The Total Synthesis of Copacamphene and Its Acid-Catalyzed Interconversion with Sativene[1]

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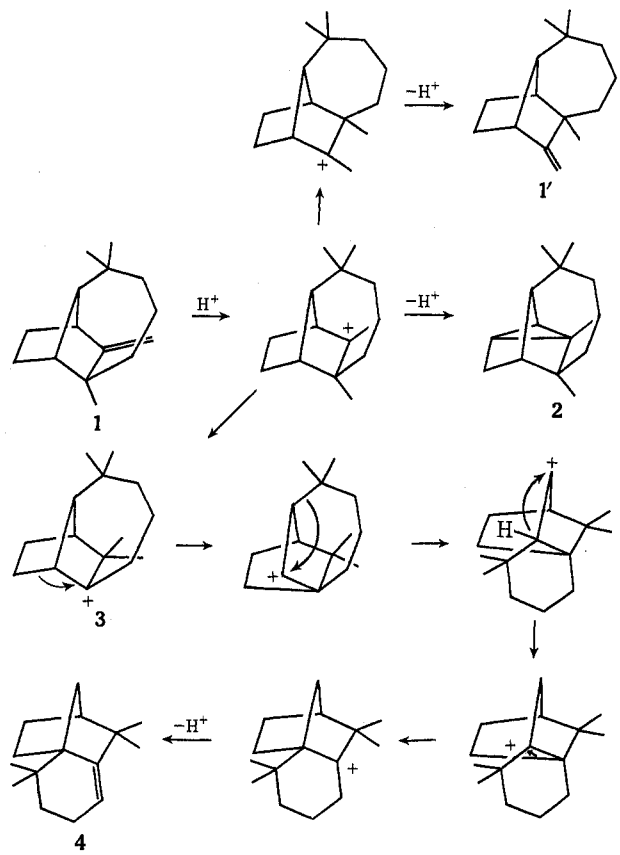
We have found that, analogous to the known behavior of longifolene, sativene (**5**) is isomerized by treatment with $Cu(OAc)_2$ in refluxing acetic acid to an equilibrium mixture of isomeric sesquiterpenes consisting of recovered sativene (7%), cyclosativene (**7**, 32%), and isosativene (**8**, 61%). We have also completed a total synthesis of copacamphene (**12**) and have found that it too is isomerized to this same equilibrium mixture on treatment with $Cu(OAc)_2$–HOAc. The key step in the synthesis is a base-catalyzed intramolecular epoxide opening (**18** → **19**). Dehydration of **19** gives the keto olefin **21** which may be hydrogenated to give either ketone **15** with sativene stereochemistry or **17** with copacamphene stereochemistry, depending on the conditions employed.

Several years ago we reported[2] a total synthesis of the sesquiterpene hydrocarbon, sativene, and remarked that, in view of its structural similarity to longifolene,[3] sativene might be expected to exhibit interesting chemical reactivity. In particular, (+)-longifolene (**1**) on treatment with refluxing $Cu(OAc)_2$–HOAc yields a three-component mixture of isomeric products consisting of racemic longifolene (51%), longicyclene (**2**, 29%), and isolongifolene (**4**, 15%).[4] The transformation has been well studied, and a mechanistic pathway accounting for the results has been proposed[5] (Scheme I).

We therefore treated (±)-sativene (**5**) with refluxing $Cu(OAc)_2$–HOAc under conditions identical with those used to isomerize longifolene and withdrew aliquots at regular intervals to follow the course of the reaction. Analysis was done by vpc (15% FFAP on 60–80 Chromosorb W; 110°). A plot of the reaction course is shown in Figure 1.

After 50 hr a three-component equilibrium consisting of recovered sativene (7%) and two new isomeric compounds A (32%) and B (61%) was established. Separation of the product mixture was readily accomplished by preparative vpc. Compound A, $C_{15}H_{24}$, was assigned structure **7** on the basis of spectral evidence and on the basis of structural analogy to longicyclene. Thus the ir spectrum showed the presence of cyclopropane C–H bonds (3055 cm^{-1}) and of the tricyclene nucleus[6] (860, 840 cm^{-1}). The nmr spectrum further confirmed the assigned structure by showing the absence of vinyl protons and the presence of two quaternary methyl groups [τ 9.01 (s, 3 H) and 9.24 (s, 3 H)], an isopropyl group [τ 9.10 and 9.12 (pair of doublets, 6 H, J = 6 Hz)], and two cyclopropane ring protons [τ 9.22 (s, 1 H) and 9.34 (d, 1 H, J = 5 Hz)]. At this point a communication appeared from Zavarin's group[7] reporting the isolation of **7** from the California red fir (*Abies magnifica* Murray). Comparison of the ir and nmr spectra of compound A and natural **7**, named cyclosativene by Zavarin, demonstrated the identity of the two samples. Zavarin further reported the isomerization of sativene and of cyclosativene into the same three-component equilibrium mixture of isomers that we obtained.

SCHEME I



Compound B, $C_{15}H_{24}$, which we have called isosativene, was assigned structure **8** on spectral grounds. Ir (CCl_4) reveals the presence of a terminal methylene (3065, 1650, 875 cm^{-1}) and of a *gem*-dimethyl group (1375 cm^{-1}, doublet). Nmr confirms the presence of the terminal methylene [τ 5.24 (s, 1 H) and 5.52 (s, 1 H)], the isopropyl group [τ 9.10 (d, 6 H, J = 6 Hz)], and one quaternary methyl [τ 9.01 (s, 3 H)]. The allylic bridgehead proton is also clearly visible at τ 7.39 (broad singlet, 1 H) [*cf.* sativene τ 7.42 (broad singlet, 1 H)].

(1) Portions of this work have been published in preliminary form: J. E. McMurry, *Tetrahedron Lett.*, 55 (1969); 3731 (1970); 3735 (1970).

(2) J. E. McMurry, *J. Amer. Chem. Soc.*, **90**, 6821 (1968).

(3) For a review of the chemistry of longifolene, see (a) J. P. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp 92–98; (b) G. Ourisson, *Proc. Chem. Soc.*, 274 (1964).

(4) J. R. Prahlad, R. Ranganathan, U. R. Nayak, T.S. Santhanakrishnan, and S. Dev, *Tetrahedron Lett.*, 417 (1964).

