DITERPENOIDS

MINORU TSUTSUI[1] AND ETHEL ASHWORTH TSUTSUI[2]
Pharmaceutical Institute, Tokyo University, Tokyo, Japan

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[1] Present address: Monsanto Chemical Company, Dayton, Ohio.

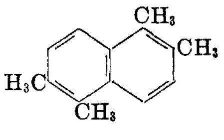
[2] Present address: Charles F. Kettering Foundation and Antioch College, Yellow Springs, Ohio.

I. INTRODUCTION

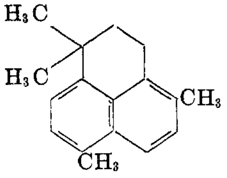
Among the important constituents of essential oils of plants are terpenes, which may be considered to be derived from isoprene, C_5H_8. Terpenes in general include: monoterpenes, $C_{10}H_{16}$ (two isoprenoid units); sesquiterpenes, $C_{15}H_{24}$ (three isoprenoid units); diterpenes, $C_{20}H_{32}$ (four isoprenoid units); polyterpenes $(C_5H_8)_n$ and related derivatives (for example, acids, alcohols, and ketones). Strictly speaking, however, the term terpene should be restricted to the acyclic or cyclic hydrocarbons from essential oils which have the composition $C_{10}H_{16}$ (monoterpenes). In a similar manner, the word diterpene should be used only to refer to the hydrocarbon constituents of essential oils which have the formula $C_{20}H_{32}$. These hydrocarbons are rarely found naturally. Diterpene derivatives (diterpenoids), i.e., acids, lactones, alcohols, ethers, and ether derivatives, are frequently found in nature in abundance. Some of these diterpene derivatives, however, do not conform to the "isoprenoid rule." This review deals with a few diterpenes (hydrocarbons) but mainly with diterpene derivatives.

The rigid establishment of the structure of abietic acid in 1941 (141) stimulated investigations by a number of workers which led to the elucidation of the structures of other diterpenes. The evidence leading to the formulation of structures for a number of diterpenes has been reviewed previously (144). The present article will attempt to review only the remarkable progress in the field of diterpenoid chemistry which has come about in the past few years, including the chemistry of certain diterpenoids not covered in recent texts (105, 158).

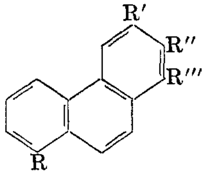
Such recent progress in the isolation, determination of structure, and total synthesis of diterpenes previously uninvestigated because of the complexity of their structures has been aided greatly by advanced techniques such as chromatography, counter-current distribution, and infrared spectroscopy. The classical procedure of dehydrogenation of the diterpenoid or of its degradation products still plays a key role, however, in the elucidation of structure. The usual products obtained upon the dehydrogenation of diterpenes have been retene (165), pimanthrene (132) and 1,7,8-trimethylphenanthrene (138). Other hydrocarbons and bases have recently been obtained by the dehydrogenation of some new diterpenoids. From cativic acid and eperuic acid, 1,2,5,6-tetramethylnaphthalene (I) (63), 1,2,5-trimethylnaphthalene (63, 90), and 1,1,4,7-tetramethylphenalan (II) (90) have been obtained. Diterpenes such as vinhaticoic and vouacapenic acids, which possess a furan ring in their structures, have yielded 1,8-dimethylphenanthrene (III), 1,6,8-trimethylphenanthrene (IV), and 2-ethyl-1,8-dimethylphenanthrene (V) (89). 1,7-Dimethylphenanthrene (130) was obtained by the dehydrogenation of the diterpenic lactones, rosenonolactone and rosololactone. The hydrocarbons 6-ethyl-1-methylphenanthrene (VI), 1-methylphenanthrene, and 6-ethyl-1-methyl-3-azaphenanthrene (LXX) (82) have been formed upon the dehydrogenation of *Aconitum* and *Delphinium* alkaloids, and 7-ethyl-1-methylphenanthrene (VII) and 7-ethyl-1-methyl-3-azaphenanthrene (LXXXII) (8) from *Garrya* alkaloids.



I

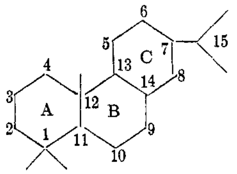


II

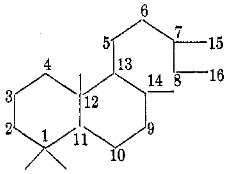


III: R, R″ = CH_3
IV: R, R′,R‴ = CH_3
V: R, R‴ = CH_3; R″ = C_2H_5
VI: R = CH_3; R′ = C_2H_5
VII: R = CH_3; R″ = C_2H_5

The assignment of a numbering system to the carbon atoms in the diterpene skeleton system is in a confused state in the literature owing to the use by the workers in this field of different individual numbering systems. The numbering to be used in general in this review follows that of phenanthrene in the case of abietic acid and the compounds related to it, as shown in formula VIII. The numbering of the bicyclic diterpenes like cativic acid is shown in formula IX.



VIII



IX

II. Acids

A. INTRODUCTION

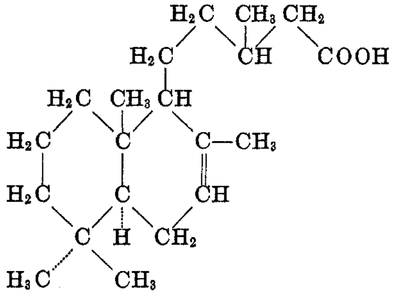
Remarkable progress in the area of the diterpenic acids has been made in the past few years; structures have been determined for several bicyclic diterpenic acids and those diterpenic acids which have a furan ring in their molecules. New acids of the retene and pimanthrene types[3] have been isolated and structures for them have been proposed.

Since resin acids form mixed crystals, some mixtures of resin acids were believed previously to be pure compounds. The improvement of separation techniques for resolving the mixed crystals led to the revelation that densipimaric acid (159) and dextrosapinic acid (102) are both mixtures of several different

[3] Tricyclic diterpenes can be classified into two types, according to the product obtained upon dehydrogenation: namely, the retene and the pimanthrene types. Some chemists still prefer to use the classification into the abietic and pimaric types. This designation, however, sometimes causes confusion. For instance, levopimaric acid belongs not to the pimaric type, but to the abietic type.

resin acids. Miropinic acid, considered previously to have an unknown structure, has been found to be identical with isodextropimaric acid (31).

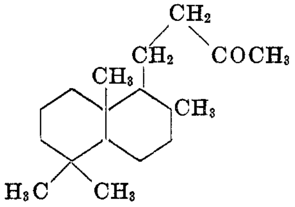
B. CATIVIC ACID



X

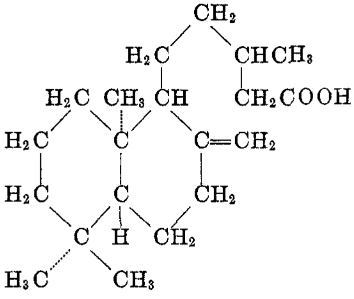
Cativic acid

Cativic acid (X), $C_{20}H_{34}O_4$, $[\alpha]_D = -6.54°$, was isolated (88) from the oleoresin exuded by *Prioria capaifera* Griseb., the cativa tree. Grant and Zeiss later succeeded in isolating the acid in crystalline form, m.p. 80–82°C., and in establishing its structure (63). The bicyclic skeleton of the acid was given conclusively by dehydrogenation experiments. With palladium–charcoal the acid was dehydrogenated to 1,2,5,6-tetramethylnaphthalene, which was also isolated from the dehydrogenation of ambreinolide (98). Upon dehydrogenation with selenium the acid gave 1,1,4,7-tetramethylphenalan, which was obtained by the dehydrogenation of agathic acid (137) and was also synthesized (34). The acid absorbed one mole equivalent of hydrogen. The position of the double bond was deduced from the results of ozonization. Since no carbon atoms were lost when the acid was ozonized, cativic acid contains one element of unsaturation which must be located in the ring system. The ozonolysis product gave a positive iodoform reaction; C-14 must therefore be one of the double-bond terminals. The ease of esterification of cativic acid indicates that the carboxyl group is not situated in the usual sterically hindered 1-position. The location of the carboxyl group and the key elucidation of the structure were given by the following degradation. A two-step Barbier–Wieland degradation of the dihydro ester yielded a methyl ketone. The semicarbazone of the ketone was found to be identical to that derivative of the methyl ketone (XI) arising from the degradation of manoöl (81). The experimental evidence outlined above leaves no doubt but that cativic acid is correctly represented by formula X as shown.



XI

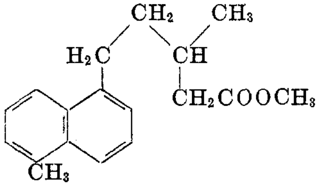
C. EPERUIC ACID



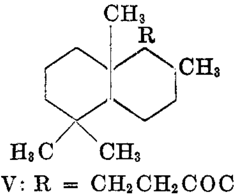
XII

Eperuic acid

Eperuic acid is the chief constituent of an oleoresin derived from the wallaba tree (*Eperua falcata* and other *Eperua* species) of British Guiana. It has been shown, principally by the investigations of King and Jones, to be a bicyclic diterpene, $C_{20}H_{34}O_2$, closely related to cativic acid and possessing formula XII (90). Since dehydrogenation of the acid gave only naphthalene derivatives, it probably possesses a bicyclic skeleton. Dehydrogenation with selenium yielded 1,2,5-trimethylnaphthalene. Under less drastic conditions two other naphthalene derivatives were obtained: 1,1,4,7-tetramethylphenalan and an ester which on hydrolysis yielded a crystalline acid (XIII). Eperuic acid, which absorbs one mole of hydrogen, has no absorption at 210 mμ, from which it follows that the ethylenic bond and the carboxyl group are not conjugated. Chemical proof of the position of the double bond was furnished by ozonolysis and degradation. Ozonolysis of methyl eperuate gave a keto ester, $C_{20}H_{34}O_3$, together with formaldehyde and formic acid; hence the double bond must reside in a terminal methylene group. The action of selenium on the keto ester yielded 1,5-dimethylnaphthalene. A two-step Barbier–Wieland degradation of the side chain of the dihydro ester gave a ketone (XIV), which establishes the relative position of the side-chain methyl group. Further oxidation with sodium hypoiodite degraded this ketone to a C_{17} acid (XV) (37), which was also obtained from ambrein. This degradation also rigidly proved the correctness of the bicyclic structure for eperuic acid.



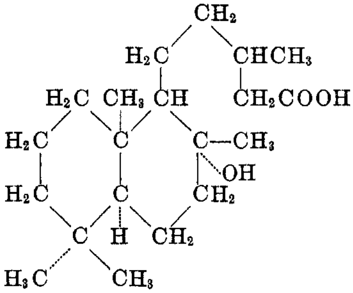
XIII



XIV: R = $CH_2CH_2COCH_3$
XV: R = CH_2CH_2COOH

The startling new fact emerged that the angular methyl group at C-12 was α-oriented, in which position the A/B ring junction is antipodal to that of the other polyterpenes and steroids. The evidence for and the discussion of this stereochemical assignation are reviewed in the discussion of labdanolic acid.

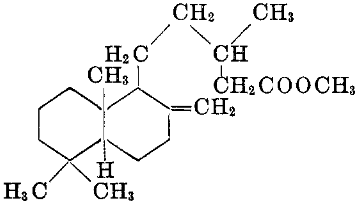
D. LABDANOLIC ACID



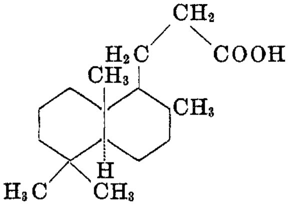
XVI
Labdanolic acid

Labdanolic acid (XVI), $C_{20}H_{30}O_2$, m.p. 114–115°C., $[\alpha]_D = +13.5°$, was first isolated from gum labdanum (39). Since dehydration of methyl labdanolate with phosgene and pyridine gave an ester (XVII) of which methyl eperuate is a stereoisomer, labdanolic acid is undoubtedly very similar in constitution to eperuic and cativic acids.

