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.

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[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

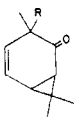
RECEIVED JULY 25, 1955

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.

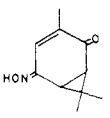
The marked tendency of eucarvone (I) to form bicyclic substitution products has been illustrated in the preceding paper on this subject[1] by a variety of examples. In these cases bicyclic carene derivatives were always formed instead of the expected monocyclic cycloheptadiene derivatives. The present 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.

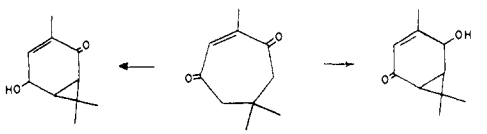


III



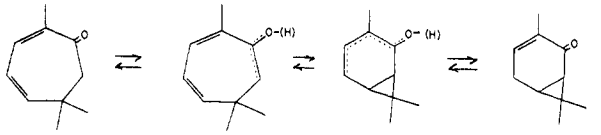
IV

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).

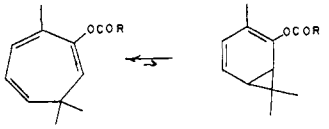
The equilibrium between the two ketonic species I and II was investigated by quantitative ultraviolet analysis of eucarvone, taking advantage of the fact that the bicyclic isomer II should show an ultraviolet absorption maximum at 229 mμ (log ε *ca.* 4)[2] and hence should be easily detectable in mixtures with the monocyclic isomer I which has only a single absorption peak at 302 mμ (log ε 3.82). Examination of the absorption spectra of various samples of eucarvone failed to reveal any absorption at 229 mμ other than slight tail absorption of the 302 mμ band and, as a consequence, the amount of the bicyclic ketone II in equilibrium with the monocyclic ketone I, must be very small, certainly less than 1%.

The presence of II in very low concentration could, however, be shown by deuterium exchange experiments. These experiments involved the quantitative measurement of deuterium exchange between eucarvone and sodium ethoxide–deuteroethanol solution and were based on the fact that if eucarvone, its enol or anion can exist only in the monocyclic form, only two of its hydrogens would be exchangeable, whereas if the bicyclic species II is present, even in trace amounts, three hydrogens should be exchangeable. Exchange reactions were carried out using the medium just mentioned and it was found that 3.0 hydrogens were exchangeable indicating the presence of II in equilibrium with eucarvone.

The greater stability of eucarvone as compared with its bicyclic isomer, which is established by the above experiment, cannot be used to estimate the relative stability of the mono- and bicyclic enols or enolate ions derived from eucarvone and so further studies were made toward this end.

Although the mono- and bicyclic enols of eucarvone are too unstable to allow a study of equilibrium, the enol esters of eucarvone, which are available by the procedure described in the preceding paper, are suitable for study as models because they possess the same ring structure.

As reported in a separate note[3] the differentiation between the mono- and bicyclic structures for the enol esters is a subtle matter because of their relationship as valence tautomers which might be in rapid equilibrium. The chemical evidence pertaining to structure is conflicting; ozonolysis of the enol acetate yields *cis*-caronic acid indicating the bicyclic structure VIII, whereas catalytic hydrogenation with palladium affords tetrahydroeucarvone enol acetate indicating the monocyclic structure VII. The validity of the monocyclic structure is shown clearly, however, by physical evidence. The nuclear magnetic resonance data[3] for the enol acetate are consistent only with structure VII. This conclusion is further substantiated by the infrared spectra of the enol esters all of which lack the absorption at *ca.* 1000 cm.$^{-1}$ which is characteristic of the three-membered ring of the carene system.[1]

