ture was shaken for 20 minutes and was then filtered. The filtrate was added to a solution of 5 g. of sodium iodide in 100 cc. of acetone and the resulting solution was boiled under reflux for 30 minutes. The tribromide LXVIb (850 mg.) was then added and refluxing was continued for 12 hr. Water and ethyl acetate were added and the organic extract was washed successively with water, sodium carbonate and sodium thiosulfate solutions. The dried extract was evaporated and the residue was boiled under reflux for 3 hr. with 10 g. of zinc dust in 100 cc. of acetic acid. The cooled mixture was then filtered, the filtrate was diluted with ethyl acetate and washed with water and sodium carbonate solution. Drying and evaporation of the solvent gave a solid residue [λ_{max} 240 mμ (ϵ 7800)] which was chromatographed on 40 g. of alumina. Elution with benzene produced 280 mg. of the saturated ketone LXVIa, m.p. 202-205°. Elution with benzene and benzene-ether (9:1) and crystallization from chloroform-ether yielded 165 mg. (31%) of the unsaturated ketone LXVII, m.p. 185-187°, [α]D — 7°, λ_{max} 240 mμ (ϵ 15,800). It was identified in the usual way[71b] with an authentic sample (m.p. 185-186°, [α]D — 8°) prepared by the Oppenauer oxidation of diosgenin.[57a]

Δ[3,5]-25D-Spirostadien-3-ol Acetate (LXX).—A solution of 150 mg. of the unsaturated ketone LXVII in 50 cc. of isopropenyl acetate was treated with 2 drops of concd. sulfuric acid and was then boiled under reflux for 3 hr. Water and ether were added to the cooled solution and the organic extract was washed with sodium carbonate solution and water. Crystallization of the product from ether-methanol gave 115 mg. (70%) of the enol acetate LXX, m.p. 181-182°, [α]D — 113°. The crude compound (m.p. 172-175°) has been reported.[59]

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.58; H, 9.25.

Diosgenin (Δ[5]-25D-Spirosten-3β-ol) (LXXI).—A solution of 100 mg. of the enol acetate LXX in 200 cc. of ethanol was added dropwise during 2 hr. to a stirred solution of 1 g. of sodium borohydride in 50 cc. of 70% ethanol kept at 5° by ice-cooling. After being kept at 5° for a further 1 hr., the solution was treated with a solution of 1 g. of sodium hydroxide in 10 cc. of water and was then heated under reflux on a boiling water-bath for 30 minutes. Water was

added and the crystalline material, isolated with ethyl acetate, was boiled under reflux for 1 hr. in 50 cc. of ethanol containing 3 drops of concd. hydrochloric acid. The product was again isolated with ethyl acetate and then chromatographed on 6 g. of alumina. The fractions eluted with benzene-ether (9:1) on crystallization from methanol yielded 66 mg. (72%) of diosgenin, m.p. 205-207°, [α]D — 119°. It was identified with an authentic sample (m.p. 207-209°, [α]D — 122°) in the usual way.[71b]

3β-Acetoxy-Δ[9(11)]-5α,25D-spirosten-12-one (LXXIVa) from Δ[9(11)]-5α,25D-Spirosten-3β-ol Acetate (LXXIII).—A solution of 75 mg. of chromium trioxide in 5 cc. of 85% acetic acid was added to 75 mg. of the Δ[9(11)]-compound LXXIII (m.p. 197-198°)[62] in 15 cc. of acetic acid. The solution was allowed to stand at 37° for 48 hr. and the excess reagent was then destroyed through addition of methanol. Isolation with ethyl acetate yielded material [λ_{max} 238 mμ (ϵ 4300)] which was chromatographed on 6 g. of alumina. The fractions eluted with pentane-benzene (1:1) on crystallization from ether-pentane yielded 22 mg. of the starting material LXXIII, m.p. 195-197°. The fractions eluted with benzene-ether (9:1) on crystallization from methanol gave 18 mg. (24%) of the unsaturated ketone LXXIVa, m.p. 217-219°, [α]D —9°, λ_{max} 238 mμ (ϵ 13,200). Identity with an authentic sample (m.p. 218-220°, [α]D — 8°)[63] was established in the usual way.[71b]

Hecogenin (3β-Hydroxy-5α,22D-spirostan-12-one) (LXXV). —A solution of 50 mg. of the unsaturated ketone LXXIVa in 20 cc. of dry ether was added dropwise during 5 minutes to a stirred solution of 100 mg. of lithium in ca. 30 cc. of liquid ammonia. The mixture was stirred for a further 5 minutes, and 2 g. of ammonium chloride was then added. The ammonia was allowed to evaporate, water was added to the residue and the product was isolated with ethyl acetate. The resulting material was boiled for 2 hr. with 20 cc. of a 3% solution of potassium hydroxide in methanol (containing 2 cc. of water). The product was again isolated with ethyl acetate and then chromatographed on 5 g. of alumina. Elution with benzene—ether (5:1) and crystallization from acetone yielded 31 mg. (68%) of hecogenin, m.p. 263-265°, [α]D + 6°. The compound was identified in the usual way[71b] with an authentic sample (m.p. 264-266°, [α]D + 8°).

The Isomerization of Thujone[1]

BY RICHARD H. EASTMAN AND A. VERNON WINN

The acid-catalyzed isomerization of thujone has been shown to follow the Markownikoff rule, and the thermal isomerization of thujone has been shown to produce nor-ketones as well as carvotanacetone. The thermal isomerization has been found to proceed at unusually low temperatures and a mechanistic scheme is proposed to account for the fact.

Among the cleavages of the bicyclo[3.1.0]-hexane system,[2] that of thujone (I) by mineral acids presents an anomaly since the reported[3] formation of carvotanacetone (II) involves a violation of the Markownikoff rule as applied to the opening of three-membered rings by acidic agents.[4]

Evidence is presented here to the effect that carvotanacetone (II) is not a product of the acid-catalyzed cleavage; that the products are those pre-

dicted by the Markownikoff rule, namely, carvenone (III), 2,3-dimethyl-4-isopropyl-2-cyclopentenone ("isothujone") (IV) and 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V); that these products

I   II   III   IV   V

are not in thermodynamic equilibrium under the conditions of the reaction; and, that the production of carvotanacetone (II) in the earlier studies was quite possibly due to fortuitous thermal isomerization of thujone which we have found to proceed at surprisingly low temperatures.[5]
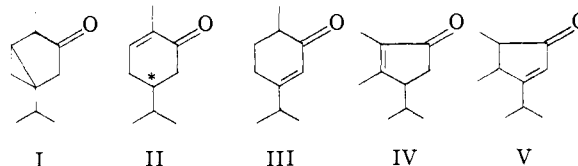
(1) Taken from the Doctoral Dissertation of A. V. Winn in the Department of Chemistry and Chemical Engineering at Stanford University.

