Cationic cyclization of bicyclic diterpenes[1]

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Manool and agathadiol cyclize in formic acid to the 13-epimeric pimara-8,15-dienes and 14α-hydroxyhibane derivatives. The mechanistic and biosynthetic implications of these results are discussed in relation to other work involving cations in tetracyclic diterpenes. The nuclear magnetic resonance spectra of relevant tricyclic and tetracyclic diterpenes are documented.

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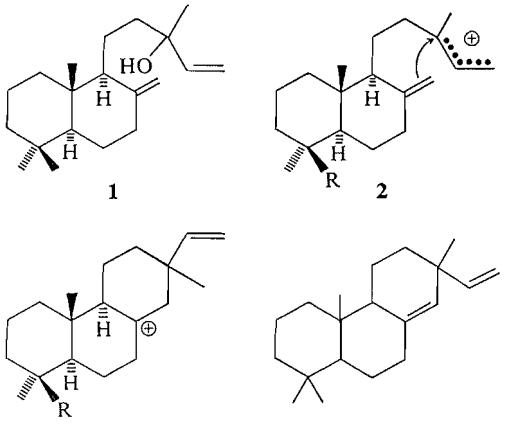
On general chemical considerations a very attractive biosynthetic route from geranylinalool to the tricarbocyclic and tetracarbocyclic diterpenes involves the bicyclic skeleton of type **1** as an intermediate (1). A logical possibility for further cyclization to pimaradienes (e.g. the resin acids) is ionization of the C—O bond of the allylic alcohol system, perhaps with pyrophosphate as the leaving group, to give ions of the type **2**. Electron flow as indicated would then



lead to cation **3**. Subsequent elimination of a proton could give the pimaradiene skeleton **4**. Alternatively, cation **3** could give rise to the tetracarbocyclic cation **5** (related to *enantio*-beyerane (hibane) (2) or isohibane (3)) by capture of the electrons of the vinyl group (4).[3]

Further rearrangement of this cation through the nonclassical ions **6** and **6***a* (4) could give the tetracarbocyclic kaurane, phyllocladane, and atisane skeletons. Elimination of a proton from **6** would give the pentacarbocyclic trachylobane (5) skeleton.

Until the present study no clear demonstration of these cyclizations has been reported.[4] However extensive studies of what has become known as the π-route to fused and bridged carbocyclic systems have recently been made (7).

Agathadiol (**7**) and manool (**1**) seemed excellent substrates for an *in vitro* study of the above cyclizations. Furthermore, the axial hydroxymethyl group at C-4 of agathadiol could prove valuable for subsequent building of the hetero ring of the diterpenoid alkaloids if tetracarbocyclic products were obtained. The cation **2** could be formed by solvolysis of an ester such as *p*-nitrobenzoate. However, the excellent model studies of Johnson and co-workers (8, see also ref. 7*b*) in cyclizations of allylic alcohols (e.g. **8** → **9**) suggested the use of formic acid on the allylic alcohols themselves.

In fact, a solution of agathadiol in 98–100% formic acid after 10 min at room temperature was converted almost completely to a mixture of products. This mixture was treated with lithium aluminium hydride to convert formates to alcohols, acetylated under mild conditions, and separated into three fractions (*a*, *b*, and *c*) by chromatography over alumina.

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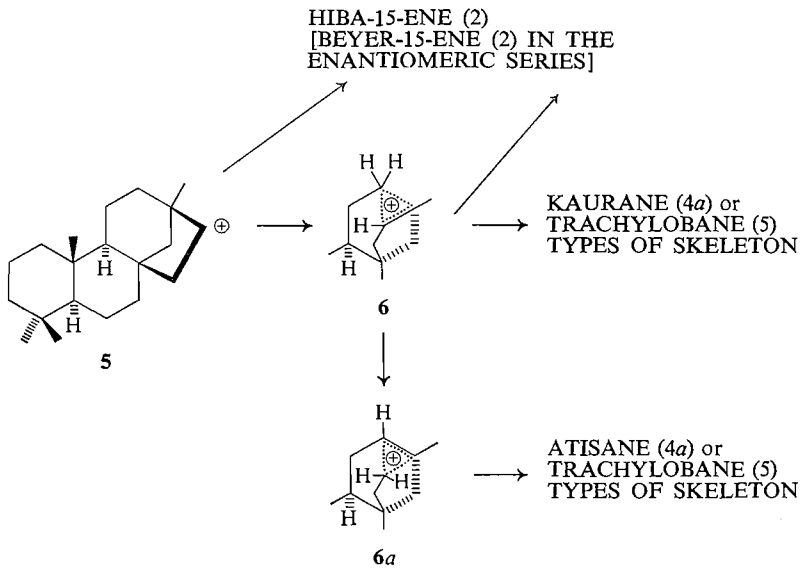
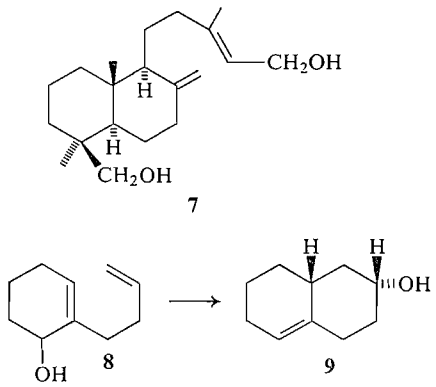
[2]NRCC Post Doctorate Fellow 1964–1966.

[3]Wenkert (4*a*) suggested that pimara-8(14),15-dienes were discrete intermediates but no cyclizations of these have been achieved in the laboratory. A direct cyclization of cation **3** is a more attractive possibility.

[4]Bory and Asselineau (6) showed that manool was converted in H_2SO_4 – HOAc to a hydrocarbon mixture from which a very small yield of a tricyclic diene was characterized. Mme. Bory has informed us (letter dated November 24, 1965) that this hydrocarbon has been identified as sandaracopimara-8,15-diene (**10***c*).



5 6 6a

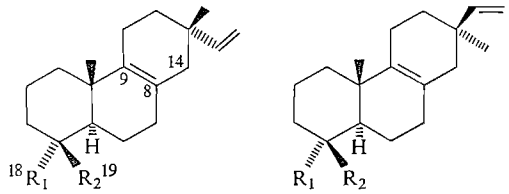


7 8 9

Similarly, a solution of manool[5] in 98—100% formic acid had completely reacted after 20 min. The reaction mixture was treated with lithium aluminium hydride and then directly separated into 3 fractions (*a*, *b*, and *c*) by chromatography.