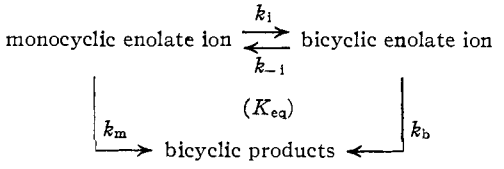


VII VIII

In agreement with the data on eucarvone enol acetate, it has also been determined that cycloheptatriene, 1,1,4-trimethylcycloheptatriene and 1,1,3,4-tetramethylcycloheptatriene exist preferentially in the monocyclic form.[3] This indicates that the cycloheptatriene system is in general more stable than the norcaradiene system and that the equilibrium position is not appreciably altered by the presence of substituents.[4,5]

Since the eucarvone enol esters as obtained represent the stable form[1] and since this form is monocyclic, it seems probable that the closely related eucarvone enol is more stable in the monocyclic than in the bicyclic form. Unfortunately, the enol esters cannot be regarded as close models of the enolate ions and so the relative stability of the mono- and bicyclic ions cannot be deduced as it can for the enols. However, it does seem quite possible from the data on the enol esters that the bicyclic ion may be less stable than the monocyclic ion. This view is subtantiated by three pieces of evidence. The ultraviolet absorption of sodioeucarvone in dioxane shows absorption which is quite similar to eucarvone (λ_{max} *ca.* 300 mμ) and quite different from what would be expected for the bicyclic enolate ion (λ_{max} *ca.* 240 mμ). In addition, careful neutralization of sodioeucarvone in dioxane with acetic acid at 0° produces only eucarvone and no detectable amount of the bicyclic isomer as determined by ultraviolet analysis and isolation using low temperature distillation. Lastly the acylation products of sodioeucarvone are always the monocyclic enol esters even when the conditions of isolation are so mild that the bicyclic enol esters should be isolable.

Unfortunately the lower relative stability and, hence, lower concentration of the bicyclic enolate ion complicates the decision between the two remaining mechanistic possibilities for the reactions of sodioeucarvone (1) bridging followed by substitution, *i.e.*, the bicyclic ion as an intermediate, and (2) simultaneous bridging and substitution. Considering the system and granting that $k_b \geqslant k_m$ as is



most likely, if K_{eq} is large (say >1) and the valence tautomerism is rapid, the bicyclic ion must be an intermediate. However, if K_{eq} is small, it is not possible to decide whether the bicyclic ion is an intermediate unless the relative magnitudes of k_b and k_m are known. Taking an extreme position, if K_{eq} is small and $k_b >> k_m$, the bicyclic ion might still be an intermediate. In summary, the lack of exact

(2) Deduced from the model compound V.

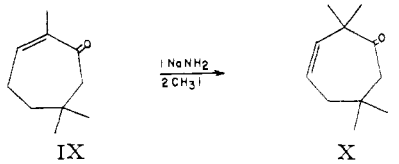
(3) E. J. Corey, H. J. Burke and W. A. Remers, THIS JOURNAL, **77**, 4941 (1955).

(4) The *gem*-dimethyl groups of the cycloheptatriene derivatives from eucarvone might be expected to stabilize the cyclopropane ring of the caradiene tautomer [see C. K. Ingold, *Ann. Repts.*, **22**, 129 (1925)].

(5) The preparation of the trimethyl- and tetramethylcycloheptatrienes from eucarvone are described in the Experimental section.

information on K_{eq} and of any information regarding k_b and k_m prevents evaluation of the bicyclic anion as an intermediate by this approach.

A clearer picture may be drawn of the alkylation of sodioeucarvone because of the structure of the product III. If bridging and alkylation were perfectly concerted, which amounts to a transannular SN2′ reaction, negative charge would be distributed on the eucarvone α-carbon and the departing anion (X) and on no other ring positions. Attack on *two* positions, both α' and γ, would be expected, as shown, with formation of a mixture of alkylation products. Actually, only the α'-alkylated β,γ-unsaturated ketone could be detected which appears to be more in harmony with alkylation of a γ-extended enolate ion than an SN2′ alkylation. Highly specific α-alkylation of γ-extended enolate ions has been observed in numerous instances and is now accepted as characteristic of such systems. The most reasonable rationale of the α-alkylation reaction[6] provides no reason for expecting exclusive α'-attack for the concerted SN2′ process described above. To verify the occurrence of α-alkylation in the γ-extended system of the bicyclic anion, the model compound γ,δ-dihydroeucarvone (IX) was prepared and alkylated *via* its sodio derivative. As expected only the α-alkylation product X was formed.