The exact configurational difference between labdanolic and eperuic acids has been clearly shown by studies of their degradation products. Comparison of various degradation products of the two acids showed that corresponding derivatives had identical or similar physical constants, but opposite rotations. This suggests the startling conclusion that eperuic acid has a carbon skeleton which is the mirror image of that of rings A and B of all the known natural di- and triterpenes and steroids. Further evidence supporting this view was given by the quantitative difference in the rotatory dispersion curves of the keto esters derived from the two acids, this result indicating that the two esters must be mirror images (37, 38). That formula XVI represents labdanolic acid was firmly established by the degradation of the acid to a known compound (XVIII), which was obtained from marrubiin (35) and ambrein (139). The only stereochemical feature of the structure of labdanolic acid which remains to be elucidated is the configuration at C-14.

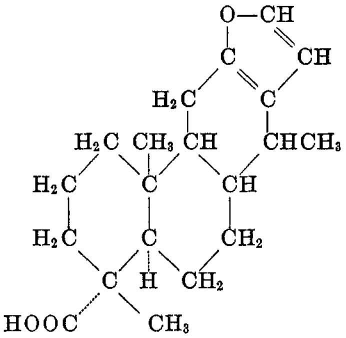


XVII



XVIII

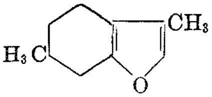
E. VINHATICOIC ACID



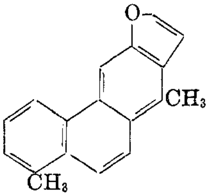
XIX

Vinhaticoic acid

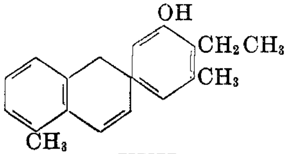
Vinhaticoic acid (XIX), $C_{20}H_{28}O_3$, m.p. 153–154°C., $[\alpha]_D = +73°$, was isolated as the methyl ester from the light-petroleum-soluble constituents of the heartwood of *Plathymenia reticulata* Benth. or *Chloroleucon vinhatico* Record, both of which are Brazilian trees of the Leguminosae family (91). The entire elucidation of the structure of this new tetracyclic diterpene acid, which has a furan ring in its molecule, has now been achieved. The existence of a furan ring was first inferred from the fact that the acid has an unreactive third oxygen atom and a conjugated diene grouping. The maleic anhydride adduct of vinhaticoic acid is relatively unstable, as are those of other furano compounds. Moreover, there is a close resemblance between certain reactions of its methyl ester and those of the authentic furanohydrocarbon, menthofuran, $C_{10}H_{14}O$ (XX). In addition to these supporting results, a series of dehydrogenation experiments afforded conclusive evidence for the presence of a furan ring and decided the point of attachment of this ring to the main skeleton of the acid (89). Dehydrogenation of methyl vinhaticoate with sulfur yielded 1,8-dimethylfuranophenanthrene (XXI). Upon dehydrogenation with selenium, 6-hydroxy-7-ethyl-1,8-dimethylphenanthrene (XXII) was obtained. The anhydro derivative of a compound obtained from methyl vinhaticoate by oxidation with perphthalic acid, a lactone (XXIII), yielded 1,7,8-trimethylphenanthrene upon dehydrogenation by selenium. The pyrolysis of an anhydro compound (XXIV) gave 7-ethyl-1,8-dimethylphenanthrene, which was later synthesized (84).



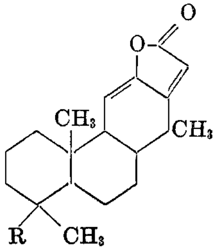
XX



XXI

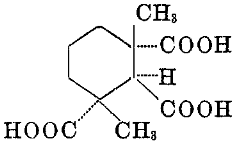


XXII



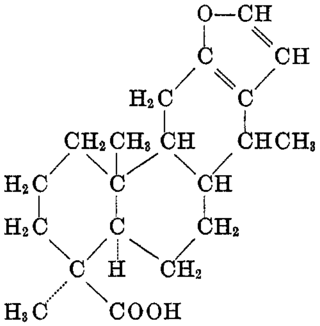
XXIII: R = $COOCH_3$
XXIV: R = CH_2OH

The stereochemistry of vinhaticoic acid at positions C-1, C-11, and C-12 was established from the products of oxidative degradation. The oxidation of methyl tetrahydrovinhaticoate with nitric acid yielded a C_{11} acid, a dimethylcyclohexanetricarboxylic acid (XXV) of known configuration, also obtained from abietic acid. The A/B ring junction in vinhaticoic acid was thus shown to have the trans fusion (94).



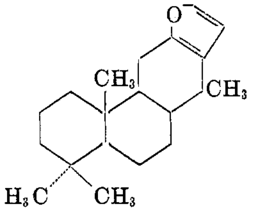
XXV

F. VOUACAPENIC ACID



XXVI
Vouacapenic acid

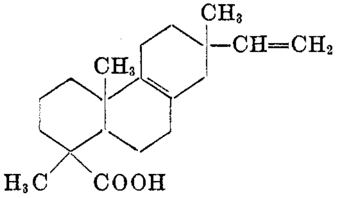
The ester of this diterpene acid, $C_{21}H_{30}O_3$, m.p. 103–104°C., $[\alpha]_D = +101°$, was first found by Spoelstra (148) in *Vouacapoua americana* and was again isolated from the wood of *V. macropetala*, where it occurs with vouacapenol acetate, the related carbinol ester (89). Since selenium dehydrogenation of vouacapenic acid (XXVI), m.p. 227–230°C. (sintering at 216°C.), $[\alpha]_D = +108°$, yielded 2-ethyl-1,8-dimethylphenanthrene, which is similarly derived from methyl vinhaticoate, the structures of vouacapenic and vinhaticoic acids must be very closely related. Conclusive evidence on this point was obtained from the reduction of the carboxyl groups at position 1 in these two diterpene acids to methyl groups, yielding identical compounds (XXVII) in both cases. The two diterpenes, therefore, are C-1 epimers, and the C-1 carboxyl and the C-12 angular methyl groups in XXVII must be in the cis configuration to each other. In view of its relationship to vinhaticoic acid, vouacapenic acid is undoubtedly correctly represented by formula XXVI. The furan ring of vouacapenic acid forms a stable adduct with maleic anhydride (1).



XXVII

G. NEOISODEXTROPIMARIC ACID (162) (ISOMERIC 7-ISODEXTROPIMARIC ACID)

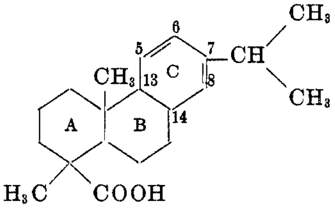
Neoisodextropimaric acid and 7-isodextropimaric acid were isolated (163, 164) as the major components exhibiting antibacterial action from the fruits of *Juniperus rigida* and *J. conferta.* The structure of neoisodextropimaric acid, $C_{20}H_{30}O_2$, m.p. 162.5–165°C., $[\alpha]_D = -18.9°$, was proposed to be that of Δ^{13}-isodextropimaric acid (XXVIII) (164). Since XXVIII, however, has a melting point of 106–107°C. and an optical rotation of +113°, this new acid must be the 9:14-isomer (59). The new acid was isomerized to Δ^{13}-isodextropimaric acid with hydrogen chloride in chloroform (58, 59).



XXVIII

H. PALUSTRIC ACID

Palustric acid was isolated from the oleoresin of *Pinus palustris* and *P. caribaea* by means of partition chromatography (101). Palustric acid, $C_{20}H_{30}O_2$, m.p. 162–167°C., $[\alpha]_D = +71.6°$, was isomerized to abietic acid with mineral acid. The maleic anhydride adduct of this acid was identical with that of levopimaric acid; hence palustric acid must belong to the retene type acids. Since palustric acid exhibits maximum absorption in the ultraviolet region at 265–266 mμ, it was suggested that the conjugated double bonds in ring C were in the 5:6 and 7:8 positions, as shown in formula XXIX (101). Recent infrared data, however, indicate that the double bonds are most probably located at positions 7:8 and 13:14 (33).

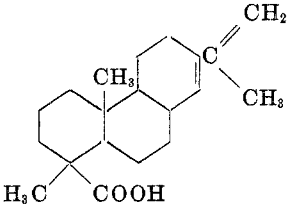


XXIX

Supporting evidence (142) for location of the two double bonds in the 7:8 and 13:14 positions has been furnished by the photosensitized oxidation of palustric acid, with determination of the nuclear magnetic resonance and stability toward base of the resulting peroxide. The transannular palustric acid peroxide was found to be stable in the presence of excess base. This stability toward base showed that the photoperoxide group is attached to two tertiary carbon atoms. The instability toward base of dialkyl peroxides in which the peroxide group is attached to one or more secondary carbon atoms has been demonstrated (107). Hence the following positions for the location of the conjugated diene system were ruled out: 5:6-7:8, 5:6-13:14, 5:13-8:14, and 6:7-8:14. The similarity of the specific rotations of palustric acid, $[\alpha]_D = +71.6°$, and dehydroabietic acid, $[\alpha]_D = +62°$, would argue for the 7:8-13:14 assignment in preference to the 6:7-5:13 arrangement.

I. TELOABIETIC ACID

Teloabietic acid[4] was isolated (160) as one of the components of so-called densipimaric acid. Teloabietic acid, m.p. 151–153°C., $[\alpha]_D = +60°$, was shown to be relatively unreactive towards maleic anhydride, even though it exhibited maximum absorption at 237.5 mμ. Partial ozonolysis yielded formic acid. Upon dehydrogenation with palladium–charcoal, the sole product was retene. Structure XXX was proposed upon consideration of all the chemical evidence.



XXX

J. CARIBEIC ACID

Caribeic acid, $C_{20}H_{30}O_3$, $[\alpha]_D = +32°$, was isolated from the oleoresin of the slash pine (69). Dehydrogenation of the acid yielded a hydrocarbon thought to be pimanthrene or retene, but further characterization has not been reported as yet.

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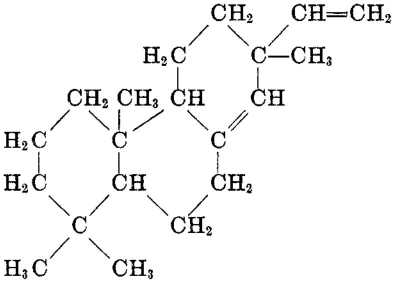
[4] The acid was first named isoabietic acid, but this name was later changed to avoid confusion.

III. Hydrocarbons, Alcohols, Lactones, and Miscellaneous Related Compounds

The structures of cafestol, columbin, and marrubiin, each of which contains a furan ring in its molecule, have been almost completely elucidated by the enthusiastic investigation of several chemists. The application of a new physical tool, proton magnetic resonance, has aided in the formulation of structures for such diterpenoids by indicating the position of substitution on the furan ring (45).

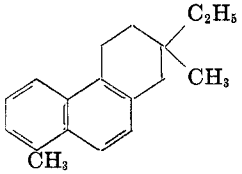
Cafestol is the first naturally occurring diterpene to be isolated which contains an ethenoid group in place of a *gem*-dimethyl group at position C-1. Since gibberellins, which possess plant-growth-promoting properties, and stevioside, considered to be the sweetest natural product yet isolated, are thought to be diterpenoid analogs, their chemistry is briefly described in this section.