Tricyclic Products

Fraction *a* of the products from agathadiol was separated into two components by chromatography over silver nitrate impregnated silica gel using the "dry column" technique (9). Their infrared and nuclear magnetic resonance (n.m.r.) spectra were consistent with structures **10***a* and **11***a*. Their mass spectra (parent ion *m/e* 330)

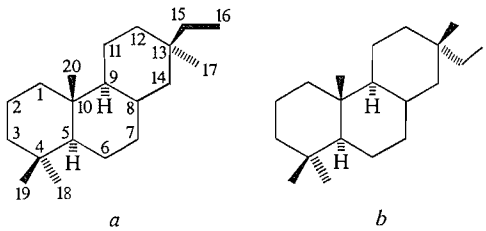


10 **11**

10 *a* $R_1 = CH_3$; $R_2 = CH_2OAc$
b $R_1 = COOCH_3$; $R_2 = CH_3$
c $R_1 = R_2 = CH_3$

11 *a* $R_1 = CH_3$; $R_2 = CH_2OAc$
b $R_1 = COOCH_3$; $R_2 = CH_3$
c $R_1 = R_2 = CH_3$

were identical to each other and similar in their fragmentation pattern to that recorded[6] for methyl isopimara-8,15-diene-18-oate (**10***b*)[7] (methyl sandaracopimarate). The configurations at



a *b*

[5]A sample of manool was obtained from Koch-Light Laboratories. After careful chromatography the product had m.p. 48–51° and the infrared and nuclear magnetic resonance spectra indicated that it was essentially pure. (Most important, this showed the absence of any of the reaction products that are to be described.)

It is of interest to note that the crude manool, which Mr. D. J. Abbot of Koch-Light Laboratories has kindly informed us came from solvent extraction of the heartwood of Dacrydium biforme, contained a small amount (ca. 2–3%) of a hydrocarbon which appeared to be 13α-pimara-7,15-diene (isopimaradiene).

[6]The mass spectra of the 8,15-dienes are more complicated than those of the 8(14),15-dienes (10).

[7]We are using the names pimarane and isopimarane (formerly sandaracopimarane) for the parent hydrocarbons *a* and *b* respectively.

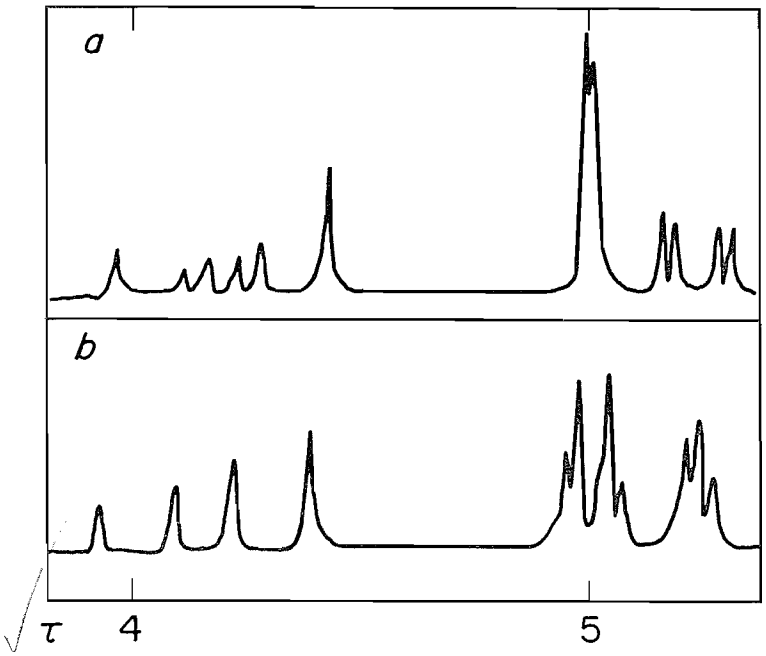


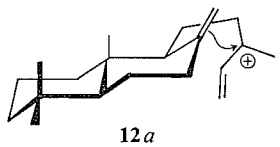
FIG. 1. Vinyl proton absorption patterns: (*a*) isopimara-8,15-diene and its 18- or 19- derivatives, and pimara-8(14),15-diene and its 18- derivatives; (*b*) pimara-8,15-diene and its 18- or 19- derivatives, and isopimara-8(14),15-diene and its 18- derivatives.

C-13 were tentatively assigned by comparison of the vinyl proton signals in their n.m.r. spectra with those of isopimara-8,15-diene and pimara-8,15-diene derivatives (**10***b* and **10***c*, and **11***b*, **11***c* respectively), (see Fig. 1). It is intriguing that moving the double bond from the 8(14) to 8(9) positions or inverting the configuration at C-13 interchanges the vinyl hydrogen patterns.

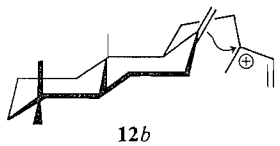
Confirmation of the structures followed from conversion to known hydrocarbons (11) by reductive cleavage of the ester, oxidation to the aldehydes, conversion to the semicarbazones, and finally Wolff–Kishner reduction. Compound **10***a* gave isopimaradiene (**10***c*) while **11***a* gave pimara-8,15-diene (**11***c*), identified by comparison with authentic specimens.

Fraction *a* of the manool products had an n.m.r. spectrum consistent with an approximately equal mixture of pimara-8,15-diene and its 13-epimer. However, the mixture could not be separated by either thin-layer chromatography (t.l.c.) or column chromatography as used above. Gas–liquid chromatography (g.l.c.) showed the presence of nearly equal amounts of two components with the expected relative retention times (11).

Since approach to the α face of the exocyclic double bond is sterically much more favorable than to the β face, the transition states for the cyclization of cations of type **2** probably resemble **12***a* and **12***b* respectively. The formation of equal amounts of the 13-epimeric dienes must then reflect similar steric requirements of the methyl and vinyl groups in the transition states.



12*a*



12*b*

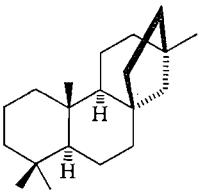
The known resin acids of the pimaric family all have their nuclear double bonds in the 7(8) or 8(14) position in contrast to the 8(9) double bond produced in the above experiments.[8] Hence if the *in vivo* cyclizations follow a comparable course to the above cyclization, the enzyme

[8]It was demonstrated that the 7(8) and 8(14) double bonds did not migrate to the 8(9)-position in formic acid under the reaction conditions.

surface must present a unique basic site aiding removal of a 7- or 14-proton.

Tetracyclic Products

Fraction *b* from the agathadiol cyclization products was converted to the alcohol using lithium aluminium hydride. Chromatography on alumina then enabled isolation of a crystalline product (ca. 5% yield) analyzing for $C_{20}H_{34}O_2$ (mol. wt. by mass spectrum 306). This gave no color with tetranitromethane and had only weak end absorption in the ultraviolet (ε at 210 mμ = 80). Its n.m.r. spectrum showed no vinylic proton signals but showed resonance for 3 quaternary methyl groups, a $—CH_2OH$ group on a quaternary carbon, and a *HC*—OH group as a sharp singlet. Hence the compound appeared to be tetracyclic and to have a hibane (**13**) or isohibane (**14**) skeleton.



