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TOTAL SYNTHESIS OF CYCLOSATIVENE

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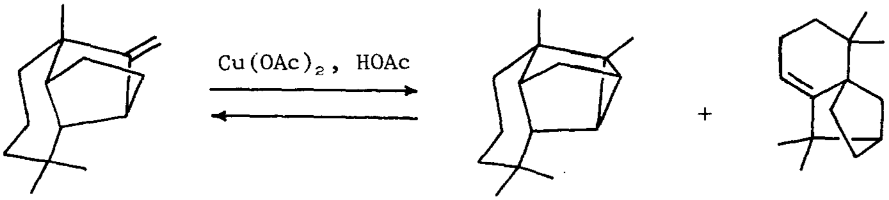
Longifolene, 1, occupies a most interesting place in sesquiterpene chemistry (1) both because of the uniqueness of its structure and because of the complexity of its chemistry. Much of this remarkable chemistry which longifolene exhibits is due to its compact tricyclic skeleton which allows for a number of interesting transannular reactions (2). For example (3) when longifolene is heated with cupric acetate in acetic acid, two isomeric hydrocarbons, longicyclene, 2, (4) (29%), and isolongifolene, 3, (15%), are obtained along with much recovered starting material (51%).



1 2 3

The tricyclic sesquiterpene hydrocarbon, sativene, 6, was isolated by de Mayo and Williams in 1965 (5) and, because of its structural similarity to longifolene, might also reasonably be expected to display interesting chemistry. We have recently reported the first total synthesis of sativene (6) and, with synthetic sativene available, (7), were interested in the transformations it might undergo. While this work was in progress, the isolation of the tetracyclic sesquiterpene cyclosativene, 8 , from California red fir (Abies magnifica, Murray) was reported (8) as well as its isomerization into sativene. We are thus prompted to record our own similar results, and to comment on the mechanism of the isomerization.

Under conditions analogous to the longifolene → longicyclene interconversion, 100 mg dl-sativene was refluxed for two days with 25 mg $Cu(OAc)_2.H_2O$ in 3 ml glacial acetic acid. Following work-up, micro-distillation of the crude product gave 85 mg of material. Examination of the product mixture by VPC using an FFAP column [15% on 60/80 Chromosorb W; 5' x ¼"; 110^o; 60 cc/min] indicated that three isomeric hydrocarbons were present and that the following equilibrium had been established:

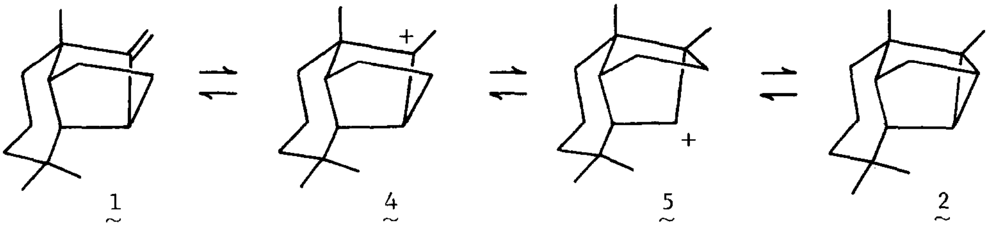
Peak 1, 32%, was assigned the structure **8**, denoted cyclosativene by Smedman and Zavarin, by spectral data: ir, (CCl_4) 3055 cm^{-1} (cyclopropane C-H), 860, 840 [tricyclene nucleus (9)]; nmr (CCl_4) τ 9.01 (s, 3 H), 9.24 (s, 3 H), 9.10 and 9.12 (pair of doublets, 6 H, J = 6 Hz), 9.22 (s, 1 H, cyclopropane C-H), 9.34 (d, 1 H, J = 5 Hz, cyclopropane C-H); mass spectrum (10) (80 ev), m/e (relative intensity), 204 (100, M^+), 189 (27), 161 (91), 133 (36), 94 (88). dl-Cyclosativene gave an nmr spectrum identical with that produced by an authentic sample of the natural material and kindly provided by Dr. L. Smedman. This reaction therefore constitutes a total synthesis of this naturally occurring material.

Peak 2, 7%, was recovered dl-sativene, **6**, identified spectroscopically and gas chromatographically.