A. RIMUENE (TOTARENE)



XXXI
Rimuene

The tricyclic diterpene rimuene (XXXI), $C_{20}H_{32}$, m.p. 55°C., $[\alpha]_D = +44.7°$, was isolated from the essential oil of the rimu tree, *Dacrydium cupressinum*, endemic to New Zealand. Totarene, isolated from the essential oil of the Totara tree, *Podocarpus Totara*, is evidently identical with rimuene (13). Dehydrogenation made it evident that rimuene has the pimanthrene type skeleton. The two double bonds in the molecule are not conjugated. One must be a methylenic double bond, since ozonolysis yielded formaldehyde. The position of the other double bond was deduced to be at position 8:14 from the following experiment. Oxidation of dihydrorimuene with monoperphthalic acid gave a liquid oxide. Dehydrogenation of the product from the reaction of the oxide and methylmagnesium iodide resulted in 1,2,8-trimethylphenanthrene. Partial catalytic dehydrogenation of dihydrorimuene yielded a compound (XXXII) which was also obtained from the dihydro derivatives of dextro- and isodextropimaric acids

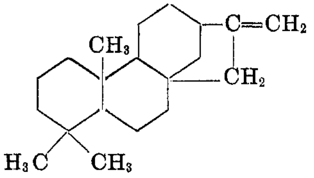


XXXII

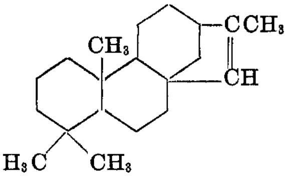
(74). The presence of a *gem*-dimethyl group in rimuene was indicated by its infrared absorption spectrum. Structure XXXI was consequently assigned to rimuene (26).

B. PHYLLOCLADENE

Phyllocladene, $C_{20}H_{32}$, m.p. 98°C., $[\alpha]_D = +15.8°$, was first isolated (2) from the leaf oil of *Phyllocladus rhomboidalis.* Phyllocladene and isophyllocladene, m.p. 110.5–112°C., $[\alpha]_D = +23°$, occur together in the essential oil of *Phyllocladus trichomanoides* (28). Phyllocladene is isomerized to isophyllocladene by treatment with alcoholic sulfuric acid. Dehydrogenation of phyllocladene with selenium yielded a mixture of pimanthrene and retene (21), together with two other hydrocarbons of undetermined constitution. Catalytic hydrogenation of isophyllocladene gave a saturated dihydrophyllocladene, which was also obtained upon hydrogenation of phyllocladene. Observations on the oxidation of phyllocladene and isophyllocladene considered in conjunction with the hydrogenation results just mentioned led to the conclusion that the two compounds are related in the same way as α- and β-pinene, that is, the double bond in the methylene group shifts into the ring. Brandt (22) suggested formula XXXIII as representative of phyllocladene, when isophyllocladene is formulated as XXXIV. A consideration (20) of the infrared spectra of phyllocladene and isophyllocladene supported the above proposed structures.



XXXIII

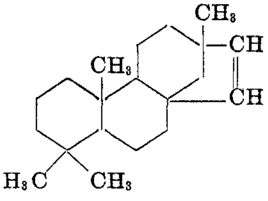


XXXIV

A study of the rotatory dispersion curve (52) of phyllocladene showed that the A/B ring junction is required to be antipodal to that of other polyterpenes and steroids, and that the angular methyl group at C-12 is most probably α-oriented.

C. MIRENE

The diterpene mirene, isolated from the leaf of *Podocarpus ferruginea,* was shown to be a mixture of phyllocladene, *d*-α-podocarprene, and a new hydrocarbon, $C_{20}H_{32}$, $[\alpha]_D = +43.8°$, m.p. 59–60°C. (27). The name mirene was then transferred to the new hydrocarbon. Mirene was isomerized to isophyllocladene by heating with glacial acetic acid. Since dihydromirene is saturated, mirene is most probably tetracyclic. Structure XXXV was inferred for mirene from a con-

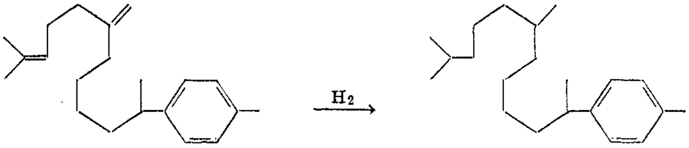


XXXV

sideration of its structural and biogenetic relationship to the diterpene pimaradiene (167).

D. ARTEMISENE AND AR-ARTEMISENE[5]

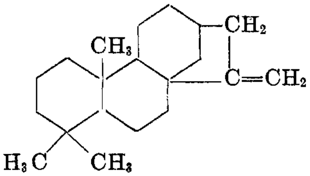
Artemisene, $C_{20}H_{32}$, $[\alpha]_D = -63°$, and ar-artemisene, $C_{20}H_{30}$, $[\alpha]_D = -19°$, both monocyclic diterpene hydrocarbons, were isolated from the fraction of wormwood oil boiling at 123°C. at 0.1 mm. pressure, by the use of chromatography (147). Upon catalytic hydrogenation of ar-artemisene, 2,6-dimethyl-*p*-tolylundecane (XXXVII) was obtained. From this evidence and from infrared data, ar-artemisene is most probably represented by formula XXXVI, 2-methyl-6-methylene-10-*p*-tolyl-2-undecene. Since artemisene and ar-artemisene exhibited practically identical infrared spectra, the authors suggested that these two diterpenes must possess identical carbon skeletons. The position of the aliphatic double bond of artemisene has not been reported, however.



XXXVI XXXVII

E. 4,4,10-TRIMETHYL-15-METHYLENE-8,13-CYCLOPENTANOPERHYDROPHENANTHRENE

A diterpene, $C_{20}H_{32}$, $[\alpha]_D = +18°$, b.p. 149–150°C., was isolated (66) from the essential oil of the wood of *Erythroxylon monogynum*. The molecular refraction of the compound indicated the presence of four rings and one double bond. Pimanthrene resulted upon dehydrogenation with selenium. Ozonolysis of the diterpene gave formaldehyde and a ketone which formed a semicarbazone with a melting point of 153–154°C. Although a tentative structure (XXXVIII) was proposed (67), no further work has been reported.



XXXVIII

A diterpenic alcohol, $C_{20}H_{32}O$, m.p. 118°C., with one double bond and a primary or secondary alcohol group, was isolated from a higher-boiling fraction of the oil (67). Upon dehydrogenation with selenium, pimanthrene resulted. No further studies on this alcohol have been reported.

F. CAFESTOL

Cafestol (formerly called cafesterol), $C_{20}H_{28}O_3$, was isolated (16) from the nonsaponifiable fraction of coffee oil. Cafestol, at the initiation of investigations on

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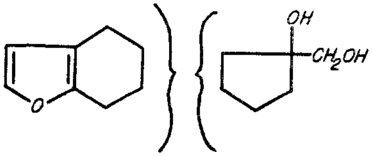
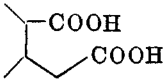
[5] The names were suggested by the authors in a private communication to the writers of this review.

its structure, was believed to possess a steroid skeleton from an erroneous report (145) that it possessed estrogenic activity. Extensive degradation experiments by Swiss workers resulted in the conclusion that cafestol is diterpenoid in nature (172). In addition to confirming an earlier report (146) of the presence of two oxygen atoms in a glycol grouping, the Swiss investigators established that the third oxygen atom formed part of a furan ring.

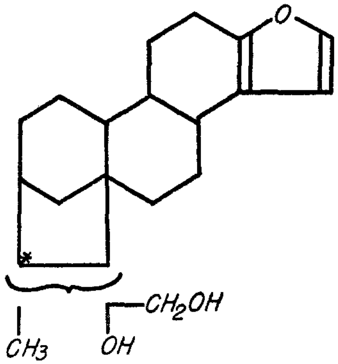
The formulation of a partial structure (XXXIX)—namely, a furan ring fused to a six-membered carbocyclic ring as well as a glycol grouping attached to a cyclopentane ring—was confirmed (55) by degradation and spectroscopic studies. Dehydrogenation (50) of partially degraded cafestol, in which the cyclopentane ring was degraded to a dibasic acid (XL) with a palladium catalyst, yielded 1-ethyl-2-hydroxyphenanthrene, the identity of which was later confirmed by synthesis (15). Structures XLI and XLII were then tentatively proposed to represent cafestol.



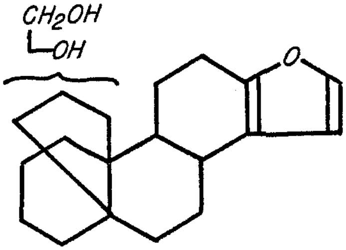
XXXIX



XL

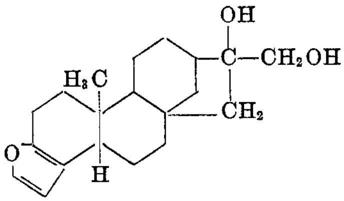


XLI



XLII

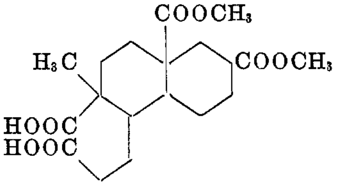
Exhaustive bromination of epoxynorcafestanone, a derivative of cafestol in which the furan ring was hydrogenated and the glycol grouping cleaved to a substituted cyclopentanone, led to a tribromo derivative (77), demonstrating that there are three active hydrogen atoms α to the carbonyl group. Furthermore, monobromination yielded monobromoepoxynorcafestanone, which was recovered unchanged after boiling with α-collidine (15). From these results, the glycol grouping is probably situated at the starred position in structure XLI. Since such substitution is reminiscent of phyllocladene, the structure of cafestol was then reformulated as XLIII.



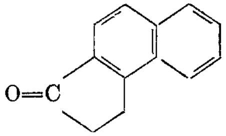
XLIII

Structure XLIII biogenetically would bear the same relation to phyllocladene that methylabietin (136) bears to abietic acid.

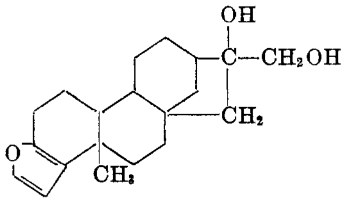
Haworth and Johnstone (76) recently suggested a different position for the angular methyl group pictured at position C-12 in structure XLIII. The evidence for this proposal follows. The conversion of cafestol into the tetrabasic acid XLIV was effected by a three-stage oxidation process. Dehydrogenation of XLIV with selenium yielded, along with other unidentified products, 4,5-benzendan-1-one (XLV) and 1-ethyl-2-methylnaphthalene. Unless one assumes the migration of an alkyl group, the formation of the latter compound cannot be explained on the basis of structure XLIII, but the dehydrogenation may be readily interpreted on the basis of structure XLVI. Structure XLVI, like that proposed for methyl vinhaticoate, cannot be divided into isoprene units. It has been suggested that such structures may be derived from a diterpenoid framework by migration of groups during the formation of the aromatic furan ring.



XLIV

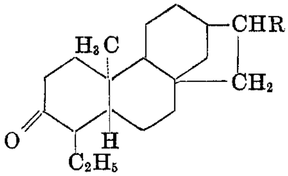


XLV



XLVI

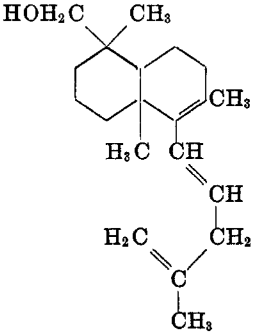
Djerassi, Cais, and Mitscher (51) emphasize that the angular methyl group in XLIII must be at C-12. Since the ketones XLVII and XLVIII and the corresponding monobromo derivatives all show negative Cotton effect rotatory dispersion curves, the A/B ring junction is required to be antipodal to that of other polyterpenes and steroids. This same configuration is the correct representation for the other members of the phyllocladene group, including the *Garrya* alkaloids. An example can be seen also in the case of eperuic acid, the structure of which was described previously. The result of Haworth and Johnstone's dehydrogenation can be interpreted most probably as a rearrangement or reduction of a carbonyl group to a methyl group (51).