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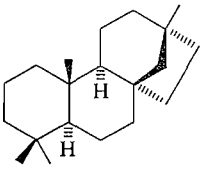

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The diol was oxidized to the keto-aldehyde which showed the expected infrared and n.m.r. spectra (see Table II). Reduction of the keto-aldehyde under vigorous Wolff–Kishner conditions gave hibane, identified by comparison with an authentic sample (2b).[9] Thus the cyclization product must have structure **15***a* (14-hydroxyl configuration undefined).

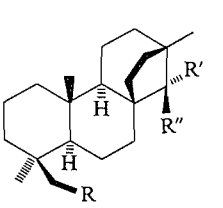
Fraction *b* from the cyclization of manool was a combination of eluates whose n.m.r., m.p., and t.l.c. indicated the presence of a single monohydroxy compound **15***b*. Only 40% acetylation of this alcohol was achieved when it was treated with acetic anhydride in pyridine at room temperature for 17 h; but treatment with acetic anhydride in acetic acid containing a trace of *p*-toluenesulfonic acid resulted in complete acetylation. Its mesylate was prepared by treatment with methanesulfonyl chloride in pyridine.

The n.m.r. spectra of these three compounds (alcohol, acetate, and mesylate) each showed signals for four quaternary methyl groups and a single unsplit ($w_{1/2}$ 3 c.p.s.) H—C—O— proton, but gave no indication of unsaturation.

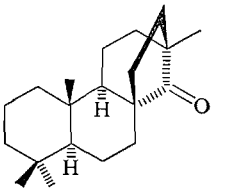
Oxidation of the alcohol **15***b* gave the ketone **16** which was then reduced under Wolff–Kishner conditions to give a hydrocarbon identical with a sample of hibane (**13**).[9] Since the oxygenated carbon atom appeared to be attached to fully substituted carbon atoms (unsplit C*H*OH signal) the alcohol arising in the cyclization reaction must be a 14-hydroxyhibane. In addition, the circular dichroism curve[10] for the ketone **16** showed a negative Cotton effect, in agreement with the proposed formula.

It appeared that we had obtained only one hydroxy isomer since it was considered unlikely that the physical data, especially the n.m.r. spectra, would be the same for both epimers of the alcohol, its acetate, and its mesylate respectively.

An attempt was made to prepare the epimeric alcohol **15***c* by reduction of the ketone. However, reaction with lithium aluminium hydride, lithium tri-*t*-butoxy aluminohydride, or lithium in ethylamine each converted it to an apparently single component identical (t.l.c., n.m.r., m.p., mixture melting point, and *x*-ray powder patterns) with each other and with the cyclization product itself. Furthermore, the acetate of the lithium tri-*t*-butoxy aluminohydride reduction product was identical with the acetate of the original alcohol.



15 *a* R = R′ = OH R″ = H
b R = R″ = H R′ = OH
c R = R′ = H R″ = OH



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Attempts to displace the mesylate of **15***b* with sodium formate in dimethyl formamide or sodium azide in dimethyl formamide, at temperatures up to 125° for up to 2.5 days, were unsuccessful. There was no reaction when the mesylate of **15***b* was heated for 3 days in refluxing aqueous acetone containing sodium acetate. On the other hand, heating overnight in refluxing formic acid

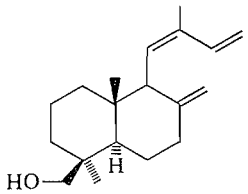
[9]A sample was kindly supplied by Dr. Y. Kitahara.

[10]Obtained through the kind cooperation of Professor R. C. Cookson.

containing sodium formate converted the mesylate in part to the formate of the starting alcohol.

The fact that all the chemical reductions of the 14-ketone yield the same alcohol indicates that this arises from "product development control" (12). Consequently, this alcohol is the least hindered of the two 14-epimers. Similarly the S_N1 solvolyses of the mesylate should have given rise to the least hindered formate (most favored approach of formate ion). Molecular models (Dreiding, Fieser) suggest that the 14α-epimer is the least hindered of the two, hence we assign this configuration to the 14-hydroxyhibanes. This assignment is also consistent with mechanistic considerations (see below). We conclude that agathadiol gave 14α,19-dihydroxyhibane (**15***a*) and manool gave 14α-hydroxyhibane (**15***b*).

Careful examination of fractions *c* of the cyclization products of manool or agathadiol, and the polar fractions of the hydrolyzate of fraction *b* from agathadiol failed to reveal any recognizable products. The materials were complex mixtures which appeared to consist largely of products of hydration of the double bonds and of rearrangement of the C-4 substituents in agathadiol. No evidence was obtained for the formation of the triene alcohol communol (**17**) (13) or its isomer **18** (14).



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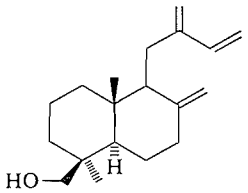

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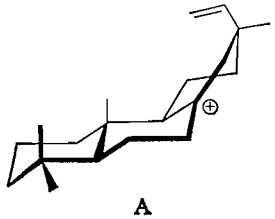
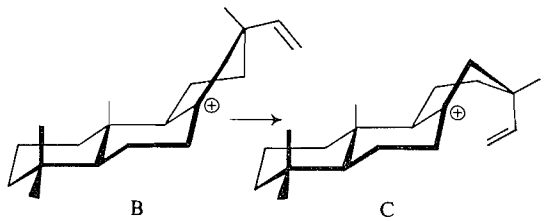
Discussion

Examination of molecular models leads us to the conclusion that the observed hibane derivatives are the most likely tetracyclic products to form by cationic cyclization. The preferred conformation for cyclization of the pimaric cation is illustrated in A.



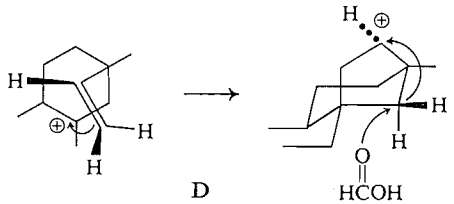
A



B C

In contrast, the isopimaric cation B, which would lead to the isohibane series (**14**), cannot cyclize until it has adopted the boat conformation C.

As the transition state, for cyclization of A, develops toward tetracyclic cation, the lowest electron density on C-16 is on its *exo* side (see D).



