[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND THE CHANDLER LABORATORY OF COLUMBIA UNIVERSITY]

The Stereochemistry of Polyene Cyclization

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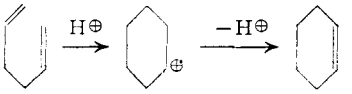
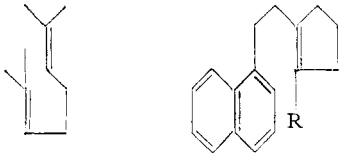
The steric course of the cyclization of polyenes is discussed with special emphasis on the cyclization of farnesic acid, farnesylacetic acid and related monocyclic isomers.

The formation of six-membered rings by the acid-catalyzed cyclization of 1,5-dienes is a well-known reaction which has been observed frequently in the terpene series.[1] The structural requirements which



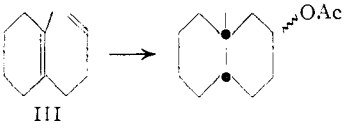
must be met before a diene will undergo this type of cyclization have been discussed by Hibbit and Linstead.[2]

It is mechanistically significant that although six-membered rings are the usual products from the cyclization of 1,5-dienes, five-membered rings also have obtained (a) in the cyclization of 2,7-dimethyl-2,6-octadiene (I)[3] and (b) in cyclizations involving attack of an aromatic ring which lead to the formation of variable quantities of spirans as with II (R = H).[4] These results are rationalized easily in the case of I which simply involves a combination of steric and electrical factors favorable to five-membered ring formation and in the case of II the low nucleophilicity of the aromatic system allows the reaction to proceed non-concertedly with the formation of the better initiating carbonium ion. The preference for the formation of six-membered rings in this reaction, *ceteris paribus*, is well illustrated by the suppression of spiran formation when R in formula II is a methyl group.[5]



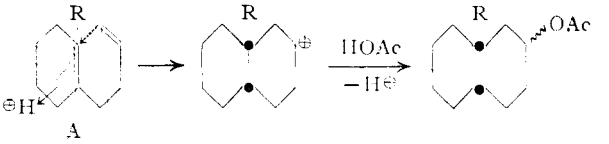
I II

A particularly important variation of the cyclization reaction is encountered when one of the double bonds of the 1,5-diene is alicyclic. In the case of butenylcyclohexene derivatives the products are hydronaphthalenes and the synthetic value of the reaction has been explored by Linstead and his collaborators who elucidated the stereochemistry of some of these cyclization reactions: They were thus able to demonstrate that under mild cyclization conditions (sulfuric acid–acetic acid–acetic anhydride at room temperature) the decalins produced from III (R = H, CH_3) have a *cis* ring junction[6,7]



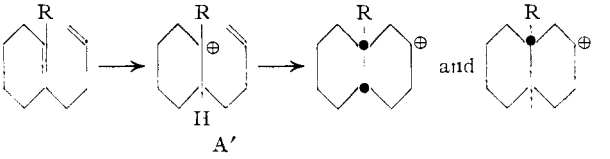
III

The stereochemical result obtained by Linstead, *et al.*, may be interpreted readily, as we have rationalized previously,[8] as the consequence of a typical concerted *trans* addition to a double bond in which a proton is the attacking cationic fragment while the second double bond plays the part of an anion. The concerted picture which we have given already[8] is repeated here



A

It is, of course, also possible to envisage a non-concerted cyclization *via* a relatively stable intermediate carbonium ion which could give rise to a mixture of *cis*- and *trans*-decalin systems[9]



II A′

It follows from the mechanism just given that if

(1) Among numerous examples which might be mentioned are the cyclization of ψ-ionone to α- and β-ionones, of geranic acid to cyclogeranic acids, etc. These and many other examples may be found in J. L. Simonsen and L. N. Owen, "The Terpenes," Vol. 1, Cambridge University Press, London, 1947. Some of the diolefins undergoing six-membered ring formation are not 1,5-dienes, but are capable of producing under acid conditions the same cationic species that can be obtained from 1,5-dienes; *cf.* ref. 2.

(2) D. C. Hibbit and R. P. Linstead, *J. Chem. Soc.*, 470 (1936).

(3) P. G. Stevens and S. C. Spalding, Jr., THIS JOURNAL, **71**, 1687 (1949).

(4) J. W. Cook and C. L. Hewett, *J. Chem. Soc.*, 365 (1934).

(5) A. Cohen, J. W. Cook, C. L. Hewett and A. Girard, *ibid.*, 653 (1934).

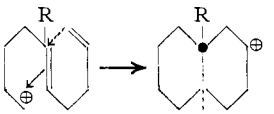
(6) R. P. Linstead, A. B. L. Wang, J. H. Williams and K. D. Errington, *ibid.*, 1136 (1937); R. P. Linstead, A. F. Millidge and A. L. Walpole, *ibid.*, 1140 (1937); V. C. E. Burnop and R. P. Linstead, *ibid.*, 720 (1940).

(7) Under drastic cyclization conditions, *e.g.*, phosphoric acid at 140°, mixtures of octalins are formed in which neither the stereochemistry nor the position of the double bond has been elucidated: The claim that when R = CH_3 the product consisted mainly of *trans*-9-methyl-Δ^2-octalin was based on the erroneous identification of its oxidation product, m.p. 163°, with *dl-trans*-1-methyl-1,2-cyclohexanediacetic acid which is now known to melt at 193° (unpublished work by Dr. Y. W. Chang of this Laboratory).

(8) G. Stork and H. Conroy, THIS JOURNAL, **73**, 4748 (1951).

(9) It is quite likely that the actual path followed in a given case depends on the stability of the initial carbonium ion and on the nucleophilic character of the junction-forming second double bond. If the latter is, for instance, part of an aromatic ring, non-concerted closure with formation of considerable amounts of *trans*-hydronaphthalene is to be expected. See, for instance, J. W. Cook, C. L. Hewett and A. M. Robinson, *J. Chem. Soc.*, 168 (1939); W. S. Johnson, D. K. Banerjee, W. P. Schneider, C. D. Gutsche, W. E. Shelberg and L. J. Chinn, THIS JOURNAL, **74**, 2832 (1952); R. Barnes, *ibid.*, **75**, 3004 (1953); F. E. King, T. J. King and J. G. Topliss, *Chemistry and Industry*, 108 (1954).

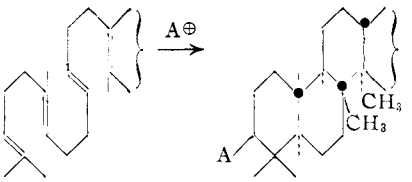
the initiating cation is not a proton, but a suitably situated carbonium ion generated within the molecule, a similar concerted reaction must lead not to a *cis*- but to a *trans*-hydronaphthalene system[10]



B

It is the purpose of this paper to draw attention to the important conclusion that *concerted* cyclization to structurally identical hydronaphthalenes will result in a *trans* system if the bicyclic precursor is an open chain triene convertible to a cation of type B[10] and a *cis* product if the precursor is monocyclic (type A). If the reactions are not concerted, mixtures of products will result.

The significance of this conclusion is quite apparent: The naturally occurring triterpenes and steroids are mostly *trans-anti-trans* structures (*e.g.*, lupeol, cholesterol) and it is an attractive hypothesis that they may be formed by concerted cyclization of polyenes in the manner shown rather



