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THE ACID CATALYZED INTERCONVERSION OF COPACAMPHENE AND SATIVENE

John E. Mc Murry[1]

Division of Natural Sciences, University of California

Santa Cruz, California 95060

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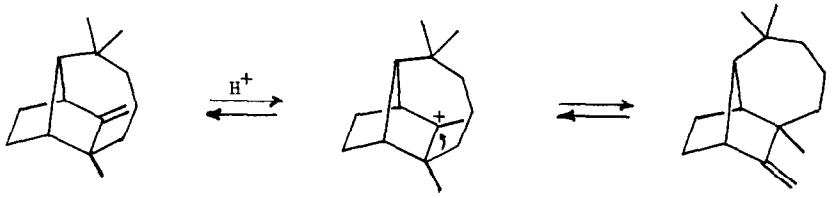
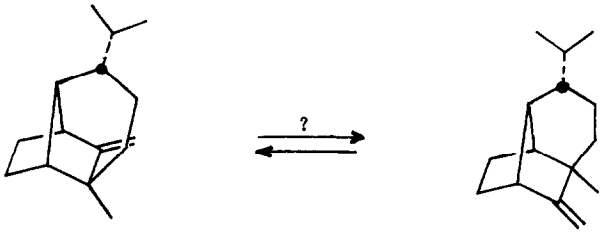
One of the many interesting facets of longifolene chemistry[2], is that when longifolene is treated with cupric acetate in refluxing acetic acid, a three component equilibrium of isomeric sesquiterpenes is established between longifolene, longicyclene, and isolongifolene[3]. Interestingly, if one starts with (+)longifolene, 1, racemic longifolene is recovered after the reaction[3]. This presumably arises via the migration pathway indicated:



1 1 (mirror image)

We[4] and others[5] have recently reported on the course of the $Cu(OAc)_2$/HOAc catalyzed rearrangement of sativene, 2, and have found similarities with the longifolene case. Sativene, when treated with $Cu(OAc)_2$ in refluxing HOAc is rearranged to an equilibrium mixture of recovered sativene (7%), cyclosativene, 4, (32%), and isosativene, 5, (61%). It is interesting however that if, in the sativene case, a migration of the type which leads to racemic longifolene were to occur, the product would not be mirror-image sativene, but would

be the new and entirely different compound 3. This is due of course to the presence in sativene of the extra asymmetric center at the isopropyl group.



2 3

In fact, neither we nor the other workers found compound 3 in the product mixture when sativene was isomerized with $Cu(OAc)_2$/HOAc. This is not surprising since in sativene the isopropyl group is equatorial while in 3 it is axial if we assume a chair conformation for the cyclohexane ring. Thus if the interconversion were to be demonstrated, it would probably be necessary to approach it by isomerization of 3 → 2 rather than 2 → 3. Compound 3 is in fact the known sesquiterpene, copacamphene. It was first prepared by rearrangement of copaborneol[6] and its structure was recently confirmed by us via total synthesis[7]. With copacamphene available, we were therefore interested in examining its behavior under acidic conditions with the expectation that sativene, cyclosativene, and isosativene would be formed.

When (+)copacamphene[8] (100 mg) was refluxed with 25 mg $Cu(OAc)_2 \cdot H_2O$ in 5 ml glacial acetic acid, and the course of the reaction was followed by vpc [15% FFAP on 60/80 Chromosorb W; 5' x 1/4"; 110°], the gradual diminution to a steady level of the peak corresponding to copacamphene, and the appearance and gradual growth of two new peaks corresponding to cyclosativene and isosativene could be detected as shown in Fig. 1. Unfortunately, copacamphene and sativene are inseparable by vpc under our conditions. The peak corresponding to copacamphene in the vpc trace of the reaction product at the various intervals therefore represents a mixture of copacamphene and sativene, and we thus cannot determine directly the rate of the isomerization.