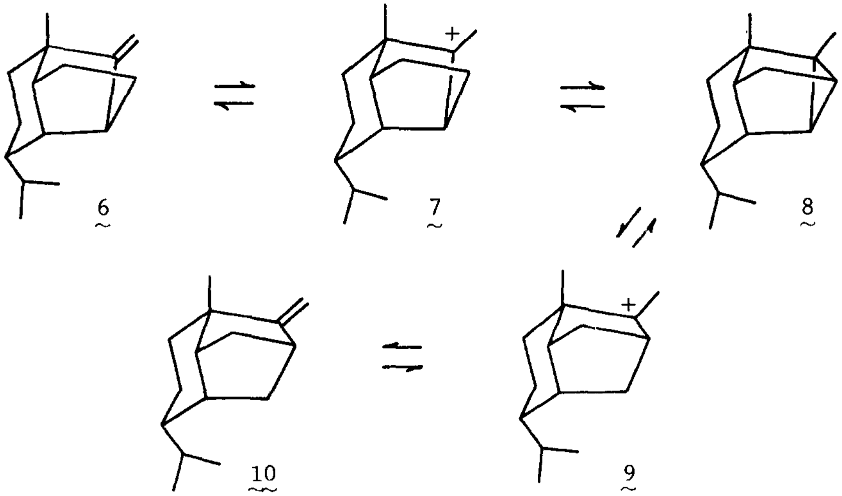
Peak 3, 61%, was a third isomeric hydrocarbon which we denote dl-isosativene and to which we assign structure **10** on the basis of spectral measurements: ir (CCl_4), 3065 cm^{-1}, 1655, 875 (terminal methylene); nmr (CCl_4), τ 5.24 (s, 1 H), 5.52 (s, 1 H), 7.39 (broad doublet, 1 H), 9.01 (s, 3 H), 9.10 (d, 6 H, J = 6 Hz); mass spectrum (80 ev), m/e (relative intensity), 204 (22, M^+), 189 (9), 161 (25), 133 (13), 94 (100).

That a true equilibrium exists between these three isomeric sesquiterpenes was demonstrated by subjecting samples of pure cyclosativene and isosativene to cupric acetate— acetic acid treatment and observing the formation of the same equilibrium mixture of products.

The mechanism of the isomerization is not clear. Dev has suggested (11) that "longifolene and longicyclene get interconverted, in all likelihood through the longibornyl cation" **5**.

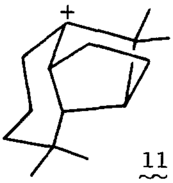


Although this is a possibility, we see no compelling reason to invoke an energetically unfavorable 3° to 2° carbonium ion rearrangement. We prefer instead the path shown below for the analogous sativene → cyclosativene interconversion, illustrated with classical carbonium ions for convenience:



In this pathway, the cation 7 formed by protonation of sativene immediately loses a proton and closes to cyclosativene, rather than isomerize to a 2° carbonium ion analogous to 5. Cyclosativene can then open by protonation in either of two directions to generate a new tertiary cation 9, or to regenerate 7. Upon deprotonation, 9 then gives isosativene. Certainly this mechanism is the obvious choice for the reverse [cyclosativene → sativene] reaction, and we therefore favor it for the forward process also, in disagreement with Dev's suggestion.

Thus there are marked differences between the acid catalyzed rearrangements of longifolene and sativene. Under the conditions described here, sativene undergoes no deep seated skeletal change analogous to the longifolene → isolongifolene rearrangement. A possible reason for this is that the bridgehead carbonium ion **11** is a presumed (2) intermediate in the longifolene isomerization. In the sativene case however, the analogous ion **12**, and all succeeding intermediates would be much more strained due to the decreased ring size, making such a path unlikely.



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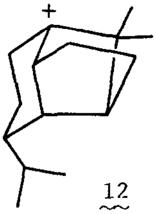

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It therefore appears that sativene, in analogy with longifolene, is capable of some interesting transformations and we are continuing the study.

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References

(1) For a review of the early chemistry of longifolene, see J. S. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp. 92-98.

(2) For a review of the molecular rearrangements which longifolene undergoes, see G. Ourisson, Simonsen Lecture, *Proc. Chem. Soc.*, 274 (1964).

(3) U. R. Nayak and S. Dev, *Tetrahedron Letters*, 243 (1963).
U. R. Nayak and S. Dev, *Tetrahedron*, *24*, 4099 (1968).

(4) Longicyclene is the first naturally occurring tetracyclic sesquiterpene and occurs as a minor portion of the oil from the oleoresin of *Pinus longifolia*; see ref. 3.

(5) P. de Mayo and R. E. Williams, *J. Am. Chem. Soc.*, 87, 3275 (1965).

(6) J. E. Mc Murry, *J. Am. Chem. Soc.*, in the press.

(7) *dl*-Sativene is far more readily available than is the natural material which occurs only in very small amounts in *helminthosporium sativum*; see ref. 5.

(8) L. Smedman and E. Zavarin, *Tetrahedron Letters*, 3833 (1968).

(9) M. Hanack and H. Eggensperger, *Liebigs Ann.*, 648, 1 (1961).

(10) The mass spectra were recorded on an Hitachi-Perkin-Elmer RMU-6E instrument.

(11) U. R. Nayak and S. Dev, *Tetrahedron*, *24*, 4102 (1968).