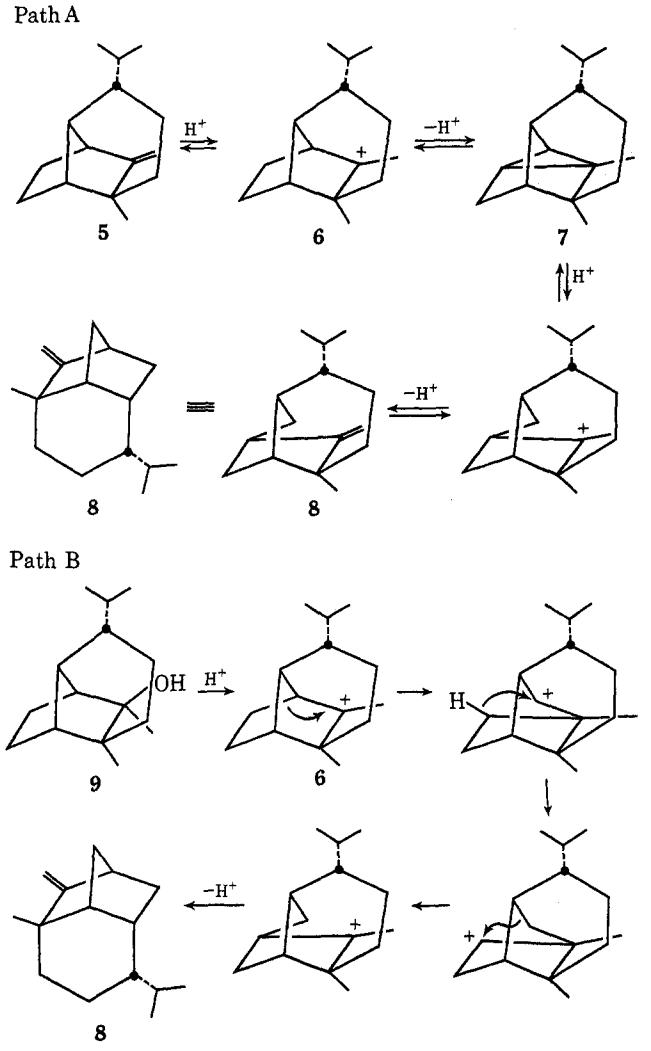
(5) (a) G. Ourisson, *Proc. Chem. Soc.*, 274 (1964); (b) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *J. Amer. Chem. Soc.*, **89**, 2590 (1967). These workers point out that endo 2,3 methyl shifts such as that proposed by Ourisson are unlikely to occur, and they suggest an alternate mechanism for the rearrangement.

(6) M. Hanack and H. Eggensperger, *Justus Liebigs Ann. Chem.*, **648**, 1 (1961).

(7) L. Smedman and E. Zavarin, *Tetrahedron Lett.*, 3833 (1968); L. A. Smedman, E. Zavarin, and R. Teranishi, *Phytochemistry*, 1457 (1969).

We further demonstrated the existence of a true equilibrium by subjecting small samples of cyclosativene and isosativene to rearrangement conditions and observing the formation of the three-component equilibrium after a 2-day reaction period. These transformations are shown in Scheme II.

SCHEME II



Mechanistically, the most economical rearrangement pathway is that pictured in path A of Scheme II where cyclosativene is an intermediate in the formation of isosativene. That this is probably the case is indicated by the fact that, as shown in Figure 1, cyclosativene reaches a maximum level after about 10 hr and then gradually diminishes to its equilibrium value as isosativene accumulates. One can postulate a pathway from sativene to isosativene which does not proceed *via* cyclosativene (path B), but we see no reason to assume that this alternate mechanism is occurring under our conditions. If, however, a hexane solution of carbinol **9** is treated with 50% aqueous sulfuric acid in a two-phase system for 1 hr, the product mixture consists of cyclosativene (3%), sativene (28%), isosativene (65%), and a fourth compound whose structure is unknown (4%). In this case, although isosativene is the major product, it clearly cannot be formed *via* cyclosativene since we have demonstrated that cyclosativene remains unchanged under the reaction conditions.

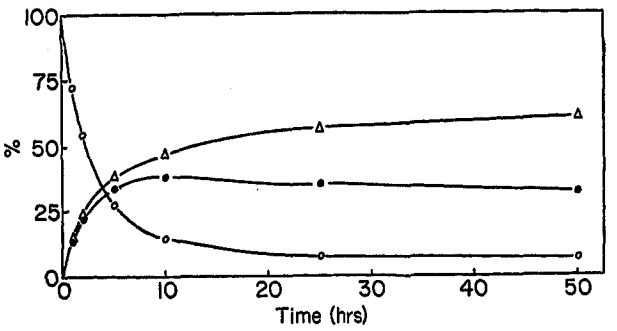
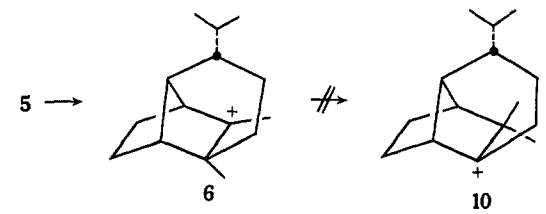


Figure 1.—$Cu(OAc)_2$–HOAc catalyzed isomerization of sativene: O, sativene; △, isosativene; ●, cyclosativene.

Under these conditions therefore, isosativene must be formed by a different path, presumably path B. We therefore appear to have the novel situation that *carbonium ion* **6** *can rearrange to isosativene by two distinct pathways depending on the reaction conditions*!

Thus, there are both similarities and differences in the reaction courses of longifolene and of sativene. Each undergoes one unique transformation (leading to iso product) and one common transformation (leading to tetracyclic product).