(2) For references to previous studies, see R. H. Eastman, P. M. Iloff, Jr., and Hart Isaacs, Jr., THIS JOURNAL, 80, 1704 (1958).

(3) A. Baeyer, *Ber.*, 27, 1922 (1894); O. Wallach, *ibid.*, 28, 1958 (1895); A. Haller, *Compt. rend.*, 140, 1630 (1905); A. E. Gillam and T. F. West, *J. Chem. Soc.*, 811 (1941).

(4) See G. Büchi and D. M. White, THIS JOURNAL, 79, 750 (1957), for an example of a non-Markownikoff opening under special conformational requirements.

Conformations of the Isomeric Thujones.—In

view of our finding that the acid-catalyzed isomerization of thujone does not follow the course described in the literature,[3] considerable effort was devoted to obtaining pure samples of *l*-thujone (VI) and *d*-isothujone (VII) for the study. Final purifications were effected by liquid–vapor partition chromatography in critical instances, and all isolation procedures were monitored with infrared absorption spectroscopy.

The assignment[6] of the equatorial position of the methyl group in *d*-isothujone (VII) is supported by the composition of the equilibrium mixture (33% *l*-thujone, 67% *d*-isothujone),[7a] and the fact that of the pair of isomers, only *d*-isothujone forms a bisulfite-addition compound.[7b] Only if *d*-isothujone has the methyl group at C-1 equatorially disposed is a diequatorial *trans* orientation (VIII) of the methyl and sulfonic groups possible, and the formation of the adduct correspondingly favored by minimization of bulk interactions.[8]
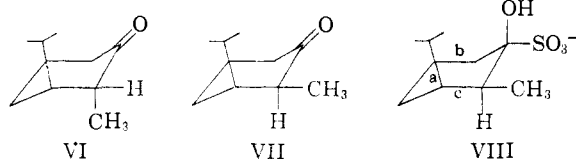
The spectroscopic properties of the thujones ($\lambda_{max}^{isooctane}$ 300 mμ, ϵ 23; λ_{max}^{film} 5.75 μ) are in agreement with those reported for cyclopentanone (λ_{max}^{hexane} 299 mμ, ϵ 20; λ_{max}^{film} 5.74 μ)[9] and thus provide no evidence for homoallylic electronic interaction[10] of the cyclopropyl and carbonyl systems.[11]

(5) Thermal isomerization of thujone to carvotanacetone at high temperatures has been reported by F. W. Semmler [*Ber.*, **27**, 895 (1894)].

(6) P. M. Illoff, Jr., Dissertation, Stanford University, 1957.

(7) (a) A similar preponderance of *d*-isothujone in the equilibrium mixture has been reported by A. J. Short and J. Read [*J. Chem. Soc.*, 2016 (1938)]. (b) It is commonly reported in the literature that thujone may be isolated by this procedure [G. Bruylants, *Ber.*, **11**, 451 (1878); F. W. Semmler, *ibid.*, **25**, 3343 (1892)]. We have found that *d*-isothujone may be separated from *l*-thujone by extraction of a mixture with sodium bisulfite solution, and were unable to prepare a bisulfite addition compound of *l*-thujone under any circumstances. Literature references to the successful use of the method presumably referred to the isolation of *d*-isothujone in each case.

(8) Although in the undistorted chain form of a cyclohexane system, the methyl–equatorial SO$_3^-$ interaction is the same whether the methyl group is axial or equatorial, in the bicyclic system under consideration the nominal 120° external bond angles imposed on the carbon atoms at the bridgeheads by the cyclopropane system flatten out the cyclopentane portion of the molecule so that there is much more interaction between methyl and equatorial (or quasi-equatorial) SO$_3^-$ when the groups are *cis* than when they are *trans*. The effect can be readily seen if one attempts to construct a model of cyclopentene wherein the double bond replaces the zero-membered bridge of the thujone system. or better, in a model in which the 120° angles at the cyclopropane carbon atoms at the bridgeheads are maintained but the 1.54 Å. separation of them in cyclopropane itself is assumed (formula VIII, *a* = 1.54 Å., angle between bond b and its projection on the plane of the cyclopropane ring = angle between bond c and its projection on the plane of the cyclopropane ring = 120°).

(9) G. Forster, R. Skobal and J. Wagner, *Z. Elektrochem.*, **43**, 290 (1937); J. Lecompte, *J. phys. radium*, **6**, 127, 257 (1945).

(10) W. D. Kumler, L. A. Strait and E. L. Alpen, THIS JOURNAL, **72**, 1463, 4558 (1950); S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, *ibid.*, **74**, 1145 (1952).

(11) The marked inflection at 230–240 mμ in the absorption spectrum reported for thujone [H. Mohler and H. Lohr, *Helv. Chim. Acta*, **20**, 1183 (1937)] suggested the existence of coupling between the two systems, but was found to be absent in the spectra of pure samples of

Acid-catalyzed Isomerization of the Thujones.—

Analysis[12] of the steam-volatile portion of the product of the action of concentrated sulfuric acid on the thujones which amounted to about 60% of the total showed that the same mixture resulted from either *l*-thujone or *d*-isothujone,[13] and that the volatile material was composed of approximately 40% carvenone (III), 40% 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) and 20% 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V). The reaction was carried out at temperatures of 0–5°, 22°, 45–50° and 95–100° without change in the nature of the products. However, higher temperatures appeared to favor slightly the formation of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V). The composition of the volatile product was the same whether 100%, 94% or 85% sulfuric acid was used.

