a general characteristic of the two conformations of the polypeptide chain.

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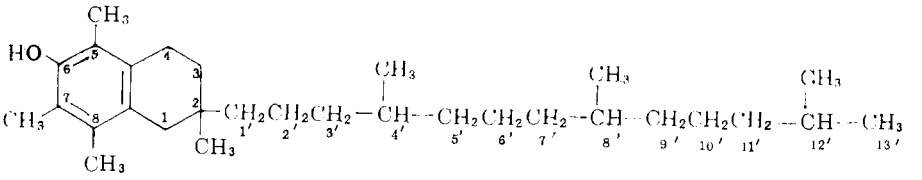
ISOLATION OF AN *l*-EPIMER OF NATURAL *d*-α-TOCOPHEROL[1]

Sir:

We wish to report the fractionation into diasteromers of synthetic α-tocopherol by means of a complex with piperazine and the isolation in pure form of an *l*-epimer of natural *d*-α-tocopherol. The α-tocopherol was prepared by reaction of natural phytol with trimethylhydroquinone. The physical properties of the *l*-epimer are reported here and its biopotency will be reported separately by Ames and Ludwig of this Laboratory. The biopotency was found to be substantially lower than that of natural *d*-α-tocopherol.

The fractionation procedure also gave a pure *d*-epimer whose properties served to identify it with natural *d*-α-tocopherol.

The synthesis of α-tocopherol by condensation of natural phytol with trimethylhydroquinone gives an epimeric mixture at the 2-position of the chroman ring. Since natural phytol contains two centers of optical activity with D-configurations,[2] the α-tocopherol so synthesized can be designated as 2-*dl*,4′D,8′D-α-tocopherol. The *l*-epimer isolated is more precisely designated as 2-*l*,4′D,8′D-α-tocopherol; the *d*-epimer isolated is correspondingly 2-*d*,4′D,8′D-α-tocopherol. The identification of the *d*-epimer with natural *d*-α-tocopherol provides evidence, heretofore lacking, that the latter has the same configuration at the asymmetric carbon atoms in the side chain as natural phytol.



The epimers were separated by repeated fractional crystallization of a solid complex, which we found that α-tocopherol forms with piperazine. This complex, which appears to be a coördination complex of two molecules of tocopherol with one of piperazine, is prepared readily by dissolving the components in approximately ten volumes of acetone and cooling the solution to effect crystallization. The tocopherol can be recovered by dissolving the complex in petroleum ether and washing with water to remove the piperazine.

The first crop of piperazine–tocopherol complex separated from a cooled (−20°) solution of the synthetic α-tocopherol (100 g., 1.0 mole proportion) and piperazine (2.5 g., 0.25 mole proportion) in acetone (200 ml.). The crystals so obtained contained a high proportion of the *d*-epimer (ratio *d*:*l* = 70:30), and after five recrystallizations yielded the pure *d*-epimer.

The original filtrate was again treated with piperazine to remove a second crop of complex enriched in *d*-epimer (ratio *d*:*l* = 61:39). The filtrate from this second crop now contained a preponderance of the *l*-epimer (ratio *l*:*d* = 59:41).

The *l*-enriched filtrate was further fractionated to obtain pure *l*-epimer. The fractionation was accomplished by repeated treatments of the recovered tocopherol with fresh portions of piperazine to precipitate the complex. The *l*-epimer was concentrated each time in the crystallized fraction, apparently because it was present in higher concentration. After seven fractionations we obtained 2-*l*,4′D,8′D-α-tocopherol, optically pure by our criteria. The yield was 1.7% without reprocessing of intermediate filtrate fractions.

TABLE I

OPTICAL ROTATION DATA

	2-*l*,4′D,8′D-α-tocopherol	2-*d*,4′D,8′D-α-tocopherol	Natural *d*-α-tocopherol
(A) Tocopherols			
$[\alpha]^{25}D$ (EtOH)	+0.36°	+0.58°	+0.65°
$[\alpha]^{25}D$ of $K_3Fe(CN)_6$ oxidation product (iso-octane)	−24.0°	+25.7°	+27.5°
(B) Acetates			
M.p., °C.	23	28[a]	28[b]
$[\alpha]^{25}D$ (EtOH)	−2.0°	+3.2°	+3.2°
(C) Acid Succinates			
M.p., °C.	51	78[c]	78[d]
$[\alpha]^{25}D$ (EtOH)	−2.9°	+3.8°	+3.8°

[a,b] Mixed melting point 28°. [c,d] Mixed melting point 78°.

The progress of the fractionation of the diasteromers was followed by the optical rotation of the fractions after oxidation. The α-tocopherol was recovered from the piperazine complex, oxidized with alkaline potassium ferricyanide and the optical rotation of the oxidized product was measured (Rudolph polarimeter, Model 70). The procedure is based on our finding[3] that the compound formed by oxidizing natural *d*-α-tocopherol with potassium ferricyanide has a relatively high specific rotation ($[\alpha]^{25}D$ +27.5°). When repeated precipitations of the complex produced α-tocopherol

(1) Communication No. 292 from the Research Laboratories of Distillation Products Industries, Division of Eastman Kodak Company, Rochester 3, New York.

(2) J. W. K. Burrell, L. M. Jackman, and B. C. L. Weedon, *Proc. Chem. Soc.*, 263 (1959).

(3) D. R. Nelan and C. D. Robeson, *Nature*, **193**, 477 (1962).

whose oxidation product showed no further change in rotation, the fraction was considered to be optically pure.

