(isomer A), m.p. 151–152°, undepressed on admixture with the above-described compound.

The acetylenic tetrol XIII (isomer B, 400 mg.) was reduced with lithium aluminum hydride as described for isomer A, except that the reflux time was 5 hr. (boiling under reflux for only 3 hr. gave less satisfactory results than those described). The product did not crystallize well directly, and was therefore chromatographed on 20 g. of alumina. Elution with chloroform–methanol (49:1) yielded 175 mg. (43%) of the *trans*-ethylenic tetrol XXVa (isomer B), m.p. 132–135°. Crystallization from ethyl acetate gave a pure sample as needles, m.p. 135–136°. The infrared spectrum (KBr disk), which showed definite differences from that of isomer A, exhibited bands at 2.80 and 2.91 μ (hydroxyl) as well as at 10.47 μ (*trans*-disubstituted double bond).[29b]

The corresponding 2,2′-diacetate XXVb (isomer B) crystallized from ethyl acetate–hexane as a monohydrate, m.p. 186–187° (depressed on admixture with isomer A); infrared bands at 2.78 μ (hydroxyl), 5.79 and 8.06 μ (acetate) as well as at 10.50 μ (*trans*-disubstituted double bond).[29b]

Anal. Calcd. for $C_{18}H_{28}O_6.H_2O$: C, 60.31; H, 8.44. Found: C, 60.67; H, 8.20.

Full hydrogenation of the 2,2′-diacetate XXVb (isomer B) in methanol over a 5% palladium–charcoal catalyst readily yielded the saturated tetrol diacetate XVa (isomer B), m.p. 129–130°, undepressed on admixture with the previously described sample.

1,2-Dicyclohexenyl-(*trans*)-ethylene (XXVI) from the (*trans*)-Ethylenic Tetrol Diacetates XXVb (Isomers A and B).—The reduction of the ethylenic tetrols XXVa and the corresponding diacetates XXVb with phosphorus diiodide was carried out under several different conditions, whereby either unchanged starting material or the conjugated triene XXVI was obtained. The following experiment to give XXVI is typical.

Phosphorus diiodide[31] (70 mg.) was added in portions during 15 minutes to a stirred solution of 60 mg. of the diacetate XXVb (isomer A) in 3 cc. of tetrahydrofuran, under purified nitrogen, and the dark brown-black reaction mixture was then stirred at room temperature for a further 20 minutes. After addition of ether, the mixture was washed successively with sodium hydroxide solution, sodium thiosulfate solution and water. The dried extract on evaporation yielded a residue (26 mg.) showing λ_{max}^{EtOH} 259, 269 and 280 mμ (ε 22,100, 25,100 and 21,800), indicating it to be mainly the triene XXVI [reported[6b]: λ_{max}^{MeOH} 260, 269 and 281 mμ (ε 23,960, 26,160 and 23,060)].

The diacetate XXVb (isomer B) on analogous treatment with phosphorus diiodide gave an essentially identical result.

[Contribution from the Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda 14, Md.]

Conformational Mobility of (−)-α-Phellandrene, Deduced from its Optical Rotatory Dispersion

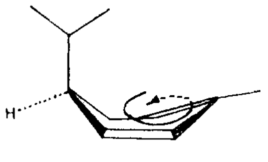
By Herman Ziffer, Elliot Charney and Ulrich Weiss

Received January 22, 1962

The optical rotations of (−)-α-phellandrene (I) and 3,5-cholestadiene (III) have been measured at 11, 23, and 82°. The observed temperature-dependence of the rotation of I, but not of III, is interpreted as indicating the existence of a mobile equilibrium between two conformations of I. The populations and relative stabilities of these conformers are discussed. It is concluded that one of these conformers Ia has the larger rotational strength, but it is present in smaller concentrations than Ib, at least at room temperature.

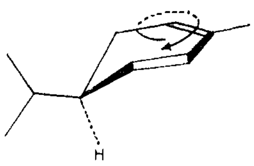
In a recent communication from this Laboratory[1] it was deduced from the rotatory dispersion curve of (−)-α-phellandrene that the preferred conformation of this molecule is that in which the isopropyl group is quasi-axial (IA). This conclusion was based on the "skewed diene" rule[2] which allows the sign of the optical rotation of a molecule containing a non-planar cisoid diene to be predicted from the skew sense or helicity of the diene: if the four carbon atoms of the conjugated system form a left-handed helix, its contribution on the long-wave length side of the diene absorption band produces levorotation, whereas a right-handed helix produces dextrorotation. Furthermore, the contribution to the optical activity produced by the skewed diene is much greater than that associated with, *e.g.*, an asymmetric carbon atom. Consequently, the rotatory dispersion in the vicinity of the diene absorption will largely reflect the relative orientation of the double bonds of the chromophore. By this reasoning, in the case of (−)-α-phellandrene of known absolute configuration, the observed *negative* rotation suggested that the predominant conformer at room temperature was the quasi-axial (IA) rather than the quasi-equatorial (IB) one, since in the former the diene system has left-handed skew sense.