Carvenone was identified by comparison of its semicarbazone, and infrared and ultraviolet absorption spectra with those of an authentic sample prepared from 1,2,8-*p*-menthantriol by the method of Wallach.[14]   2,3-Dimethyl-4-isopropyl-2-cyclopentenone (IV) was identified by its infrared [λ_{max}^{film} 5.90μ, 6.08μ] and ultraviolet [λ_{max}^{alc} 237 mμ (ϵ 15,000), 300 mμ (ϵ 60)[15]] absorption spectra which showed it to be a conjugated cyclopentenone with an α- and a β-substituent,[16a] and the preparation of its semicarbazone[16b] corresponding to the formula C$_{10}$H$_{16}$O.

The third ketone in the mixture, 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V), was a new compound and the structure assignment is based upon its infrared (λ_{max}^{film} 5.89 μ, 6.23 μ) and ultraviolet [λ_{max}^{alc} 230 mμ (ϵ 14,900), 312 mμ (ϵ 51)] absorption spectra which show it to be a conjugated cyclopentenone with one substituent on the double bond,[16] its oxidation to a keto-acid, C$_9$H$_{16}$O$_3$, containing but one fewer carbon atoms than the parent ketone, and its isomerization to 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) by hot sodium carbonate solution.

The possibility that carvotanacetone (II) was initially formed in the reaction and subsequently underwent isomerization to carvenone (III) (or, *vice versa* in the earlier studies[3]) was disposed of by demonstrating that neither of these ketones

the isomers. The inflection was present in the spectra of aged samples of *d*-isothujone, and is due to the presence of carvotanacetone (λ_{max}^{alc} 236 mμ) which is slowly formed from *d*-isothujone, even at room temperatures.

(12) Analyses were made by liquid–vapor partition chromatography on 3-meter × 8 mm. i.d. Carbowax–4000 firebrick columns operated at 180–200°, by infrared absorption spectroscopy using authentic samples for reference, by fractional distillation and by the selective preparation of semicarbazones. The percentages quoted are approximate.

(13) No unreacted thujone was recovered, even when the reaction time was shortened to one minute so it is not possible to say whether equilibration of the thujones preceded their conversion to products.

(14) O. Wallach, *Ann.*, **277**, 110 (1886).

(15) Reported by Gillam and West.[4] λ_{max}^{alc} 237.5 mμ (ϵ 12,000), 310 mμ (ϵ 80).

(16) (a) A. E. Gillam and E. S. Stern, "Electronic Absorption Spectroscopy," Edward Arnold, Ltd., London, 1954. (b) The semicarbazone had m.p. 221–222°, and hydrolysis of it regenerated the original ketone with unchanged spectroscopic properties. The melting points reported[3,15] for this semicarbazone lie around 208°. In view of the practical impossibility of separating mixtures of ketones IV and V by fractional distillation, it would appear that earlier preparations of the semicarbazone were not homogeneous.

suffered any isomerization on hour-long solution in concentrated sulfuric acid. It is clear, therefore, that the acid cleavage of the cyclopropane ring in the thujones formally involves the species IX and X but not XI as would be required if carvotanacetone were indeed a product, and thus that the cleavage is in the sense predicted by the Markownikoff rule.[17]

IX   X   XI
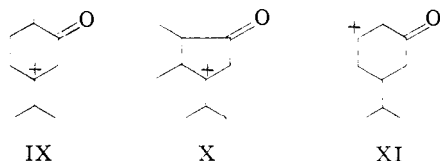
When *l*-thujone was heated with dilute sulfuric acid it was converted into a mixture of 5% *p*-cymene, 45% 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) and 50% carvenone (III), and the results of treating thujone with 48% hydrobromic acid or a saturated solution of hydrogen chloride in glacial acetic acid were essentially the same.[18]

Thermal Isomerization of the Thujones.—We have confirmed the report[5] that thermal isomerization of the thujones at 280° yields carvotanacetone (II). However, our reinvestigation of the reaction produced several new items of interest:
1. The reaction proceeds at measurable rates at remarkably low temperatures (12% in 90 hours at 100°) (7).[19]
2. The composition of the volatile product is independent of the degree of dilution of the starting material with a hydrocarbon solvent (1,2).
3. The carvotanacetone formed is optically inactive although it is formed from optically-active starting materials and contains an asymmetric carbon atom at C-4 (starred in II and in XIX).
4. The isomerization is not significantly inhibited by α-methylstyrene indicating that it does not involve a radical chain process (12,13).
5. The isomerization proceeds more rapidly in the case of *d*-isothujone than in the case of *l*-thujone, although to the same products in both cases (1,3). It may be that only *d*-isothujone is isomer-

(17) The recently-reported, elegant proof of the equivalence of the hydrogen atoms at the 1-, 3- and 5-positions during the solvolysis of the toluenesulfonate of bicyclo[3.1.0]-3-hexanol [S. Winstein, J. Sonnenberg and L. de Vries, THIS JOURNAL, 81, 6523 (1959)] raises the possibility that the conjugate acid of thujone which should have a tris-homocyclopropenyl ion structure may play a part in the acid-catalyzed isomerization. However, the formations of IX and X for III, IV and V) from such an intermediate is not straightforward, and the over-all course of the reaction is adequately described in terms of direct attack of the acid on the cyclopropane ring with the production of IX and X.
(18) The failure of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) to appear as a product in these isomerizations is attributed to its conversion to IV under the conditions which are favorable to enolization [cf. C. G. Swain, THIS JOURNAL, 72, 4578 (1950)]. When V was heated with concentrated sulfuric acid for three hours no conversion to IV was observed. It follows that the formation of IV does not proceed through initial formation of V with subsequent isomerization in concentrated sulfuric acid. Thus, X must lose a proton not only from the methylene group adjacent to the carbonyl group but also from the ring carbon atom bearing the methyl group and adjacent to the carbonium carbon. Isomerization of the resulting unconjugated cyclopentenone to the conjugated IV through protonation of the double bond would be expected, since the intermediate carbonium ion would be tertiary in character.
(19) The numbers in parentheses refer to the relevant items in the table in the Experimental part.

ized, since at 120° *no* isomerization of *l*-thujone was observed during a heating period that produced measurable amounts of products from *d*-isothujone (5,6). At temperatures higher than 120°, *l*-thujone was also isomerized, but analysis of recovered starting material showed it to be a mixture of *d*-iso- and *l*-thujone so that interconversion of the isomers through their common enol was taking place.
6. The isomerization of *d*-isothujone proceeds more rapidly in glacial acetic acid solution than in the absence of solvent (6,8), and more rapidly than the isomerization of the equilibrium mixture of the two thujones (8,9) in glacial acetic acid.
7. The isomerization rate is markedly enhanced by the addition of small amounts of *p*-benzoquinone (10,11).
8. At 280° the thermal isomerization of thujone produces small amounts of two C₉-ketones believed to be 2-methyl-4-isopropyl-2-cyclopentenone (XII) and 5-methyl-3-isopropyl-2-cyclopentenone (XIII) on spectroscopic evidence.