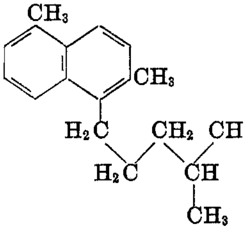
XLVII: R = H
XLVIII: R = CH_3

G. ELLIOTINOL

Elliotinol, $C_{20}H_{32}O$, $[\alpha]_D = +10.2°$, was isolated as the *p*-nitrobenzoate, m.p. 128–130°C., $[\alpha]_D = +74°$, from the neutral fraction of commercial gum rosin collected mainly from *Pinus elliotti* (129). Elliotinol is triply unsaturated, as shown by catalytic hydrogenation. Studies of the ultraviolet absorption curve of elliotinol showed that two of the double bonds are conjugated; one is tetrasubstituted, one is trans-disubstituted, and the remaining double bond is found in an isolated terminal methylene group. The reaction of maleic anhydride with elliotinol or its acetate readily gave an adduct having no specific ultraviolet absorption from 220 to 230 mμ. This adduct contained a terminal methylene group and a new substituted double bond. This result accounts for the arrangement of the three double bonds as shown in formula XLIX. Dehydrogenation of tetrahydroelliotinol yielded a trialkylnaphthalene, $C_{18}H_{24}$, probably 2,5-dimethyl-1-isohexylnaphthalene (L). The hydroxyl group in elliotinol is probably primary. Structure XLIX, which may well interpret all these results, was proposed for elliotinol.



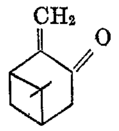
XLIX



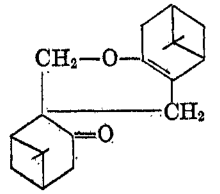
L

H. ARITASON

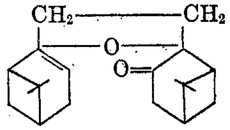
Aritason, $C_{20}H_{20}O_2$, m.p. 105–106°C., $[\alpha]_D = -118.8°$, was isolated from the essential oil of wild *Chenopodium ambrosioides* L. (155). Since distillation of aritason *in vacuo* at 80–150°C. gave *l*-pinocarvone (LI) in good yield, aritason is probably the dimer of LI. Structures LII and LIII, therefore, were first suggested for aritason (154). Attempts to obtain carbonyl derivatives of aritason ended in the isolation of the *l*-pinocarvone derivatives. For example, aritason did not give an oxime, semicarbazone, or phenylhydrazone by the usual methods, but it reacted with 2,4-dinitrophenylhydrazine in ethanolic sulfuric acid to give a monohydrazone. This hydrazone was identical with that yielded from LI by refluxing in ethanolic 1 per cent hydrochloric acid solution at 80°C. Comparison of the infrared spectrum of aritason with those of pinocamphone, a dimer of 2-methylenecyclohexanone, 2-methylcyclohexanone, and 2-ethylcyclohexanone indicated that structure LIII is more likely to represent aritason than is LII.



LI



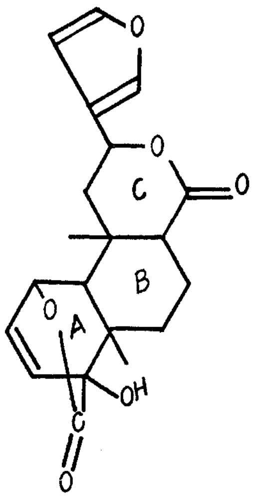
LII



LIII

I. COLUMBIN

Columbin, $C_{20}H_{22}O_6$, m.p. 182°C., optically inactive, was isolated from the neutral bitter component of the root of *Jatrorrhiza palmata* Miers, the Colombo root (61, 171). The principal skeleton of the structure of columbin is probably bicyclic, because dehydrogenation of various columbin derivatives afforded 1,2,5-trimethylnaphthalene, 1-methyl-2-naphthoic acid, and 1,5-dimethyl-2-naphthoic acid. Since hydrolysis of columbin yielded two new carboxyl and two new hydroxyl groups without the loss of any carbon atoms, the presence of two lactone rings was inferred. The first lactone ring, presumably located in ring A, was characterized as a *β*, *γ*-unsaturated *α*-hydroxy-*δ*-lactone system. The other lactone, most likely situated in ring B, is saturated and may be a *γ*- or *δ*-lactone



LIV

system. It was found that a hydrogen in the position (probably C-13) adjacen to the carbonyl group is epimerizable.

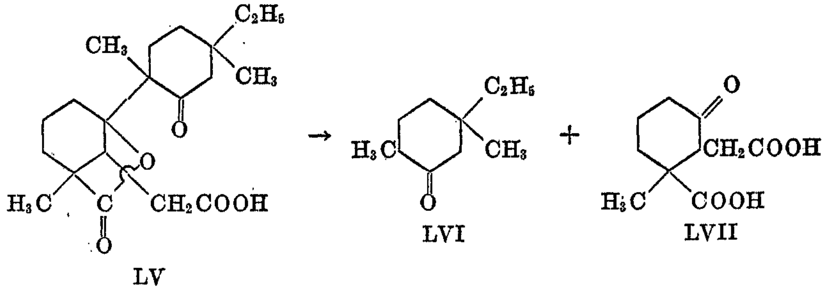
Columbin also possesses a β-substituted furan ring which was suggested to b positioned with its ether oxygen (ring C) alpha with respect to the β-position o the furan ring by magnetic resonance studies (45). From the above evidence anc other observations, as well as extensive earlier work, structure LIV was proposec for columbin (11).

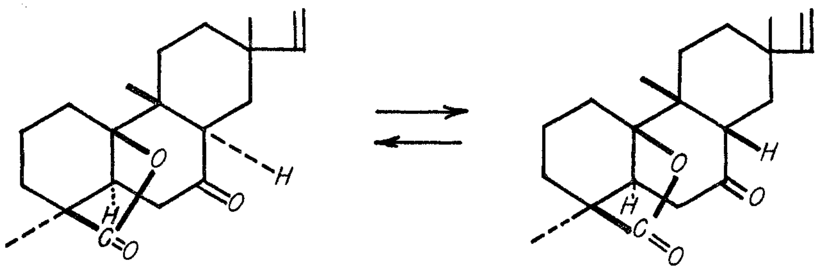
J. ROSENONOLACTONE AND ROSOLOLACTONE

Rosenonolactone, $C_{20}H_{28}O_3$, and rosololactone, $C_{20}H_{30}O_3$, were isolated fron the mycelium of *Trichothecium roseum* Link from decaying apples (130). Rosenonolactone can be reversibly isomerized with acid to isorosenonolactone; botl compounds yielded a mixture of 1,7-dimethylphenanthrene and 1,7-dimethyl-9-hydroxyphenanthrene upon dehydrogenation. Rosenonolactone was thus considered to have a tricyclic skeleton. Infrared data showed the presence of a viny group and a γ-lactone system in rosenonolactone. Further structural evidence was given by ozonolysis and hydrolysis experiments. The oxidation of dihydrorosenonolactone yielded rosoic acid (LV), which in alkaline solution furnished a C_{10} cyclic ketone (LVI) and a C_{10} dibasic keto acid (LVII) with fission of the intermediate β-hydroxyketone. A structure was then assigned to rosenonolactone without stereochemical implications, while the rosenonolactone ⇄ isorosenonolactone interconversion was ascribed to inversion at C-14 (72).

Later it was found that alkaline degradation of LV yielded a mixture of two diastereoisomeric C_{10} acids (LVII), which were claimed to be trans and cis acids. This result led to the conclusion that the stereochemical configuration of rosenonolactone and isorosenonolactone is trans-syn-trans and trans-syn-cis, respectively. Acetylation of the triols obtained from lithium aluminum hydride reduction of dihydrorosenonolactone and dihydroisorosenonolactone or hydrolysis of the triol acetates, however, showed that the C-9 carbonyl group in dihydrorosenonolactone is sterically unhindered, while the C-9 carbonyl in dihydroisorosenonolactone *is* hindered. A model clearly showed that the C-9 carbonyl group is hindered by the C-7 substituent in the trans-syn-cis, but not in the trans-syn-trans, system. Rosenonolactone and isorosenonolactone, therefore, *may* be correctly represented by the relative trans-syn-trans (LVIII) and trans-syn-cis (LIX) configurations, respectively (65).

These structures do not obey the classical isoprene rule, but can be derived from a tricyclic precursor by migration of an angular methyl group from the

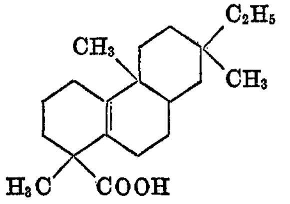




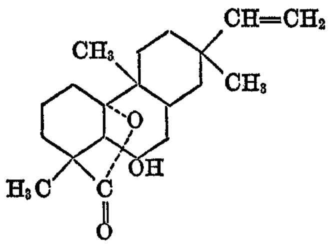
LVIII LIX

C-12 to the C-13 position, a type of reaction which is encountered in steroid biosynthesis. Biosynthesis of rosenonolactone from $CH_3C^{14}OOH$ (19) and 2-C^{14}-mevalonic lactone (29) supported these proposed structures.

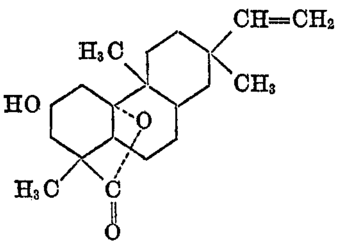
Rosololactone was oxidized to the corresponding ketone, dehydrorosololactone, $C_{20}H_{28}O_3$, isomeric with but not identical to, rosenonolactone. Dehydrogenation of rosololactone and dehydrorosololactone provided pimanthrene. Rosololactone contains a secondary alcohol group and a vinyl group. Dehydrorosololactone was readily isomerized by acid to an α,β-unsaturated keto acid, isodehydrorosololactone. Dehydration of dihydrorosololactone readily gave dihydrorosenic acid, which on hydrogenation was converted into tetrahydrorosenic acid. Lactonization of this acid yielded a mixture of allo- and neohydroxyrosanoic γ-lactones, identical with the two γ-lactones from iso(?)ros-11,12-en-16-oic acid (probably LX), derived from rosenonolactone, thereby establishing a close structural relationship between rosololactone and rosenonolactone. These and other facts indicated formulas LXI and LXII as possible structures for rosoloactone (73).



LX



LXI



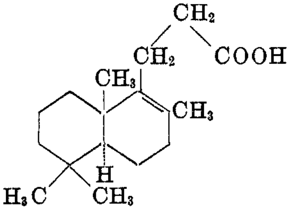
LXII

K. MARRUBIIN

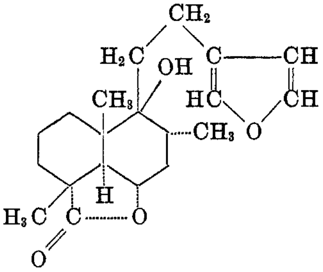
The diterpenoid lactone marrubiin, $C_{20}H_{28}O_4$, m.p. 158°C., which constitutes the bitter principle of horehound (*Marrubium vulgare*), was first obtained pure by Mercier and Mercier (106). Marrubiin was assumed to be bicyclic, because dehydrogenation yielded 1,5,6-trimethylnaphthalene. This supposition was further proved correct by degradation of marrubiin to a compound (LXIII) also obtained from the degradation of ambrein (36). The presence of a lactone ring was established by facile alkaline hydrolysis to the monobasic hydroxy acid, marrubic acid, $C_{20}H_{30}O_5$ (80). Studies of infrared data indicated that the lactone system is probably a γ-lactone, with attachment at C-10 to a secondary hydroxyl group (42, 71).

One of the two oxygen atoms not associated with the lactone system in marrubiin could be removed from the molecule by dehydration with either phosphorus trichloride or thionyl chloride. This oxygen, in a hydroxyl group, was tentatively located at C-13. Upon investigation of infrared data it was suggested that the other oxygen atom, which is quite reactive, is probably present in a furan ring which may be β-substituted (41). Proton magnetic resonance measurements on marrubiin could be used to provide further evidence for the nature of the substitution of the furan ring. Structure LXIV was tentatively proposed for marrubiin (40).