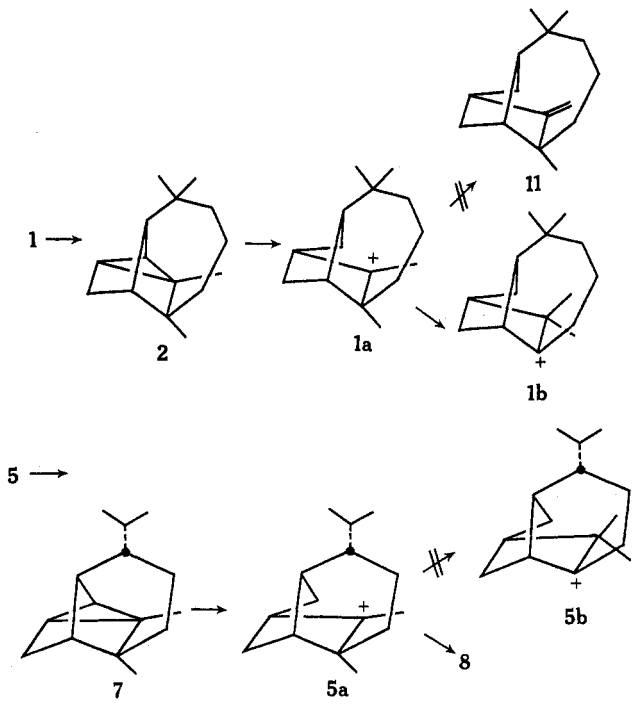
The reason for these differences can be understood by examination of the rearrangement mechanisms which have been proposed. Ourisson[5a] has postulated that longifolene is protonated and undergoes an endo 2,3 methyl shift to give the bridgehead carbonium ion **3**, which then undergoes a series of further rearrangements to give isolongifolene. If such a path were followed in the sativene case, the analogous bridgehead ion **10** would be formed. In **10**, however, the ion is contained in a bicyclo[3.2.1]octane system while in **3** the ion is in the more flexible bicyclo[4.2.1]nonane system. The consequent strain increases on moving to the smaller ring system would probably prevent the rearrangement from occurring in the sativene series, thus explaining the difference.



Alternatively and quite convincingly, Berson has pointed out[5b] that endo 2,3 methyl shifts occur only with great difficulty and has postulated that the rearrangement of longifolene proceeds through ion **1a** which undergoes an exo 2,3 methyl shift to give **1b** and thence to isolongifolene. If this path were followed in the sativene series, the more strained bridgehead ion **5b** would be formed, and this path should therefore be unfavorable. Berson, however, has postulated an unnecesarily complex scheme to reach **1a**, and we envision this intermediate as arising simply from protonation of longicyclene.

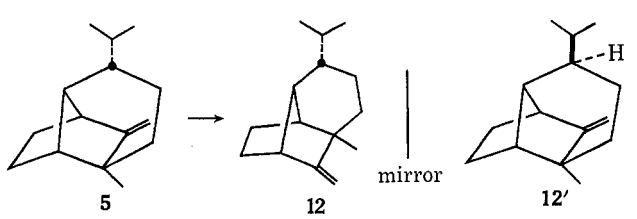
Assuming Ourisson's mechanism to be correct, it is considerably more difficult to see why the type of rearrangement leading from sativene to isosativene does not also occur in the longifolene case to give **11**, since the necessary intermediate **1a** looks perfectly accessible

and in fact lies along the Berson pathway to isolongifolene.[8] We believe that the Berson mechanism is in fact correct and that **1a** is formed but rearranges further rather than lose a proton to give **11**. Ion **5a**, however,



cannot rearrange further and so loses a proton. Thus both isolongifolene and isosativene do arise from the same type of rearrangement path.

One further point of difference between the isomerizations of longifolene and sativene is that the longifolene recovered from the reaction is racemized. This racemization is due to yet another carbonium ion rearrangement (**1** → **1′** in Scheme I).[5] Were a rearrangement of this type to occur in the sativene series, it would lead, not to racemic sativene, but to a new compound, **12**, differing from sativene by being epimeric at the isopropyl group.

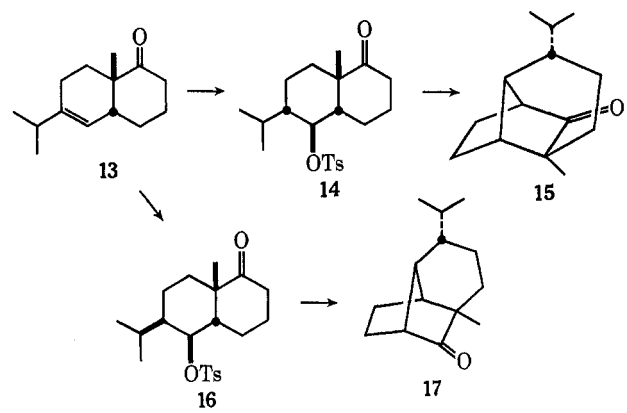


In fact, neither we nor the other workers found such a product in the sativene isomerization. This is not surprising since, if we assume the six-membered ring in sativene to have a chair conformation, the isopropyl group is equatorial. In the possible rearrangement product, the isopropyl group is axial; thus sativene is clearly the more stable of the two. Therefore if we were to demonstrate the existence of an interconversion between sativene and its epimer, it would be necessary to start with the epimer and examine its rearrangement under acid catalysis. We predict that **12** will first isomerize to sativene which will then further react to give the usual product mixture.

(8) A rearrangement product with the carbon skeleton of **11** has recently been isolated from the acetolysis of longicamphenilyl tosylate: R. Coates and J. P. Chen, *Chem. Commun.*, 1481 (1970).

Compound **12** is in fact the structure assigned to copacamphene, a rearrangement product recently prepared by Westfelt from copaborneol.[9] Copacamphene has not itself been isolated from natural sources although closely related compounds (*e.g.*, cyclocopacamphenic acid, cyclocopacamphene)[10] have been found recently in vetiver oil. The published structure proof of copacamphene seemed to us to be based rather more heavily on intuition than on chemical data, and we therefore undertook a total synthesis of **12** to verify the proposed structure of copacamphene and to obtain a sample for rearrangement studies.

In our earlier synthesis of sativene, we used the keto olefin **13** as an intermediate. Cis–anti Markovnikov addition of water to the double bond followed by tosylation gave keto tosylate **14** which, when treated with methylsulfinyl carbanion, cyclized to norsativone (**15**). Conceptually, in devising a synthesis of copacamphenilone (**17**) we would like to effect a trans–anti Markovnikov addition of water to **13**. Tosylation and cyclization should then give **17**.



