271 mμ (log ε 4.12, 3.45); ν_{max} 1760, 1643, 1018 cm.$^{-1}$

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.26; H, 8.33.

Saponification of Eucarvone Enol Ethoxyformate (XII).—Eucarvone enol ethoxyformate (700 mg.) was dissolved in a solution of 880 mg. of potassium hydroxide in 20 ml. of water with the aid of a small amount of ethyl alcohol. After standing overnight the solution was acidified at 0° and extracted with ether. The extract was dried over magnesium sulfate and concentrated to a yellow oil which was fractionated at 2.3 mm., and gave only eucarvone, b.p. 54–55°, $n^{20}D$ 1.5083.

Eucarvone Enol Monoethylpyrocarbonate.—The intermediate fraction from the preparation of the enol carbonate was refractionated and yielded 6.70 g. (7.6%), a light yellow liquid, b.p. 92–94.5° (2 mm.), $n^{20}D$ 1.4750; λ_{max} 207.5, 271 mμ (log ε 4.54, 3.84); ν_{max} 1815, 1757, 1720, 1019 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.82. Found: C, 62.99; H, 7.77.

Δ^2-4-Methylcaren-5-one (XVI).—To the sodioeucarvone solution from 3.77 g. (0.0965 mole) of sodium amide and 11.50 g. (0.0766 mole) of eucarvone was added with stirring, at 10°, 15.2 g. (0.107 mole) of methyl iodide. No reaction occurred, so the cooling bath was removed. When the reaction was checked again an hour later the solution had turned the usual light yellow-brown and the internal temperature was 38°. Stirring at room temperature was continued for one hour more, then the solution was neutralized with glacial acetic acid, a small amount of solid potassium bicarbonate was added to destroy excess acetic acid, and one liter of saturated salt solution was added.

This solution was extracted with two 100-ml. portions of ether, the extract dried over sodium sulfate, and the ether removed *in vacuo*. Fractionation *in vacuo* produced a few drops of forerun, 10.86 g. (88%), b.p. 86–90° (12 mm.), and *ca.* 1 g. of still residue. Refractionation of a portion of the product for analysis showed b.p. 70° (5 mm.), $n^{20}D$ 1.4809, strong orange color with tetranitromethane; λ_{max} 206, 300 mμ (log ε 3.71, 2.89); ν_{max} 1698, 1665, 1007 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.34; H, 9.95.

Δ^2-4-Benzylcaren-5-one (XVII).—To the sodioeucarvone solution from 4.88 g. (0.125 mole) of sodium amide and 15.49 g. (0.103 mole) of eucarvone was added, at 5°, 15.85 g. (0.125 mole) of freshly distilled benzyl chloride. The reaction was warmed slowly to *ca.* 70°, at which temperature the reaction became somewhat exothermal. The temperature was allowed to rise slowly to reflux, but the suspension remained red-orange. An excess of benzyl chloride was added, causing the color to change to yellow orange. Refluxing was continued for 10 minutes, then the reaction mixture was cooled to room temperature. The total time of heating at 80–102° was *ca.* 2.5 hours.

Glacial acetic acid was added until the color changed to yellow, then the suspension was poured into one liter of salt solution and worked up in the same manner as the methyl analog (see above). Fractionation of the yellow residue yielded 18.33 g. (74%) of yellow oil, b.p. 117–119° (1 mm.), $n^{20}D$ 1.5389. An analytical sample showed b.p. 119° (1 mm.), $n^{20}D$ 1.5390, λ_{max} 206, 290 mμ (log ε 4.01, 2.05); ν_{max} 1695, 1611, 1004 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.91; H, 8.17.

Ozonolysis of Δ^2-4-Benzylcaren-5-one (XVII).—A solution of 7.86 g. (0.033 mole) of XVII in 50 ml. of ethyl acetate was ozonized for three hours at −80°. The ozonide was decomposed with hot 50% hydrogen peroxide and the ethyl acetate evaporated in a current of air. The solution was made basic with sodium carbonate, gas evolution was allowed to cease, and the solution was extracted with ether. It was then made strongly acidic with hydrochloric acid, saturated with salt, and extracted continuously for 24 hours with ether. The extract was concentrated *in vacuo* to oily white crystals which were washed with a few ml. of chloroform to leave 1.73 g. of white crystals, m.p. 161–173°. Extractive recrystallization in about 20 ml. of chloroform yielded 1.39 g., m.p. 168–174°. Recrystallization from water raised the melting point to 174–176°, yield 1.17 g. (25%). Identity with authentic *cis*-caronic acid was established by mixture melting point and comparison of infrared spectra.