D

This suggests that the developing secondary cation, in this medium of low nucleophilicity (formic acid) is stabilized by bridging[11] from C-14. Formic acid would then complete the process by attack on the opposite face of C-14, leading to the prediction that the secondary hydroxyls in **15***a* and **15***b* have the configuration illustrated. As indicated earlier, this is in accord with other evidence.

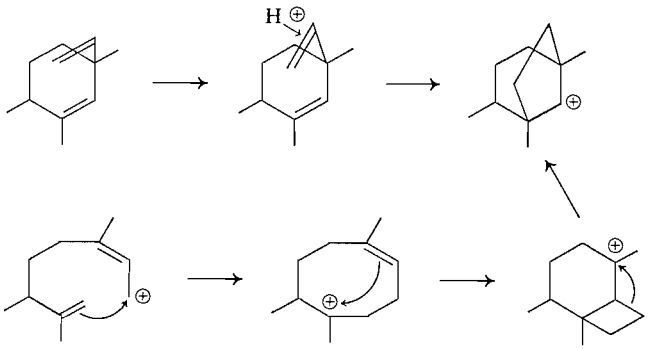
While transannular hydride migrations in consort with solvolyses etc. in bridged and medium ring systems are well established (15) a precise analogue of this migration in a bicyclo[3·2·1] system has apparently not been observed previously. However, the above route to the tetracyclic product gives an elegant explanation of the predominant hibane geometry (rather than iso-hibane) that was observed.

Two alternate routes to 14-oxygenated hibane follow. Pimara-8(14),15-dienes are not appreciably transformed into the Δ^8 isomers under our reaction conditions. Therefore, since nearly equal amounts of 13-epimers are formed and no isopimara-8(14),15-diene was found, the amount of the 13β isomers available for cyclization must

[11]For comparable 2 → 6 hydride shifts in norbornyl compounds, there is evidence that a protonated cyclopropane is an intermediate (15*a*), i.e. carbon–carbon participation provides the initial charge delocalization.

(*a*)

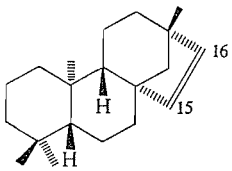
(*b*)



have been small. Hence if route (*a*) were operative it would have to be very efficient. Experiment showed however that the 8(14),15-dienes did not give detectable amounts of 14-oxygenated hibanes under our cyclization conditions, hence (*a*) can be eliminated from consideration.

Route (*b*) is implausible because: (1) The allylic cation will have most of its charge density on the tertiary carbon. (2) Cationic cyclization to an eight membered ring is improbable unless under enzyme control. (3) Cyclization of the cyclooctenyl cation to the 6,4 system should, because of steric interactions with the 10-methyl group, give predominantly the isohibane skeleton contrary to what is observed.

It is of interest to compare the proposed fate of the cation on C-16 with that of cations formed on that carbon by alternative processes. McCrindle and colleagues (16) described the hydrogen chloride catalyzed conversion of beyer-15-ene (**19**) in aprotic solvents to a mixture of (—)kaur-15-ene **20**, (—)kaur-16-ene (isokaurene), and atis-16-ene. Sobti and Sukh Dev (17) found that solvolysis of 16β-tosyloxybeyerane (**21**) gave (—)kaur-15-ene, (—)isokaurene and kauran-16α-ol. Ghisalberti and Jefferies (18) studied the solvolysis of the related tosylate **22** obtaining the substituted kaurene and isokaurene. Kapadi and Sukh Dev (19*a*) treated 15β, 16β-epoxybeyerane (**23**) with boron trifluoride etherate. The product was a mixture of 14-hydroxykaur-15-ene (**24**) and the corresponding 16-ene. Similar observations have been made by Hanson (19*b*) and Kitahara and colleagues (19*c*).



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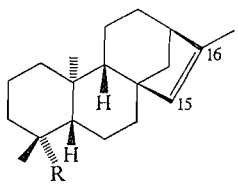

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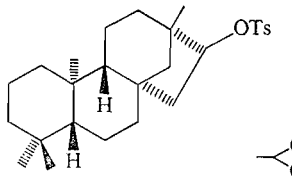

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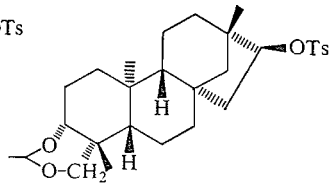

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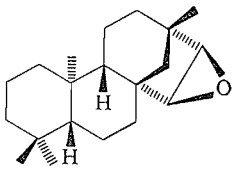

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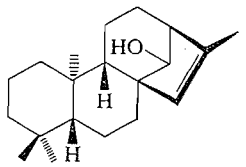

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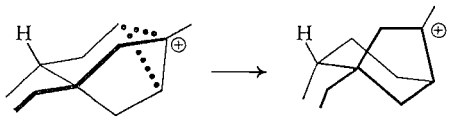
In each of these cases the major electron deficiency developed initially on the *endo* size of C-16, in contrast to the situation in our cyclization studies. This was ideal for participation of the 12,13 C—C bond leading to ions of type **25** from which the kaurane cation **26** arose.



25 26

At present then, the 14 → 16 hydride shift mechanism seems the most plausible route to the 14-oxygenated hibanes but further work is needed to test the hypothesis.

A most interesting related study is that of Ourisson and co-workers (20) on the acid-

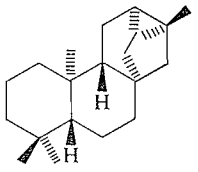
TABLE I

Methyl group absorptions in τ units

	—CH_3	Hydrocarbon	19-OH	19-OAC	19-oxo	19R*
Isopimara-8,15-diene	4	9.12, 9.15	9.02	9.04	8.98	8.95
	10	9.04	9.06	9.04	9.16	9.18
	13	9.04	9.04	9.04	9.03	9.04
Pimara-8,15-diene	4	9.12, 9.15	9.01	9.03	8.97	8.97
	10	9.04	9.07	9.03	9.16	9.18
	13	9.07	9.07	9.07	9.08	9.08
	—CH_3	Hydrocarbon	18-OH	R′†	18-oxo	18-R*
Isopimara-8(14),15-diene	4	9.13, 9.14	9.20	8.81		8.90
	10	9.20	9.16	9.17		9.15
	13	8.96	8.96	8.97		8.97
Pimara-8(14),15-diene	4	9.13, 9.15	9.20	8.81	8.92	8.90
	10	9.27	9.22	9.21	9.21	9.20
	13	9.02	9.01	9.01	9.01	9.01

*R = semicarbazone.
†R′ = equatorial 4-methoxycarbonyl.

catalyzed reactions of trachylobane (**27**). However these seem readily accounted for as reactions of edge-protonated cyclopropanes.