Experimentally, however, we were unable to accomplish this goal. Brown has reported[11] a method for preparing *cis*-2-methylcyclohexanol from 1-methylcyclohexene, a net trans–anti Markovnikov addition of water to the olefin, by epoxidation followed by $NaBH_4$–BH_3 reduction. We therefore attempted to use this method in the present case. Keto olefin **13** was treated with 1 equiv of *m*-chloroperbenzoic acid to produce the oily epoxide **18** in 95% yield. The reaction occurs stereospecifically from the convex face of the *cis*-octalone system as demonstrated by nmr which shows the proton on the epoxide ring as a sharp singlet at τ 7.50 unsplit by the neighboring bridgehead proton. The dihedral angle between the two protons must therefore be near 90°, a situation which, as is clear from an examination of Dreiding models, can only obtain if reaction occurs from the top face.

Reduction of **18** under the Brown conditions did not result in epoxide cleavage. The use of more severe conditions gave an extremely complex mixture of products and we therefore abandoned this approach.

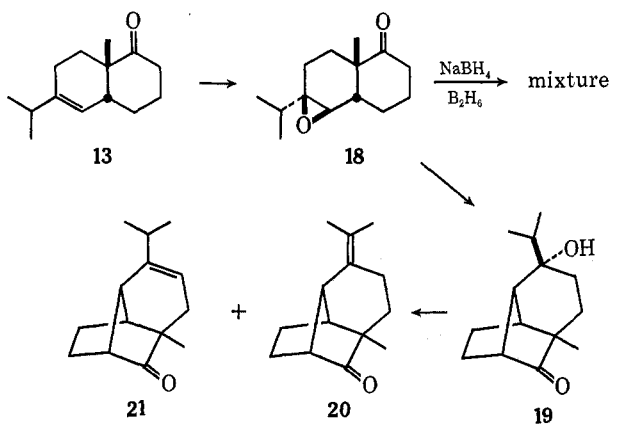
Since establishment of the stereochemistry at the isopropyl group at this early stage proved difficult, we decided to first form the tricyclic skeleton and then to set the stereochemistry at a later stage. Our keto

(9) M. Kolbe and L. Westfelt, *Acta Chem. Scand.*, **21**, 585 (1967).

(10) F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, *Tetrahedron Lett.*, 3169 (1969), and ref 7 therein.

(11) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **90**, 2686 (1968).

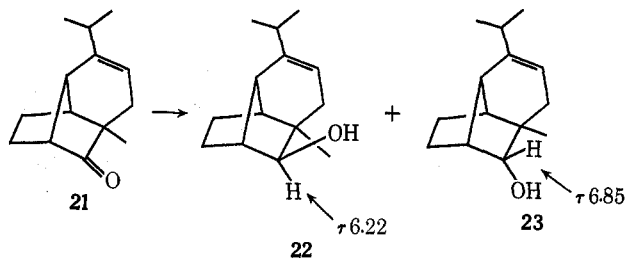
epoxide **18** seemed ideally suited for this purpose if it could be induced to undergo a base-catalyzed intramolecular epoxide opening. The resulting tricyclic keto alcohol **19** would then have a synthetic handle at the exact position necessary for stereochemical control of the isopropyl configuration. When **18** was treated with 1.2 equiv of methylsulfinyl carbanion in DMSO[12] at 60° for 4 days or with 2 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol at reflux for 7 days, cyclization occurred in 95% yield to give **19**. Dehydration was accomplished most readily by brief treatment of a hexane solution of **19** with 50% aqueous sulfuric acid to give, in quantitative yield, a 31:69 mixture of the two olefins **20** and **21**. Spectral data allowed an unambiguous structural assignment to be made (see Experimental Section). Rather than work with a mixture we separated the two olefins by column chromatography and carried out our further work on **21**, the major isomer. The minor isomer could be reequilibrated with **20** by treatment with acid allowing **21** to be obtained in high overall yield.



13 18 21 20 19

It is evident from an inspection of models that catalytic hydrogenation of **21** from the less hindered side would lead to a saturated ketone having the sativene stereochemistry and not the desired copacamphene stereochemistry. In the hope that a small amount of desired product might be obtained however, catalytic hydrogenation of **21** in acetic acid over Adams catalyst was attempted. Initial attempts were most unrewarding in that even under vigorous hydrogenation conditions (50 psi, 80°) no reduction took place. The olefin sample we were using for reduction had been prepared from **18** by methysulfinyl carbanion catalyzed cyclization. Evidently traces of sulfur-containing impurities remained with the material to poison the catalyst even after acid treatment, chromatography, and treatment with activated charcoal because reduction of a sample of **21** prepared *via tert*-butoxide catalyzed cyclization occurred smoothly and quantitatively under mild conditions to give a single saturated ketone which was spectrally identical with pure norsativone (**15**)[2]. Treatment of **15** with methyllithium followed by dehydration with thionyl chloride in cold pyridine gave pure (±)-sativene with no trace of copacamphene impurity detectable by nmr.

We were therefore forced to devise a more circuitous route to saturate the double bond in **21** from the more hindered side. Reduction of **21** with $LiAlH_4$ in ether gave a 42:58 mixture[13] of the two hydroxy olefins **22** and **23**. Structural assignments were based both on spectral data and on subsequent chemical reactivity of the two alcohols. The major alcohol was assigned structure **23** based on its nmr spectrum showing the proton on the alcohol carbon at τ 6.85 (broad singlet, 1 H) strongly shielded by lying above the plane of the double bond[14] while in the minor isomer **22**, the corresponding proton appears at τ 6.22 (d, 1 H, J = 5 Hz). Strong confirmation of these assignments comes from the ir spectra of the two epimeric alcohols taken in CCl_4. Alcohol **22** shows hydroxyl absorption at 3640 cm^{-1} (sharp) and at 3450 cm^{-1} (broad), the latter being due to internal hydrogen bonding with the double bond.[15] Alcohol **23** shows only a single sharp absorption at 3560 cm^{-1} since no internal hydrogen bonding is sterically possible.



21 22 23

The minor isomer **22** was the desired product because of the proximity of the hydroxyl and the double bond. We felt that if **22** were to be hydrogenated in a nonpolar solvent, the hydroxyl might bond to the catalyst and thus promote hydrogenation from that side.[16] Fortunately **22** could be made the major product by carrying out the reduction with lithium in liquid ammonia. Under these conditions, a 59:41 ratio of **22** to **23** was obtained.