XII   XIII   XIV

XV   XVI   XVII
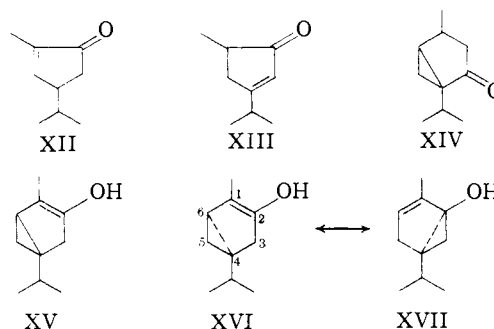
It seems remarkable that conversion of the cyclopropane ring in thujone to the equivalent double bond should take place at temperatures as low as 100°. Only 4-carene[20a] and the pinenes[20b] undergo thermal isomerization at comparable low temperatures and in these cases there may be allylic resonance stabilization of the intermediate biradical[21] generated by homolytic scission of one of the bonds of the small ring. Thujyl alcohol, in contrast to thujone, does not isomerize when heated,[22] and kinetic studies[23] on the rate of isomerization of cyclopropane itself required heating to temperatures of 440–520°. Further, β-dihydroumbellulone (XIV), of structure closely related to that of thujone, shows only traces of isomerized products under reaction conditions that bring about rapid and complete isomerization of the thujones. It would appear that the unique structural features of the thujone molecule somehow facilitate its isomerization.

We would like to suggest that the reaction involves the formation of the enol XV of thujone and proceeds to the intermediate XVI, which differs from the enol XV in that carbon atoms 1–6 of the *p*-menthane system of XVI lie in a single plane;

(20) (a) K. N. Menon, T. Madras Univ., 23B, 92 (1953). C. A., 49, 7528 (1955). (b) R. E. Fugnitt and T. E. Hawkins, THIS JOURNAL, 67, 242 (1945); L. A. Goldblatt and S. Palkin, ibid., 63, 3517 (1941).
(21) R. L. Burwell, ibid., 73, 4461 (1951).
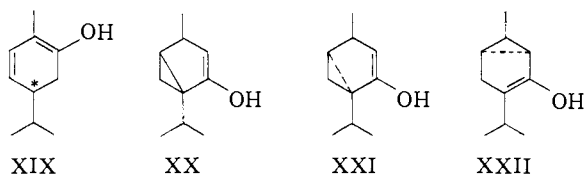(22) J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, New York, N. Y., 1949, p. 26.
(23) E. S. Corner and R. N. Pease, THIS JOURNAL, 67, 2067 (1945).

XVI is envisioned as arising from XV by the movement of the methylene group at C-5 into coplanarity with the cyclopentene system made up by carbon atoms 1, 2, 3, 4 and 6. As the methylene group at C-5 comes into the plane the bonding between C-4 and C-6 becomes π. The dotted line in structure XVI corresponds on this basis to a 1–3 π-bond above and below the plane hexagon, produced by the overlap of p-carbon orbitals at C-4 and C-6. In XVI, carbon atoms 1, 2, 4 and 6 are sp2-hybridized, carbon atoms 3 and 5 are sp3-hybridized. The geometry of XVI is such that the interaction of the isopropyl group (in the plane) with the hydrogen atoms (above and below the plane) at C-3 and C-5 is minimized. Furthermore, the planar symmetry of XVI is such that the resonance XVI⟷XVII should be essentially equivalent. On these two counts the energy of XVI⟷XVII is lowered, and although it is recognized that a 1–3 overlap which is π is quantum mechanically inferior,[24] it is regarded as not unreasonable in this case.[25]

Inspection of XVI⟷XVII reveals that it contains the π-electron system of cyclopentadiene, and is an analog of that system in which the σ-bond of one of the double bonds has been replaced by an intercalated methylene group (at C-5 in XVI, C-3 in XVII). Since at the same time the methylene groups at C-3 and C-5 correspond to that of cyclopentadiene, hydrogen at these positions would be expected to be somewhat acidic, that is, the anions XVIa and XVIIa should reflect the stability of the cyclopentadiene anion XVIII and the removal of a proton from the methylene groups in question should be facilitated.

XVIa　　　　XVIIa　　　　XVIII
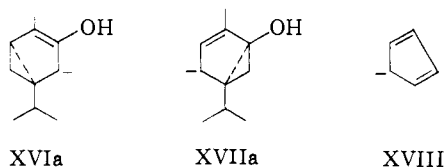
The migration of a proton from C-5 to C-4 of XVII leads directly to the enol of carvotanacetone XIX[25a] which would revert to carvotanacetone under the conditions of the thermal isomerization of thujone.

XIX　　　XX　　　XXI　　　XXII

Although our data do not make this mechanism for the thermal isomerization of thujone necessary, it provides a rational explanation for several of the experimental results given above. Since the intermediate XVI⟷XVII is planar, the carvotanacetone would be expected to be racemic, as observed;

since the first step involves enolization, the reaction would be expected to proceed more rapidly in the polar solvent acetic acid; and since the proton which migrates in the formation of the enol XV is presumably axial in d-isothujone, it might be expected to enolize more rapidly,[26] hence isomerize more rapidly, than l-thujone. The accelerating effect of p-benzoquinone on the isomerization could well be due to the formation of an unstable Diels–Alder adduct between it and the cyclopentadieneoid intermediate XVI⟷XVII.[27]

Although a very similar mechanism can be envisaged for β-dihydroumbellulone (XIV) which does not readily isomerize upon being heated, the formation of the required enol XX involves an unfavorable enolization to a secondary carbon atom, and the cyclopentadienoid intermediate (XXI⟷XXII) for this case involves coplanarity of the enolic hydroxyl group and the bond joining the isopropyl group to the ring at C-4 with concomitant serious bulk interaction of the hydroxyl oxygen atom and the methyl groups of the isopropyl group.