27

Table I summarizes the methyl group absorptions in the n.m.r. spectra of the pimaradienes encountered in this work. Some of the figures for the 8(14),15-dienes (e.g. **4**) have been reported by Wenkert *et al.* (21), but there appears to be an error in the assignments of the signals of pimara-8(14),15-diene. On the basis of Wenkert's assignments, inversion at C-13 to isopimara-8(14),15-diene results in a large shift of one of the C-4 methyl groups. No other such large shift is apparent in derivatives of these hydrocarbons or in the series of 8,15-dienes described in this paper.

The structures of the acetoxy pimaradienes **10***a* and **10***b* described earlier were also supported by other features of their n.m.r. spectra. The center of the pair of doublets arising from the 19-protons in the acetates **10***a* and **10***b* falls at τ 5.85 and 5.86 (*J*, 11 c.p.s.) respectively; in the derived alcohols at τ 6.37 and 6.36 (*J*, 11 c.p.s.); and in the derived aldehydes at τ 0.21 and 0.24 (*J*, 1.2 c.p.s.). These figures are in close agreement with the corresponding absorptions for analogous axial C-4 oxygenated compounds and quite different from the corresponding equatorial C-4 oxygenated derivatives (including those derived from isopimara-8(14),15-diene and pimara-8(14),15-diene-18-oic acids (2*a*, 21, 22).

In the 8(14),15-dienes epimerization at C-13 causes a shift of 0.04–0.06 p.p.m. in the 13-methyl group signal while a similar shift of 0.03–0.05 p.p.m. is observed in the 8,15-dienes. On the other hand, epimerization at C-13 in the 8(14),15-dienes causes a shift of 0.04–0.07 p.p.m. of the 10-methyl group signal whereas in the 8,15-dienes essentially no change in this absorption occurs. The shift to lower field of the 10-methyl signal when the 8(14)-olefin is isomerized to 8(9) is similar to that observed in the steroids (23) and bicyclic diterpenes (24).

Table II summarizes the data for methyl group absorptions relevant to the 14-substituted hibane product.

Insertion of the 14α-hydroxyl group into hibane (*enantio*-beyerane) or its 19-hydroxy derivative has very little effect on the protons attached to C-17 and C-20. A similar behavior is shown by 16β-hydroxybeyerane. The deshielding effect by the 14-ketone group on the protons on C-17 and C-20 would be expected for the structure assigned. In contrast, a 14-ketone in the kaurane series results in a shielding effect, of approximately 0.14 p.p.m., on the 20-protons (19*a*) and a similar effect would be expected for a 14-oxoisohibane structure.

TABLE II

Methyl group absorptions in τ units

	C-18,C-19	C-20	C-17
16α-(—)-Kaurane	9.15, 9.19	8.99	9.09
Isohibane	9.13, 9.18	9.00	8.99
Beyerane (*enantio* hibane)	9.15, 9.19	9.06	9.06
14α-Hydroxyhibane	9.15, 9.19	9.08	9.08
19-Hydroxybeyerane (calcd)*	9.05	9.08	9.06
14α-19-Dihydroxyhibane	9.05	9.08	9.08
16β-Hydroxybeyerane†	9.14, 9.18	9.06	9.09
14-Oxohibane	9.14, 9.18	8.96	9.01
19-Oxobeyerane (calcd)*	9.01	9.21	9.06
14,19-Dioxohibane	9.00	9.11	8.99
14α-Acetoxyhibane	9.15, 9.19	9.15	9.06
14α-Mesyloxyhibane	9.14, 9.20	9.06	8.98

*Calculated from the known effect of insertion of these substituents into the beyerane skeleton (2*a*, 22). Additivity of these effects is observed when (*i*) there are no conformation differences between the singly- and multisubstituted molecules, and (*ii*) no dipolar or hydrogen bonding interactions occur between these substituents (2*a*, 22, see also ref. 25).

†Unpublished observations in this laboratory.

The 14β-proton absorbs at τ 7.07, 5.55, and 5.89 in the alcohol **15***b*, its acetate, and its mesylate respectively with a $w_{1/2}$ of 3 c.p.s. in each case.

Experimental

Infrared spectra were of Nujol mulls unless otherwise specified and nuclear magnetic resonance (n.m.r.) spectra were determined for deuteriochloroform solutions with tetramethylsilane as internal reference. Optical rotations are of solutions in absolute alcohol unless otherwise noted. Woelm neutral alumina was used for chromatography.

Agathadiol as Substrate

Cyclization of Agathadiol in Formic Acid

Finely powdered agathadiol (2.57 g), prepared by reduction of methyl agathate by lithium aluminium hydride, was dissolved in 98–100% formic acid (200 ml). After 10 min at room temperature (ca. 25°) the solution was poured into a slurry of ice and water containing potassium hydroxide (330 g), extracted with ether, washed with saturated sodium bicarbonate solution, dried, and the volume of the solution reduced to approximately 100 ml. After addition of lithium aluminium hydride, the solution was refluxed for 15 min. The excess reagent was destroyed with a saturated solution of sodium sulfate, the solution dried and then evaporated, leaving a pale-yellow gum (2.49 g).[12] The gum was then acetylated during 2 days in acetic anhydride – pyridine at room temperature. The resulting pale-yellow oily acetate was dissolved in hexane and chromatographed over 50 g of activity III alumina. Elution with hexane (400 ml) gave fraction *a* (1.84 g); hexane–benzene (4:1, 600 ml.) eluted fraction *b* (0.65 g); and finally ether eluted fraction *c* (0.43 g), as colorless oils.

[12]Preliminary experiments had shown that the crude cyclization product was at least partially formylated.

Tricyclic Products

The infrared spectrum of fraction *a* showed the absence of any hydroxylic material. The fraction (900 mg) was chromatographed using the "dry column" technique (9) over 300 g of silica gel impregnated with 75 g of silver nitrate. Hexane–ether (3:1) was used as eluent and 15 ml fractions were collected. The composition of the eluate was determined using vapor-phase chromatography (v.p.c.).[13] Fractions 1–16, 57 mg of oils containing at least 6 components; fractions 17–22, 240 mg of crystals mainly component 1; fractions 23–25, 96 mg of oily mixture of 1 and 2; fractions 26–44, 200 mg of crystals, mainly component 2; fractions 45–155, 105 mg of oils rich in component 2. The balance of fraction *a* combined with fractions 23–25 from the above chromatogram was separated in the same way. The total isolated yields were then 510 mg of component 1 and 440 mg of component 2. However, the total yields estimated using the v.p.c. of the mixed fractions was approximately 600 mg of each component.

