837. *Further Rearrangements of Eucarvone Derivatives.*

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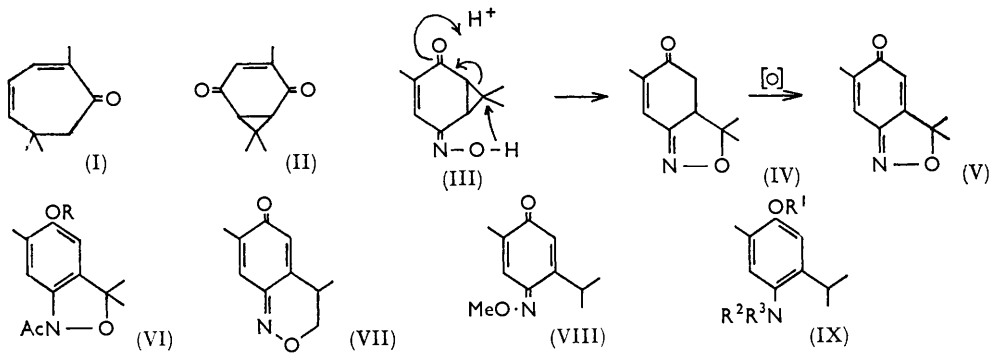
Hydroxyiminocarenone (III) is rearranged by acid to compound (IV) which affords a compound (V) containing a quinone imine grouping. The structure of α-dihydroeucarvone is discussed and the dienone previously derived from it by oxidation with selenium dioxide, followed by dehydration, is shown to be 1-acetyl-5,5-dimethylcyclohexa-1,3-diene (XVI).

The versatile monocyclic terpene eucarvone (I) has already been shown to undergo transformations leading to derivatives of bicyclo[4,1,0]heptanone,[1] bicyclo[3,2,0]heptanone,[2] and bicyclo[2,2,1]heptanone.[3] This paper describes new rearrangements of the eucarvone skeleton which lead to cyclohexadiene derivatives.

An interest in the synthetic applications of eucarvone or its transformation products led us to seek a more practicable route to carenedione (II) than the published method [1b] of selenium dioxide oxidation of eucarvone. An alternative involved the hydrolysis of

[1] Corey and Burke, *J. Amer. Chem. Soc.*, (*a*) 1954, **76**, 5257; (*b*) 1956, **78**, 174.
[2] Büchi and Burgess, *J. Amer. Chem. Soc.*, 1960, **82**, 4333.
[3] Hurst and Whitham, *Proc. Chem. Soc.*, 1961, 116.

hydroxyiminocarenone (III), which is readily available.[1b] Deoximation was best accomplished by nitrous acid, but during the study of other methods it was found that heating the oxime (III) with lævulic acid and hydrochloric acid produced a yellow solid A, $C_{10}H_{11}NO_2$. Better yields were obtained by a two-phase acid treatment.



The spectral properties of material A indicated the presence of a conjugated carbonyl group [ν (in CCl_4) **1655** cm.$^{-1}$] and an extended chromophore ($\lambda_{max.}$ **329** mμ; ε **23,500**). The colour was discharged by mild reducing agents and regenerated by air. Reductive acetylation (zinc–acetic acid–acetic anhydride) yielded a colourless product, $C_{14}H_{17}NO_4$, showing infrared absorption typical of an aryl acetate (**1765** cm.$^{-1}$) and an *N*-acetyl (**1670** cm.$^{-1}$) group with aromatic bands at **1620** and **1500** cm.$^{-1}$. Catalytic reduction of compound A in acetic acid–acetic anhydride yielded a phenolic amide [ν (in CCl_4) **3615** and **1668** cm.$^{-1}$] which was converted into the *O*-acetate described above by acetylation. Neither of these products showed N–H absorption in the infrared spectrum. The most reasonable structure for the rearrangement product (A) appeared to be (V), arising as indicated (III ⟶ IV ⟶ V) and leading to the phenol (VI; R = H) and its acetate (VI; R = Ac) by reductive acetylation. An alternative formulation (VII) for A was consistent with the available evidence and, although mechanistically less likely, it demanded consideration. Both structures contain the same chromophore and the ultraviolet absorption is in good agreement with that found for the oxime-ether [4] (VIII) ($\lambda_{max.}$ **320** mμ; ε **20,100**). A decision between these alternatives was made on the basis of hydrogenolysis. Vigorous catalytic reduction of compound A yielded an unstable product, whose stable mono- and di-acetyl derivatives were shown to have structures (IX; $R^1 = R^2 = H$, $R^3 = Ac$; and $R^1 = R^2 = Ac$, $R^3 = H$) by comparison with synthetic specimens prepared from 5-isopropyl-2-methyl-4-nitrosophenol. The substitution pattern of the carbocyclic ring was thus verified and the loss of an oxygen atom under these conditions clearly favoured structure (V) which alone contains a benzyloxy-group. The ready formation of this compound (V) from hydroxyiminocarenone seems to establish the geometry of this oxime as shown in (III).