There remains for discussion the two C9-cyclopentenones formed in the thermal isomerization reaction. The possibility that they were present as impurities in the starting materials is rendered remote by the fact that their formation was observed in the isomerizations of both d-isothujone and l-thujone which in turn came from different natural sources. The analytical figures indicate but do not definitely prove that they are C9-ketones. However, their retention times in liquid–vapor chromatography indicate most strongly that they are in fact C9-compounds. The retention times of the compounds thujone[28] (I), 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) and carvenone (III) were, respectively, 11, 33, 47 and 48 minutes on the column used, under the same conditions of flow rate and temperature. It is evident that conversion of the cyclopropane ring into an equivalent double bond which is conjugated to the carbonyl group produces a very large increase in retention time which is in accord with the polar nature of the stationary phase used (Carbowax 4000) on the column. One of the C9-cyclopentenones (XII) had the same retention time as thujone and the second (XIII) followed thujone by 3 minutes. The low retention times of XII and XIII taken in conjunction with the much longer retention times of the C10-ketones is taken as conclusive evidence that they must be of lower molecular weight, hence C9 as indicated by the analyses. Tentative structure assignments are made to the two ketones on the basis that the infrared spectrum of XII, like that of carvotanacetone (II) has but one band in the double bond region, the carbonyl and olefinic absorptions not being resolved, while in XIII as in carveneone (III), they are.[29]

(24) S. Winstein, THIS JOURNAL, **81**, 6524 (1959).

(25) A similar model has been proposed by W. E. Doering, et al., for the ground state of tropilidene [ibid., **78**, 5448 (1956)]; see also, M. V. Evans and R. C. Lord, ibid., **82**, 1876 (1960).

(25a) It was pointed out by J. W. Wheeler, Jr., that migration of a proton from C-3 to C-4 would also lead to carvotanacetone via the less likely enol form with double bonds in the 2,3- and 6,1-positions.

(26) One of the referees made this point.

(27) Suggested in substance by Professor W. H. Urry, Univ. of Chicago.

(28) Mixtures of d-isothujone and l-thujone could not be resolved, a symmetrical peak being obtained.

(29) It is of further interest that within the pairs XII and XIII, II and III, it is the isomer which has an α-hydrogen on the α,β-double bond that has the longer retention time.

The loss of a methylene group necessary for the formation of XII and XIII seems *a priori* rather mysterious. However, a straightforward path exists from the postulated intermediate XVI↔ XVII, if it is assumed that carbene is eliminated in the form of the methylene group at C-5 in XVI↔ XVII with concomitant formation of a σ-bond between C-4 and C-6. In these terms the elimination corresponds to the reversal of the known[30] addition of carbene to double bonds.
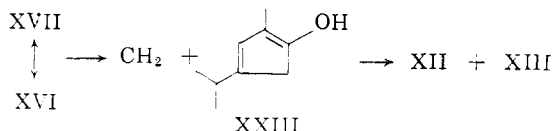
In view of the small yield of the C_9-cyclopentenones, the fate of the carbene was not determined,[31] nor was the conversion of XII into XIII investigated.

If it be granted that the mechanism proposed for the formation of the C_9-ketones is correct, then it follows from the principle of microscopic reversibility that the addition of carbene to a cyclopentadienoid system such as that in XXIII would proceed through a transition state in which the carbene approaches the double bond with its carbon atom in the nodal plane of the π-orbital of the double bond with disruption of the σ-bond of the olefinic linkage. The formation of the tropilidene system[25] might well proceed in the same manner.

Acknowledgment.—We wish to express our appreciation to the Hercules Powder Co., Wilmington, Del., for their generous fellowship aid in support of this investigation.

Experimental

l-Thujone (VI).—A 2200-ml. sample of Cedar Leaf oil (Fritsche Brothers, New York, N.Y.) was fractionated from a 3-foot Stedman column (70 TP) using a reflux ratio of 100:1. An 800-ml. forerun was rejected, whereupon a 700-ml. cut of *l*-thujone of b.p. 83.8–84.1° at 17 mm., $n^{25}D$ range 1.4490–1.4483 and $\alpha^{22}D$ range −19.2° to −14.3° (neat, 1-dm. tube)[32] was collected.

A later fraction (80 ml., b.p. 84.4–85.5° at 17 mm., $n^{24}D$ 1.4490, $\alpha^{23}D$ +32.1°) had an infrared absorption spectrum practically identical with that of the equilibrated mixture (see below) of *l*-thujone and *d*-isothujone. When 30 ml. of this fraction was extracted with sodium bisulfite solution as described below, there was obtained 7.2 ml. of *d*-isothujone of $\alpha^{23}D$ +67.1°.

The pot residue was found to contain carvotanacetone by comparison of infrared absorption spectrograms.

d-Isothujone (VII).—To 500 ml. of saturated sodium bisulfite solution was added 60 g. of sodium bicarbonate, 160 ml. of alcohol and 450 ml. of Tansy oil.[33] The resulting mixture was agitated for 14 hours during which time a large mass of crystalline material separated. The precipitate was separated by filtration and washed with three portions of a 1:1 alcohol–ether mixture and then decom-

posed by the addition of excess 6 N sulfuric acid.[34] The oil so obtained was distilled with steam to give 195 ml. of crude *d*-isothujone, $\alpha^{25}D$ +61.9°. The crude ketone was distilled through a 2-foot Fenske fractionating column (13TP) at reduced pressure and a reflux ratio of 15:1. After a small forerun, there came over 120 ml. of pure *d*-isothujone of b.p. 85.7–86.2° at 17 mm., $\alpha^{27}D$ range 66.5 to 62.4°; reported[7] b.p. 76° at 10 mm., $\alpha^{15}D$ 72.46.