IX X

The above argument is by no means a proof of the bicyclic enolate ion intermediate, but it does provide evidence against a perfectly concerted transannular SN2′ mechanism. Mechanisms between the two extremes of a perfectly concerted transannular SN2′ reaction and a true bicyclic intermediate are not excluded, although they would appear reasonable only if bridging leads substitution by a substantial margin.

A different situation may exist in the case of the low temperature (−80°) ozonolysis of the enol esters of eucarvone. In this case k_m and k_b are probably both large compared to k_i and k_{-i} and it looks very much as though the predominating monocyclic enol undergoes bridging simultaneously with electrophilic attack by ozone. In this event, it seems probable that electrophilic attack leads and, indeed, induces the bridging step.

(6) See G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).

The selenium dioxide oxidation of eucarvone to give the hydroxy ketone V may be mechanistically akin to the ozonolysis of the enol esters, although this question must remain open because of the present lack of knowledge of the mechanism of selenium dioxide oxidations.

Thus, at least two mechanisms, differing in the timing of the bridging and substitution processes may be available for the formation of bicyclic products from eucarvone. The importance of these pathways may be due, not only to the ease of bridging, but also to the steric effect of the *gem*-dimethyl groups which probably serve to shield the adjacent α-methylene group of eucarvone and to retard the normal bimolecular substitution reactions of eucarvone enol and enolate ion at the α-carbon.

Experimental[7]

Deuterium Exchange.—To a solution of 0.240 g. (0.0104 mole) of sodium in 10 ml. of absolute deuteroethanol[8] (C_2H_5OD) was added 1.510 g. of eucarvone, $n^{20}D$ 1.5082, and the resulting solution was stored at 25°. After the periods of time specified below *ca.* 3.5 ml. samples were withdrawn and added to *ca.* 2 ml. of deuterium oxide. The deuteroethanol was removed under reduced pressure (15 mm.) and the remaining liquid was extracted with petroleum ether–ether (6 to 1) mixture. The extract was dried over sodium sulfate, concentrated and distilled at 1 mm. in a microcolumn. The center cut of pure eucarvone, $n^{20}D$ 1.5079–1.5088, was used for combustion and deuterium analysis by the falling drop method.[9] The number of exchangeable hydrogens in eucarvone was then calculated for various exchange reaction times. It was found that over two hydrogens were exchanged within five minutes of mixing and that a third hydrogen exchanged considerably more slowly. After five hours a limiting value of 3.0 exchangeable hydrogens per molecule of eucarvone was reached. In 6:4 deuteroethanol–deuterium oxide it was also found that the first two hydrogen atoms were replaced much more rapidly than the third and that the rate of exchange is slower than in deuteroethanol. Insofar as can be judged from these limited experiments it seems that the monocyclic anion is protonated to form eucarvone at a much faster rate than it bridges to form the bicyclic species.

1,1,4-Trimethylcycloheptatriene.—To a solution of 1.20 g. (0.0315 mole) of sodium borohydride in 8 ml. of methanol was added 4.50 g. (0.030 mole) of eucarvone with ice-bath cooling. After 40 minutes the methanol was removed under reduced pressure and the residue was treated with 50 ml. of saturated salt solution and 15 ml. of ether–methylene chloride. The organic layer was separated, dried, concentrated and distilled to give 3 g. of eucarvol, b.p. 67–69° (1.4 mm.), $n^{20}D$ 1.5040, λ_{max} 247 mμ (log ε 3.85), showing hydroxyl but no carbonyl absorption in the infrared. Dehydration of eucarvol was carried out by heating in a distilling flask to 120° at 20 mm. pressure with a minute drop of sulfuric acid. The reaction products, 1,1,4-trimethylcycloheptatriene and water, distilled as rapidly as formed under these conditions. The distillate was dried over sodium hydroxide and redistilled through a micro-column, b.p. 65° (70 mm.), $n^{20}D$ 1.4960 (all fractions), λ_{max} 268 mμ (log ε 3.64).