The physical properties of 2-*l*,4′D,8′D-α-tocopherol are given in Table I. It has a slight positive rotation of 0.36°. However, the specific rotation (−24°) of its oxidation product is opposite in sign to that of the oxidation product from natural *d*-α-tocopherol and the 2-*d*,4′D,8′D-α-tocopherol prepared *via* the fractionation procedure. The rotations of the *l*-acetate and acid succinate esters were negative and lower in value than the corresponding *d*-esters.

Melting points for the *l*-acetate and acid succinate were lower than for the corresponding *d*-esters.

The 2-*d*,4′D,8′D-α-tocopherol prepared by the fractionation procedure was judged to be identical with natural *d*-α-tocopherol from the data shown in Table I for the free tocopherols, oxidation products, crystalline acetates and acid succinates.

This procedure for preparing 2-*l*,4′D,8′D-α-tocopherol makes it available for determining the relation between stereochemical configuration and vitamin E activity of α-tocopherol in human and animal nutrition. Such studies are in progress.

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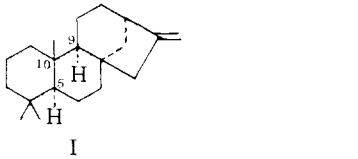
RECEIVED JUNE 13, 1962

STEREOCHEMISTRY OF THE DITERPENOIDS: ABSOLUTE CONFIGURATION OF CAFESTOL[1]

Sir:

The recent disclosure[2] of the absolute configurations of steviol, kaurene and the diterpene alkaloids, together with the unequivocal assignment of absolute stereochemistry (I) to phyllocladene,[3,4a] suggests a concerted *trans-anti* cyclization in the biosynthesis of the diterpenoids from a geranylgeraniol precursor[5] (II → III). Earlier speculations[4,5,6] regarding the stereochemical nature of the primary diterpenoids cyclization have, however, been tempered by the presence of a small but important group of C_{20} compounds which apparently[6] possessed a *syn*-9,10 backbone. These include isopimaric acid (IV),[7] rosenonolactone (V)[8] and its relatives (VI, VII), gibberellic acid (VIII)[9], eperuic acid (IX),[10] rimuene (X),[11a,b] cafestol (XI),[4a,12] and kahweol (XII).[4a]



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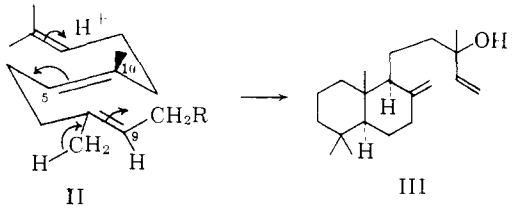

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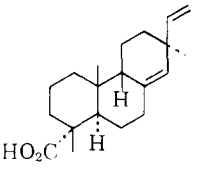

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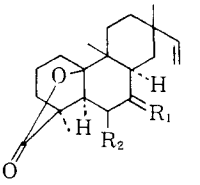
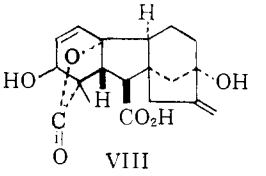
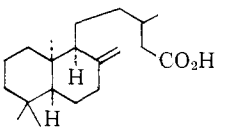


V, $R_1 = O$, $R_2 = H$
VI, $R_1 = H_2$, $R_2 = OH$
VII, $R_1 = H_2$, $R_2 = H$



VIII



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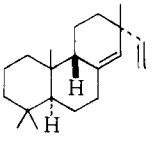
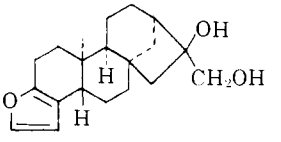
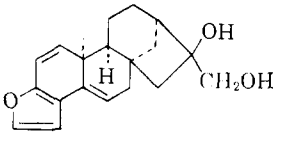


X



XI



XII

We now suggest that the entire family of di-, tri- and tetracarbocyclic diterpenoids is based on the backbone of rings A and B in the *trans-anti* configuration (as III and its mirror image). The exceptions to the 9,10-*anti* configuration can be eliminated as follows.

Stereospecific syntheses[11b] of structure (IV) epimeric at C_9 and C_{13} representing rimuene have demonstrated that the proposed formulation is untenable and suggest that the isomerism of (IV) and (X) with their respective relatives is structural.[13] A process such as XIII→VII[14] in the biosynthesis

(1) Circular Dichroism Studies. II. Part I: F. McCapra, A. I. Scott, G. A. Sim and D. W. Young, *Proc. Chem. Soc.*, in press, 1962.

(2) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge and L. H. Briggs, *J. Am. Chem. Soc.*, **83**, 3720 (1961).

(3) P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960).

(4) (a) C. Djerassi, M. Cais and L. A. Mitscher, *J. Am. Chem. Soc.*, **81**, 2386 (1959); (b) E. Wenkert and J. W. Chamberlain, *ibid.*, p. 688.

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(6) W. B. Whalley, *Tetrahedron*, **18**, 43 (1962).

(7) (a) B. Green, A. Harris and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958); O. E. Edwards and R. Howe, *Canad. J. Chem.*, **37**, 760 (1959).

(8) A. Harris, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1799, 1807 (1958); W. B. Whalley, B. Green, D. Arigoni, J. J. Britt and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5520 (1959).

(9) B. E. Cross, *J. Chem. Soc.*, 3022 (1960); G. Stork and H. Newman, *J. Am. Chem. Soc.*, **81**, 5518 (1959).

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(13) The revised structure for isopimaric acid (Edwards, *et al.*, *J. Org. Chem.*, **27**, 1930 (1962); Ireland, *et al.*, *ibid.*, **27**, (1962) is in full accord with our prediction.

(14) A. J. Birch, R. W. Rickards, H. Smith, A. Harris and W. B. Whalley, *Tetrahedron*, **7**, 241 (1959).