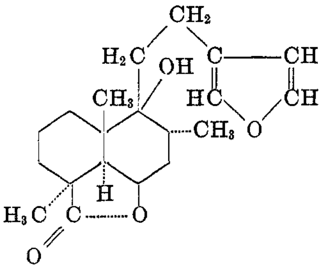
The stereochemistry of carbon atoms 10 and 14 is uncertain as yet. A reassessment of molecular rotation data indicated that marrubiin has the configuration at C-1 shown in formula LXV, and not that suggested previously in LXIV. By applying Klyne's lactone rule (95) to the molecular rotation contribution of the bridging lactone, it was ultimately deduced that the potential C-10 hydroxyl group must be β-oriented and that, in consequence, the C-1 carboxyl group must also be β-oriented (43). Burn and Rigby, however, have suggested that there is no stereochemical reason for omitting from consideration a "skewed" lactone bridge (1α–10β or 1β–10α), so that the configuration at C-1 may not necessarily follow from knowing that at C-10 (36).



LXIII



LXIV



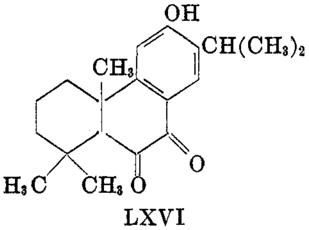
LXV

L. QUASSIN AND NEOQUASSIN

Quassin, $C_{20}H_{22}O_4(OCH_3)_2$, m.p. 222°C., $[\alpha]_D = +34.5°$, and neoquassin, $C_{20}H_{24}O_4(OCH_3)_2$, m.p. 228°C., $[\alpha]_D = +41°$, were isolated from a mixture of the bitter constituents of Quassia wood. On reduction quassin gives neoquassin. It was suggested that quassin and neoquassin were tricyclic diterpenes because selenium dehydrogenation of the product obtained from the Martin–Clemmensen reduction of neoquassin yielded 1,2,8-trimethylphenanthrene (14). Quassin is an unsaturated lactone containing two (or possibly three) C-methyl groups, a tertiary hydroxyl group, and a ketonic group. With hot mineral acid, quassin is demethylated, giving nor- or bisnorquassin, while with warm alcoholic potassium hydroxide it gives an unsaturated acid, isoquassinic acid. Neoquassin, which forms quassin on oxidation, is an unsaturated ketone containing two hydroxyl groups. Postulated structures for these two compounds have not been reported as yet.

M. XANTHOPEROL

Hydrolysis of the neutral portion of the extract of the wood of *Juniperus communis* L. yields sugiol, a component which is a mixture of ferruginol and Δ^9-dehydroferruginol, and a yellow compound which is probably an artifact, xanthoperol, $C_{20}H_{26}O_3$, m.p. 255–270°C. with decomposition, $[\alpha]_D = +132.5° (\pm 2.5°)$ (24). Clemmensen reduction of xanthoperol gave 9-ketoferruginol. Retene is probably the dehydrogenation product of xanthoperol. A C-methyl determination gave a value of 1.98. From these results, it has been suggested that xanthoperol may be represented by formula LXVI.



LXVI

N. CRYPTOPINONE

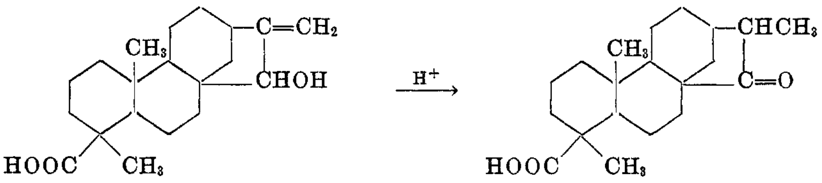
Cryptopinone from the Scots fir, *Pinus sylvestris* L., was rigidly proved to be dextropimarinal by partial synthesis from dextropimaric acid. The 2,4-dinitrophenylhydrazone of cryptopinone was identical with that of dextropimarinal prepared by chromic acid oxidation of dextropimarinol, obtained in turn by the reduction of dextropimaric acid by means of lithium aluminum hydride (10).

O. DARUTIGENOL

This carbinol is one of the rare diterpenes which exists in nature as a glycoside. Hydrolysis of darutoside, isolated from *Siegesbeckia orientalis* L., yielded one mole of darutigenol and one mole of D-glucose. Darutigenol, $C_{20}H_{34}O_3$, m.p. 168–170°C., $[\alpha]_D = -11°$, was isomerized with acid to two isodarutigenols, m.p. 155°C., $[\alpha]_D = -64°$ and m.p. 183°C., $[\alpha]_D = +15°$ (122). Upon dehydrogenation darutigenol yielded pimanthrene. The compound contains one double bond, a 1,2-glycol grouping, and one primary hydroxyl group. No structure has yet been proposed.

P. STEVIOSIDE

A crystalline glycoside, stevioside, $C_{38}H_{60}O_{18}$, m.p. 198°C., $[\alpha]_D = -39.3°$, was isolated from the leaves of *Stevia Rebaudiana* Bertoni from Paraguay (25). This glycoside proved to be some three hundred times as sweet as sucrose and thus the sweetest natural product yet isolated. Acid hydrolysis of stevioside gave crystalline D-glucose as the only sugar component and a crystalline nonsugar product, isosteviol, presumed to be an aglucon, which contains a carbonyl group and a carboxyl group. Enzymatic hydrolysis of stevioside yielded steviol, a nonsugar product which has one double bond, a hydroxyl group, and a carboxyl group. Steviol was isomerized to isosteviol with dilute sulfuric acid. Steviol was inferred to be a tetracyclic diterpene, the structure of which is very closely related to that of phyllocladene, since isosteviol, dehydrogenated with palladium–charcoal, gave pimanthrene in a yield of only 2.5 per cent. A Zerewitinoff determination showed the presence of two active hydrogen atoms in steviol. Comparison of the ultraviolet spectrum of steviol with that of phyllocladene showed that the double bond in steviol cannot be more highly substituted than that in phyllocladene. Other spectroscopic data confirmed that the double bond in steviol must be a disubstituted ethylenic linkage $\left(\rangle C{=}CH_2 \right)$. Structures for steviol and isosteviol were tentatively formulated as LXVII and LXVIII, respectively (108).

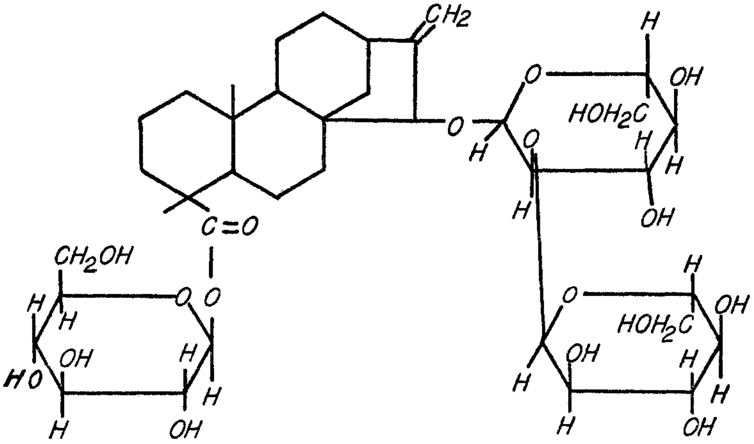


LXVII LXVIII

Uncertainties exist as to the nature of the five-membered ring and the positions of the functional groups. The positions and linkages of the three glucose moieties have been suggested to be those shown in formula LXIX by chemical evidence (177). A study of the rotatory dispersion curve of phyllocladene showed that the configuration of the angular methyl group at C-12 in steviol is still uncertain, but that the α-orientation is the most likely (52).

Q. GIBBERELLINS

Yabuta and Hayashi found that *Gibberella fujikuroi* (Saw) Wr, the causative organism of Bakanae disease in rice, produces a substance which they named gibberellin A (178). Later, the isolation of a mixture of three acids, gibberellin A_1, gibberellin A_2, and gibberellic acid was reported (179). Stodola's group at Peoria (149) and Cross's group in England (48) isolated gibberellin A, which appeared to be different from the gibberellin isolated by the Japanese workers; later, however, it was found that this gibberellin A is almost certainly the same



LXIX

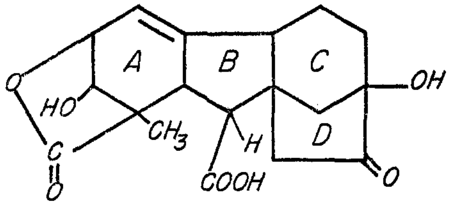
as the A_1 of Yabuta's group, despite the difference in decomposition point (table 1).

It was confirmed that gibberellin A_1 is a dihydro derivative of gibberellic acid and that gibberellin A_2 is tetrahydrogibberellic acid, but the direct relationship is not clear. Acid hydrolysis of gibberellic acid at room temperature yields allogibberic acid with loss of carbon dioxide and the elements of water. On more vigorous treatment with acid, allogibberic acid is isomerized to gibberic acid. It was found that gibberellic acid is tetracyclic and has a carboxyl, a secondary hydroxyl, a tertiary hydroxyl, a vinyl, and a tetrasubstituted ethylenic group, as well as a saturated γ-lactone system in its molecule. Structures LXX and LXXI were tentatively proposed for gibberellic acid (46). More definite evidence supporting these structures was given by the establishment of the structures of allogibberic acid (LXXII) and gibberic acid (LXXIII) (47). Despite the fact that gibberellic acid has only nineteen carbon atoms, it may be regarded as a relative of the diterpenes. The gibberellins and diterpenes are both isoprenoid. The proposed ring D meta-5-ring bridge in gibberellic acid is now well recognized in diterpene chemistry. Ring B could arise by ring contraction of a diterpene ring B, one of the carbon atoms being extruded as a carbonyl group. Structure LXX for gibberellic acid is more in accord with the hydroxylation pattern found in the triterpenes.

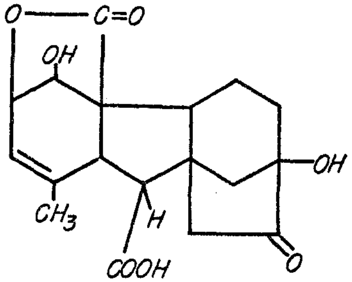
TABLE 1

Physical constants of gibberellins

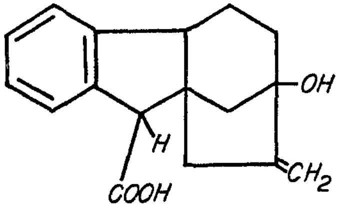
	Formula	Decomposition Point	$[\alpha]_D$
		°C.	
Gibberellic acid	$C_{19}H_{22}O_2$	233–235	+93°
Gibberellin A_1	$C_{19}H_{24}O_6$		
Yabuta, Sumiki, and Aso		232–235	+42°
Stodola, Nelson, and Spence		255–258	+36°
Gibberellin A_2	$C_{19}H_{26}O_6$	235–237	+12°



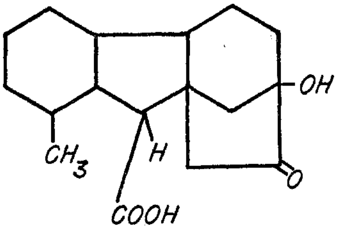
LXX



LXXI



LXXII



LXXIII

R. GRAYANOL

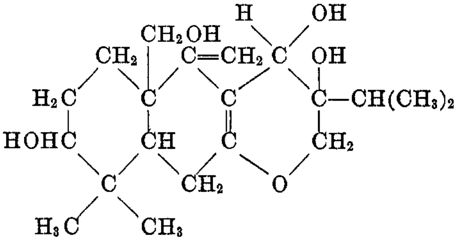
Grayanol (85), $C_{20}H_{32}O_5$, m.p. 198°C., $[\alpha]_D = -42°$, first called grayanotoxin II, was isolated (152) from the leaf of *Leucothoe grayana* with grayanotoxin I (96), $C_{22}H_{36}O_7$, m.p. 238–238.5°C. Grayanol and grayanotoxin I cause nasal irritation and have found use as nemicides. Deacetylation of grayanotoxin I gave grayanotoxin III (85), $C_{20}H_{34}O_6$, m.p. 248–250°C., which yielded grayanol upon dehydration (153). It was recently confirmed that grayanotoxin I and III are identical with acetylandromedol and andromedol, respectively, which were isolated from *Andromeda, Kalmia, Leucothoe,* and *Lyonia* species (156). Grayanotoxins I and III are known to be potent hypotensive agents. Since grayanol readily absorbs bromine and is easily hydrogenated with palladium–barium sulfate to dihydro derivatives, it contains at least one double bond. Upon ozonolysis, grayanol tetraacetate produced formaldehyde, which identifies the double bond as belonging to a methylene group. From observations on the catalytic hydrogenation of grayanol, it was concluded that the double bond is located near the hydroxyl group and that the methylene group is linked directly to the nucleus (109). The results of oxidation with potassium permanganate indicated that grayanol possesses the linkages (110)

$$\text{—C—CH}_2\text{—CH}_2\text{—C— and —C—C(CH}_3)_2\text{—C— (A)}$$

Three acids, oxalic acid,

$$(CH_3)_2CHCOOH, \text{ and } (CH_3)_2CHC(CH_3)(OH)COOH \text{ (B)}$$

were produced upon fusion with potassium hydroxide (111). From these results, the positions of fourteen carbon atoms in grayanol can be deduced; among these fourteen carbon atoms, ten (two in the two methyl radicals of group A, six in acid B, and two carbon atoms associated with the methylene group and the primary hydroxyl group) cannot be ring carbon atoms. Ten other carbon atoms probably form a decahydronaphthalene ring. Of the five oxygen atoms, four are in hydroxyl groups and one is probably an inactive ether oxygen. Structure LXXIV, which satisfies the isoprenoid rule, was tentatively assigned to grayanol. Grayanol gives a positive Liebermann color reaction, which seems to be the only evidence at present that grayanol is a diterpenoid.