When **22** was reduced over 10% palladium on charcoal in hexane solution at atmospheric pressure, nmr revealed the presence of two products. The product mixture was homogeneous by vpc on a variety of columns, however, and separation could not be effected. The product mixture was therefore oxidized with Collins reagent[17] to a mixture of saturated ketones, **15** and **17**, which was again homogeneous on a variety of vpc columns. Reaction of the product mixture with methyllithium followed by dehydration with thionyl chloride in cold pyridine gave a mixture of hydrocarbons which by nmr was an 85:15 mixture of copacamphene and sativene. This mixture once again was homogeneous by vpc, but separation could be effected by careful column chromatography on silver nitrate impregnated silica gel (see Experimental Section). The pure (±)-copacamphene obtained was identical in all respects (ir, nmr, mass spectrum, vpc) with a sample of the material prepared from natural copaborneol and kindly supplied by Dr. Westfelt.

(12) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(13) At the time of our preliminary communication of this work, we had not been able to effect this separation and were therefore working with this mixture.

(14) For a discussion, see E. D. Becker, "High Resolution NMR," Academic Press, New York, N. Y., 1969, pp 73–79.

(15) For a good discussion of hydrogen bonding, see H. E. Hallam in "Infra-red Spectroscopy and Molecular Structure," M. Davies, Ed., Elsevier, Amsterdam, 1963, pp 405–440.

(16) *Cf.* C. H. Heathcock, R. A. Badger, and J. W. Patterson, *J. Amer. Chem. Soc.*, **89**, 4133 (1967).

(17) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

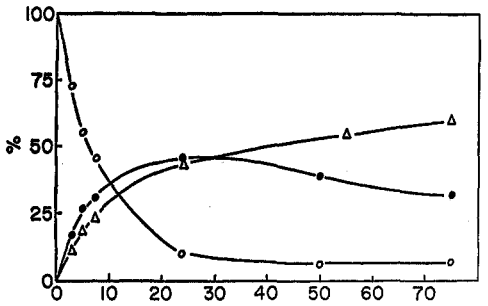
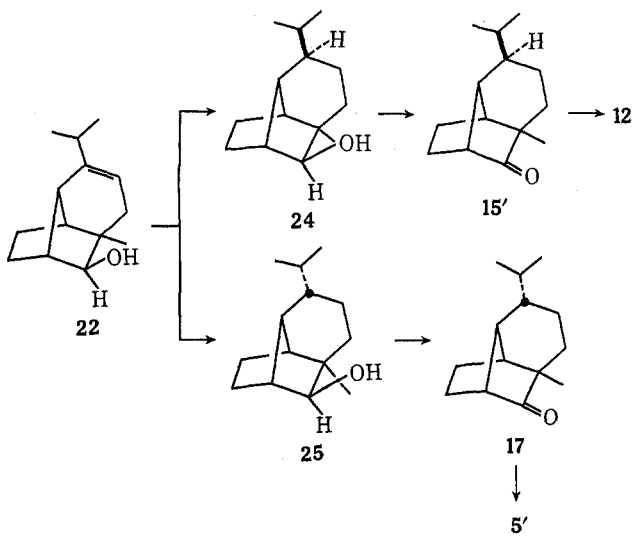


Figure 2.—$Cu(OAc)_2$–HOAc catalyzed isomerization of copacamphene: ○, sativene + copacamphene; △, isosativene; ●, cyclosativene.

Reduction of **23** in hexane solution over a 10% Pd/C catalyst also gave a product which, although homogeneous by vpc, was a mixture of two epimers. Oxidation, treatment with methyllithium, and dehydration gave a 45:55 mixture of copacamphene and sativene. From a practical standpoint, it was easiest to hydrogenate directly the mixture of **22** and **23** resulting from Li/NH_3 reduction of **21**. If this was done, a 70:30 mixture of copacamphene and sativene was obtained. Depending on the reduction conditions, therefore, enone **13** can be readily transformed in good yield either into pure sativene by two different stereospecific routes or into copacamphene by a stereoselective route requiring a rather difficult separation at the final step.

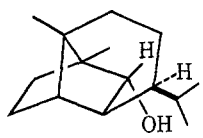
One additional reduction attempt was made on **22** which, had it been successful, might have led stereospecifically to copacamphene. Reduction of **22** was attempted with lithium in refluxing ethylamine[18] and with sodium in HMPA/*tert*-butyl alcohol,[19] the thought being that the intermediate anion radical resulting from addition of an electron to **22** might be protonated by the internal hydroxyl from the desired side. The attempt was unsuccessful, however, for no reduction of the hindered double bond took place.



With copacamphene available, we turned next to an examination of its acid-catalyzed isomerization. When (±)-copacamphene was treated with $Cu(OAc)_2$ in refluxing acetic acid and the reaction course followed by vpc analysis of aliquots at given intervals, the vpc peak corresponding to copacamphene rapidly diminished and two new peaks corresponding to cyclosativene and isosativene appeared, as illustrated in Figure 2.

After 75 hr, the vpc trace of the reaction mixture was identical with that obtained from isomerization of sativene. The peaks were collected and identified by ir, nmr, and mass spectral analysis as sativene (7%), (+)-cyclosativene (32%), and isosativene (61%). Unfortunately sativene and copacamphene were inseparable by vpc under our conditions and we therefore could not follow directly the rate of isomerization. Our original prediction of a copacamphene → sativene interconversion is therefore borne out.

In closing, one further result of this work has been to elucidate the absolute stereochemistry of (+)-copaborneol. If, as is probably the case,[20] (+)-cyclosativene has the absolute configuration given in **7**, then (+)-copacamphene must be **12**. Thus (+)-copaborneol is defined as **26**.



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Experimental Section

Micronalyses were performed by Micro-Tech Laboratories, Skokie, Ill. Nmr spectra were run in CCl_4 solution (TMS internal standard) on a Varian A-56/60A instrument, and ir spectra were run on a Perkin-Elmer 337. Mass spectra were taken on a Hitachi Perkin-Elmer RMU6E. Melting points are uncorrected.

$Cu(OAc)_2$–HOAc-Catalyzed Isomerization of (±)-Sativene.—(±)-Sativene (100 mg) and $Cu(OAc)_2 \cdot H_2O$ (25 mg) were dissolved in 3 ml of glacial acetic acid and refluxed under nitrogen. At intervals small portions were withdrawn from the reaction *via* syringe and analyzed by vpc [5 ft × 0.25 in., 15% FFAP on 60–80 Chromosorb W, 110°]. After 50 hr an equilibrium had been reached. The reaction was cooled, diluted with water, and extracted with hexane. The extracts were combined, washed with 5% NaOH and with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated. The residue was microdistilled to yield 85 mg of product which was separated by preparative vpc into its three components.