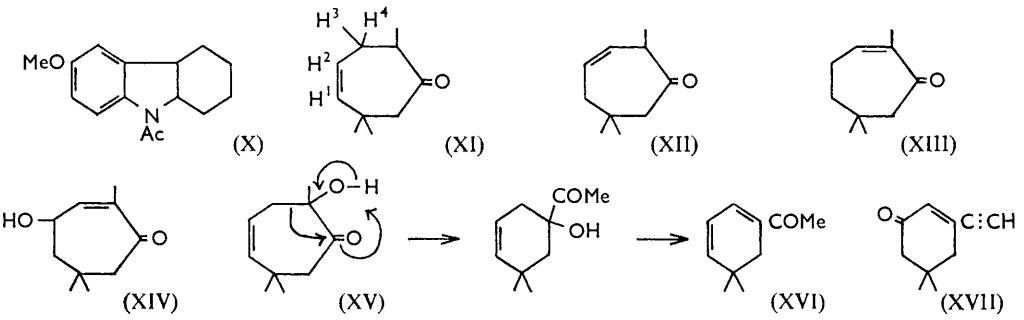
The ultraviolet absorption of both the phenol (VI; R = H) and its acetate showed (see Table) the intensities and wavelengths to be expected by extrapolation from model systems,[5] but the hydrogenolysis products (IX; $R^1 = R^2 = Ac$, $R^3 = H$; and $R^1 = R^2 = H$, $R^3 = Ac$) absorbed much less intensely whilst the derived triacetyl compound

Substance	$\lambda_{max.}$ (in EtOH)	ε	Substance	$\lambda_{max.}$ (in EtOH)	ε
VI; R = H	269	15,500	IX; $R^1 = R^2 = H$, $R^3 = Ac$	280	2260
VI; R = Ac	268	15,000	IX; $R^1 = R^2 = R^3 = Ac$ ...	266, 274	915, 845
IX; $R^1 = R^2 = Ac$, $R^3 = H$	274	1030	X (ref. 6)	261, 295	15,500, 3680

[4] Sherk, *Amer. J. Pharm.*, 1921, **93**, 221.
[5] Le Rosen and Smith, *J. Amer. Chem. Soc.*, 1948, **70**, 2705.

(IX; $R^1 = R^2 = R^3 =$ Ac) showed even weaker absorption. It may be concluded that, in the monocyclic series, steric crowding forces the amide grouping out of the plane of the aromatic ring, thus hindering delocalisation involving the amide group and the benzene ring. On the other hand, the bicyclic structures, like the model (X),[6] are rigidly coplanar, thus assuring complete delocalisation. Indeed, the intense absorption of the products (VI; R = H and Ac) is, in itself, evidence for the presence of the heterocyclic ring.

The mechanism suggested for the transformation (III ⟶ V) involves an oxidation and assumes an intermediate (IV) which was not isolated in reactions as above. This intermediate was, however, the sole product when hydroxyiminocarenone (III) was treated



with cold concentrated sulphuric acid, and it was converted into compound (V) under the conditions which afforded the latter directly from the oxime (III). Alternatively, the intermediate (IV) could be oxidised to (V) by gaseous oxygen. The structure of the intermediate followed from its ultraviolet absorption ($\lambda_{max.}$ 300 mμ; ε 9030) which is similar to that of (III) ($\lambda_{max.}$ 295 mμ; ε 10,000), its ready oxidation to (V), and its infrared carbonyl absorption (1660 $cm.^{-1}$) with no indication of N–H or O–H bands.