IA



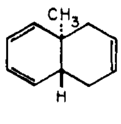
Levorotatory

IB

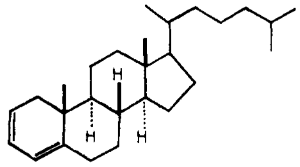


Dextrorotatory

II



III



As Table I shows, the molar rotation, [M], of (−)-α-phellandrene at the first extremum is much lower than that of (+)-*trans*-9-methyl-1,4,9,10-tetrahydronaphthalene[2] (II), although the λ_{max} and ϵ_{max} of the two compounds are almost identical. Similarly, 2,4-cholestadiene (III), with only twice the value of ϵ_{max}, has an [M] about ten times that of (−)-α-phellandrene. These facts suggested the

---

(1) A. W. Burgstahler, H. Ziffer and U. Weiss, *J. Am. Chem. Soc.*, **83**, 4660 (1961).

(2) A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, *ibid.*, **83**, 4661 (1961).

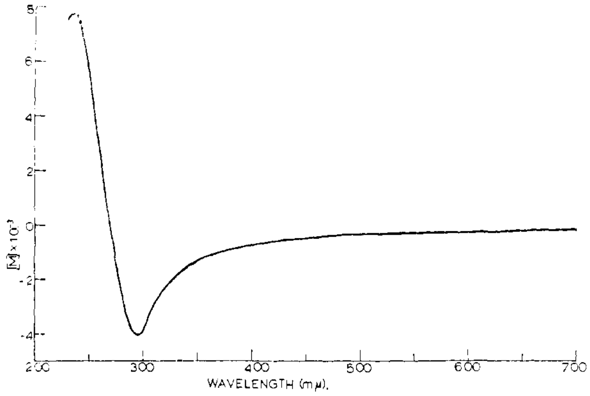


Fig. 1.—The rotatory dispersion of (−)-α-phellandrene at room temperature; solvent, isoöctane.

possibility that (−)-α-phellandrene may exist as an equilibrium mixture of the conformers IA and IB of opposite rotation.

TABLE I

	ϵ_{max} (mμ)	[M] (21 ± 1°)
(−)-α-Phellandrene	3360 (262)	4,000 (trough)
(+)-*trans*-9-Methyl-1,4,9,10-tetrahydronaphthalene	3460 (261)	18,000 (peak)
2,4-Cholestadiene	6450 (267)	38,000 (peak)

Furthermore, the ease with which the two conformations may be interchanged in Dreiding models, and the lack of obvious repulsive interactions in either conformation (such as seems to exist in an alternate conformation of III), indicates that the energy barrier to the interchange of IA and IB may be of the order of thermal energies. An investigation of the temperature dependence of the optical activity of (−)-α-phellandrene was therefore undertaken to determine whether the conformational equilibrium changes appreciably at readily accessible temperatures. For comparison, a similar study of III was made.

Experimental

(−)-α-Phellandrene from an Eastman Kodak Co. sample was purified by gas chromatography on an Apiezon column. 2,4-Cholestadiene was prepared by Dr. A. W. Burgstahler, University of Kansas, by the procedure described by Bergmann, *et al.*[3]; m.p. 67–68°, [α]D +164° (ether).

The absorption spectra of both (−)-α-phellandrene and III were measured with a Cary model 14 spectrophotometer in jacketed 1-cm. quartz cells at temperatures ranging from 11 to 82°. In both cases, the solutions could be reversibly heated and cooled without any change in the room-temperature spectrum. The spectra at other temperatures, of course, reflected the change in density of the solution. The solvent was Spectro Grade isoöctane; concentrations: (−)-α-phellandrene, 6.12 × 10^{-4} mole/liter; III, 8.13 × 10^{-5} mole/liter.