Fraction 1 (32%) was cyclosativene (**7**): ir (CCl_4) 3055 (cyclopropane CH), 860, 840 cm^{-1} (tricyclene nucleus[5]); 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 CH), 9.34 (d, 1 H, J = 5 Hz, cyclopropane CH); mass spectrum (80 eV) m/e (rel intensity) 204 (100 M^+), 189 (27), 161 (91), 133 (36), 94 (88). The ir and nmr of (±)-cyclosativene were identical with those of the natural material.

Fraction 2 (7%) was recovered (±)-sativene (**5**), identified by micro ir and by vpc comparison with an authentic sample.

Fraction 3 (61%) was (±)-isosativene (**8**): ir (CCl_4) 3065, 1655, 875 cm^{-1} (terminal methylene); nmr (CCl_4) τ 5.24 (s, 1 H), 5.52 (s, 1 H), 7.39 (broad singlet, 1 H), 9.01 (s, 3 H), 9.10 (d, 6 H, J = 6 Hz); mass spectrum (80 eV) m/e (rel intensity) 204 (22 M^+), 189 (9), 161 (25), 133 (13), 94 (100).

$Cu(OAc)_2$–HOAc-Catalyzed Isomerizations of Cyclosativene and Isosativene.—Cyclosativene (5 mg) and $Cu(OAc)_2 \cdot H_2O$ (2 mg) were refluxed in 0.5 ml of glacial acetic acid for 2 days and then analyzed as described above. The product consisted of cyclosativene (32%), sativene (7%), and isosativene (61%). Similarly, isosativene (5 mg) was isomerized over a 2-day period to the same three-component equilibrium.

Isomerization of 7-Hydroxy-3-isopropyl-6,7-dimethyltricyclo-[4.4.0.$0^{2,8}$]decane (9) with Aqueous Sulfuric Acid.—Carbinol **9** (60 mg) was dissolved in 15 ml of hexane, and 15 ml of 50%

(18) See M. Smith in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, p 129.

(19) G. M. Whitesides and W. J. Ehmann, *J. Org. Chem.*, **35**, 3565 (1970).

(20) F. Kido, R. Sakuma, H. Uda, and A. Yoshikoshi, *Tetrahedron Lett.*, 3169 (1969).

aqueous sulfuric acid was added. The reaction was stirred for 2 hr at room temperature and then poured into cold water. The organic layer was drawn off, dried ($MgSO_4$), filtered, and evaporated. Analysis of the colorless residue (55 mg) by vpc showed the presence of four products.

Fraction 1 (3.2%) was identified as cyclosativene by vpc comparison with an authentic sample.

Fraction 2 (4.3%) was not identified.

Fraction 3 (27.7%) was identified as (±)-sativene by comparison of the ir spectra and vpc behavior of an authentic sample.

Fraction 4 (64.8%) was identified as isosativene by comparison of its ir and nmr spectra with an authentic sample.

Attempted Isomerization of Cyclosativene in Aqueous Sulfuric Acid.—Cyclosativene (5 mg) was dissolved in 5 ml hexane, and 5 ml 50% aqueous sulfuric acid was added. After being stirred for 2 hr at room temperature vpc of the product showed only recovered starting material.

2-Isopropyl-4aβ-methyl-3,4,4a,7,8,8aβ-hexahydronaphthalen-5(6*H*)-one β-Epoxide (18).—Keto olefin **13** (4.12 g, 0.020 mol) was dissolved in 75 ml of $CHCl_3$ at 0° and *m*-chloroperbenzoic acid (4.90 g, 0.024 mol) in 75 ml of $CHCl_3$ was added dropwise. The reaction was allowed to come to room temperature and was stirred for 15 hr. The solution was then washed with 5% aqueous NaOH and with saturated NaCl and then was dried ($MgSO_4$), filtered, and evaporated to yield epoxide **18** (4.1 g, 93%) as a colorless oil: ir (film) 1710, 1240, 755 cm^{-1}; nmr (CCl_4) τ 7.50 (s, 1 H), 8.90 (s, 3 H), 8.98 and 9.02 (two doublets, 6 H, J = J' = 6 Hz).

7-Oxo-3-hydroxy-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]decane (19). Procedure A.—Methylsulfinyl carbanion catalyzed cyclization of **18**.

A solution of methylsulfinyl carbanion (30 mmol) in 60 ml of DMSO was prepared according to Corey's procedure[12] from 1.2 g of NaH (60% dispersion in mineral oil). A solution of keto epoxide **18** (4.1 g, 18.5 mmol) in 40 ml of DMSO was added, and the reaction was stirred for 4 days at 60°. The reaction was then diluted with water and extracted with 1:1 pentane–ether (five 50-ml portions). The organic extracts were combined, washed with water and with brine, dried ($MgSO_4$), filtered, and evaporated. The product (3.86 g, 94%) crystallized from isopropyl ether to give the analytical sample: mp 78–79.5°; ir (CCl_4) 3600, 1750 cm^{-1}; nmr (CCl_4) τ 7.68 (s, 1 H), 9.05 (s, 3 H), 9.11 (d, 6 H, J = 7 Hz); mass spectrum (80 eV) *m/e* (rel intensity) 222 (3 M^+), 204 (3), 179 (100), 161 (25).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.88; H, 10.19.

Procedure B.—Potassium *tert*-butoxide catalyzed cyclization of **18**.

The keto epoxide **18** (3.5 g, 15.75 mmol) was dissolved in 100 ml of dry *tert*-butyl alcohol under nitrogen, and 10 g (0.089 mol) of KO-*tert*-Bu was added. The reaction was refluxed for 7 days and the solvent was then removed by rotary evaporation. The residue was partitioned between ether–water, and the organic layer was drawn off, washed with brine, dried ($MgSO_4$), filtered, and evaporated. The yield of **19** was 3.35 g (95%).