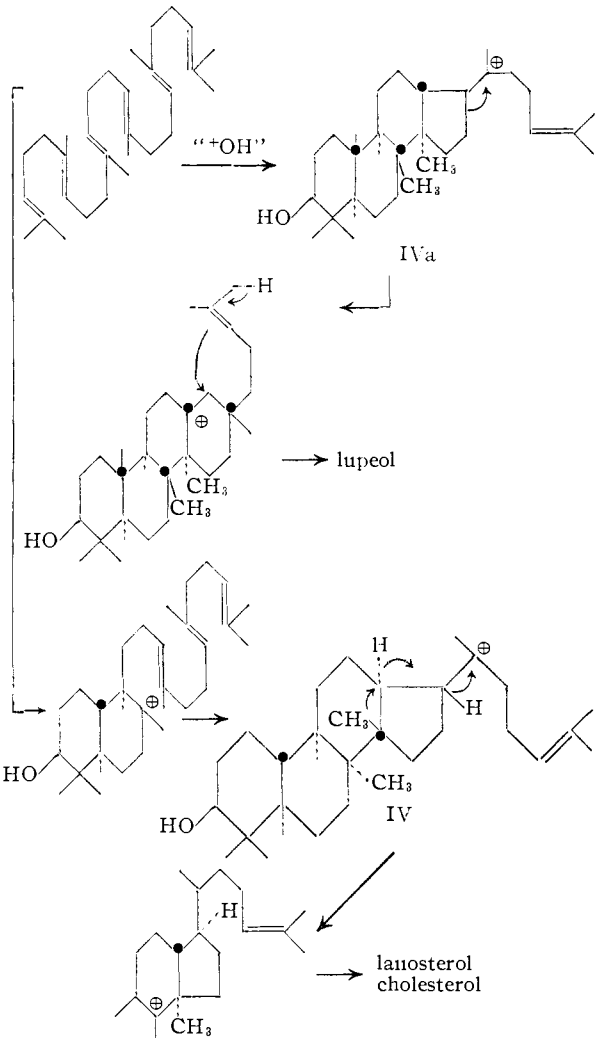
than, for instance, by step-wise cyclizations involving formation of one ring at a time, a path which would have led to *cis* stereochemistry. At the time we began to consider this hypothesis,[11] the stereochemistry of the triterpenes was not yet defined completely, nor had the similar origin of triterpenes and steroids received the striking support afforded by the establishment of the structure of lanosterol.[12] The intervening events thus have added plausibility to the occurrence of this biogenetic pathway and we may envisage the following routes leading (a) to lupeol and (b) to lanosterol (and hence to cholesterol). It will be noted that it is necessary to assume *two different paths* rather than a common intermediate for lupeol (and related triterpenes) and the sterols: The β-orientation of the methyl attached to C_{13} in lanosterol necessitates a β-methyl at C_{14} in its precursor IV, while an α-methyl at C_{14} is required in the precursor IVa of lupeol. This is easily envisaged if III is formed by a concerted closure of four rings while IV is produced by the concerted formation of the first two rings, *followed* by concerted closure of the last two.[13]

(10) This conclusion is valid only if the middle double bond has R,H *trans*, the usual stable configuration for compounds of this type. Should the bond be *cis* with respect to R and H, the concerted process would give a *cis*-hydronaphthalene.

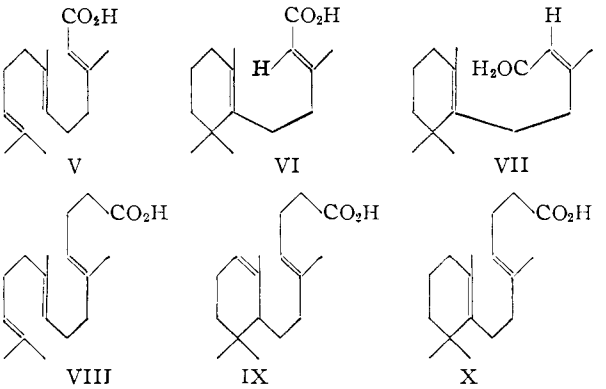
(11) G. Stork, Organic Colloquium, Harvard University, March 14, 1950.

(12) *Cf. Ann. Reps. Chem. Soc.*, **49**, 184 (1953).

(13) Dr. Eschenmoser has informed us that he has concluded independently that the scheme published in *Experientia* (L. Ruzicka, *Experientia*, **9**, 357 (1953)) which utilizes the *same* intermediate to triterpenoids and steroids had to be modified along such lines as indicated here.



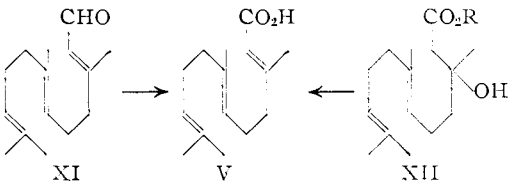
We now will describe our work on the cyclization of farnesic acid (V), β-monocyclofarnesic acids (VI, VII), farnesylacetic acid (VIII) and α- and β-monocyclofarnesylacetic acids (IX, X). This was undertaken to determine to what extent concerted polyene closures to *trans*-hydronaphthalene systems could be carried out experimentally.



Farnesic Acid Series.—At the outset of our work the cyclization of the farnesic acids had not been studied. In recent years, however, a number of papers have appeared in which these cyclizations

have been carried out under various conditions,[14] but the stereochemical problems involved have not been considered and the results have been confusing and sometimes misleading.

The farnesic acid (V) used was prepared by the silver oxide oxidation[14a] of farnesal (XI) which was itself made from nerolidol by the procedure of Stoll and Commarmont.[15] Farnesic acid also was prepared by Reformatsky reaction with geranylacetone followed by dehydration of the intermediate hydroxy ester XII with phosphorus oxychloride and pyridine in benzene solution. The acid produced by hydrolysis of the unsaturated ester appeared to consist mostly of farnesic acid as it gave the same crystalline S-benzylthiuronium salt as the farnesal oxidation product, although in a state of lower purity. Caliezi and Schinz[14d] dehydrated the hydroxy ester XII *via* the pyrolysis of its acetate, but did not characterize the acid which resulted after hydrolysis.

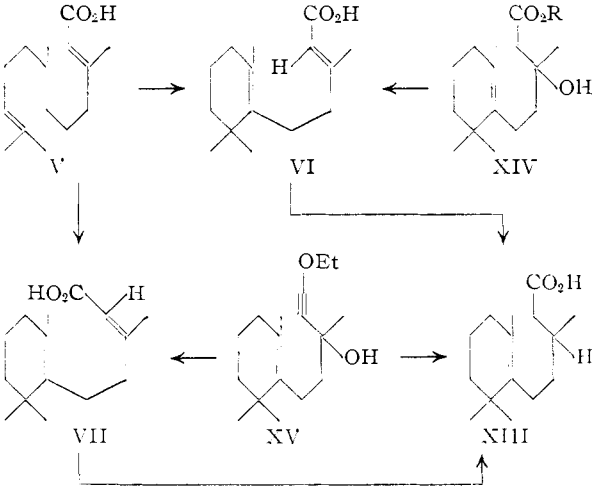


All our cyclization experiments were carried out with farnesic acid made from farnesal and regenerated from its crystalline thiuronium salt. We found that better results were obtained by the use of boron trifluoride etherate in benzene solution than with the formic acid–sulfuric acid system described by Bernhauer and Forster[16] for the cyclization of geranic acid, and used by Caliezi and Schinz[14a,d] with farnesic acid.

In contrast to the cyclizations with formic acid–sulfuric acid which gave only bicyclic acids from farnesic acid, we found it possible to isolate monocyclic acids (dihydro-β-ionylideneacetic acids) by conducting the cyclization below 5°. Under these conditions two acids were obtained, one (VI) was crystalline and was isolated in about 25% yield (crude); it melted at 115–117° when pure and gave a benzylthiuronium salt, m.p. 134.5–135°, which depressed the melting point of the corresponding derivative, m.p. 132–133°, from farnesic acid. A second (VII), liquid monocyclic acid was obtained in small yield from the mother liquors of the crystalline isomer. It was characterized by its benzylthiuronium salt, m.p. 158–159.5°. This last thiuronium salt was much less soluble than that of the crystalline isomer and could be separated easily from it.

These two acids are *monocyclic* since they are identical with acids which have been prepared from dihydro-β-ionone: Lederer, *et al.*,[14c] obtained the 117° acid from the bisulfate dehydration of the hydroxyester XIV while the thiuronium salt, m.p. 158–159.5°, was obtained by Caliezi and Schinz[14b] from the ethoxyacetylenic carbinol XV.[17]

We have now found that both acids are formed concurrently during the dehydration of the hydroxyester XIV with phosphorus oxychloride or thionyl chloride in pyridine at 60°, a method which we found superior to the bisulfate dehydration. The two monocyclic acids are obviously geometric isomers, since they are both α,β-unsaturated acids as shown by ultraviolet absorption spectra and by the strong double bond absorption at 6.1 μ, which seems characteristic of such α,β-unsaturated acids. In agreement with this view, VI and VII were reduced smoothly in the presence of palladium-on-strontium carbonate to an *identical* liquid dihydro acid XIII as shown by the fact that both preparations gave the same infrared spectra and were converted to thiuronium salts, m.p. 159–159.5°, which did not depress each other, but gave a strong depression with the derivative of the same melting point from the liquid acid VII. The geometric isomerism of the 117° and the liquid monocyclofarnesic acids is undoubtedly as represented by VI and VII, respectively, since the 117° acid is the major product of the cyclization of a farnesic acid which has the more stable *trans*[18] configuration, since it is derived from farnesal (XI).



The nature of the isomerism of VI and VII is confirmed further by their cyclization to *epimeric* bicyclic acids as will now be discussed.