Equilibration of *l*-Thujone.[7]—Five grams of *l*-thujone was added to a solution of 1 g. of sodium in 24 ml. of absolute alcohol, and the mixture was allowed to stand for 40 hours. Following distillation with steam, the oily product was distilled at 24 mm. and the portion boiling above 87° was collected. Its infrared spectrum showed that it was a mixture of *l*-thujone and *d*-isothujone, and it had $\alpha^{27}D$ +38.0°. The same mixture was obtained, starting with *d*-isothujone.

Acid-catalyzed Isomerization of Thujone.—A 92-g. sample of *l*-thujone was added to 300 g. of concentrated sulfuric acid at such a rate that the temperature of the reaction mixture did not rise above 25° with ice cooling. After 2 hours of stirring, the mixture was poured onto ice and the oily product was extracted with ether. (Subsequently it was found that it made no difference whether the mixture was stirred 1 hour or 4 hours.) The crude product was distilled with steam and then fractionated on a 13TP Fenske column packed with glass-helices. Eighteen fractions were collected in the boiling point range 100–111° at 15 mm. and individually analyzed by gas chromatography and infrared spectroscopy.

4,5-Dimethyl-3-isopropyl-2-cyclopentenone (V) was separated from the early fractions using a gas chromatographic column. The product had $\alpha^{23}D$ + 56.0° and showed in the infrared λ^{film}_{max} 5.89μ, 6.23μ and in the ultraviolet $\lambda^{isooctane}_{max}$ 222 mμ (ε 11,500), 325 mμ (ε 36); and λ^{alc}_{max} 230 mμ (ε 14,900), 312 mμ (ε 51).

Anal.[32] Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.80; H, 10.54.

Treatment of 0.9 g. of ketone with excess semicarbazide acetate in alcohol for 10 hours followed by dilution of the reaction mixture with water gave 1.06 g. of crude semicarbazone of m.p. 140–162°.[32] Recrystallization from methanol gave crystals of m.p. 172–173°, λ^{alc}_{max} 276 mμ.

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.12; H, 9.15. Found: C, 63.26; H, 9.06.

Hydrolysis of the semicarbazone with saturated oxalic acid solution regenerated a ketone of infrared absorption identical with that of the starting material.

Oxidation of 1.35 g. of the ketone V in a solution of 11.4 g. of periodic acid in 421 ml. of water by the addition of 56 ml. of 0.01 M potassium permanganate in portions, followed by acidification with dilute sulfuric acid and ether extraction gave a crude, oily acidic product. The crude product was evaporatively distilled to give a colorless, viscous oil, electrometric titration of which showed pK_a 5.1.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36; neut. equiv., 172. Found: C, 62.41; H, 9.68; neut. equiv., 176.

The semicarbazone was prepared in alcohol using semicarbazide acetate and had m.p. 169° after one crystallization from ethanol.

Anal. Calcd. for $C_{10}H_{19}O_3N_3$: C, 52.38; H, 8.35; N, 18.33. Found: C, 52.20; H, 8.03; N, 18.10.

On the basis of its source and properties, the liquid acid is assigned the structure of 2,3,5-trimethyl-4-oxohexanoic acid.

Forty drops of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) was heated under reflux with 5 ml. of 10% potassium carbonate solution. Samples of the oil taken during the first 6 hours showed a progressive decrease in the infrared band at 6.23 μ characteristic of V and the coincident development of a band at 6.08 μ characteristic of 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV); after 50 hours of reflux, the spectrum of the oil was identical with that of IV.

Two milliliters of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) was stirred with 10 ml. of concentrated sulfuric acid for 3 hours. On gas chromatotraphy of the oil recovered by dilution of the reaction mixture with water, two components were isolated. The major component was shown

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(30) See H. M. Frey and G. B. Kistiakowsky, THIS JOURNAL, 79, 6373 (1957).

(31) The liquid in the sealed tubes in which the pyrolyses were carried out effervesced when the seal was broken. An infrared spectrum of the gas showed it to be hydrocarbon in nature with prominent bands at 3.4, 4.7, 4.8, 6.8 and 7.2 μ, but its composition could not be inferred from the spectrum.

(32) All optical rotations were measured under these conditions unless otherwise indicated. Melting points are not corrected. Analyses are by Microchemical Specialties, Berkeley, Calif.

(33) Obtained from the A. M. Todd Co., Kalamazoo, Mich., through the courtesy of Dr. Robert Reitsema.

(34) An attempt to decompose the bisulfite adduct with alkali was only partially successful.

to be starting material by its infrared absorption spectrum. The minor component, which had only a slightly longer retention time, had an infrared absorption spectrum practically identical with that of the starting material. It is assumed that the second component was an epimer of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) produced by inversion of configuration at C-1 through enolization. There was no evidence for the presence of 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) in the product, although in a separate experiment where V was boiled with formic acid for 48 hours, a small amount of IV was formed as judged by the infrared absorption which showed the small band at 6.08 μ characteristic of IV.

2,3-Dimethyl-4-isopropyl-2-cyclopentenone (IV).—To a solution containing 4.12 g. of semicarbazide hydrochloride and 3.3 g. of anhydrous sodium acetate in 9.25 ml. of alcohol plus 9.4 ml. of water was added 5.62 g. of the last fraction (b.p. 108–111° at 15 mm.) from the distillation of the thujone–sulfuric acid reaction product (see above). The mixture was kept 15 hours at room temperature, and then stored at 5° for 24 hours. The crystals (4.5 g., m.p. 176–185°) which had appeared were separated, crystallized three times from methanol, four times from dioxane and finally once again from methanol to yield material of m.p. 217–218° dec. At a later time, several further crystallizations from alcohol gave material melting at 221–222° dec.[16]

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.12; H, 9.15. Found: C, 63.15; H, 8.93.

The semicarbazone was hydrolyzed by heating with 6 N sulfuric acid, and the ketone distilled with steam. The product had $n^{25}D$ 1.4822 (reported $n^{20}D$ 1.4823), λ_{max}^{alc} 237 mμ (ϵ 15,000), 300 mμ (ϵ 60), in substantial agreement with those reported.[15] The infrared spectrum showed λ_{max}^{film} 5.90 μ (C=O), 6.08μ (C=C), and was practically identical with that of the material obtained by isomerizing 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V) with sodium carbonate solution.