19-Acetoxy-isopimara-8,15-diene—Crude component 1 from above chromatogram was recrystallized from aqueous methanol and then sublimed at 115° and 0.02 mm; m.p. 57.5–58.5°; $[\alpha]_D$ +90° (*c*, 0.9). ν_{max}: 1742 cm^{-1} (ester); 3075, 1638, and 906 cm^{-1} (vinyl group). The position of the last band is in agreement for the data of Ireland and Schiess (11*a*) for similar isopimaradienes. The n.m.r. data (see the appropriate section of the discussion) was in agreement with the structural proposals.

Anal. Calcd. for $C_{22}H_{34}O_2$(mol. wt., 330.49): C, 79.95; H, 10.4. Found (mol. wt., mass spectrum, 330): C, 79.8; H, 10.2.

19-Hydroxy-isopimara-8,15-diene—The acetate (445 mg) was treated with excess lithium aluminium hydride during 1 h at room temperature. Working up in the usual

[13]Vapor-phase chromatography was at 200° with a flow rate of 100 ml/min, over a 1 m 15% diethylene glycol succinate on chromosorb W column, in a Perkin–Elmer model 154C gas chromatograph.

way, followed by filtration through 12 g of activity III alumina in hexane–benzene (1:1) gave the alcohol as a colorless solid (335 mg). After recrystallization from aqueous-methanol and sublimation at 125° and 0.02 mm this had m.p. 107–108.5°; $[\alpha]_D$ +101° (*c*, 0.18). ν_{max}: 3240 cm^{-1} (hydroxyl) and 3070, 1637, 1001 and 909 cm^{-1} (vinyl group). The n.m.r. data showed the presence of an axial hydroxymethyl group, three quaternary methyl groups, and the vinyl group (see also the appropriate section of the discussion).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 82.4, 82.5; H, 11.0, 11.1.

19-Oxo-isopimara-8,15-diene and its semicarbazone—The alcohol (145 mg) was dissolved in acetone (10 ml), the solution cooled in ice, and then titrated with Jones' reagent (26). The mixture was poured into water and worked up with ether in the usual way to give the crystalline aldehyde (130 mg), $\nu_{max}(CCl_4)$: 1720 cm^{-1} (aldehyde) and 915 and 1002 cm^{-1} (vinyl group). The n.m.r. spectrum included a peak at τ 0.21 (axial aldehyde proton) as a partially resolved doublet, with *J*, ca. 1.2 c.p.s.

The semicarbazone was prepared in pyridine (10 ml). using a solution of semicarbazide acetate (from 300 mg of semicarbazide hydrochloride and 300 mg of sodium acetate which were dissolved in 0.5 ml of water and 9.5 ml of ethanol) during 2 days at room temperature (27). The mixture was worked up with ether in the usual manner to give 145 mg of the crystalline semicarbazone which was recrystallized first from hexane – ethyl acetate and then from aqueous methanol to give sheaves of colorless needles, m.p. 215°. The n.m.r. spectrum included a maximum at τ 2.97 (—CH=N).

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.4; H, 9.7; N, 12.2. Found: C, 73.6; H, 9.75; N, 12.1.

Isopimara-8,15-diene—The semicarbazone (120 mg) and 5 g of KOH in diethylene glycol (17 ml) were refluxed for 3 h at 200–205° under a nitrogen atmosphere. The mixture was poured into water and worked up with hexane to give 92 mg of a pale-yellow oil which was then chromatographed on 5 g of activity II alumina in 35 ml of hexane to yield 76 mg of a colorless solid. This material gave a single peak on gas chromatography which had the same retention time as an authentic sample (prepared as described by Ireland and co-workers (11)). After recrystallization from methanol and sublimation at 80° and 0.02 mm the material showed m.p. 51–52.5°, $[\alpha]_D$ +119° (*c*, 0.92) undepressed on admixture with an authentic sample.

Anal. Calcd. for $C_{20}H_{32}$ (mol. wt., 272.46): C, 88.2; H, 11.8. Found (mol. wt., 272, mass spectrum): C, 88.4; H, 11.7.

Identity was also established by the infrared (liquid film) (ν_{max} 3078, 1638, 907 cm^{-1}) and n.m.r. spectra and *x*-ray powder patterns.

19-Acetoxypimara-8,15-diene—Crude compound 2 from the above chromatogram was recrystallized from aqueous methanol; m.p. 66–68°, $[\alpha]_D$ +67° (*c*, 0.17). It had ν_{max}: 1745 cm^{-1} (ester); 3080, 1636, and 908 cm^{-1} (vinyl group). The n.m.r. data was in agreement with the structural proposals (see Fig. 1 and Table I).

Anal. Calcd. for $C_{22}H_{34}O_2$ (mol. wt., 330.49): C, 79.95; H, 10.4. Found (mol. wt., 330, mass spectrum): C, 79.7; H, 10.4.

The same sequence was used to prepare the hydrocarbon as for component 1.

19-Hydroxypimara-8,15-diene—After recrystallization from aqueous-methanol this had m.p. 95–97°; $[\alpha]_D$ +78° (*c*, 0.92); ν_{max}, 3369 cm^{-1} (hydroxyl) and vinyl absorption at 3075 and 906 cm^{-1}.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.4; H, 11.0.

Semicarbazone of 19-oxopimara-8,15-diene—The aldehyde was obtained as an oil, $\nu_{max}(CCl_4)$, 1720 cm^{-1} (aldehyde) and 910 and 998 cm^{-1} (vinyl group); while the n.m.r. spectrum included a peak at τ 0.24 (axial aldehyde proton). This signal was a poorly resolved doublet with *J*, ca. 1.2 c.p.s.

The semicarbazone was obtained as plates from aqueous-methanol and had m.p. 192°. The n.m.r. spectrum included a maximum at τ 2.85 (—CH=N—).

Anal. Calcd. for $C_{21}H_{33}N_3O$: C, 73.4; H, 9.7; N, 12.2. Found: C, 73.25; H, 9.5; N, 12.1.

Pimara-8,15-diene—The diene was obtained as a colorless oil which was distilled at 85° and 0.02 mm. Identity with an authentic sample (prepared as described in 11) was established by infrared (liquid film) (ν_{max} 3075, 910 cm^{-1}), n.m.r., and mass spectra and gas chromatography.

Anal. Calcd. for $C_{20}H_{32}$ (mol. wt., 272.46): C, 88.2; H, 11.8. Found (mol. wt., 272, mass spectrum): C, 88.1.; H, 11.7.

Tetracyclic Product

Hiban-14α,19-diol—Fraction *b* from the cyclization sequence showed no hydroxyl or vinyl absorption in its infrared spectrum.