Cyclization of the 117° acid VI has been carried out previously with phosphoric acid by Lederer, *et al.*,[14c] who were unable to isolate crystalline substances. We made use of boron fluoride etherate in benzene at 40° and obtained in 35% yield a pure bicyclofarnesic acid (XVII), m.p. 131°, identical with the solid acid obtained in about 10% yield by Caliezi and Schinz[14a,d] from the cyclization of farnesic acid. With formic acid–sulfuric acid the 117° acid VI gave a low yield of the α,β-unsaturated isomer XVI, m.p. 153–154°,

(14) (a) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **32**, 2556 (1949); (b) **33**, 1129 (1950); (c) C. Collin-Asselineau, M. E. Lederer and J. Polonsky, *Bull. soc. chim.*, **17**, 715 (1950); (d) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **35**, 1637 (1952); (e) R. E. Wolff, *Compt. rend.*, **238**, 1041 (1954).

(15) M. Stoll and A. Commarmont, *Helv. Chim. Acta*, **32**, 1356 (1949).

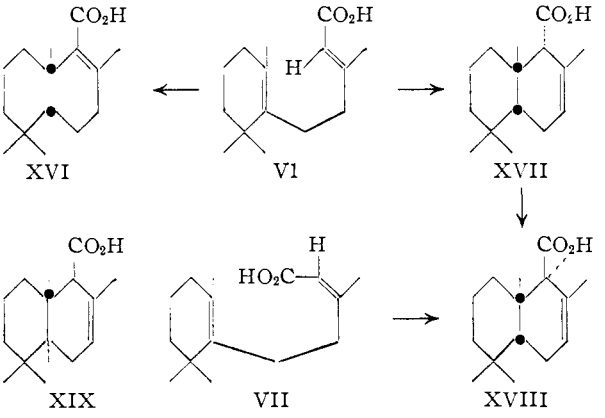
(16) K. Bernhauer and R. Forster, *J. prakt. Chem.*, [2] **147**, 199 (1936).

(17) It was not possible, of course, to be sure that the liquid acid of Caliezi and Schinz[14b] was not merely an impure sample of the 117° acid prepared by Lederer, *et al.*,[14c] until we prepared the thiuronium salt of the latter acid and showed it to be clearly different from that of the liquid acid.

(18) *trans* refers to the long alkyl chain and the carboxyl group.

evidently identical with one of the products obtained by Caliezi and Schinz from the cyclization of farnesic acid.[14d]

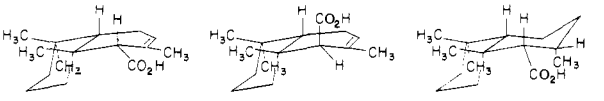
When the geometrically isomeric liquid monocyclofarnesic acid (VII)[19] was treated with boron fluoride etherate no cyclization could be effected up to 70°. When formic acid–sulfuric acid was used, according to Caliezi and Schinz,[14b] we succeeded in isolating in low yield a third bicyclofarnesic acid (XVIII), previously unreported, which melted at 138°.



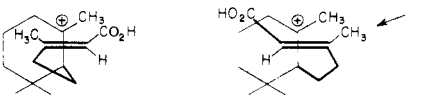
Now, Caliezi and Schinz[14b] previously had carried out this cyclization using a liquid β-monocyclofarnesic acid, from which the thiuronium salt of VII could be obtained, and had shown the presence in the cyclization products of a *liquid* acid which gave rise to an alcohol, the allophanate of which melted at 193.5–194.5°. That the liquid acid of Caliezi and Schinz is a mixture is shown by the fact that the same allophanate, m.p. 193.5–194.5°,[20] was obtained in the present work from the alcohol derived from our crystalline bicyclic acid XVIII, m.p. 138°.

The three bicyclofarnesic acids (XVI, XVII and XVIII) thus obtained can be shown to possess the *same stereochemistry at the ring junction:* The α,β-unsaturated acid XVI could be obtained from the 131° acid XVII by treatment with thionyl chloride, followed by hydrolysis of the acid chloride; that the 131° acid is epimeric with the 138° acid at the carbon bearing the carboxyl group was demonstrated by treating the methyl ester of XVII with 10% alcoholic base at 150–160° for 24 hours when XVIII was isolated in 45% yield. On the other hand, the methyl ester of XVIII merely gave back the parent acid under similar conditions.

Careful infrared comparison showed that none of the three acids was identical with the natural (*trans*) degradation product XIX from ambrein[21] and consequently all three crystalline acids XVI, XVII and XVIII, obtained in the cyclization of farnesic acid are derivatives of *cis*-decalin. The assignment of the particular orientation of the carboxyl group shown in XVII and XVIII is tentative and based on the behavior of the two acids on hydrogenation: The 131° acid XVII is *readily* reduced catalytically to a single dihydro compound XX, m.p. 164°, as claimed by Caliezi and Schinz[14a] and confirmed by us, while we found that under similar conditions the 138° isomer XVIII gave a mixture of dihydro acids. Examination of models shows that the 131° acid should give only one dihydro acid if it has the configuration shown in XVII and elaborated in XVIIa, while the reduction of XVIII (see XVIIIa) should not be as stereospecific.



The configuration XVII of the 131° acid requires that the cyclization of its precursor, the *trans* 117° monocyclic acid VI, proceed in the confirmation shown in VIa rather than VIb. This is made plausible by examination of models and may be due to repulsion between the two methyl groups in VIb.



There are two further corollaries of the assignments just made: (a) The more stable 138° epimer (XVIII = XVIIIa) has its carboxyl *axial* rather than equatorial. This is presumably the result of the special circumstance that it interferes with only one axial hydrogen, while the equatorial carbonyl of the (less stable) 131° acid (XVII = XVIIa) is hindered by the doubly bonded methyl group. (b) The dihydro acid XX derived from XVII must have its carboxyl group equatorial and we ascertained that its methyl ester gives back unchanged XX on vigorous base hydrolysis. This is what might be anticipated except that in XX the equatorial carboxyl finds itself flanked by two axial substituents, a situation which might lead to a reversal of the usual stability order.[22]

We then have shown that the cyclization of the monocyclic acids VI and VII gives, as isolable crystalline substances, the bicyclic acids of *cis* configuration, XVI, XVII and XVIII, which are required by concerted cyclization of a 1,5-diene. The cyclization reaction is, however, not necessarily concerted: The conjugation of a carboxyl group with one of the double bonds in VI and VII reduces electron availability and nucleophilic character of that bond so that the cyclization may well take place *via* an intermediate carbonium ion such as A′. This is to some extent borne out by the difficulty experienced in cyclizing the acid VII and would lead to the inference that some of the *trans*-acid XIX is probably present among the cyclization products. Although no definite evidence for this was obtained in this series, the correctness of this conclusion is indicated by the following facts: Caliezi and Schinz[14d] showed that the cyclization of a monocyclic acid similar to VI

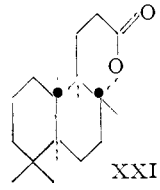
(19) The acid used here was regenerated from its thiuronium salt.

(20) Our allophanate did not depress the melting point of the allophanate of Caliezi and Schinz (this determination was carried out through the kindness of Dr. Caliezi).

(21) We wish to thank Dr. O. Jeger for his kindness in making the acid XIX available to us.

(22) See D. H. R. Barton, *Chemistry & Industry*, 663 (1953).

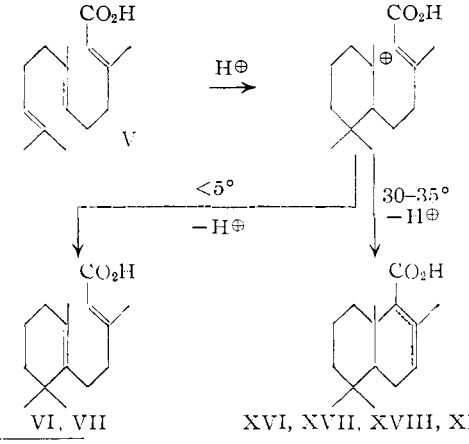
but derived from dihydro-α-ionone[23] leads to a liquid bicyclic acid fraction reducible to an alcohol which gives an allophanate melting at 193.5–194.5°. As we already have mentioned, we have shown that this allophanate is derived from the *cis* 138° acid XVIII); the liquid bicyclic acid of Caliezi and Schinz must, however, be a mixture and *obviously contains also the trans* isomer XIX, since Wolff[14e] was able to obtain from it some *dl*-ambreinolide (XXI), a substance in which the decalin junction is *trans*.[24]



XXI

The situation thus is relatively complex with the simple monocyclic acids, and on the basis of the preceding discussion one might anticipate that the cyclization of the open chain trienic acid, farnesic acid (V), would lead to essentially the same mixture as that obtained from the monocyclofarnesic acids. The cyclization of farnesic acid has been studied using formic acid–sulfuric acid by Caliezi and Schinz[14d] who obtained the acids XVII, m.p. 131°, and XVI, m.p. 154°, in addition to liquid acids which must have contained our 138° isomer (XVIII) since its allophanate, m.p. 191–192°, was obtained from the derived alcohol mixture. We studied this cyclization again with boron fluoride etherate in benzene and found that at 30–35° cyclization proceeds to the bicyclic stage, and up to 35% of the 131° acid XVII could be obtained. The isomer XVIII, m.p. 138°, was obtained in small amounts from the mother liquors. It is thus clear that the cyclization was in large part non-concerted, leading to the same *cis*-acids obtained from the monocyclic acids.