Carvenone (III).—The filtrate remaining after the separation of the semicarbazone of 2,3-dimethyl-4-isopropyl-2-cyclopentenone (IV) (above) was poured into water and the resulting suspension was extracted with ether. On reducing the volume of the ether extract, a solid of m.p. range 159–184° was obtained. Three crystallizations of this material from methanol gave carvenone semicarbazone of m.p. 190–192°, alone or mixed with a sample of m.p. 196° prepared from an authentic sample[14] of carvenone.

Hydrolysis of the semicarbazone using 6 N sulfuric acid produced the ketone, identical with an authentic sample[14] in infrared and ultraviolet absorption.

Carvenone (1 ml.) recovered after 3 hours of solution in concentrated sulfuric acid (15 ml.) by the addition of ice and water showed only a single peak on gas chromatography (carvenone and carvotanacetone were found to be separable on the column employed) and the infrared absorption of material collected by gas chromatography was identical with that of the starting material. Carvotanacetone was similarly recovered unchanged from its solution in concentrated sulfuric acid.

It should be pointed out here that the infrared absorption spectra of carvenone and carvotanacetone (III) show marked difference in the region of skeletal vibrations, so that the presence of as little as 5% of one in a mixture of the two was readily detected.

Hydrobromic Acid.—Two grams of l-thujone was stirred with 10 ml. of 48% hydrobromic acid for 24 hours. A portion of the oil was removed and washed with water. A Beilstein test on the crude product was positive. Gas chromatography showed three peaks, corresponding to p-cymene, unreacted thujone (the infrared spectrum corresponded to that of the equilibrated mixture of l-thujone and d-isothujone), and the mixture of carvenone and 2,3-dimethyl-4-isopropyl-2-cyclopentenone (V).

When the crude product was steam distilled from the acid solution before gas chromatographic analysis, it was shown that the steam distilled product contained 4,5-dimethyl-3-isopropyl-2-cyclopentenone (V). Apparently the crude product from the hydrobromic acid treatment contained 3-bromo-4,5-dimethyl-3-isopropylcyclopentanone.[35]

(35) This bromoketone has been proposed to be a product of the action of hydrobromic acid on acetic acid solution of thujone; I. Kondakow, *Chem. Ztg.*, **26**, 720 (1901); *Chem. Zentr.*, **73**, 641 (1902).

Hydrochloric Acid.—Hydrogen chloride was bubbled slowly through a solution of 10 ml. of l-thujone and 10 ml. of glacial acetic acid for 4 days. Gas chromatography and infrared analysis showed that the products were carvenone (III) and 2,3-dimethyl-4-isopropyl-2-cyclopentenone. Various methods were used for working up the crude product, but in no case was the presence of 3,4-dimethyl-3-isopropyl-2-cyclopentenone (V) indicated.

Thermal Isomerization of the Thujones.—The thermal isomerizations were carried out in glass-stoppered flasks, in sealed tubes and by heating the ketones under a reflux condenser. The results were independent of the method. The course of the reaction was followed by taking gas chromatograms of the volatile portions of the isomerized material at various intervals of time, and by measuring the infrared absorption spectra of the components separated by gas chromatography. Typical results are contained in the following table in which temperatures are accurate to ±5° and analyses to ±5%.

	Sample	Hours	Temp., °C.	Gas chromatography fractions,[a] % A	B	C
1	l-Thujone	48	280	57, 58	5, 5	38, 37
2	l-Thujone[b]	48	280	57, 59	4, 5	39, 36
3	d-Isothujone	48	280	28, 29	14, 11	57, 61
4	Thujone[c]	48	280	58, 59	5, 5	37, 36
5	l-Thujone	116	120	100	0	0
6	d-Isothujone[d]	116	120	92	1	7
7	d-Isothujone	117	120	83	0	17
8	d-Isothujone[e]	144	121	74	0.5	25.5
9	Thujone[c]	145	120	82	0	18
10	l-Thujone[f]	6	280	83, 84	1, 1	16, 15
11	d-Isothujone[f]	6	280	57, 57	4, 7	39, 36
12	l-Thujone	16	280	66, 65	8, 7	26, 28
13	l-Thujone[g]	16	280	71, 73	5, 6	24, 21

[a] Fraction A was a mixture of isomeric thujones approximately the equilibrium mixture (67% d-iso- and 33% l-thujone) when the reaction was carried out at 280°; and under those circumstances contained in addition, traces of 2-methyl-4-isopropyl-2-cyclopentenone (XII). Fraction B was 5-methyl-3-isopropyl-2-cyclopentenone (XIII). Fraction C was carvotanacetone (II), but contained traces of carvenone (III) when the reaction was carried out at 280°. Where two percentages figures are entered, they correspond to the results of duplicate experiments. [b] 50% solution in mineral oil. [c] The equilibrium mixture of d-iso- and l-thujone. [d] These samples were purified by gas chromatography immediately prior to isomerization in sealed tubes. [e] Diluted with three times its volume of acetic acid. [f] 1 mole % p-benzoquinone added. [g] 2 mole % α-methylstyrene added.

Identification of Thermal Isomerization Products.—Fraction A in the gas chromatograms gave an unsymmetrical peak indicating the presence of at least two components, one of which was thujone. Since the other component could not be separated from the mixture, a sample of d-isothujone was heated under reflux for 235 hours to effect complete conversion of it to products. A gas chromatogram of the product showed a symmetrical peak corresponding to fraction A in retention time, and a sample of the material corresponding to the peak was collected; spectra: λ_{alc}^{max} 229 mμ (ϵ 7200), 314 mμ (ϵ 69); λ_{max}^{film} 5.90 μ (C=O).

Anal. Calcd. for $C_9H_{14}O$: C, 78.31; H, 10.21. Found: C, 77.88, 77.75; H, 10.48, 10.45.

Fraction B in the gas chromatogram of the material which had been heated for 235 hours was well resolved and gave a symmetrical peak. A sample was collected; spectra: λ_{max}^{alc} 230 mμ (ϵ 7100), 309 mμ (ϵ 41); λ_{max}^{film} 5.88μ (C=O), 6.09μ (C=C).

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.13, 77.93; H, 10.66, 10.56.