Ozonolysis of 2-Benzylidene-Δ^3-caren-5-one (XVIII, Monobenzylidene Eucarvone) (by W. A. Remers).—A solution of 1.02 g. of monobenzylidene eucarvone, prepared as described by Wallach,[6] in 30 ml. of ethyl acetate was ozonized at −78° for 1 hour and at 0° for 20 hours The solution of the ozonide was added dropwise to hot (80°) 30% hydrogen peroxide and the ethyl acetate was evaporated in a stream of air. The remaining solution was made basic with potassium carbonate and extracted well with ether. Acidification of the aqueous phase, extraction with ether, evaporation of the ether layer and recrystallization from benzene yielded colorless crystals of crude caronic acid (180 mg.), m.p. 162–171°. Recrystallization from acetic acid yielded pure caronic acid, m.p. 179–179.5°, undepressed upon admixture with an authentic sample.

Neither ozonolysis nor permanganate oxidation of the benzoxybenzylidene derivative of eucarvone[6] (XX), which is along with the monobenzylidene derivative XVIII, yielded caronic acid. In addition, although the benzoxybenzylidene derivative is formed simultaneously with the monobenzylidene derivative from benzaldehyde and sodium ethoxide, it is not formed from the monobenzylidene derivative and benzaldehyde under the same conditions.

Attempted Synthesis of Δ^3-Caren-5-one (XXI).—To the solution of sodioeucarvone prepared from 5.22 g. (0.134 mole) of sodium amide and 10.09 g. (0.0672 mole) of eucarvone was added, at 12–15°, a solution of 7.80 g. (0.130 mole) of glacial acetic acid in 50 ml. of absolute dioxane. The slurry was kept at a stirrable consistency by addition of ether through the condenser as needed. The grey slurry was filtered and the yellow filtrate concentrated *in vacuo* with a nitrogen capillary at 25–30°. The red-orange oil, when fractionated in a micro-column, yielded only eucarvone, identified by its boiling point, refractive index and ultraviolet spectrum.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Nature of the Ring-bridging Step in the Transformation of Eucarvone to Carene Derivatives

BY E. J. COREY, H. J. BURKE AND W. A. REMERS

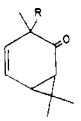
RECEIVED JULY 25, 1955

Evidence is presented that eucarvone (I), eucarvone enol and eucarvone enolate ion all exist predominately in the monocyclic forms. In the case of eucarvone itself, the presence of a small amount of the bicyclic isomer II has been demonstrated by deuterium exchange experiments. Whereas acylation of sodioeucarvone proceeds directly from the predominating monocyclic anion, alkylation appears to take place by way of the less stable bicyclic anion and not by a concerted transannular SN2′ reaction of the monocyclic species. Ozonolysis of the enol esters of eucarvone, on the other hand, appears to involve simultaneous substitution and bridging.

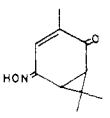
The marked tendency of eucarvone (I) to form bicyclic substitution products has been illustrated in the preceding paper on this subject[1] by a variety of examples. In these cases bicyclic carene derivatives were always formed instead of the expected monocyclic cycloheptadiene derivatives. The present article is concerned with the details of these unusual transformations, especially the exact sequence of the bridging and substitution parts.

The formation of carene derivatives from eucarvone might take place in one of three distinct ways: (1) by way of the anion or enol of the bicyclic isomer of eucarvone (II) or some other bicyclic intermediate, (2) by a process in which bridging and substitution are simultaneous and (3) by a process in which bridging follows substitution.

Fortunately, the third of these possibilities can be ruled out on the basis of the very nature of the bicyclic products. Thus, the alkylation products of sodioeucarvone (III) could not possibly have been formed by bridging subsequent to alkylation.

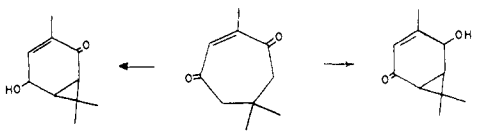


III



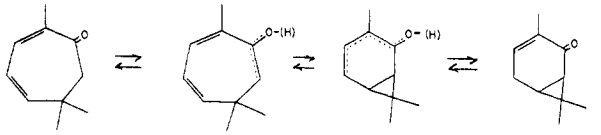
IV

Also, it is unlikely that the oximation product of eucarvone (IV) could be formed by prior oximation followed by bridging, especially since the substance can be made directly from sodioeucarvone and butyl nitrite in dioxane. Lastly, if the selenium dioxide oxidation product V were formed by bridging of the monocyclic dione VI two position isomeric hydroxy ketones would be expected in roughly equal amounts, contrary to fact. It thus appears that the possibility of bridging after substitution can be discounted.



V VI

In connection with the remaining two possibilities (1 and 2 above) we first sought to obtain data concerning the equilibria



I monocyclic enol or enolate ion bicyclic enol or enolate ion II

(1) E. J. Corey and H. J. Burke, THIS JOURNAL, **78**, 174 (1956).