Anal. Calcd. for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.03; H, 10.95.

Methyleucarvol.—To a solution of *ca.* 0.06 mole of methyllithium in 50 ml. of anhydrous ether at reflux was added dropwise a solution of 9.00 g. (0.033 mole) of eucarvone in 50 ml. of ether. After 40 minutes the addition was completed and the reaction mixture was heated to reflux for an additional 2 hours, decomposed with aqueous ammonium chloride and separated into ethereal and aqueous fractions. The ethereal solution was dried, concentrated

(7) Microanalyses by Mr. Joseph Nemeth and associates.

(8) J. D. Roberts, C. M. Regan and I. Allen, THIS JOURNAL, **74**, 3679 (1952).

(9) A. S. Keston, D. Rittenberg and R. Schoenheimer, *J. Biol. Chem.*, **122**, 227 (1942).

and distilled to give 3.18 g. of methyleucarvol, b.p. 58° (0.9 mm.), $n^{20}D$ 1.5070.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.14; H, 11.63.

1,1,3,4-Tetramethylcycloheptatriene.—This material, previously prepared by Rupe[10] by the reaction of methylmagnesium bromide on eucarvone without isolation of the intermediate alcohol, was obtained by dehydration of methyl eucarvol using the procedure given above, b.p. 61° (10 mm.), $n^{20}D$ 1.5072, λ_{max} 275 mμ (log ε 3.68).

γ,δ-Dihydroeucarvone.—This substance was prepared from eucarvone by a modification of the previously described methods.[11,12] A solution of 8.00 g. (0.053 mole) of eucarvone in 160 ml. of ethanol was shaken with 0.40 g. of Lindlar palladium–lead catalyst and hydrogen overnight. The theoretical amount of hydrogen for reduction of one double bond was taken up in about 3 hours and the uptake had stopped after the overnight period at about 1.2 equivalents of hydrogen. Filtration, evaporation and distillation afforded 6.8 g. (85%) of γ,δ-dihydroeucarvone, b.p. 83° (10 mm.), $n^{20}D$ 1.4808, λ_{max} 239.5 mμ (log ε 3.9), ν_{max} 1673 cm.$^{-1}$.

Δ³-2,2,6,6-Tetramethylcyclohepten-1-one (Methyldihydroeucarvone).—In an apparatus flushed with nitrogen, sodium amide (1.0 g., 0.0256 mole), dioxane (41 ml.) and γ,δ-dihydroeucarvone (3.0 g., 0.02 mole) were combined and heated to reflux with stirring. After three hours the theoretical amount of ammonia had been evolved and the brown solution was cooled and treated with 3.64 g. (0.0256 mole) of methyl iodide at room temperature for 2 hours. The mixture was then neutralized with glacial acetic acid, concentrated and treated with ether-saturated salt solution. The ether extract was dried, concentrated and distilled to give 1.6 g. of methyldihydroeucarvone, b.p. 79–80° (15 mm.), $n^{22}D$ 1.4609, ν_{max} 1710 cm.$^{-1}$, no high intensity ultraviolet absorption, yellow color with tetranitromethane.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.69; H, 11.24.

URBANA, ILLINOIS

(10) H. Rupe and W. Kerkovius, *Ber.*, **44**, 2702 (1911).
(11) O. Wallach, *Ann.*, **403**, 73 (1914).
(12) Y. Naves and P. Ardizio, *Helv. Chim. Acta*, **32**, 329 (1949).