One point is worthy of note: In spite of the fact that the cyclization is not concerted, it does not lead to bicyclic acids *via* the monocyclic unsaturated acids, since the monocyclic acids are harder to cyclize to bicyclic structures than farnesic acid. The reaction is thus depicted as



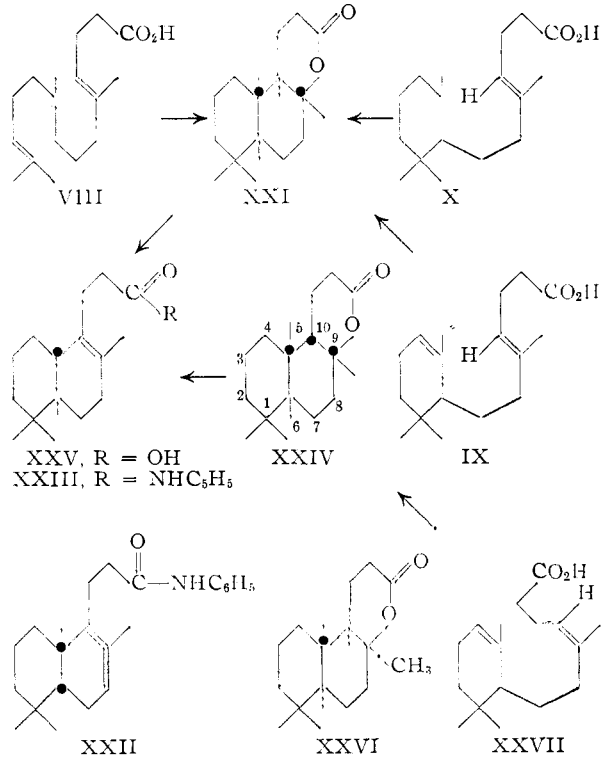
(23) It seems likely that the same mixture would result from β-ionone derivatives as equilibration would probably take place under the cyclization conditions.

(24) W. Klyne, *J. Chem. Soc.*, 3072 (1953).

Cyclization of Farnesylacetic Acid and the Monocyclofarnesylacetic Acids.—The greater nucleophilic character of the double bond involved in forming the second ring should lead to more concerted closure in the case of farnesylacetic acid (VIII). This was selected as a good case to study since the product of completely concerted closure is *dl*-ambreinolide (XXI), the active form of which is well known as a degradation product of ambrein.

When this work was started, nothing was known of the feasibility of cyclizing farnesylacetic acid (VIII) to tricyclic lactones. It recently has been shown, however, that some *dl*-ambreinolide may be obtained from farnesylacetic acid: Dietrich and Lederer[25] claim a yield of 12.4% of crystalline *dl*-ambreinolide by the use of formic acid on farnesylacetic acid. This is incorrect; their figures correspond to 4.5% of *crude* (m.p. 120–134°) *dl*-ambreinolide. Careful repetition gave us 1.6% of *pure dl*-ambreinolide, m.p. 135–137°. A variety of cyclizing agents was tried, but, although stannic chloride and stannic bromide both gave better results than formic acid, the yields of *pure dl*-ambreinolide (XXI) were only 2.3 and 2.9%, respectively.[26]

The presence in the cyclization products of lactones of the *cis*-decalin series was demonstrated by the transformation of crude lactone mixtures to an anilide XXII m.p. 169–170°, different from that, m.p. 130.5–132°, corresponding to ambreinolide and assigned structure XXIII.



The conclusion might then be reached that, to a small extent, completely concerted cyclization is

(25) P. Dietrich and E. Lederer, *Helv. Chim. Acta*, **35**, 1148 (1952).

(26) Other cyclization conditions are discussed in the Experimental section.

taking place in this series. This is, however, quite possibly unwarranted. We have now shown that *dl*-ambreinolide also can be obtained from the *monocyclic* acids IX and X, derived from dihydro-α-ionone and dihydro-β-ionone, respectively. These monocyclic acids have not been prepared previously. Their synthesis is unexceptional and is described in the Experimental section, but one point is of interest: Both acids gave thiuronium salts melting at 144–145° which did not give any depression of melting point on mixing. They were, however, different as shown by infrared spectra (12.2 μ band in CS_2 in α-isomer) and especially by their different behavior on cyclization: The acid X from dihydro-β-ionone gave, either with formic acid or stannic chloride, 2% yield of pure *dl*-ambreinolide. Surprisingly, only traces were obtained with stannic bromide.

The cyclization of monocyclofarnesylacetic acid (IX) proved very interesting: With stannic chloride under the same conditions as with the β-isomer (35–40°) a crystalline "ambreinolide" fraction was obtained. This was much more difficult to purify than in the β-series and could be separated by chromatography into *dl*-ambreinolide (XXI) and a new isomer, *dl*-isoambreinolide (XXIV) m.p. 103–106°. Under milder conditions, at room temperature, relatively little of the isoambreinolide was formed and *dl*-ambreinolide was obtained in 1.6% yield. With stannic bromide, however, the ambreinolide fraction gave pure *dl*-isoambreinolide in 7.2% yield.

It is easy to show that *dl*-isoambreinolide is also a *trans*-decalin: Treatment with methanolic sulfuric acid, followed by saponification, gave the same unsaturated acid XXV, m.p. 139–140°, that can be obtained from *dl*-ambreinolide under the same conditions.[27] It follows, therefore, that the structure of the isoambreinolide must differ from that of ambreinolide in that its lactone ring, which infrared data show to be also six-membered, must be *cis* fused (the other *trans* possibility is not feasible as it would be diaxial). Of the two possibilities, XXIV and XXVI, XXIV is undoubtedly correct as XXVI would certainly epimerize to the stable *dl*-ambreinolide (XXI) under the conditions of its formation while XXIV would be expected to be stable (*trans-syn-cis* better than *trans-syn-trans*[28]). The isoambreinolide from the cyclization of α-monocyclofarnesylacetic acid is therefore 9-*epi*-ambreinolide (XXIV).

The occurrence of 9-*epi*-ambreinolide is explained easily by the presence in the α-monocyclofarnesic acid of the geometric isomers XXVII as well as IX.[29]

(27) The position of the double bond in acid XXV was proved to be tetrasubstituted by ultraviolet absorption data for which we take pleasure in thanking Dr. Henbest of the University of Manchester; see also P. Dietrich, E. Lederer and D. Mercier, *Helv. Chim. Acta*, **37**, 705 (1954). The substance, m.p. 122–123°, reported by Dietrich and Lederer[25] is possibly an impure sample of XXV.

(28) W. S. Johnson, THIS JOURNAL, **75**, 1498 (1953).

(29) The α-monocyclofarnesylacetic acid used was purified through its thiuronium salt which appeared homogeneous although, as mentioned earlier, it did not depress the melting point of the corresponding derivative of the β-series. It is possible that either the acid was a mixture of IX and XXVII or that XXVII was formed from IX during the cyclization reaction. It is of practical interest that the highest yield of the *trans*-decalin acid XXV is obtainable *via* 9-*epi*-ambreinolide from α-monocyclofarnesylacetic acid.

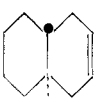
Again, as in the farnesic acid series, even though now cyclization from monocyclic acids to tricyclic lactone is apparently as easy as cyclization from acyclic acid to tricyclic lactone, the latter reaction must not proceed through the intermediacy of the monocyclofarnesylacetic acids as the results, especially with stannic bromide as catalyst, are different whether the starting material is acyclic or monocyclic.

It is probable that some of the desired concerted *trans* cyclization has been obtained in this series, at least with stannic bromide, but the extent to which it has been realized is certainly very small. This may be due to two factors: (a) Steric interference to concerted approach and (b) unfavorable arrangement of the relevant double bonds in solution.