Fractions A and B were assigned the structures of 2-methyl-4-isopropyl-2-cyclopentenone (XII) and 5-methyl-3-isopropyl-2-cyclopentenone (XIII) on the basis of their absorption spectra.

Fraction C was shown to be carvotanacetone (II) by comparison of its infrared spectrum with that of an authentic sample prepared from carvomenthone by the method of

Wallach[36] which in our hands gave a mixture of carvomenthone, carvotanacetone and carvacrol that had to be resolved by extraction with alkali followed by gas chromatography. Pure carvotanacetone showed λ_{max}^{alc} 236 mμ (ε 8650), 317 mμ (ε 45), in accord with the reported values,[16]

(36) O. Wallach, *Ann.*, **414**, 353 (1918).

and λ_{max}^{film} 5.98μ(C=O). The semicarbazone had m.p. 176–179°, reported[37] 177–178°. The semicarbazones from the two sources had identical infrared absorption spectra (KBr disks) and the mixture had m.p. 176–178°.

(37) I. Heilbron and H. M. Bunbury, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.
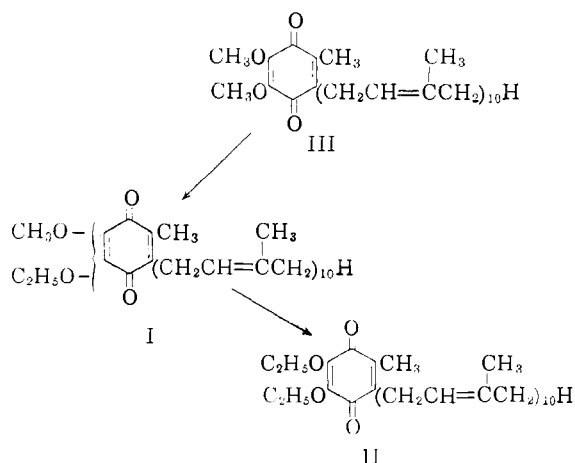

Coenzyme Q. XIX. Alkoxy Homologs of Coenzyme Q_{10} from Methoxy Group Exchange

By Clifford H. Shunk, Donald E. Wolf, James F. McPherson, Bruce O. Linn and Karl Folkers

The reactivity of the methoxy groups of coenzyme Q_{10} has been utilized to prepare the diisoamoxy- and diisopropoxy homologs of coenzyme Q_{10}. The monoethoxy homolog of Q_{10} obtained during the isolation of Q_{10} from beef heart has been shown by degradation and synthetic studies to be a mixture of the two monoethoxy oriented derivatives, indicating comparable reactivity of the two methoxy groups of Q_{10}. The syntheses have made available the new 4-ethoxy-2-methyl-3,5,6-trimethoxy- and 5-ethoxy-2-methyl-3,4,6-trimethoxyphenylacetic acids.

Our initial experience on the isolation and structural elucidation of ethoxy homologs of coenzyme Q_{10} was reported,[1] and the extended study of the reactions of coenzyme Q_{10} with ethanol has been described.[2] It was found that during the hot alkaline saponification in ethanolic solution, which is a step in the isolation of coenzyme Q_{10} from beef heart tissue, the monoethoxy- (I) and diethoxy- (II) homologs of coenzyme Q_{10} (III) were formed. The extent of the conversion of coenzyme Q_{10} to these ethoxy homologs depends upon several aspects of the reaction conditions. These ethoxy homologs were not obtained when methanol was substituted for ethanol in the procedure. It was shown that the ethoxy derivatives are artifacts of isolation. The presence of pyrogallol and nitrogen atmosphere for the hot saponification step minimizes the exchange reaction, but does not always

It is evident that the reactivity of the methoxy group of 1,4-benzoquinone is much more similar to that of a carboxylic methyl ester than to that of typical aliphatic or aromatic methyl ethers. The reaction of methoxy-1,4-benzoquinone with various nucleophilic reagents to cause displacement of the methoxy group has been studied previously.[3–5]

Nucleophilic displacement of a methoxy group of a benzoquinone derivative by RO^-, such as $C_2H_5O^-$, has not been seen in the literature, but the ethoxy homologs of coenzyme Q_{10} appear to be examples of such a reaction.

This reactivity of the methoxy groups of coenzyme Q_{10} offers an approach to the preparation of radioactive coenzyme Q_{10} (IV), higher alkoxy homologs (V), and nitrogen- and sulfur-containing derivatives (VI) by reaction with appropriate nucleophiles. We have utilized this approach

and prepared the diisoamoxy (VII) and diisopropoxy- (VIII) homologs of coenzyme Q_{10}. These homologs are of interest to study for possible inhibition of coenzyme Q_{10} in various succino- and cytochrome enzyme systems.[6]

completely suppress this reaction, particularly when the exposure of coenzyme Q_{10} to these conditions is prolonged.
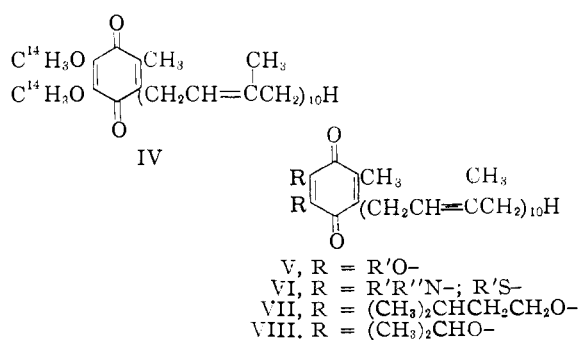
(1) B. O. Linn, N. R. Trenner, C. H. Shunk and K. Folkers, This Journal, **81**, 1263 (1959).

(2) B. O. Linn, N. R. Trenner, B. A. Arison, R. G. Weston, C. H. Shunk and K. Folkers, *ibid.*, **82**, 1647 (1960).

(3) D. Buckley, H. B. Henbest and P. Slade, *J. Chem. Soc.*, 4891 (1957).

(4) D. Buckley, S. Dunstan and H. B. Henbest, *ibid.*, 4901 (1957).

(5) J. A. D. Jeffreys, *ibid.*, 2153 (1959).

(6) D. Hendlin and T. Cook, *J. Biol. Chem.*, **235**, 1187 (1960).