Fraction *b* (600 mg) was dissolved in ether and treated with excess lithium aluminium hydride and after the usual work-up a glass (470 mg) was obtained which was dissolved in hexane–benzene (2:1) and chromatographed on activity IV alumina. Benzene–ether (19:1) eluted a crystalline material (147 mg)[14] which after recrystallization from hexane–acetone had m.p. 204° $[\alpha]_D$—10° (*c*, 0.18). There was only end absorption in the ultraviolet (ε = 80 at 210 mμ in 95% ethanol solution) and no color was obtained with tetranitromethane. The n.m.r. spectrum ($CDCl_3$ and pyridine solutions) showed the presence of three quaternary methyl groups, a —C—CH_2OH (quartet centered at τ 6.40) and a *H*—C—OH group (singlet at τ 7.09) but no olefinic protons.

Anal. Calcd. for $C_{20}H_{34}O_2$ (mol. wt., 306.47): C, 78.4; H, 11.2. Found (mol. wt., 306, mass spectrum): C, 78.2; H, 11.0.

Hibane—Hiban-14α,19-diol (90 mg) was dissolved in acetone (10 ml) and titrated with the Jones reagent (26), the mixture poured into water, and extracted with ether to give the crystalline 14,19-dioxohibane (80 mg), ν_{max} (CCl_4) (measured on a Perkin–Elmer model 21 spectrometer), 2740 and 1737 cm^{-1} (aldehyde) and 1725 cm^{-1} (ketone). The n.m.r. spectrum showed the presence of three quaternary methyl groups, and an axial aldehyde

[14]From subsequent work in the manool series it became known that acetylation of the 14α-hydroxyl is only approximately 70% complete under the conditions used in the work-up of the product from cyclization of agathadiol. Hence the "true" yield of this diol may be nearer 200 mg (i.e., 7–8%).

group (τ 0.22, poorly resolved doublet with J, ca. 1.2 c.p.s.).

The keto-aldehyde (70 mg) was refluxed with diethylene glycol (8 ml) and 95% hydrazine (1 ml) for 1½ h under a nitrogen atmosphere. The solution was cooled and pieces of sodium (1 g) added slowly followed by a further 5 ml of diethylene glycol and the mixture refluxed at 220° for 3.5 h, then poured into water and extracted with hexane. A pale-yellow oil (43 mg) was obtained which was chromatographed over activity II alumina in hexane yielding a colorless oil (31 mg) which crystallized on seeding with authentic hibane.[9]

After recrystallization from methanol this had m.p. 39–41.5°, raised to 39–42.5° on admixture with authentic material (m.p. 41–43°). Identity was also established by infrared (measured on a Perkin–Elmer model 21 spectrometer), n.m.r., and mass spectra, and by x-ray powder patterns.

Manool as Substrate

Cyclization of Manool in Formic Acid

Finely powdered manool[15] (6.40 g) was shaken with 98–100% formic acid (100 ml; ca. 0.2 M) for 20 min at room temperature (ca. 25°). All of the solid dissolved within 5 min while an oil began to separate. The mixture was poured onto ice and water containing sodium hydroxide (146 g) and extracted with ether. The residue (6.21 g) was a pale-yellow oil whose n.m.r. spectrum showed the presence of at least some formate group. The ultraviolet spectrum (cyclohexane) had a shoulder near 230 mμ, ε 320 (biformene had λ_{max} 228 mμ ε = 15 300 (28)). The residue was redissolved in ether and treated with excess lithium aluminium hydride at room temperature for 30 min. Extraction in the usual manner gave a pale-yellow oil (5.98 g) which was dissolved in hexane and chromatographed on 100 g of activity III alumina. Hexane eluted a colorless oil ((4.29 g) fraction *a*) while hexane–benzene (9:1) eluted several crystalline fractions whose melting points and thin-layer chromatograms indicated a single component (fraction *b*; 675 mg).

Tricyclic Product

Isopimara-8,15-diene and pimara-8,15-diene—The n.m.r. spectrum of fraction *a* was that expected of an approximately equal mixture of the two hydrocarbons. The mixture, however, could not be separated. Gas–liquid chromatography on a 6 ft column of 15% diethylene glycol succinate on chromosorb W at 125 °C and flow rate of 20 ml/min (using an F and M model 700 with flame ionization detector) showed the presence of isopimar-8,15-diene and pimara-8,15-diene in the ratio 55:45 (±5%). These were identified by their relative retention times (11) and peak enhancement with authentic materials.

Tetracyclic Products

Hiban-14α-ol—A sample of fraction *b* was recrystallized from aqueous methanol and sublimed at 125° and 0.1 mm; m.p. 114–115°, $[\alpha]_D$ −6° (*c*, 0.91). ν_{max}($CHCl_3$) 3620 cm^{-1} (OH). The n.m.r. spectrum included a singlet at τ 7.58 (H—C—OH).

[15]This had m.p. 48–51° and its infrared and n.m.r. spectra showed it to be free of any of the reaction products to be described below. We thank Professor G. Buchi for a reference sample of crystalline manool.

Anal. Calcd. for $C_{20}H_{34}O$: C, 82.7; H, 11.8. Found: C, 82.55; H, 11.6.

Hiban-14-one—Hiban-14α-ol (209 mg) was dissolved in acetone (20 ml) and titrated with Jones' reagent (26). The mixture was poured into water and extracted with ether to give a pale-yellow solid (202 mg) which was dissolved in hexane and chromatographed on 5 g of activity III alumina to give a colorless solid (140 mg). After recrystallization from aqueous methanol and sublimation at 115° and 0.1 mm it had m.p., 107–108°, ν_{max} 1733 cm^{-1}, $[\alpha]_D$ +11° (*c*, 0.15).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.25; H, 11.1.

Circular dichroism[10] λ_{max} 297 mμ (ΔE − 1.8).

Hibane—Sodium (400 mg) was dissolved in diethylene glycol (15 ml) under a nitrogen atmosphere. Ninety-five percent hydrazine (2.0 ml) and hiban-14-one (85 mg) were added, the mixture refluxed at 180° for 2 h, the temperature then raised to 217° by distillation, and reflux continued for 2 h. The mixture and the distillate were then poured into water and extracted with hexane to give a colorless oil (75 mg). The oil was chromatographed on activity III alumina in hexane (20 ml) to give a colorless oil (73 mg) which crystallized from methanol; m.p. 41.5–43.5°, undepressed on admixture with a recrystallized authentic sample, m.p. 41.5–43.5°. Identity was also established by infrared (liquid film) and n.m.r. spectra and x-ray powder patterns.