Dehydration of 19.—Alcohol **19** (3.3 g, 0.0149 mol) was dissolved in 100 ml of hexane and 100 ml of 50% aqueous sulfuric acid was added. The reaction was stirred for 2 hr at room temperature after which time the organic layer was drawn off, washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield 3.0 g of a 69:31 mixture of two keto olefins. The olefin mixture could be readily separated by column chromatography on acid washed alumina. Elution with benzene gave 2.1 g of the oily Δ^3-3-isopropyl-6-methyltricyclo[4.4.0.0^{2,8}]decan-7-one (**21**): ir (film) 1750 cm^{-1}; nmr (CCl_4) τ 4.88 (t, 1 H, J = 3 Hz), 7.40 (broad singlet, 1 H), 8.98 (s, 3 H), 9.02 (d, 6 H, J = 7 Hz); mass spectrum (80 eV) *m/e* 204 (M^+).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.89; H, 9.86.

Further elution with 10% ether in benzene gave 0.9 g of 3-isopropylidene-6-methyltricyclo[4.4.0.0^{2,8}]decan-7-one (**20**) as a colorless oil: ir (film) 1750 cm^{-1}; nmr (CCl_4) τ 8.32 and 8.40 (two broad singlets, 6 H), 9.01 (s, 3 H); mass spectrum (80 eV) *m/e* 204 (M^+).

Catalytic Reduction of 21 to Norsativone (15).—A sample of keto olefin **21** (500 mg) cyclized by procedure B above was dissolved in 10 ml of glacial acetic acid and hydrogenated over 100 mg of PtO_2 at room temperature and atmospheric pressure. Reduction was complete after 10 hr, and the reaction was stopped and filtered free of catalyst. The filtrate was diluted with ether, washed with 5% aqueous NaOH, washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield a colorless oily product (480 mg, 96%), identical with authentic norsativone by ir, nmr, and vpc criteria.

According to the method previously described,[2] norsativone was transformed into (±)-sativene by treatment with methyllithium followed by dehydration ($SOCl_2$–pyridine). The sativene thus obtained was free of copacamphene by nmr.

$LiAlH_4$ Reduction of 21.—A slurry of $LiAlH_4$ (380 mg, 10 mmol) was prepared in 20 ml of dry ether, and a solution of keto olefin **21** (500 mg, 2.45 mmol) in 10 ml of dry ether was added dropwise. The reaction was stirred overnight at room temperature and then carefully quenched by dropwise addition of saturated aqueous NH_4Cl. $MgSO_4$ was added to coagulate the aluminum salts, and the reaction was filtered and evaporated to yield 500 mg of crude product. The product could be separated preparatively by vpc (5 ft × 0.25 in. 15% Carbowax 20M on 60–80 Chromosorb W, 180°) into two oily epimeric alcohols.

Fraction 1 (58%) was assigned structure **23** by spectral criteria: ir (CCl_4) 3560 cm^{-1} (sharp); nmr (CCl_4) τ 4.59 (t, 1 H, J = 3 Hz), 6.85 (broad singlet, 1 H), 8.91 (s, 3 H), 8.98 (d, 6 H, J = 7 Hz); mass spectrum (80 eV) *m/e* 206 (M^+).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.40; H, 10.62.

Fraction 2 (42%) was assigned structure **22**: ir (CCl_4) 3640 (sharp), 3475 cm^{-1} (broad, H-bonded); nmr (CCl_4) τ 4.74 (t, 1 H, J = 2 Hz), 6.22 (d, 1 H, J = 5 Hz), 8.99 (d, 6 H, J = 7 Hz), 9.09 (s, 3 H).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.58; H, 10.49.

Li–NH_3 Reduction of 21.—A solution of Li (175 mg, 25 mmol) in 50 ml of liquid ammonia–30 ml of ether was prepared, and keto olefin **21** (500 mg, 2.45 mmol) in 20 ml of ether–0.5 ml of ethanol was added dropwise. After being stirred for 10 min, the reaction was quenched by addition of solid NH_4Cl. The ammonia was evaporated, and the ether filtered free of salts. The ether layer was washed with water and with brine, dried ($MgSO_4$), filtered, and evaporated to yield 480 mg of a mixture of products which by vpc was shown to consist of 59% **22** and 41% **23**.

(±)-Copacamphene.—Hydroxy olefin **22** (260 mg, 1.26 mmol) was dissolved in 5 ml of cyclohexane and hydrogenated over 100 mg of 10% Pd/C catalyst at room temperature and atmospheric pressure. The reaction was complete after 24 hr. The solution was filtered free of catalyst and evaporated to yield 255 mg of a colorless oil which was homogeneous by vpc but which appeared by nmr to be a mixture of products. This product mixture was therefore oxidized to a mixture of saturated ketones. A solution of Collins reagent was prepared by stirring CrO_3 (2.4 g, 24 mmol) and dry pyridine (3.80 g, 48 mmol) in 50 ml of dry CH_2Cl_2 for 1 hr at room temperature.[21] The mixture of alcohols in 10 ml of CH_2Cl_2 was added, and the reaction stirred for 1 hr under nitrogen. The solution was then poured into aqueous $NaHCO_3$ solution and extracted with ether. The organic extracts were combined, washed with cold 6 *N* HCl, washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield a colorless oil (240 mg), ir (film) 1748 cm^{-1}. This oil was homogeneous by vpc.

This product mixture was dissolved in 10 ml of dry ether and a solution of methyllithium (5 ml of 1.7 *M* solution) was added. The reaction was stirred overnight at room temperature and then quenched by dropwise addition of saturated aqueous NH_4Cl. The organic layer was drawn off, washed with water and with brine, dried ($MgSO_4$), filtered, and evaporated to yield a colorless oil (225 mg). This oil was dissolved in 10 ml of dry pyridine at 0°, and $SOCl_2$ (0.5 ml) was added. The reaction was stirred for 15 min and then poured into water and extracted with ether. The organic extracts were combined, washed with cold 6 *N* HCl and with brine, dried ($MgSO_4$), filtered, and evaporated. The mobile residue was microdistilled to yield 200 mg of colorless oil which homogeneous by vpc. Nmr showed this oil to be 85% (±)-copacamphene and 15% (±)-sativene.