The rotations were measured on a Rudolph recording spectropolarimeter, using a 5-mμ half-band width, in 5-cm. jacketed quartz cells at temperatures from 11 to 82°. The complete rotatory dispersion curve of (−)-α-phellandrene is shown in Fig. 1. The temperature dependence of the optical activity of (−)-α-phellandrene was measured at 320 mμ, that of III at 302 mμ. The optical densities of the solutions and the concentrations (in mole/l.) utilized were: (−)-α-phellandrene: 0.215, 4.44 × 10^{-2}; III: 0.875, 2.71 × 10^{-3}; solvent, Spectro Grade isoöctane.

The concentrations of the solutions at each temperature were calculated from the temperature dependence of the intensity of the peak of the absorption band (no marked changes in band width were observed with temperature). The optical rotations at each temperature were also corrected for change in refractive index of the solvent by dividing the observed rotations by the ratio of $(n^2 + 2)/3$ at the temperature of measurement to the value at room temperature. The refractive index of the isoöctane was taken to be n^{25}D 1.390 and its change with temperature as 4.7 × 10^{-4} per degree centigrade.[4]

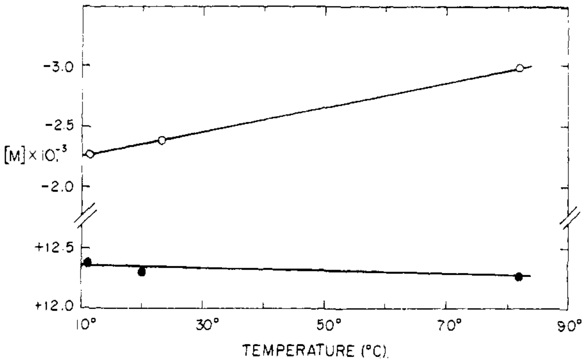


Fig. 2.—The molar rotation of (−)-α-phellandrene, ○, at 320 mμ and of 2,4-cholestadiene, ●, at 302 mμ as a function of temperature; solvent, isoöctane.

Results and Discussion

An increase in temperature in an equilibrium system such as IA⇄IB should increase the population of the constituent of higher energy.[5] If the equilibrium concentrations of the constituents change significantly as the temperature is varied, then the energy difference between the conformers is of the order of thermal energies; furthermore, if equilibrium is established quickly, the energy barrier between the conformations is not very large. The observed rotation of (−)-α-phellandrene at room temperature can accept two alternative interpretations: (1) if the rotational strengths of IA and IB are the *same*, as would be the case if the skew angles of the two conformers were approximately equal,[6] then the observed negative rotation at room temperature leads to the conclusion suggested earlier, namely that IA predominates. In this case, an *increase* in temperature should result in a *decrease* in the fraction of molecules in this form and consequently a *decrease* of levorotation; (2) on the other hand, if one conformer has a considerably larger rotational strength than the other, *e.g.*, if the rotational strength of the quasi-axial form IA is much larger than that of the quasi-equatorial form IB, it would be possible to observe a net negative rotation even if the latter conformer predominated at room temperature. In this case, however, the fraction of molecules of IA would *increase* with increasing temperature with a subsequent *increase* in levorotation.

As Fig. 2 shows, the rotation of (−)-α-phellandrene becomes more negative with higher tempera-

---

[3] E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

[4] A. Weissberger, E. S. Proskauer, J. A. Riddick and E. E. Toops, Jr., Organic Solvents ("Technique of Organic Chemistry," Vol. VII), Interscience Publishers, Inc., New York, N. Y., 1955.

[5] A significant difference in the entropy of the two conformers could drive the equilibrium in the other direction; there seems to be no reason, however, to believe that the entropy contribution to the difference in free energy of the quasi-axial and quasi-equatorial forms of (−)-α-phellandrene would be large enough to produce this effect.

[6] Dreiding models of IA and IB of course do not show any difference in skewness.

ture, showing that a conformational interchange takes place readily and that the levorotatory quasi-axial conformer is the form of *higher* energy, since its concentration increases with increasing temperature. This is consistent with the second alternative discussed above, subject only to the restriction with regard to a lack of significantly large entropy differences between the conformers. In contrast, the rotation of III under the same conditions remains practically constant; in this case, therefore, the energy difference between the two possible conformations appears to be much larger than that of (−)-α-phellandrene, thus favoring one of the conformations to the practical exclusion of the other.