Hiban-14α-yl acetate—Hiban-14α-ol (93 mg) was treated with acetic anhydride (2.0 ml) and pyridine (4.5 ml) for 17 h at room temperature (ca. 25°). Working up in the usual way gave a partly solid residue whose n.m.r. spectrum showed only about 40% acetylation. The residue was treated with acetic anhydride (1.5 ml), acetic acid (3 ml) and *p*-toluenesulfonic acid (100 mg) at room temperature overnight. Extraction with ether yielded the acetate (95 mg). This was chromatographed on 5 g of activity III alumina with hexane (70 ml) to give 94 mg of material which after recrystallization from aqueous methanol and sublimation at 105° and 0.1 mm had m.p. 85–86°, ν_{max} 1742 cm^{-1}. The n.m.r. spectrum included a singlet at τ 5.48 (H—C—OAc).

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.5; H, 10.9. Found: C, 79.6; H, 11.1.

Hiban-14α-yl mesylate—Hiban-14α-ol (240 mg) was dissolved in pyridine (20 ml) cooled in ice, methanesulfonyl chloride (1.0 g) added, and the mixture left overnight at room temperature. The excess mesyl chloride was destroyed with ice, the mixture poured onto ice-hydrochloric acid, and then extracted with ether to give a solid residue (315 mg). After chromatography on activity I alumina it crystallized from hexane as needles with m.p. 135° ν_{max}($CHCl_3$): 1175 cm^{-1} (—SO_2—O—). The n.m.r. spectrum included a singlet at τ 5.88 (H—C—OMs).

Anal. Calcd. for $C_{21}H_{36}O_3S$: C, 68.8; H, 9.35; S, 8.7. Found: C, 68.7; H, 9.2; S, 8.7.

Reductions of Hiban-14-one

(1) Lithium tri-t-butyoxyaluminohydride—The ketone (99 mg) was treated with excess reductant in tetrahydrofuran for 2 h at room temperature. After the work-up there was obtained 100 mg of a solid whose n.m.r. spectrum was identical to the cyclization product. The residue was chromatographed on 7 g of activity III alumina with hexane (20 ml fractions)—the m.p. and t.l.c. of the frac-

tions showed that there was only one alcohol produced which after recrystallization from aqueous methanol had m.p. 114–115° undepressed on admixture with the cyclization product. The *x*-ray powder pattern was also identical with that of the cyclization product.

A sample of the reduction product (52 mg) was acetylated with acetic acid (2 ml), acetic anhydride (1 ml) and *p*-toluenesulfonic acid (10 mg). After working up with ether, chromatography on 5 g of activity II alumina in hexane, recrystallization from aqueous methanol, and sublimation at 105° and 0.1 mm, the acetate had m.p. 83.5–85° raised to 84.5–86° on admixture with authentic material. The *x*-ray powder pattern was also identical with that of the acetylated cyclization product.

(2) Lithium aluminium hydride—Hiban-14-one (93 mg) was reduced with excess reductant in refluxing ether during 40 min. The product was examined as in (1) above and was also found to be a single compound identical to the cyclization product. The acetate was not prepared.

(3) Lithium in ethylamine reduction—Hiban-14-one (97 mg) was reduced with lithium in ethylamine using ethanol as the proton source. The product was examined as in (1) and (2) above and was also found to be a single compound identical to the cyclization product. The acetate was not prepared.

Reactions of Hiban-14α-yl Mesylate

(1) Sodium formate in dimethyl formamide—Sixty-two mg of the mesylate in dimethyl formamide (10 ml) were heated with sodium formate (190 mg) at 125° for 2.5 days. The n.m.r. spectrum of the product indicated no apparent reaction.

(2) Sodium azide in dimethyl formamide—The mesylate (104 mg) in dimethyl formamide (12 ml) was heated with sodium azide (200 mg) at 125° for 16 h. The infrared spectrum of the product showed only a trace of absorption at 2100 cm^{-1} (—N_3).

(3) Sodium acetate in aqueous acetone—The mesylate (63 mg), sodium acetate (180 mg), acetone (10 ml), and water (0.5 ml) were refluxed for 3 days. The n.m.r. spectrum of the product showed no apparent reaction.

(4) Sodium formate in formic acid—A solution of the mesylate (98 mg) and sodium formate (27 mg) in formic acid (10 ml) were refluxed for 23 h. Extraction with ether gave a pale-yellow oil (73 mg) whose n.m.r. spectrum showed that it was entirely in the form of a formate (singlets at τ 5.5 and 1.73). This product was treated with excess lithium aluminium hydride in ether at room temperature during 10 min. The colorless solid (72 mg) obtained had an n.m.r. spectrum very similar to the original cyclization product. The product was chromatographed on 7 g of activity III alumina, eluting with hexane (20 ml fractions). The t.l.c. of the fractions showed that only one alcohol (35 mg) was produced. Only 58 mg of material was eluted from the column of which 15 mg had a high R_f on t.l.c. and was presumably an olefinic product while a further 8 mg gave several spots of lower R_f than the mono alcohol. After recrystallization of the product from aqueous methanol it had an n.m.r. spectrum and an *x*-ray powder pattern identical to those of the original alcohol.

Action of Formic Acid on Isopimara-8(14),15-dien-19-oic Acid

To a solution of 66 mg of the acid in 1 ml of chloroform was added 10 ml of 98% formic acid. After 20 min at room temperature the mixture was diluted with 20 ml of water and the resin acids extracted into methylene chloride. After two washes with 20 ml of water to remove formic acid, the methylene chloride solution was dried and distilled. The residue crystallized spontaneously and its n.m.r. spectrum was indistinguishable from that of starting material. The specific rotation however showed a small positive shift (+8°) showing that a slow change was taking place.

Action of Formic Acid on Methyl Pimara-8(14),15-dien-18-oate

The methyl pimarate (116 mg) dissolved within 1 min in 10 ml of 100% formic acid. After 30 min at room temperature the solution was diluted with 25 ml of water and the product extracted into methylene chloride. The organic layer was washed with water, then sodium carbonate solution, dried, and distilled, yielding 117 mg of pale-yellow gum. The n.m.r. spectrum of the gum was nearly identical to that of starting material although the total vinyl hydrogen count had dropped by 30% relative to the OCH_3 signal. No C*H*O—CO— or *H*COO signals were present in the spectrum.

Action of Formic Acid on Pimara-8(14),15-diene

The diene (42 mg) was stirred mechanically with 5 ml of 100% formic acid at room temperature for 75 min. Solution was not complete, some oil drops (formic acid dissolved in diene?) being evident. This simulates closely the conditions during manool cyclization. The reaction mixture was diluted with 20 ml of water, the product extracted into methylene chloride, and the methylene chloride solution washed with sodium carbonate solution. The 44 mg of gum recovered from the solvent had an n.m.r. spectrum very similar to that of starting materials, except for a 20% reduction in intensity of the vinyl proton signals. A weak broad *H*COO— band was present near τ 8.1 but no C*H*O—CO signal was detectable. After hydrolysis with potassium hydroxide in methanol, no C*H*OH signal could be detected in the n.m.r. spectrum.

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