Separation was effected by careful column chromatography on 140 g of 15% $AgNO_3$ impregnated silica gel. Purified ligroin was used as eluent and 5-ml fractions were collected every 10 min by means of an automated fraction collector. Fractions 80–90 (60 mg) were a mixture of sativene and copacamphene. Fractions 90–115 (140 mg) were pure (±)-copacamphene, identical by ir,

(21) According to the procedure of R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970). We thank Professor C. H. Heathcock for informing us of this method prior to publication.

nmr, mass spectrum, and vpc with an authentic sample: ir (CCl_4) 3090, 1655, 872 cm^{-1}; nmr (CCl_4) τ 5.21 and 5.50 (two singlets, 2 H), 7.55 (broad singlet, 1 H), 9.00 (s, 3 H), 9.10 (d, 6 H, J = 6 Hz); mass spectrum (80 eV) m/e (rel intensity) 204 (19 M^+), 189 (21), 161 (78), 108 (100).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.13; H, 11.95.

In a similar manner, olefin **23** was hydrogenated, oxidized, treated with methyllithium, and dehydrated to give a product which, by nmr, was a 45:55 mixture of copacamphene and sativene.

Acid-Catalyzed Rearrangement of (+)-Copacamphene.—In a manner similar to that described above for sativene, (+)-copacamphene[22] (100 mg) was isomerized by treatment with $Cu(OAc)_2 \cdot H_2O$ (25 mg) in 3 ml of refluxing glacial acetic acid, and the course of the reaction was followed by vpc. After 4 days, equilibrium was reached and the product consisted of a mixture of three isomeric compounds.

Fraction 1 (32%) was found to be (+)-cyclosativene (**7**), α_D +61° [c 0.46 (lit.[20] +67.8°)], by comparison of ir, nmr, and mass spectrum with an authentic sample.

Fraction 2 (7%) was found to be sativene by micro ir.

Fraction 3 (61%) was identified as isosativene by comparison of its ir, nmr, and mass spectrum with an authentic sample.

(22) We thank Dr. Westfelt for a generous sample of (+)-copaborneol, the precursor of (+)-copacamphene.

Registry No.—**7**, 30541-92-5; **8**, 22415-05-0; **12**, 29642-51-1; **18**, 29642-52-2; **19**, 30541-95-8; **20**, 29642-54-4; **21**, 29642-55-5; **22**, 30541-98-1; **23**, 30597-80-9.

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[*m*][*n*]Ferrocenophanes.[1] Derivatives Containing Tri-, Tetra-, and Pentamethylene Bridging Groups

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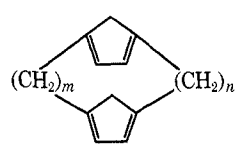
Doubly bridged ferrocenes ([*m*][*n*]ferrocenophanes) containing tri-, tetra-, and pentamethylene bridging groups have been synthesized and characterized. Ring closure reactions of [*m*]ferrocenophanylpropionic acids provide a convenient route to these compounds in contrast to schemes designed to form an interannular bridge by linking acetyl groups on different rings in diacetylferrocenophanes.

The possibility of using metallocenophanes as starting compounds for the synthesis of tricyclic tetraenes such as **1**, or positional isomers, led us to prepare a series of doubly bridged ferrocene derivatives.



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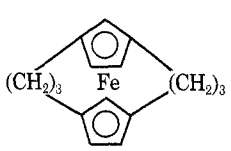

2

The only examples of such ferrocenophenes reported[3] are those which have three atoms in each bridge. In a previous note[4] we contrasted the difficulty encountered in attempting to cleave [3][3]-1,3-ferrocenophane (**2**) with the ease of reducing 1,1′-dialkylferrocenes, which react vigorously with lithium in propylamine to form substituted cyclopentadienes.

Although no conclusive evidence exists concerning the mechanism of these reductive cleavage reactions, Trifan and Nicholas[5] suggested that two steps were involved in the reduction of ferrocene, the first being a one-electron transfer to form a cyclopentadienide ion and a cyclopentadieneiron radical. The second step was postulated to be another one-electron transfer to the radical forming a second cyclopentadienide ion and metallic iron. Clearly **2** is an unlikely candidate to undergo such a process because of the restrictions placed on the molecule by the two trimethylene bridges. An examination of molecular models suggested to us that ferrocenophanes **5a–f** which have more than three atoms in one or both bridges would be more likely to undergo reductive cleavage, and we have prepared a number of these compounds which we now report (see Scheme I).

Results and Discussion

Rinehart and coworkers showed[6] that β-ferrocenylpropionic acid reacts in the presence of trifluoroacetic anhydride (TFAA) to form [3]ferrocenophan-1-one (**14**) to the virtual exclusion of other possible products such as a fused ring ketone or intermolecular condensation product. We have found that identical conditions afford good yields of **4a–d** from β-ferrocenophenylpropionic acids **3g–j**. These acids were prepared from acetylferrocenophanes **3c–f**[7] *via* sodium hydride catalyzed condensation with ethyl carbonate, hydrogenolysis, and saponification.[6] Only in the ring closure reaction of **3i** was more than one product isolated, a small amount of **4g** being formed along with the major product, **4a**. Based on the fact that one product is formed in predominant amounts in all ring closure reactions, we initially assigned structures **4a–d** to the products. The possibility exists, however, in the case of the [3][5]- and [4][5]ferrocenophanes, of construct-

(1) Ferrocenophane nomenclature conforms to that suggested by B. H. Smith ("Bridged Aromtic Compounds," Academic Press, New York, N. Y., 1964, pp 8–23) and used by T. H. Barr, W. E. Watts, and coworkers, in their recent papers which are cited. For a review, see W. E. Watts, *Organometal. Chem. Rev.*, **2**, 231 (1967).

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(3) K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Amer. Chem. Soc.*, **85**, 970 (1963); K. Schlögl, M. Peterlik, and H. Seiler, *Monatsh. Chem.*, **93**, 1309 (1962).

(4) A. D. Brown, Jr., and H. Reich, *J. Org. Chem.*, **35**, 1191 (1970).

(5) D. S. Trifan and L. Nicholas, *J. Amer. Chem. Soc.*, **79**, 2746 (1957).

(6) K. L. Rinehart, Jr., R. J. Curby, Jr., D. H. Gustafson, K. G. Harrison, R. E. Bozak, and D. E. Bublitz, *ibid.*, **84**, 3263 (1962).

(7) T. H. Barr, E. S. Bolton, H. L. Lentzner, and W. E. Watts, *Tetrahedron*, **25**, 5245 (1969).