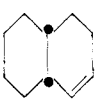
It is possible that the second factor could be affected by carrying out the acid cyclizations on surfaces which might hold the molecules in different arrangements from those in solution (this may be an important factor in the stereospecificity of such reactions in nature). The first factor could be made much less important by removing certain groups around the double bonds involved. For instance, removal of the methyl group marked by an arrow in *VIb* might make concerted cyclization easier but would alter the structural features found in the natural substances.

There is one final point to which we would like to draw attention. We have encountered in this work, as products of acid-catalyzed reactions, substances which belong to the *cis*-octalin series and which have the double bond as shown in XVII and XVIII. On the other hand, at least one substance of the *trans*-octalin series, formed again in an acid-catalyzed dehydration, has been shown to have its double bond as shown in XXV.

It is thus clear that great caution must be exercised before one may conclude that a *trans*-octalin is *necessarily* more stable with its double bond as shown in XXVIII, and a *cis*-octalin with its double bond as shown in XXIX. In complex cases, such as those we are dealing with, other factors may well alter the situation found in simple cases.[30]



XXVIII



XXIX

Experimental

Farnesic Acid (V). (a) From Farnesal (XI).—Farnesal was prepared by the procedure of Stoll and Commarmont[15] from nerolidol and was oxidized with silver oxide, according to Caliezi and Schinz,[14a] to farnesic acid, b.p. 158–162° (0.5 mm.), $n^{23}D$ 1.4955. It was converted into its benzylthiuronium salt, m.p. 132–133° as reported,[14a] and the salt was used as a source of pure farnesic acid.

(b) From Geranylacetone.—Geranylacetone was prepared by the alkylation of ethyl acetoacetate with geranyl bromide, followed by hydrolysis with 2% aqueous alcoholic sodium hydroxide. It has b.p. 145–150° (22 mm.), $n^{25}D$ 1.4661 (lit.,[31] b.p. 99–101° (4 mm.), $n^{20}D$ 1.4683). This was converted essentially by the procedure of Caliezi and

(30) The conclusion, for instance, that the position of the double bond in the natural degradation acid XIX supports a *trans* ring junction in that acid (A. J. Birch, *Ann. Reps. Chem. Soc.*, **47**, 201 (1951), is not warranted.

(31) M. F. Carroll, *J. Chem. Soc.*, 704 (1940).

Schinz[14d] into the hydroxy ester XII, b.p. 128–132° (0.3 mm.), $n^{25}D$ 1.4689 (lit.[14d] b.p. 128–130° at 0.2 mm.). The hydroxy ester (30 g., 0.107 mole) was dissolved in three times its volume of a 2:1 mixture of pyridine (dried over BaO) and benzene, and a solution of 20 g. of phosphorus oxychloride in 20 ml. of benzene was added dropwise, with stirring, at room temperature. The reaction was initiated by heating the mixture slowly, with rapid stirring, to 60–65° and it was kept at that temperature for 20 minutes. The mixture then was cooled, poured on crushed ice and worked up in the usual manner. The unsaturated ester (no OH absorption in the infrared, pronounced absorption at 6.15 μ due to conjugated double bond) was hydrolyzed by keeping overnight at room temperature with 5% aqueous alcoholic sodium hydroxide to give crude farnesic acid, b.p. (bath temp.) 160–165° (0.3 mm.), $n^{25}D$ 1.4951, in 17% over-all yield from geraniol. The benzylthiuronium salt had m.p. 124–126° after one crystallization and the infrared spectrum was nearly identical with that of authentic farnesic acid from farnesal.

Cyclization of Farnesic Acid (V). (a) Model Experiment with Geranic Acid.—To a rapidly stirred solution of boron trifluoride etherate (20 g.) in dry benzene (150 ml.), a solution of 20 g. of geranic acid (prepared by silver oxide oxidation of citral[16]) in 25 ml. of dry benzene was added dropwise at room temperature during 15 minutes. The resulting deep brown solution was warmed to 50° for 30 minutes. Decomposition with ice-water gave an organic layer which was washed with water and dried. Distillation after removal of solvent gave 19.0 g. (95%) of nearly colorless α-cyclogeranic acid, b.p. (bath temp.) 170–180° (20 mm.), m.p. 93–104°. One crystallization from petroleum ether containing a small amount of benzene gave 15.0 g. of pure acid, m.p. 105–107° (lit.[16] m.p. 105–107°).

(b) **Partial Cyclization of Farnesic Acid.**—To a rapidly stirred solution of boron trifluoride etherate (15 ml.) in dry benzene (200 ml.), 20 g. of farnesic acid (from farnesal) in 50 ml. of dry benzene was added dropwise at 2–3° over a 45-minute period. After standing overnight at 4–5°, the reaction mixture was worked up as described above. The product was a viscous oil, b.p. (bath temp.) 160–165° (0.4 mm.), which gradually crystallized in the cold from 15 ml. of petroleum ether. The yield of colorless, crystalline material, m.p. 95–110°, was 5.0 g. (25%). On recrystallization, this furnished 2.6 g. (13%) of the pure crystalline β-monocyclofarnesic acid (VI), m.p. 115–117°, identical with the acid prepared according to Lederer, *et al.*,[14c] by bisulfate dehydration of the hydroxyester XIV from dihydro β-ionone, as a mixture of the two acids produced no depression of the melting point. No other crystalline product could be isolated from the above cyclization. The infrared spectrum of this acid in carbon disulfide showed no band around 12.3 μ, thus supporting a β- rather than α-structure. The ultraviolet spectrum has been published by Lederer, *et al.*[14c]

The benzylthiuronium salt was recrystallized from acetone–ethanol and formed clusters of needles, m.p. 134.5–135°, depressed to 120–126° on admixture with the pure thiuronium salt, m.p. 133–134°, of farnesic acid.

Anal. Calcd. for $C_{23}H_{34}O_2N_2S$: C, 68.61; H, 8.51. Found: C, 68.36; H, 8.61.

From the mother liquors of the crystalline 117° acid the isomeric liquid **β-monocyclofarnesic acid (VII)** could be isolated, in low yield, by conversion into the thiuronium salt which is considerably less soluble than that of the 117° acid. The crude thiuronium salt thus obtained was purified easily by crystallization from ethanol. It had m.p. 158.5–159.5°, as reported for the acid obtained by Schinz[14b] from the ethoxyacetylenic carbinol XV. Regeneration of the pure acid by shaking with dilute hydrochloric acid and ether afforded the mobile, colorless, liquid β-monocyclofarnesic acid (VII), b.p. (bath temp.) 152–156° (0.15 mm.), $n^{25}D$ 1.4935 (lit.[14b] b.p. 130–132° at 0.05 mm.).

Variation of catalyst concentration and reaction time did not appear to alter the above results appreciably, provided the temperature was not allowed to exceed 10°. Above that temperature varying amounts of bicyclic acids were formed.

Monocyclofarnesic Acids from Dihydro-β-ionone.—The hydroxyester XIV was prepared substantially according to Lederer, *et al.*[14c] In an effort to improve the yield of the 117° monocyclofarnesic acid (VI), the dehydration was studied in some detail. Among the methods which produced very little dehydration are: (a) distillation from powdered potassium bisulfate at 180–200° (20 mm.), (b) treatment with phosphorus oxychloride in pyridine at room temperature, (c) heating with phosphorus pentoxide in triethylamine at 60–70°, (d) refluxing in toluene in the presence of iodine, (e) refluxing the hydroxy acid with acetic anhydride. Slow distillation of the hydroxy acid from XIV as described by Lederer, *et al.*,[14c] gave the crystalline acid VI in only 6–8% yield. The procedure employing phosphorus oxychloride in pyridine–benzene at 60–65°, as has been described above for the dehydration of XII, gave, after mild hydrolysis as described in the preparation of farnesic acid from XII, a mixture containing the two isomeric bicyclofarnesic acids in 70–75% over-all yield; b.p. (bath temp.) 160–165° (0.5 mm.). On cooling the mixture in an equal volume of low boiling (20–40°) petroleum ether, the crystalline isomer VI was deposited in 10–15% yield as fine colorless needle clusters, m.p. 105–112°, raised to 115–117°, as reported,[14c] on recrystallization from 30–60° petroleum ether. The benzylthiuronium salt was identical with that prepared by partial cyclization of farnesic acid.

The liquid acid VII was isolated readily from the mother liquors of the 117° acid as its thiuronium salt, as described in the partial cyclization of farnesic acid.

Both acids took up one equivalent of hydrogen on reduction with palladium-on-strontium carbonate in ethanol and gave the same dihydro acid XIII characterized as its benzylthiuronium salt, m.p. 159–159.5°. This depressed the melting point of the derivative (m.p. 158.5–159.5°) of the liquid bicyclic acid VII to 153–156°.