A further example of ring contraction was found in the chemistry of α-dihydroeucarvone. This unsaturated ketone has been formulated as (XI), but the available evidence does not exclude the alternative structure (XII).[7] Indeed, the light absorption ($\lambda_{max.}$ 290 mμ; ε 37) [7] and the ready isomerisation [7] to the conjugated β-dihydroeucarvone (XIII) are more readily understood in terms of (XII).

Re-examination of " α-dihydroeucarvone " revealed that it was a mixture of, mainly, two components (~3 : 1), separable by gas–liquid chromatography. Furthermore, the isomerisation to β-dihydroeucarvone (XIII), although ready, occurred under basic or acidic conditions to the extent of only 17% and 29%, respectively; this suggests that the βγ-unsaturated ketone (XII) is the minor component of the mixture. The major bands in the nuclear magnetic resonance spectrum of " α-dihydroeucarvone " comprised a strong doublet centred at τ 4·8, which must be due to H^1 split by coupling with H^2 (XI) ($J_{1,2}$ 10 c./sec.) and a cluster of four weak doublets centred at τ 4·6 assigned to H^2 coupling with H^1 and with H^3 and H^4 ($J_{2,3}$ 2 c./sec.). Structure (XII) would produce a much more complex spectrum and is therefore not abundant in the mixture, whose major component is clearly (XI).

A previous paper [7] described the oxidation of " α-dihydroeucarvone " to a mixture of two ketols (XIV) and (XV), and it is now possible to speculate that these originated respectively from (XII) and (XI). Heating with boric acid dehydrated the secondary alcohol (XIV) smoothly to eucarvone, but under identical conditions the tertiary isomer (XV) underwent skeletal rearrangement to an isomer of eucarvone which we have now proved synthetically to be the cyclohexadienone (XVI) formed by ring-contraction as shown. Treatment of the enol ether of dimedone with ethynylmagnesium bromide,

[6] Chalmers, Openshaw, and Smith, *J.*, 1957, 1115.
[7] Campbell, Islam, and Raphael, *J.*, 1956, 4096.

followed by acid, gave the conjugated enynone (XVII). The carbonyl group was then selectively reduced by borohydride and the resulting alcohol was converted, without isolation, into this isomer (XVI) in one operation by hot formic acid: the bright crimson 2,4-dinitrophenylhydrazones from the two samples were identical.

Experimental

Car-1(6)-ene-2,5-dione (II).—Hydroxyiminocarenone (1·06 g.) in acetic acid (12 ml.) was treated with sodium nitrite (4·8 g.) in water (10 ml.). After 4 hours with occasional shaking, the red colour formed initially had disappeared and the solution was poured into a large volume of aqueous sodium acetate and extracted with benzene. The product obtained on evaporation was chromatographed in benzene on grade III neutral alumina. Elution with 1 : 9 ether–benzene afforded the carenedione (0·75 g., 71%), m. p. 89—90°. For larger-scale preparations continuous stirring was necessary to duplicate this yield.

3,3,6-*Trimethyl-1,2-benzisoxazol-5(3H)one* (V).—(*a*) Hydroxyiminocarenone (1·6 g.) in lævulic acid (9 vol.) and N-hydrochloric acid (1 vol.) were heated at 100° for 2½ hr., diluted with water, and extracted with methylene chloride. The extract was washed until neutral, concentrated, and extracted with hot benzene, giving the *dienone*, which crystallised from light petroleum (b. p. 60—80°) in yellow needles, m. p. 152—153° [Found: C, 67·4; H, 6·0; N, 8·0%; *M* (mass spectroscopy), 177. $C_{10}H_{11}NO_2$ requires C, 67·8; H, 6·3; N, 7·9%; *M*, 177].

(*b*) Hydroxyiminocarenone (8 g.) was heated for 1½ hr. at 100° in a two-phase system of light petroleum (b. p. 100—120°) and 2N-sulphuric acid, with stirring, the organic layer being removed at 30 min. intervals and replaced with fresh solvent. The combined extracts were concentrated and redissolved in benzene, and this solution was washed with aqueous sodium hydrogen carbonate, then with water, dried, and evaporated. The product was chromatographed in benzene on grade III alumina; elution with benzene gave the dienone in *ca.* 40% yield. Further elution afforded *ca.* 30% of the starting material.