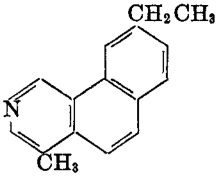
LXXIV

IV. Alkaloids

Remarkable progress has occurred recently in the field of investigation of the diterpene alkaloids: the *Erythrophloeum* alkaloids, the *Aconitum* and *Delphinium* alkaloids, and the *Garrya* alkaloids (104). The *Erythrophloeum* alkaloids are alkamine esters of monocarboxylic acids of the diterpene series. The *Aconitum* and *Delphinium* alkaloids and the *Garrya* alkaloids have a diterpenic skeleton in their structures. The structures for several of these alkaloids have been assigned. Only a brief review of the recent research on these compounds will be included here.

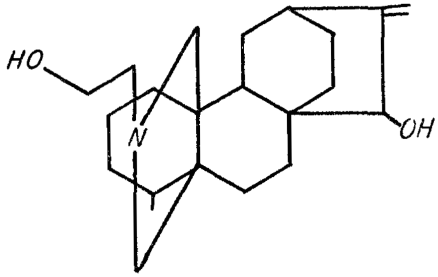
A. ATISINE

Atisine, one of the *Aconitum* and *Delphinium* alkaloids, $C_{22}H_{33}O_2N$, m.p. 57–60°C., $[\alpha]_D = +28°$, is the alkaloid long known to occur in the root of atis, *Aconitum heterophyllum* Wall. On mild alkaline treatment of atisine, a molecular rearrangement to isoatisine takes place. Dehydrogenation of atisine with selenium yielded a hydrocarbon, 6-ethyl-1-methylphenanthrene (82) and a $C_{16}H_{15}N$ base, for which structure LXXV was rigidly established by synthesis (100).



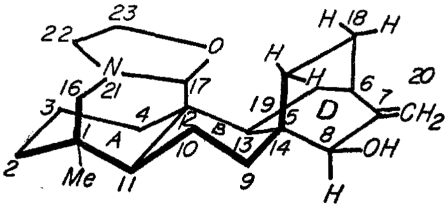
LXXV

On the basis of these results and the similarity of the chemistry of the *Garrya* alkaloids to that of atisine (86), the suggestion was made (173) that dihydroatisine be formulated as LXXVI.

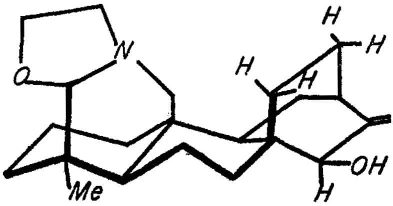


LXXVI

The oxazolidine type of structure for atisine (LXXVII) and isoatisine (LXXVIII) was suggested almost simultaneously by Bartlett (7) and by Pelletier and Jacobs (119).



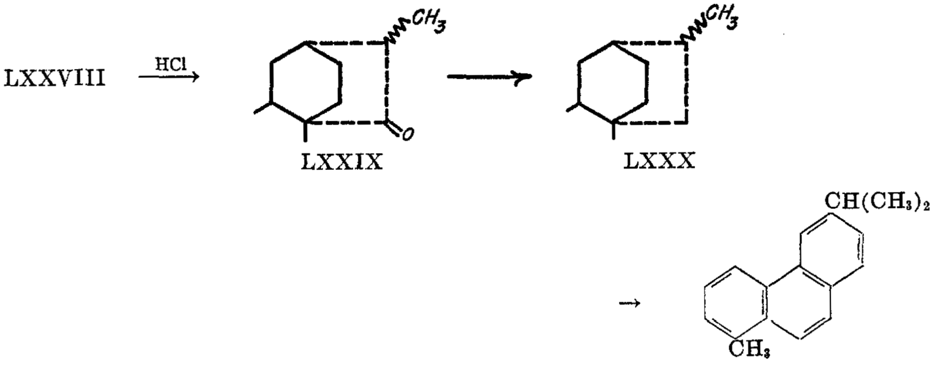
LXXVII



LXXVIII

Me = CH_3.

The location of the allyl alcohol system was demonstrated by procedures carried out independently by two groups of investigators (57, 117). Treatment of isoatisine with hydrogen chloride yielded a ketone (LXXIX), which was then reduced to desoxytetrahydroatisine (LXXX). Upon dehydrogenation, LXXX yielded 6-isopropyl-1-methylphenanthrene (LXXXI). This result provides clear evidence for locating the termethylene group at position C-18; the allylic hydroxyl group, therefore, must be at C-19. Structure LXXVIII was suggested for isoatisine on the basis of the similarity of the chemistry of atisine and isoatisine



LXXIX

LXXX

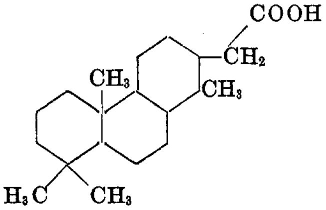
LXXXI

to that of veatchine and garryine (see page 1058) (118, 119, 175). The configurations of the hydroxyl groups at C-19, shown in structures LXXVII and LXXVIII, are tentative (117).

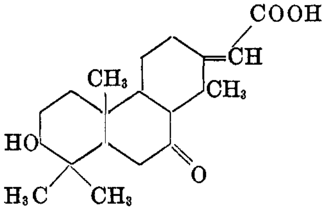
B. CASSAINE

Cassaine, one of the *Erythrophloeum* alkaloids, $C_{24}H_{39}O_4N$, m.p. 142.5°C., $[\alpha]_D = -113°$, was isolated from the bark of *Erythrophloeum quineese* (49). Cassaine is an alkamine ester of a diterpene α,β-unsaturated monocarboxylic acid. The corresponding acid, cassaic acid, $C_{19}H_{29}O_2COOH$, possesses remarkable cardiac activity coupled with intense local anesthetic action. Cassaic acid has a secondary hydroxyl group and a carbonyl group. The oxidation of dihydrocassaic acid gave dioxocassanic acid, which on Wolff–Kishner reduction formed cassanic acid (LXXXII). Since dehydrogenation of cassanic acid gave 1,2,8-trimethylphenanthrene (133), the acid is probably tricyclic. The location of the carboxyl group in the side chain was clearly established in the following way. Methyl cassanate, on reaction with methylmagnesium iodide followed by dehydrogenation, afforded a hydrocarbon (135) identified as 7-isobutyl-1,8-dimethylphenanthrene by synthesis (83).

The absorption spectrum of cassaic acid showed that the double bond is in the α, β-position with respect to the carboxyl group and that a *gem*-dimethyl group is present. From this evidence, formula LXXXIII was subsequently assigned to cassaic acid (83). The correctness of structure LXXXIII was further confirmed by partial synthesis of the acid from methyl vouacapenate (94). The A/B ring junction in cassaic acid, therefore, has the trans arrangement. The synthesis of 7-keto compounds obtained by oxidative cleavage of the double bond has furnished further evidence for the correctness of structure LXXXIII for cassaic acid (161).



LXXXII



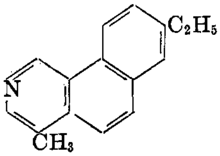
LXXXIII

C. GARRYINE AND VEATCHINE

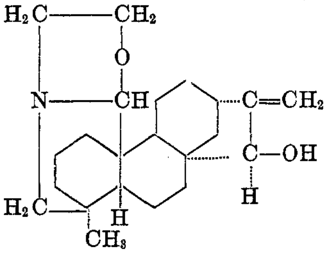
The two alkaloids garryine and veatchine were isolated from the bark of *Garrya veatchii* Kellog (115). They have both been given the empirical formula $C_{22}H_{32}O_2N$. Garryine crystallizes as a monohydrate, m.p. *ca.* 96°C. Veatchine crystallizes without water of crystallization and melts at 122–123°C. Veatchine when treated with methanolic potassium hydroxide quantitatively isomerizes to garryine (173), thus paralleling the atisine–isoatisine isomerization.

The chemistry of veatchine and garryine is very closely related to that of atisine and isoatisine (174, 176). The only structural difference between garryine and isoatisine probably lies in the point of attachment of the allyl alcohol group. Since dehydrogenation of veatchine and garryine yielded 7-ethyl-1-methylphenanthrene and azaphenanthrene (LXXXIV), identified by synthesis (8), the point of attachment of the allyl alcohol and the location of the nitrogen atom were consequently inferred to be those shown in formulas LXXXV and LXXXVI for veatchine and garryine, respectively.

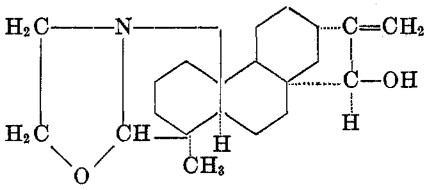
It was rigidly proved that isomerization from veatchine to garryine occurs only in the oxazolidine ring, similar to the isomerization of atisine to isoatisine, since the cyclopentane rings in both compounds, which include the allyl alcohol groups, remain unchanged after the isomerization. The evidence for this view is as follows. The presence of a terminal methylene group in veatchine and garryine was confirmed by the isolation of formaldehyde in ozonolysis experiments. On catalytic hydrogenation, both alkaloids absorbed two moles of hydrogen and gave the same tetrahydro compound. Kuhn–Roth oxidation of tetrahydroveatchine indicated a content of two C-methyl groups, whereas the analysis of both veatchine and garryine indicated only one such group. The presence of a hydroxyl group in both alkaloids was shown by infrared absorption and by acetylation.