Since the reduced rotational strength of skewed dienes is known[2] to be ~25, as compared to ~200 for hexahelicene[7] and ~2.5 for cyclic ketones, the rotatory contributions of IA and IB, while different, should be of the same order of magnitude. Consequently, the relatively low rotation of (−)-α-phellandrene (Table I) shows that the concentration of IA does not differ from that of IB by more than an order of magnitude at room temperature; *i.e.*, a substantial concentration of the quasi-axial form exists at room temperature. An unequivocal quantitative evaluation of the composition of the conformational equilibrium mixtures would require the experimental determination or theoretical calculation[2,8] of the rotational strength of both conformers. In the case of the theoretical calculations, the determination of the skew angles would have to take into account non-bonded repulsions which cannot be determined from Dreiding models.

Acknowledgment.—We express our appreciation to Mr. Joseph Colony of the Department of Biochemistry, Walter Reed Hospital, Washington, D. C., for the gas-chromatographic purification of (−)-α-phellandrene and to Mr. H. K. Miller of this Institute for making available the Rudolph recording spectropolarimeter on which these measurements were made.

(7) A. Moscowitz, Ph.D. Thesis, Harvard University, March, 1957.

(8) A. Moscowitz, *Rev. Mod. Phys.*, **32**, 440 (1960).

[COMMUNICATION 281 FROM THE RESEARCH LABORATORIES OF DISTILLATION PRODUCTS INDUSTRIES, DIVISION OF EASTMAN KODAK CO., ROCHESTER 3, N. Y.]

The Oxidation Product from α-Tocopherol and Potassium Ferricyanide and Its Reaction with Ascorbic and Hydrochloric Acids

BY DONALD R. NELAN AND CHARLES D. ROBESON

RECEIVED JANUARY 27, 1962

Interest in oxidation products of vitamin E as possible metabolic intermediates has led us to investigate some of the physical and chemical properties of a product from the oxidation of α-tocopherol with potassium ferricyanide. A dimeric structure, containing a dihydropyran ring and dienone group, is postulated for the compound. Structures are also postulated for its reaction products with ascorbic and hydrochloric acids. All three compounds had less than 2% of the activity of *d*-α-tocopheryl acetate in the rat gestation–resorption bioassay.

We have oxidized α-tocopherol (both *d*- and *dl*-) with potassium ferricyanide and have investigated the structure of the oxidation product. This product had an absorption maximum in the ultraviolet at 300 mμ with a weaker broad band at 337 mμ. Such oxidation products assume interest in view of current studies on metabolic transformations of α-tocopherol (*e.g.*, Alaupovic, *et al.*[1]).

The properties of the oxidation product indicated that it has the dimeric structure I arising by coupling through *o*-methyl groups and ring closure to form a new dihydropyran ring. An analogous structure has been reported for the oxidation product from 2,4-di-*tert*-butyl-6-methylphenol and silver oxide.[2]

Martius and Eilingsfeld[3] described the oxidation of α-tocopherol with alkaline potassium ferricyanide and obtained a yellow compound of undetermined structure which was stated to have an ultraviolet absorption maximum at 235–236 mμ with a weaker band at 300 mμ. We followed the oxidation procedure described by these authors, but did not obtain a compound having this property. Issidorides[4] has reported the formation of a dimer by oxidation of α-tocopherol with potassium permanganate and Boyer[5] has described a dimer formed from α-tocopheroxide, but from the reported properties of these products, neither appears to have structure I.

The proposed structure I was based on the following findings: (1) molecular weight determination and elementary analyses determined on a sample purified by chromatography indicated a compound formed from two molecules of the parent tocopherol; (2) the infrared absorption spectrum showed bands characteristic of a conjugated unsaturated ketone, but no band characteristic of a hydroxy compound; a strong band at 9.13 μ, not shown by α-tocopherol, indicated the presence of an additional ether group; (3) the ultraviolet absorption spectrum showed maxima at wave lengths (300, 337 mμ) in the range characteristic of linearly conjugated, dieneone systems[6]; (4) further slow oxidation (Fig. 1) of the compound occurred on reaction with ferric chloride in the Emmerie–Engel assay procedure[7] suggesting the

(1) P. Alaupovic, B. C. Johnson, Q. Crider, H. N. Bhagavan and B. J. Johnson, *Am. J. Clin. Nutrition*, **9**, Part II (1961).

(2) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 243 (1954).

(3) C. Martius and H. Eilingsfeld, *Ann.*, **607**, 159 (1957).

(4) A. Issidorides, *J. Am. Chem. Soc.*, **73**, 5146 (1951).

(5) P. D. Boyer, *ibid.*, **73**, 733 (1951).

(6) H. Wynberg, *Chem. Rev.*, **59**, 169 (1959).

(7) H. Rawlings, *Oils and Soap*, **21**, 257 (1944).