Reductive Acetylation of the Benzisoxazolone (V).—(*a*) The ketone (156 mg.) in 1 : 1 acetic acid–acetic anhydride (10 ml.) was hydrogenated (1 mol./hr.) over platinum oxide (98 mg.), and the solution was then freed from catalyst, concentrated *in vacuo*, and poured on ice. 1-*Acetyl-1,3-dihydro-5-hydroxy-3,3,6-trimethylbenzisoxazole* (VI; R = H) crystallised from aqueous ethanol in plates, m. p. 193—194° (Found: C, 65·25; H, 6·6; N, 6·6. $C_{12}H_{15}NO_3$ requires C, 65·1; N, 6·8; N, 6·3%). Acetylation by refluxing acetic anhydride converted this phenol into the acetate described below.

(*b*) The ketone (V) (41 mg.) was heated under reflux with zinc dust (100 mg.) in 1 : 1 acetic acid–acetic anhydride (3 ml.). The mixture was finally poured on ice and the precipitated *acetate* (VI; R = Ac), crystallised from light petroleum (b. p. 60—80°), had m. p. 135—136° [Found: C, 63·9; H, 5·9; N, 5·5%, *M* (mass spectroscopy), 263. $C_{14}H_{17}NO_4$ requires C, 63·9; H, 6·5; N, 5·3%; *M*, 263].

Synthesis of 4-Amino-5-isopropyl-2-methylphenol Derivatives.—The 4-nitrosophenol [8] (820 mg.) in 1 : 1 acetic acid–acetic anhydride (20 ml.) was hydrogenated over platinum oxide (520 mg.) until the colour was discharged (*ca.* 1 hr.). After the catalyst had been removed, the solution was concentrated and poured on ice, affording *4-acetamido-5-isopropyl-2-methylphenol*, m. p. 180—181° (from aqueous alcohol) (Found: C, 69·5; H, 8·1; N, 7·3. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3; N, 6·8%). This phenol (52 mg.) in 2N-sodium hydroxide was shaken with dropwise addition of acetic anhydride until the mixture was permanently acid. The precipitated *4-acetamido-5-isopropyl-2-methylphenyl acetate*, crystallised from ethyl acetate–light petroleum, had m. p. 161—162° (Found: C, 67·2; H, 7·6; N, 5·5. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7; N, 5·6%). When the acetamidophenol was refluxed for 1 hr. in acetic anhydride and decomposed with ice, *4-diacetylamino-5-isopropyl-2-methylphenyl acetate*, m. p. 73—74° [from light petroleum (b. p. 40—60°)], was precipitated (Found: C, 66·2; H, 7·05; N, 5·0. $C_{16}H_{21}NO_4$ requires C, 65·95; H, 7·3; N, 4·8%).

Hydrogenolysis of the Benzisoxazolone (V).—The ketone (V) (690 mg.) in acetic acid (75 ml.) was hydrogenated at 5 atm. in the presence of 10% palladium–charcoal (300 mg.) for 30 min. at room temperature and for a further 20 hr. at 55°. An excess of acetic anhydride was added to the mixture which was then freed from catalyst and concentrated under nitrogen. The

[8] Kremers, Wakeman, and Hixon, *Org. Synth.*, Coll. Vol. I, 1946, p. 511.

residual solvent was finally removed *in vacuo*, and the residue was dissolved in ethanol–ethyl acetate and filtered through a silica gel–Celite column. Evaporation afforded an almost colourless oil which crystallised from light petroleum (b. p. 60—80°) and recrystallised from light petroleum–ethyl acetate to give a product, m. p. 161°. The m. p. was not depressed on admixture with the 4-acetamido-acetate (above).

On evaporation, the light-petroleum mother-liquors gave an oil, b. p. 90—100°/0·5 mm., which was refluxed for 20 min. with 2N-sodium hydroxide. The mixture was washed with ether, acidified, and extracted with ether, and the extract was washed with water, dried, and concentrated. The solid residue crystallised from ethyl acetate–light petroleum, then having m. p. 177—179° alone and mixed m. p. with the 4-acetamido-phenol.