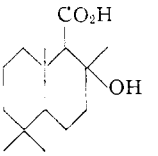
The infrared spectra of the dihydro acids from VI and VII were identical.

Cyclization of the 117° β-Monocyclofarnesic Acid (VI). (a) With Boron Trifluoride Etherate. Isolation of the 131° Bicyclofarnesic Acid (XVII).—To a solution of 10 ml. of boron trifluoride etherate in 40 ml. of benzene, 1.0 g. of the crystalline monocyclofarnesic acid (VI), m.p. 115–117°, dissolved in 10 ml. of benzene was added slowly at 40° with stirring. After six hours at 40° the reaction was worked up as usual and gave an acidic fraction which was partly crystalline. Recrystallization from petroleum ether gave 0.41 g. (41%) of crude bicyclofarnesic acid (XVII), m.p. 124–130°. One recrystallization from benzene–petroleum ether sufficed to raise this m.p. to 130–131°. The mixed melting point with the substance obtained by Caliezi and Schinz[14a,d] by formic acid cyclization of farnesic acid was undepressed.

(b) With Formic Acid at 40°. Isolation of the 154° Bicyclofarnesic Acid (XVI).—To a well-stirred mixture of 0.5 ml. of concentrated sulfuric acid and 20 ml. of 98–100% formic acid was added 1 g. of the 117° monocyclofarnesic acid (VI). After a half-hour at 40–45° the light tan mixture was kept overnight at room temperature. After working up as usual the acid portion obtained did not show any of the absorption at 6.15 μ characteristic of the starting material. Trituration with petroleum ether gave a crystalline fraction (0.15 g.) which melted at 115–135° and could not be purified further. From the mother liquors a second crystalline fraction, m.p. 143–148°, gradually precipitated (0.20 g.). Three crystallizations from 20–40° petroleum ether were required to raise the melting point of the acid XVI to 153–154°. It gave no color with tetranitromethane and is obviously identical with one of the products subsequently obtained by Caliezi and Schinz[14d] from farnesic acid and characterized as an α,β-unsaturated bicyclofarnesic acid.

(c) With Formic Acid at 55°.—From the cyclization of 2 g. of the 117° monocyclofarnesic acid (VI) with 25 ml. of 98–100% formic acid containing 0.2 ml. of concentrated sulfuric acid at 55° for 6 hours a crystalline acid precipitate was obtained, m.p. 195–200° (0.15 g.). Recrystallization from ethanol–benzene afforded what is apparently the bicyclic hydroxy acid shown below as colorless prisms, m.p. 206–208°. This substance showed no absorption in the ultraviolet and gave no color with tetranitromethane.

Anal. Calcd. for $C_{15}H_{26}O$: C, 70.83; H, 10.30. Found: C, 70.85; H, 10.29.



From the mother liquors a small amount of the 154° bicyclofarnesic acid (XVI) was obtained.

Cyclization of the Liquid Monocyclofarnesic Acid (VII).—Treatment of the acid VII (regenerated from its thiuronium salt) with boron trifluoride etherate in benzene at temperatures ranging from 20 to 70° failed to effect its cyclization, as evidenced by the fact that the absorption at 6.15 μ exhibited by VII did not change.

Cyclization with formic acid–sulfuric acid according to Caliezi and Schinz[14b] gave a bicyclic acidic product which readily crystallized from petroleum ether containing a little benzene as colorless elongated prisms, m.p. 137–138°, yield 0.30 g. (5.8%). No other crystalline product could be isolated. The acid XVIII gave a deep coloration with tetranitromethane in chloroform.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.39; H, 10.44.

Lithium aluminum hydride reduction of the ester prepared from XVIII and diazomethane gave the corresponding alcohol, the allophanate of which melted at 191–192°, undepressed[23] when mixed with the allophanate of the same melting point obtained by Caliezi and Schinz[14b] from a liquid bicyclofarnesic acid mixture.

Interrelation of the Bicyclofarnesic Acids XVI, XVII and XVIII. (a) Conversion of XVII into XVI.—The 131° bicyclic acid XVII was transformed into its acid chloride with thionyl chloride in ether. Attempted Rosenmund reduction of this chloride gave no detectable aldehyde, but hydrolysis of the reaction mixture gave a crystalline acid, m.p. 145–152°, which after recrystallization from benzene–petroleum ether was brought to m.p. 152–154°. Admixture with an authentic sample of XVI produced no depression.

(b) Conversion of XVII into XVIII.—The methyl ester of the 131° bicyclic acid XVII was prepared with diazomethane. Hydrolysis of the methyl ester was carried out by heating with a 10% solution of potassium hydroxide in alcohol in a sealed tube at 150–160° for 24 hours. Hydrolysis under these conditions was essentially complete and gave as the only acid that could be isolated the 138° acid XVIII obtained by crystallization from petroleum ether in 45% yield. The melting point on admixture with authentic XVIII was not depressed and infrared spectra further confirmed the identity of the acid.

Under similar conditions, the methyl ester of the 138° acid XVIII merely regenerated unchanged XVIII.

Hydrogenation of XVII and of XVIII.—Reduction of the 131° acid XVII over Adams catalyst in acetic acid solution yielded the dihydro compound XX, m.p. 164–164.5°, as reported already by Caliezi and Schinz[14a]; yield 85%.

The methyl ester of XX gave back XX in 75% yield on heating with 10% potassium hydroxide in alcohol at 150–160° in a sealed tube.

Hydrogenation of the 138° bicyclic acid XVIII proceeded rather more slowly than that of XVII with the absorption of an equivalent of hydrogen. The product was a mixture which could not be resolved completely by fractional crystallization.

(c) Direct Cyclization of Farnesic Acid to Bicyclic Acids.—Under the conditions described for the partial cyclization of farnesic acid, but at 30–40°, followed by standing overnight at room temperature, the bicyclofarnesic acid melting at 131° (XVII) was obtained in 15–35% yield depending on the purity of the farnesic acid (highest with farnesic acid regenerated from its thiuronium salt) and the temperature of cyclization (best at 35°). The acid fraction was worked up as usual and was crystallized from petroleum ether. One recrystallization usually sufficed to obtain the product in a state of purity.

By careful concentration and cooling (0 to −5°) of the mother liquors from the 131° acid it was possible to obtain small amounts (2–5%) of the 138° isomer XVIII. The separation of these isomers in this manner was facilitated by the distinctly smaller solubility of the 131° acid in petroleum ether.

Efforts to obtain any other crystalline material from the mother liquors of the 138° acid were unavailing. Fischer esterification (one hour reflux with methanol–sulfuric acid[14a]) removed most of the colored impurities in the resulting ester fraction; from the remaining acidic material (*ca.* 60%) only small additional quantities of the above two isomeric bicyclic acids XVII and XVIII could be isolated. Chromatography of the remaining mother liquors on activated acid-washed alumina, followed by thiuronium salt formation, likewise did not lead to further crystalline products.

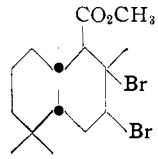
Cyclization of farnesic acid with other catalysts under a variety of conditions gave results which are summarized in part below. In each case the bicyclic acid XVII was isolated by crystallization of the distilled acidic fraction from petroleum ether.

Catalyst	Condition	Time	Yield of 131° acid, %
$ZnCl_2$–CH_3CO_2H	10° then 35°	2 hr.	3.2
H_2SO_4–CH_3CO_2H(3:2)	5° then 25°	20 min.	<0.5
BF_3(gas)–benzene	55°	1 hr.	4.0
$SnCl_4$–benzene	40° then 25°	12 hr.	2.5

A number of reactions were carried out on the 131° acid XVII. Some of these are described below.

Bromination of the 131° Acid.—A solution of 1.60 g. (0.01 mole) of bromine in 10 ml. of acetic acid was added to 2.50 g. (0.01 mole) of the methyl ester of XVII dissolved in 15 ml. of acetic acid. After 12 hours at room temperature the solution was concentrated under water-pump vacuum on the steam-bath and the product was crystallized from dilute methanol to yield 2.03 g. (49.5%) of the dibromo ester as colorless needle clusters, m.p. 110–114°, raised to 113–114° on recrystallization.

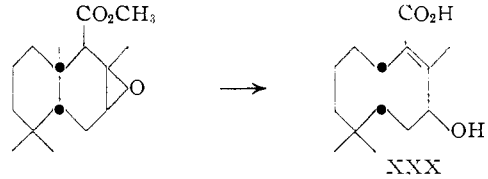
Anal. Calcd. for $C_{16}H_{26}O_2Br_2$: C, 46.84; H, 6.39. Found: C, 46.75; H, 6.47.