LXXXIV



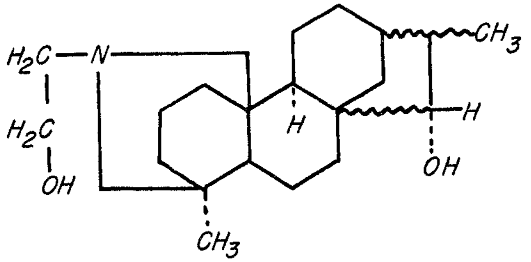
LXXXV



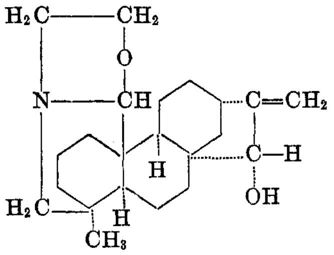
LXXXVI

D. GARRYFOLINE AND CUAUCHICHICINE

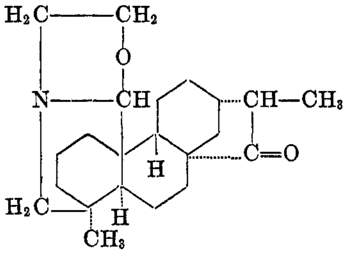
Garryfoline, $C_{22}H_{33}NO_2$, m.p. 130–133°C., $[\alpha]_D = -60°$, and cuauchichicine, $C_{22}H_{33}NO_2$, m.p. 152–155°C., $[\alpha]_D = -71.4°$, were isolated from *Garrya laurifolia* Hartw., a Mexican tree commonly known as "cuauchichic" (53, 54). Garryfoline is isomerized to cuauchichicine by acid. Infrared spectroscopy of cuauchichicine showed the complete absence of amine or hydroxyl absorption but a strong carbonyl band which can be attributed to a five-membered ring ketone. Ozonization of cuauchichicine did not yield formaldehyde. This indicates the absence of an exocyclic methylene group. A Kuhn–Roth determination indicated that cuauchichicine possesses two C-methyl groups. It is clear that the structures of cuauchichicine and veatchine are very similar to each other, because the reduction of cuauchichicine with lithium aluminum hydride led to tetrahydroepiveatchine (LXXXVII), which has been synthesized (176). Thus the carbonyl group of cuauchichicine must be located at C-19. The termination point (C-16 or C-17) of the oxazolidine ring could be assigned on the basis of the basicity of the alkaloid, since it had been observed earlier that veatchine (pK = 11.5) and garryine (pK = 8.7) differ enormously in that respect. Cuauchichicine was found to exhibit a pK of 11.15. Garryfoline was of the same order of basicity (pK = 11.8). Hence acid isomerization of garryfoline to cuauchichicine demonstrated that only the pentane ring D could be involved in this isomerization. Infrared spectroscopy showed that garryfoline has only hydroxyl absorption, thus resembling veatchine. Ozonization of garryfoline gave formaldehyde, which established the presence of an exocyclic methylene group. Garryfoline, therefore, should be considered the C-19 epimer of veatchine. Thus structures for garryfoline and cuauchichicine were formulated as LXXXVIII and LXXXIX, respectively.



LXXXVII



LXXXVIII



LXXXIX

V. Total Synthesis of Diterpenes

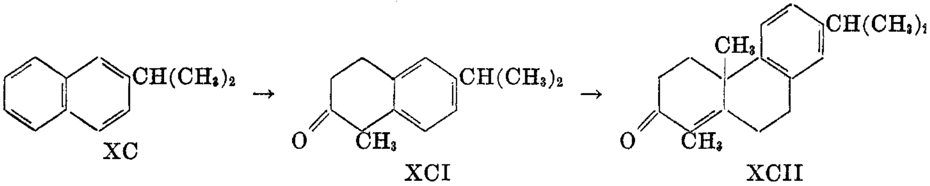
Only one diterpenic acid, *dl*-podocarpic acid, was totally synthesized prior to the past decade (17, 78). Uncertainty existed, however, as to the exact identity of the synthetic acid until 1956. In the last ten years a number of diterpenes have been totally synthesized, in one case by a stereospecific route. These syntheses have aided the elucidation of the absolute structure of diterpenes.

A. FROM SUBSTITUTED NAPHTHALENES

1. dl-Dehydroabietic acid

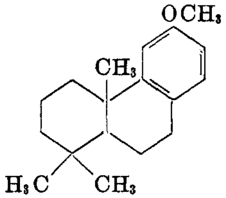
Total synthesis of *dl*-dehydroabietic acid was achieved by Stork and Schulenberg (151). 2-Isopropylnaphthalene (XC) was converted to 6-isopropyl-1-methyl-2-tetralone (XCI), which was then condensed with 1-diethylamino-3-

pentanone methiodide, or ethyl vinyl ketone, to give the α,β-unsaturated ketone (XCII). After the introduction of a carboxyl group at the 1-position and the removal of a carbonyl group at C-2, *dl*-dehydroabietic acid was obtained. The infrared spectrum of the synthetic acid, m.p. 179.5–180.5°C., was identical with that of *d*-dehydroabietic acid, m.p. 171°C., from a natural source.



2. dl-6-Methoxypodocarpane

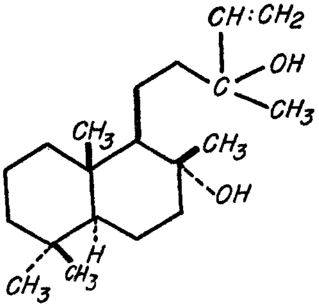
Synthesis of *dl*-6-methoxypodocarpane (XCIII) was initiated with 1-methyl-7-methoxy-3,4-dihydronaphthalene. The method involved the oxidation of the 2-position to a carbonyl group with lead oxide, followed by condensation with 4-diethylaminobutanone 2-methiodide to form the phenanthrene skeleton by cyclization (123).



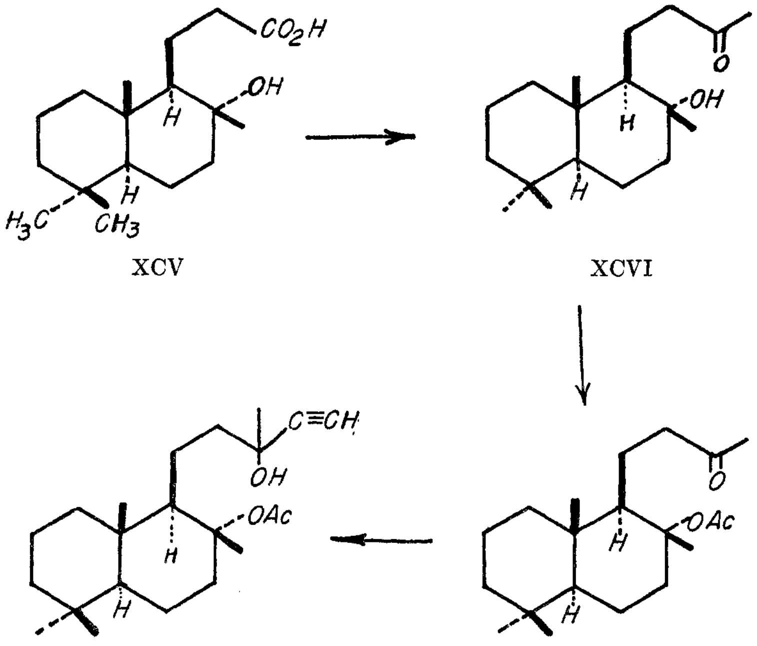
XCIII

3. Sclareol

Sclareol (XCIV) (140) was synthesized (3) from (+)-ambreinolide (18). Treatment of the lithium salt of (+)-ambreinolide (XCV) with methyllithium gave a mixture of the hydroxyketone (XCVI) and the enol-ether identical with the oxidation product of sclareol. The hydroxyl group of XCVI was first protected by acetylation and ethynylation was then carried out on the acetoxyketone (XCVII), giving a mixture of ethynylcarbinols (XCVIII), separable into the nonhydrogen-bonded and the hydrogen-bonded isomers. Reduction by lithium aluminum hydride of the two isomers yielded sclareol, m.p. 103°C., $[\alpha]_D = -3.3°$, and 13-episclareol, m.p. 131.5°C., $[\alpha]_D = +7°$, respectively.



XCIV



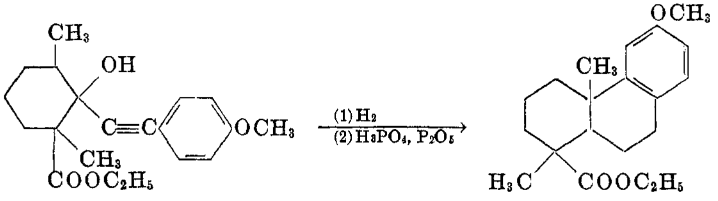
XCV XCVI

XCVII XCVIII

B. FROM SUBSTITUTED CYCLOHEXANONE AND *m*- OR *p*-METHOXYPHENYLACETYLENE

1. *dl-Podocarpic acid*

Haworth and Moor (78) and Bhattacharyya (17) independently obtained an unidentified racemate of podocarpic acid by very similar routes of synthesis. Later it was found that this racemate must be *dl*-podocarpic acid by its identity with the product of the following synthesis (93). 2-Carboethoxy-2,6-dimethylcyclohexanone and the Grignard reagent from *p*-methoxyphenylacetylene reacted to give 2-carboethoxy-1-(*p*-methoxyphenyl)ethynyl-2,6-dimethylcyclohexanol (XCIX). Upon catalytic hydrogenation XCIX was converted to 2-carboethoxy-1-β-(*p*-methoxyphenyl)ethyl-2,6-dimethylcyclohexanol, which was then cyclized to C using polyphosphoric acid. Hydrolysis of C gave *dl*-methoxypodocarpic acid, m.p. 200–202°C., which was identified by infrared spectroscopy. Further hydrolysis yielded *dl*-podocarpic acid, m.p. 264–265°C., which was undepressed by the corresponding products of Haworth and Moor and of Bhattacharyya.

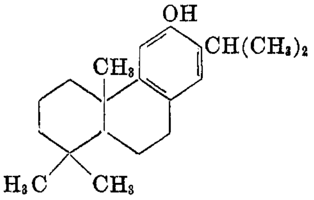


XCIX C

2. dl-Ferruginol

2,2,6-Trimethylcyclohexanone and sodium *p*-methoxyphenylacetylene were used as starting materials for the synthesis of *dl*-ferruginol (CI) (92). The reaction of these compounds in liquid ammonia gave 1-β-(*p*-methoxyphenyl)-ethyl-2,2,6-trimethylcyclohexanol, which was then cyclized with phosphorus pentoxide to 6-methoxy-1,1,12-trimethyl-1,2,3,4,9,10,11,12-octahydrophenanthrene. Incorporation of an isopropyl group at the C-7 position was carried out through acetylation by means of a Friedel–Crafts reaction followed by reaction with a methyl Grignard reagent. Dehydration and reduction of the product then yielded *dl*-ferruginol methyl ester. The infrared absorption of its benzoate was completely identical with that of the natural benzoate.

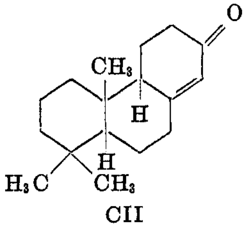
Ferruginol with the A/B ring junction in the trans configuration was stereospecifically synthesized from 1-methyl-7-methoxy-3,4-dehydronaphthalene (126).



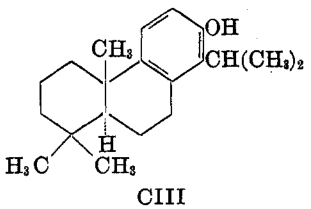
CI

3. Totarol

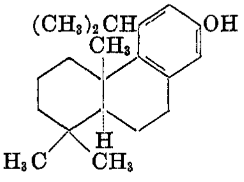
Although the structure of totarol had been the subject of a series of investigations (143), it was rigidly established by synthesis. The total synthesis of *dl*-totarol (CIII) was achieved (5, 6) from $\Delta^{8,14}$-podocarpen-7-one (CII) or $\Delta^{13,14}$-podocarpen-7-one, which were obtained from the condensation and subsequent cyclization of 2,2,6-trimethylcyclohexanone and *m*-methoxyphenylacetylene, by alkylation and bromination with *N*-bromosuccinimide followed by dehydrobromination. This synthesis established the structure of totarol to be CIII and



CII



CIII

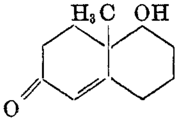


CIV

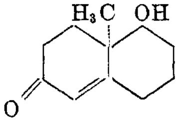
not CIV (23), which obeys the isoprene rule but is difficult to reconcile with the infrared absorption spectrum.

C. INTERMEDIATES IN DITERPENE SYNTHESIS

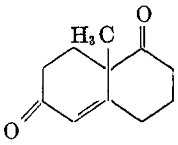
One of the difficulties in the synthesis of diterpenes is that of obtaining optically pure compounds. Attempts at resolution of synthesized racemic diterpenes have all failed. It might be advantageous to use the optically active diastereoisomers CV and CVI, hydroxydecalones, as starting materials. This would offer the opportunity of establishing the configuration of the angular methyl group at position C-12 of the diterpenes. Compounds CV and CVI can be obtained from CVII (113) by microbiological reduction (121). A number of other decalin derivatives which would be useful intermediates for the synthesis of diterpenes have been reported (68).