3a,4-*Dihydro*-3,3,6-*trimethylbenzisoxazol*-5(3H)-*one* (IV).—Hydroxyiminocarenone (0·77 g.), dissolved in concentrated sulphuric acid, was set aside for 18 hr. at room temperature and then poured on ice. The precipitated *ketone* sublimed in prisms, m. p. 129—131° [Found: C, 67·1; H, 6·95; N, 8·0%; *M* (mass spectroscopy), 177. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%; *M*, 177].

Oxidation of the Dihydrobenzisoxazolone (IV).—Oxygen was passed through a solution of the ketone (IV) (95 mg.) and potassium hydroxide (200 mg.) in ethanol (60 ml.) for 1½ hr. The bulk of the solvent was then removed *in vacuo* and the residue was taken up in water and acidified. Ether-extraction gave a brown solid which was chromatographed in benzene on grade I neutral alumina and, when crystallised from light petroleum (b. p. 60—80°), had m. p. 152—153°. It was identical (mixed m. p. and infrared spectrum) with the benzisoxazolone (V) already described.

Experiments on "α-Dihydroeucarvone."—Gas–liquid chromatography of the ketone on 5% Apiezon L revealed two major components in amounts of 73% and 21%.

"α-Dihydroeucarvone" (440 mg.) and potassium acetate (480 mg.) in ethanol (25 ml.) were heated under reflux for 20 hr., concentrated to small bulk, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated, yielding an oil, b. p. 80—90°/15 mm., n_D^{22} 1·4672, $\lambda_{max.}$ (in EtOH) 238 mμ (ε 1047). From the spectral data of β-dihydroeucarvone [$\lambda_{max.}$ (in EtOH) 238 mμ (ε 6166)], this corresponds to 17% conversion. When the rearrangement was carried out in acid as previously described,[7] the product, b. p. 89—94°/13 mm., had $\lambda_{max.}$ (in EtOH) 240 mμ (ε 1778), corresponding to 29% conversion, and on increasing the time of heating to 8 hr. an essentially similar value was obtained.

1-*Acetyl*-5,5-*dimethylcyclohexa*-1,3-*diene* (XVI).—3-Ethoxy-5,5-dimethylcyclohex-2-enone (10·7 g.) in tetrahydrofuran (50 ml.) was added in 1 hr. to ethynylmagnesium bromide (from 2·4 g. of magnesium) in tetrahydrofuran (100 ml.), and the mixture was heated under reflux in nitrogen for 2 hr. 10% Sulphuric acid (10 ml.) was then added and heating was continued for a further 1 hr. The usual extraction procedure gave the ketone (XVII) (1 g.), b. p. 62—64°/0·9 mm., n_D^{25} 1·5110, $\lambda_{max.}$ (in EtOH) 262 mμ (ε 16,200), $\nu_{max.}$ 3250, 2100, 1660, 1600, 1365, and 1350 cm.$^{-1}$. It was set aside in methanol for 1 hr. at room temperature with an excess of sodium borohydride, then poured into a large volume of water, and the whole was extracted with methylene chloride. The extract was washed with 4N-sodium hydroxide, then with water, dried, and evaporated. The resulting oil ($\nu_{max.}$ 3300, 2095, 1630 cm.$^{-1}$), which gave a positive test for C:CH with ammoniacal silver nitrate, was heated under reflux for 1 hr. with an excess of 90% formic acid. The ketone next isolated by ether-extraction gave a crimson 2,4-dinitrophenylhydrazone, m. p. 174° (from butan-1-ol), $\lambda_{max.}$ (in $CHCl_3$) 397 mμ (ε 27,000) (Found: N, 17·4. Calc. for $C_{16}H_{18}N_4O_4$: N, 16·95%), identical (mixed m. p. and infrared spectrum) with that derived by dehydration of the keto-alcohol (XV)

Microanalyses were carried out by Mr. J. M. L. Cameron, B.Sc., and his staff, mass spectra were measured by Dr. R. I. Reed and associates, nuclear magnetic resonance spectra (neat) on an A.E.I. R.S.2 instrument by Miss M. Mackay, and infrared spectra on a Unicam S.P. 100 instrument by Mrs. F. Lawrie. The authors are indebted to Drs. A. L. Porte and G. Eglinton for advice on the interpretation of the nuclear magnetic resonance and infrared spectra, respectively, also to The Carnegie Trust for the Universities of Scotland for a research scholarship (to I. W. J. S.).

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