Attempts to dehydrobrominate the substance to a dienic ester with potassium *t*-butoxide did not yield definite products.

Formation and Rearrangement of the Epoxide of XVII.—A solution of the methyl ester of the 131° acid in 20 ml. of anhydrous ether was mixed with a slight excess of monoperphthalic acid in ether and was kept at 0° for 3 days. The neutral product obtained by washing the ether solution with 5% aqueous sodium carbonate exhibited a new band at 9.35 μ, presumably due to the epoxide group. Hydrolysis of the epoxide with 13% alcoholic potassium hydroxide at 160° in a sealed tube gave 0.4 g. of an acid, presumably XXX. This crystallized from ethanol–benzene in fine colorless needles, m.p. 202–203°.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.10; H, 9.48.



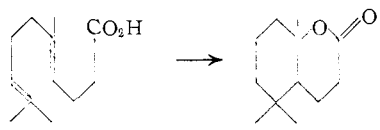
XXX

XXX was unsaturated to bromine in carbon tetrachloride and to potassium permanganate in acetone solution. It gave no color with tetranitromethane in chloroform solution, gave no reaction with dinitrophenylhydrazine, and its methyl ester (diazomethane) displayed a strong hydroxyl band at 2.9 μ.

Cyclization of Farnesylacetic Acid (VIII). (a) Model Cyclization of Geranylacetic Acid.—A solution of geranylacetic acid[32] in 20 ml. of 98–100% formic acid containing 1.5 ml. of concd. sulfuric acid was cyclized essentially according to the conditions used by Caliezi and Schinz for the related cyclization of farnesic acid.[14a] After 2 days at 0°, the deep red solution was diluted with 75 ml. of ether and extracted with water, and with 10% sodium bicarbonate solution. Evaporation of the dried (magnesium sulfate) solution gave 3.9 g. of neutral product, b.p. 110–115° (0.5 mm.). Redistillation gave 2.0 g. (25%) of the bicyclic lactone as a colorless oil having a strong cedar odor; b.p. 112° (0.5 mm.), $n^{25.5}D$ 1.4808.

(32) M. O. Forster and D. Cardwell, *J. Chem. Soc.*, 1338 (1913).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.44; H, 10.59.



XXXI

The lactone XXXI was a δ-lactone (absorption at 5.8 μ) and was bicyclic (no absorption of hydrogen over platinum; no uptake of perbenzoic acid.

(b) **Cyclization of Farnesylacetic Acid.**—Farnesylacetic acid was prepared essentially as later described by Dietrich and Lederer,[25] starting from either farnesol or nerolidol. The farnesylacetic acid thus obtained had b.p. (bath temp.) 155–160° (0.3 mm.), $n^{25}D$ 1.4865 (reported[25] $n^{19}D$ 1.4870). It gave a benzylthiuronium salt, m.p. 116.5–117° after crystallization from ethyl acetate, which decomposed readily on standing and did not give good analytical data.

Cyclization of Farnesylacetic Acid (VIII) to *dl*-Ambreinolide.—Farnesylacetic acid (27 g.) was cyclized with 65 ml. of 98–100% of formic acid at 100° for 20 minutes.[25] The neutral fraction which resulted (8 g.) was hydrolyzed with 5% aqueous alcoholic potassium hydroxide; the hydrolysis mixture was poured into water and was extracted repeatedly with ether. After cooling to 5° the aqueous layer was acidified with 20% hydrochloric acid and immediately re-extracted with ether. The ether layer was washed with water and quickly extracted twice with 5% aqueous potassium carbonate. The neutral portion (fraction 1) was collected (0.6 g.) and consisted mostly of 5-membered lactones as determined by infrared absorption. Acidification of the aqueous layer, followed by ether extraction, gave a solution of the remainder of the material which was allowed to stand overnight with anhydrous magnesium sulfate. Filtration and extraction of the ether solution with 5% potassium carbonate solution gave 1.2 g. of neutral substance (fraction 2) in the ether. Acidification of the aqueous extract and ether extraction gave, after removal of the ether on the steam-bath, an oil which was kept overnight at room temperature. It then yielded 1.5 g. of neutral product (fraction 3) and an acidic fraction which gave 2.5 g. of neutral product (fraction 4) after warming on the steam-bath for 6 hours. The final acidic material weighed 1.5 g.

The infrared spectra of fractions 2 and 3 were essentially identical, but fraction 2 contained a small amount of γ-lactone (5.7 μ), wholly absent in fraction 3.

Fractions 2 and 3 were combined and chromatographed on a 17 × 30 mm. column of activated 80-mesh alumina (Merck). The portions eluted by 3:1 petroleum ether–benzene up to 1:1 petroleum ether–benzene crystallized on standing overnight. Recrystallization of these fractions from petroleum ether gave 120 mg. of crude *dl*-ambreinolide (XXI), m.p. 124–130°. Three further crystallizations from the same solvent afforded 25 mg. of beautifully formed colorless prisms, m.p. 135.5–137° (lit.[25] m.p. 136–138°). The infrared spectrum was identical with that of natural *d*-ambreinolide (obtained through the courtesy of Dr. E. Lederer).

In subsequent experiments the isolation procedure was conveniently simplified by omitting the separation of fraction 1 and combining the spontaneous lactonization steps for fractions 2 and 3 above. Further, the chromatographic separation proved unnecessary since, on seeding a petroleum ether solution cooled to 0°, the lactone-fraction (corresponding to 1, 2 and 3 above) readily gave crystalline *dl*-ambreinolide.

Effect of Cyclization Conditions on Yield of *dl*-Ambreinolide.—(a) From 10 g. of farnesylacetic acid cyclized by 35 ml. of formic acid under the previously described conditions and worked up in the simplified manner just outlined, 200 mg. of *dl*-ambreinolide, m.p. 128–134°, was obtained. One recrystallization from benzene–petroleum ether raised the m.p. to 135–137°, yield 155 mg.

(b) From 20 g. of farnesylacetic acid cyclized by dropwise addition during a half-hour to 200 ml. of a well-stirred benzene–petroleum ether (3:1) solution of stannic chloride (25 g.) held at 35–40° for 2 hours, 650 mg. of *dl*-ambreinolide, m.p. 130–135°, was isolated from the spontaneous lactone fraction weighing 2.3 g. (total initial lactonic product weighed 12.4 g.). One recrystallization gave 550 mg., m.p. 135.5–137°.

(c) From 5 g. of farnesylacetic acid cyclized with a solution of 15 g. of stannic bromide in 100 ml. of 3:1 benzene–petroleum ether, at 25° overnight, a yield of 145 mg. of recrystallized *dl*-ambreinolide, m.p. 135–137°, was obtained from the spontaneous lactone fraction weighing 0.65 g.

With ether formic acid–sulfuric acid, under the conditions described earlier for the cyclization of geranylacetic acid, or with stannic chloride in nitromethane at room temperature, considerable quantities of γ-lactones were present in the original neutral fraction as shown by infrared spectra. With boron trifluoride etherate in benzene or stannic chloride in benzene at 40° very little γ-lactone appeared to be formed.

Also examined but found unsatisfactory or ineffective were 85% phosphoric acid, 66% sulfuric acid, anhydrous aluminum bromide in benzene and trace amounts of stannic chloride in benzene–petroleum ether, all studied at various temperatures ranging from −20 to +50°.

Bicyclofarnesylacetic Acid (XXV) from *dl*-Ambreinolide.—Treatment of 1.0 g. of *dl*-ambreinolide with methanolic sulfuric acid, following the procedure described by Ruzicka and Lardon for the natural substance,[33] but in the presence of a few drops of pyridine, gave an unsaturated ester fraction which was hydrolyzed to an acid which crystallized readily in contact with petroleum ether. It had m.p. 139–140° after recrystallization from benzene–petroleum ether (lit.[25] m.p. 122–123°); yield 300 mg. (30%).

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.42; H, 10.81.

The acid was treated with an excess of oxalyl chloride in benzene at room temperature for a few hours and, after removal of solvent and excess reagent in vacuum on the steam-bath, with aniline in benzene. Recrystallization of the crude anilide from methanol gave the pure anilide XXIII, m.p. 130.5–132°.

Anal. Calcd. for $C_{23}H_{33}ON$: C, 81.36; H, 9.80. Found: C, 81.38; H, 9.92.