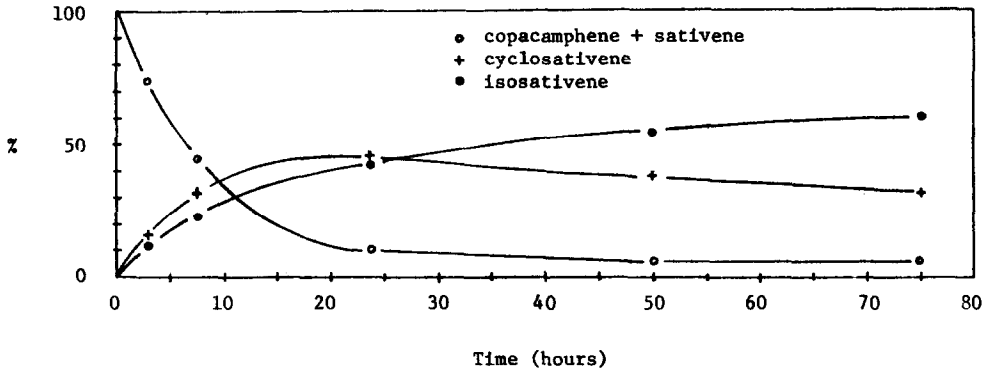


Fig. 1 Isomerization of copacamphene in cupric acetate - acetic acid.

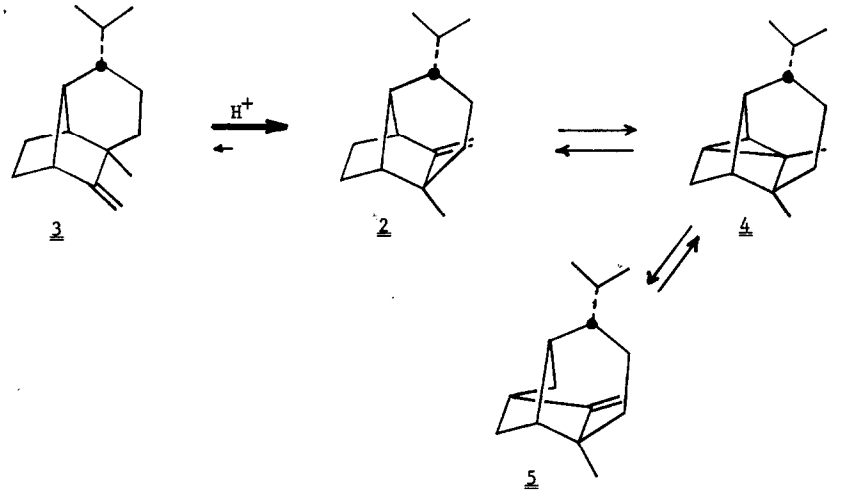
After 4 days, the vpc trace of the reaction product mixture was identical to that from the sativene rearrangement[4]. The reaction was worked up and the product mixture separated into its three components by preparative vpc.

Peak 1, 32%, was identified as (+)cyclosativene, α_D +61°, c = 0.46 (lit[9] +67.8°), by comparison of its ir, nmr, and mass spectrum with those of an authentic sample of (±)cyclosativene[4]. The ir spectrum of cyclosativene is quite different in the fingerprint region from that of cyclocopacamphene[10] which might have been expected to be a rearrangement product.

Peak 2, 7%, was identified as sativene (and not recovered copacamphene) by micro ir comparison with an authentic sample[4]. Thus, although we do not know the rate of the copacamphene → sativene isomerization, the equilibrium between the two favors sativene to a high extent.

Peak 3, 61%, was identified as isosativene by comparison of its ir, nmr, and mass spectrum with those from an authentic sample of (±)isosativene[4].

It therefore appears that sativene and copacamphene are interconvertible on acid treatment as predicted, and that the four-component equilibrium shown below is established.



It follows that if, as is probably the case[9], (+)cyclosativene has the absolute configuration shown in 4, then (+)copacamphene must have absolute configuration as given in 3. This therefore defines the absolute configuration of copaborneol[6].

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References

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7. See accompanying communication.

8. We are grateful to Dr. Westfelt for providing us with a generous amount of (+) copaborneol, the precursor of (+)copacamphene.

9. F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, Tetrahedron Letters, 3169 (1969).

10. We thank Dr. Kido for sending us this ir spectrum of cyclocopacamphene.