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

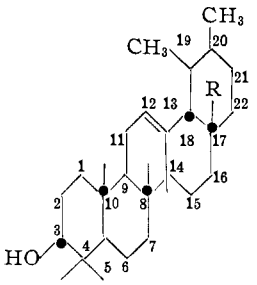
The Stereochemistry of the α-Amyrins

BY ELIAS J. COREY AND JOSEPH J. URSPRUNG

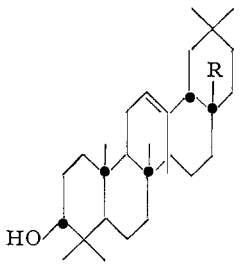
RECEIVED AUGUST 16, 1955

Evidence is presented for stereoformula I for α-amyrin and consideration is given to other proposals recently made.

In a previous communication[1] we proposed stereoformula I for α-amyrin, the parent member of the important ursane or α-amyrin family of pentacyclic triterpenes. This formula was derived by starting



I, α-amyrin, R = CH_3
II, ursolic acid, R = COOH



III, β-amyrin, R = CH_3
IV, oleanolic acid, R = COOH

out with the previously established configurations for C_3, C_5, C_8 and C_{10} and adding assigned configurations for C_9, C_{14}, C_{17}, C_{19} and C_{20}, in that order, as deduced from chemical evidence. This evidence is reviewed herein and that portion which was presented only briefly in the preliminary note on this subject is described in more detail together with the pertinent experimental data.

The α-orientation of the hydrogen at C_9, which results in a *trans-anti-trans* arrangement for the A, B and C rings of α-amyrin, follows from the facts (1) that this center is not epimerizable when adjacent to the 11-keto function and (2) that the hydrogen at C_9 is axial to ring C. The axial orientation of the 9-hydrogen relative to ring C is indicated by the well known ease with which 11α-(axial)-bromo-12-ketones undergo dehydrobromination to give Δ^{10}-12-ketones.[2] Identical behavior is observed in the β-amyrin series (III, IV)[3] in which the 9-hydrogen is also α-oriented.

The configurations at C_{14} and C_{17} in the α-amyrins were determined by two interlocking lines of evidence and are the same as at the corresponding centers in the β-amyrin (oleanane) series (III, IV).[4,5] First the acid $\rightleftarrows$ γ-lactone equilibrium constants for ursolic (II) and oleanolic (IV) acids are 0.33 and 0.11, respectively, indicating that the energy differences between γ-lactone and free acid due to strain and steric interactions are about the same in both cases. Eight structures, differing in configuration at C_{14}, C_{17} and C_{18}, are possible for ursolic acid and are noted in Table I. Second, acid–γ-lactone optical rotation differences for ursolic and oleanolic acid and the corresponding γ-lactones are essentially identical (Table II). After ruling out the possibilities in which there is a large amount of strain in the γ-lactone relative to the acid and the possibilities which are not in agreement with optical rotation differences, only one possibility remains for the configurations at C_{14} and C_{17}, that with the substituents at C_{14} and C_{17} α- and β-oriented, respectively, as in the β-amyrin series. This conclusion has subsequently been

(1) E. J. Corey and J. J. Ursprung, *Chemistry and Industry*, 1387 (1954).
(2) D. E. Seymour, K. S. Sharples and F. S. Spring, *J. Chem. Soc.*, 1075 (1939).
(3) (a) C. W. Picard, K. S. Sharples and F. S. Spring, *ibid.*, 1045 (1939); (b) R. Budziarek, J. D. Johnston, W. Manson and F. S. Spring, *ibid.*, 3019 (1951).
(4) D. H. R. Barton and N. J. Holness, *ibid.*, 78 (1952).
(5) A. M. Abd El Rahim and C. H. Carlisle, *Chemistry and Industry*, 279 (1954).