The bicyclic acid XXV has a tetrasubstituted bond as shown by the absence of infrared absorption at 12.3 μ (in carbon disulfide). The ultraviolet spectrum confirmed this.[27]

Bicyclic Anilide XXII from Crude Tricyclic Lactone. Application of the procedure just described to 1.5 g. of the total lactone product obtained by formic acid–sulfuric acid cyclization of farnesylacetic acid (*cf.* cyclization of geranylacetic acid previously described) gave an oily anilide which crystallized on trituration with methanol to give *ca.* 35 mg. of anilide, m.p. 164–168°. Recrystallization from methanol gave the pure bicyclic anilide XXII, m.p. 169–170°.

Anal. Calcd. for $C_{23}H_{33}ON$: C, 81.36; H, 9.80. Found: C, 81.59; H, 9.90.

Synthesis of β-Monocyclofarnesylacetic Acid (X).—To a solution of 1.5 moles of freshly prepared sodium acetylide in 1 liter of anhydrous liquid ammonia was added dropwise, with rapid stirring, a solution of 52.5 g. (0.271 mole) of dihydro-β-ionone in 400 ml. of anhydrous ether. After evaporation of the ammonia the product was obtained by adding ice and ammonium chloride and extracting with ether. The unreacted ketone was removed as its semicarbazone[14b] and the ethynylcarbinol was removed by extraction with petroleum ether. Distillation of the dried extracts afforded 34.5 g. (58%) of carbonyl-free (infrared) product, b.p. 106–108° (0.5 mm.), $n^{25}D$ 1.4876.

Semi-hydrogenation of the pure ethynylcarbinol was carried out by treating a solution of 34.0 g. (0.154 mole) of the substance in 175 ml. of pyridine with hydrogen in the presence of 3 g. of a 2% Pd–$CaCO_3$ catalyst. The absorption of one equivalent of hydrogen took about 30 minutes and the hydrogenation then was interrupted. Removal of catalyst and solvent gave an oily residue which was distilled to give 34.0 g. (98%) of colorless vinylcarbinol, b.p. 105–107° (0.5 mm.), $n^{25}D$ 1.4897. The infrared spectrum indicated the complete absence of any unreduced ethynylcarbinol, while the characteristic terminal methylene absorption (6.1 and 11.2 μ) was sharply defined.

For transformation into the allylic primary bromide a solution of 40 g. (0.180 mole) of the vinylcarbinol in 250

(33) L. Ruzicka and F. Lardon, *Helv. chim. Acta*, **29**, 912 (1946); *cf.* ref. 27.

ml. of petroleum ether containing 2 ml. of pyridine was cooled to 0° and was treated under nitrogen, with stirring, with a solution of 19.5 g. of phosphorus tribromide in 50 ml. of petroleum ether. After standing overnight at room temperature, the bromide was recovered in the usual manner, giving a crude yield of *ca.* 50 g. (98%).

This was used directly to alkylate the sodium salt of malonic ester (from 32 g. of malonic ester and 4.8 g. of sodium hydride in 3:1 benzene–dimethyl formamide). After two days at room temperature, the neutral product was recovered in the usual manner and hydrolyzed directly with 20% aqueous potassium hydroxide with stirring on the steam-bath for 10 hours. The acidic material obtained from the hydrolysis was decarboxylated during the distillation to give 33 g. (69.5%) of β-monocyclofarnesylacetic acid (X), b.p. 150–155° (0.5 mm.), $n^{25}D$ 1.4953. The acid was characterized as its benzylthiuronium salt which crystallized in small plates, m.p. 144–145°, from ethanol.

Anal. Calcd. for $C_{25}H_{38}O_2N_2S$: C, 69.70; H, 8.90. Found: C, 69.46; H, 8.87.

Synthesis of α-Monocyclofarnesylacetic Acid (IX).—Pure dihydro-α-ionone was prepared essentially according to the directions of Kandel[34] in 60% yield from α-ionone.

In the formation of the ethynylcarbinol from this ketone lithium acetylide gave a somewhat better yield (68%) than sodium acetylide by the procedure described above in the β-series. The carbinol had b.p. 101–103° (0.3 mm.), $n^{26}D$ 1.4875. The infrared spectrum was similar to that of the compound of the β-series but had an additional band at 12.3 μ (in carbon disulfide).

The corresponding vinylcarbinol, b.p. 100–102° (0.3 mm.), $n^{26}D$ 1.4872, was obtained in 95% yield by the partial catalytic hydrogenation described for the β-series. Its conversion into the bromide, followed by malonic ester alkylation, hydrolysis and decarboxylation, as previously described, led to α-monocyclofarnesylacetic acid (X), b.p. 150–155° (0.3 mm.), $n^{25}D$ 1.4950. The yield from the vinylcarbinol was 72%. The benzylthiuronium salt, m.p. 144–144.5°, crystallized in small plates from ethanol.

Anal. Calcd. for $C_{25}H_{38}O_2N_2S$: C, 69.70; H, 8.90. Found: C, 69.71; H, 9.00.

A mixed m.p. of this derivative with the thiuronium salt (m.p. 144–145°) from β-monocyclofarnesylacetic acid (IX) gave no depression. The infrared spectrum of the α-acid showed a band at 12.2 μ (in carbon disulfide) which was not present in the isomer.

Cyclization of β-Monocyclofarnesylacetic Acid. (a) With Formic Acid.—From 25 g. of β-monocyclofarnesylacetic acid cyclized with 65 ml. of 98–100% formic acid at 100° for 20 minutes, 14 g. of neutral product was obtained from which by hydrolysis and spontaneous relactonization, as described with farnesylacetic acid, 580 mg. of racemic ambreinolide, m.p. 125–134°, was obtained. Recrystallization from benzene–petroleum ether gave 490 mg. of pure *dl*-ambreinolide (XXI), m.p. and mixed m.p. 135–137°.

(b) **Stannic Chloride Cyclization.**—From 9.0 g. of α-monocyclofarnesylacetic acid (IX) cyclized with 15 g. of stannic chloride in 125 ml. of benzene–petroleum ether (3:1) at 35–40°, 200 mg. of *dl*-ambreinolide (XXI), m.p. 128–134°, was isolated by the usual procedure. One recrystallization gave 180 mg., m.p. 135–137°.

Use of stannic bromide in place of stannic chloride gave no more than a trace of *dl*-ambreinolide as the only crystalline product isolated.

Cyclization of α-Monocyclofarnesylacetic Acid. (a) Stannic Chloride Cyclization.—From 10 g. of acid IX cyclized with 15 g. of stannic chloride in 150 ml. of 3:1 benzene–petroleum ether at 35–40°, followed by standing overnight at 20–25°, 800 mg. of crystalline product, m.p. 105–120°, was obtained from the spontaneous lactone fraction. Recrystallization from benzene–petroleum ether or methanol failed to improve the melting point. Chromatography on activated, acid-washed alumina achieved only a partial separation into *dl*-ambreinolide (XXI) (first crystalline fraction), m.p. 130–135° after one recrystallization, and *dl*-isoambreinolide (XXIV), described below. Repetition of this cyclization with 7.5 g. of IX and 15 g. of stannic chloride in the same solvent pair, at room temperature, resulted in a somewhat lower yield of crystalline product (120 mg.) which, however, appeared to be largely *dl*-ambreinolide (m.p. and mixed m.p. 134–137° after one recrystallization from benzene–petroleum ether).

(b) **Stannic Bromide Cyclization. Isolation of *dl*-Isoambreinolide (XXIV).**—From 7.5 g. of the acid IX cyclized with 15 g. of stannic bromide in 150 ml. of 3:1 benzene–petroleum ether at room temperature overnight, 445 mg. of crystalline product, m.p. 104–115°, was isolated from the spontaneous lactone fraction. On recrystallization from benzene–petroleum ether this gave 320 mg. of colorless, rectangular prisms, melting largely at 103–107° (clear at 115°). Repetition of this experiment gave 570 mg. of crude crystalline product, m.p. 100–107°, which gave on recrystallization 540 mg., m.p. 103–106°. Two further crystallizations from benzene–petroleum ether gave pure *dl*-isoambreinolide (XXIV), m.p. 103–104°.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.07; H, 10.87.

The isoambreinolide thus obtained was shown to have the same ring junction stereochemistry as *dl*-ambreinolide since treatment of 50 mg. of the pure XXIV, m.p. 103–104°, with methanolic sulfuric acid, followed by hydrolysis, as described in the case of ambreinolide itself, gave 22 mg. of the unsaturated acid XXV. On recrystallization from benzene–petroleum ether this acid had m.p. 138–139°, and a mixed m.p. with the *dl*-β-bicyclofarnesylacetic acid (XXV) from *dl*-ambreinolide was undepressed.

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(34) J. Kandel, *Ann. chim.*, **11**, 73 (1939).