CV

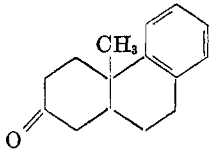


CVI

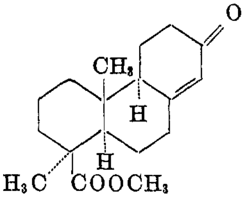


CVII

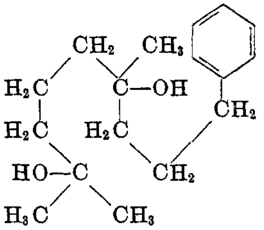
The tricyclic ketone CVIII (170) and the tricyclic keto ester CIX (18) would also be useful as intermediates in the synthesis of diterpenes. *dl*-Ambreinolide has been synthesized from CIX (18). Substituted benzene compounds have also served as intermediates. Compound CXI, which has the tricyclic skeleton of the diterpenes, has been obtained by the cyclization of the substituted benzene compound CX (112).



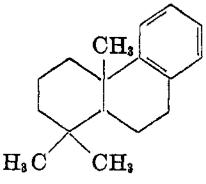
CVIII



CIX

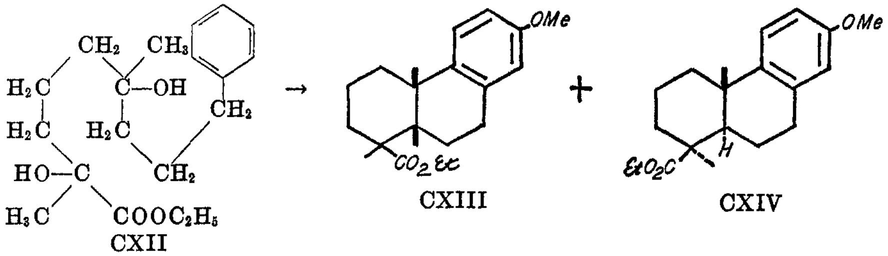


CX

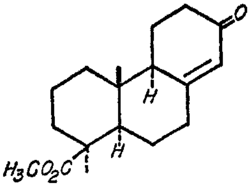


CXI

Cyclization (4) of a modification of compound CX, the tertiary alcoholic ester CXII, with phosphoric oxide gave the *cis*- and *trans*-octahydrophenanthrene carboxylic esters, CXIII and CXIV. The latter mixture of esters was converted



CXII CXIII CXIV



CXV

Me = CH_3; Et = C_2H_5.

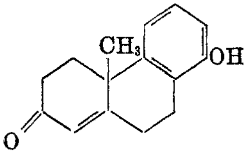
into the tricyclic (±)-keto ester CXV, identical to a degradative product of agathenedicarboxylic acid.

VI. Approaches to Steroid Synthesis from Diterpenes

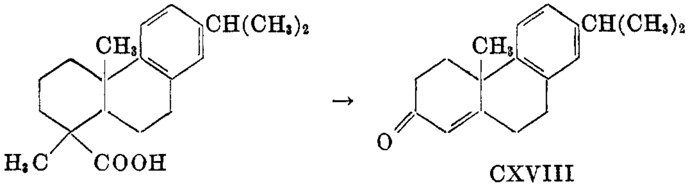
The transformation of diterpenic acids into the molecule CXVI, which possesses a known relationship to the steroid molecule, would be an important contribution to the chemistry of the diterpenes. Such a partial steroid synthesis would provide an unequivocal answer to the question of the stereochemistry of the C-12 methyl group in diterpenic acids and present an alternate route to the synthesis of steroids from abundant and cheap raw materials. There are two degradation sequences in this proposed transformation: namely, the degradation of the methyl and carboxyl groups at the 1-position in ring A of the diterpenic acid CXVII to the α,β-unsaturated ketone CXVIII through the 1-keto compound, and the degradation of the isopropyl group in ring C.

The degradation of C-1 of CXVII to ketonordehydroabietane (CXIX) has been achieved by dehydration of dehydroabietinol followed by ozonolysis of the resulting mixture containing exocyclic olefins (30). Stork and Burgstahler subsequently synthesized compound CXIX (150). The translocation of the carbonyl group from the 1-position to the 2-position was carried out by the following steps (180). The ketone was condensed with benzaldehyde to give the 1-keto-2-benzylidine derivative (CXX). Reduction of CXX accompanied by elimination of the hydroxyl group yielded the 2-benzylidine-$\Delta^{1,11}$ product (CXXI). From selective ozonolysis of CXXI, 2-keto-$\Delta^{1,11}$-nordehydroabietene (CXXII) was isolated.

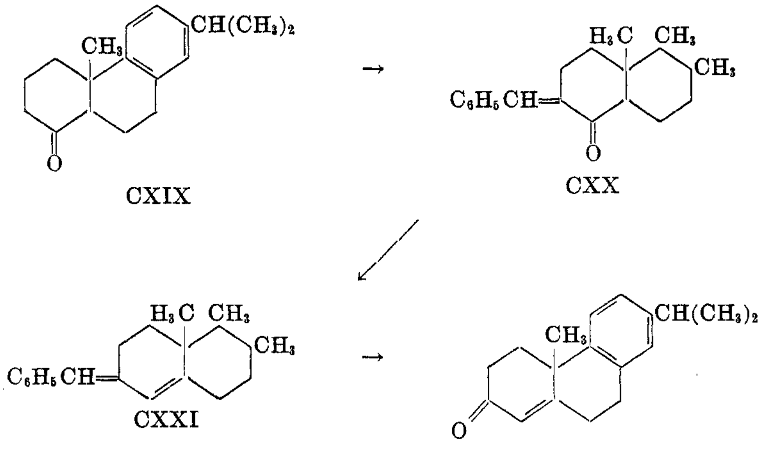
The degradation of the isopropyl group at C-7 has also been studied separately. Several investigators (103, 157) have studied the absorption of oxygen by diterpenic acids, presumably by the isopropyl group, but in only one case was a reaction product completely characterized (56). The main reaction product from the oxidation of dehydroabietic acid with oxygen was shown to be 9-ketodehydro-



CXVI

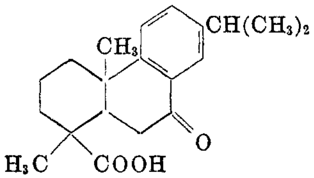


CXVII CXVIII

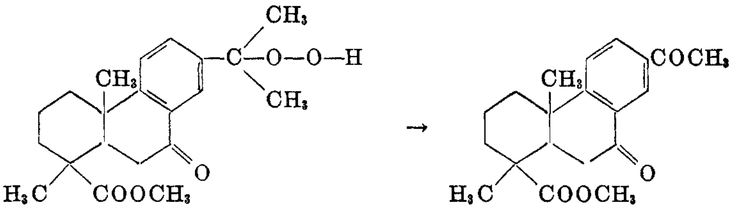


CXIX CXX CXXI CXXII

abietic acid (CXXIII). A recent study of the autoöxidation of methyl dehydroabietate has indicated that oxygen attack occurs mainly at C-9, apparently accompanied, however, by some attack at the C-15 position in the isopropyl side chain (127). Oxidation of methyl 9-ketodehydroabietate with molecular oxygen (128) gave a mixture of products which contained methyl 9-oxo-14-hydroperoxydehydroabietate (CXXIV), which was then converted to the 7-acetyl compound (CXXV).



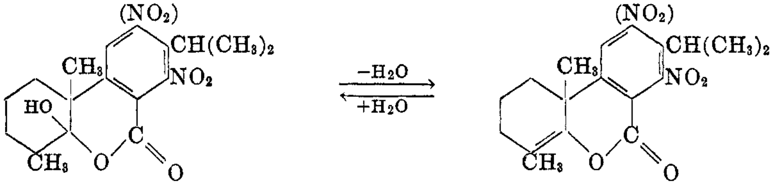
CXXIII



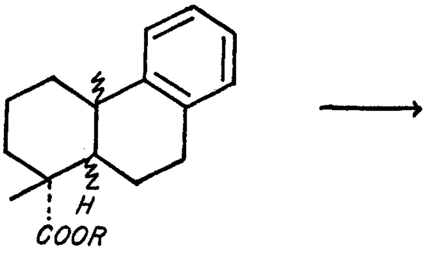
CXXIV CXXV

Chromic acid oxidation of methyl 6,8-dinitrodehydroabietate (70) and methyl 8-nitrodehydroabietate (181) did not result in the oxidation of the isopropyl group, but the 9,10-position was cleaved through the 9-oxo-8-nitrodehydroabietate (44), giving a lactol (CXXVI) and a lactone (CXXVII). It was found, however, that the oxidation of methyl dehydroabietate under conditions similar to those used for the nitro derivatives yielded 17–20 per cent of the 7-acetyl-9-keto compound (CXXVIII) (181).

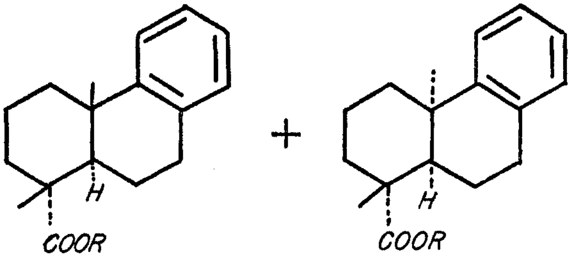
Another successful deisopropylation of methyl dehydroabietate was achieved by a reverse Friedel–Crafts reaction (116). The action of hydrogen chloride on methyl dehydroabietate in benzene solution in the presence of aluminum chloride gave compound CXXVIII in good yield. Chromatographic investigation of this product showed that it is a mixture of CXXIX and CXXX (114). Wenkert and Chamberlin also found that such a reverse Friedel–Crafts reaction causes isomerization at the 12-position of dehydroabietonitrile (169).



CXXVI CXXVII



CXXVIII



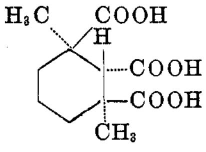
CXXIX CXXX

Thus degradations of C-1 and C-7 have been achieved separately. Both degradations on the same resin acid, however, have not been reported. Introduction of a hydroxyl group at C-8 would be the last step in achievement of the transformation of a resin acid to an α,β-unsaturated ketone (CXVI).

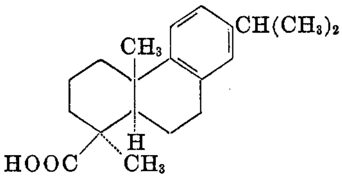
VII. STEREOCHEMISTRY

Vigorous oxidation of abietic acid and of dextropimaric acid gives a $C_{11}H_{16}O_6$ tricarboxylic acid (CXXXI) derived from ring A (62). This acid is optically inactive, so that the carboxyl groups at positions 1 and 3 must be in the cis relationship to each other. Although there are still many arguments concerning the absolute orientation of the angular methyl group at C-12, Barton and Schmeidler (12) have established from dissociation constant data that the A/B ring fusion in abietic acid and related acids must be trans. The angular methyl group at C-12 is arbitrarily defined as having the β-oriented position and is represented as projecting in front of the plane of the paper (full line). In dehydroabietic acid (CXXXII), the carboxyl group is β-oriented and the C-1 methyl group is α-oriented (dotted line) with respect to the asymmetric center at C-12.

Klyne (95) correlated the stereochemistry of rings A/B of the triterpenes with that of the steroids by the method of molecular rotational differences, suggesting that the rotations of a ring A ketone compound and its corresponding saturated derivative are both positive and, therefore, that the A/B angular methyl group is β-oriented. Since this positive shift of rotation has been observed with a large number of steroids and triterpenoid ketones, as well as with the 2-keto-$\Delta^{1,6}$ product prepared from lanostadienol (166), the ring A/B angular methyl groups of the triterpenes and the steroids would not be in a mirror image relationship to each other. From the establishment of the stereochemical identity of rings A and B of abietic acid and manoöl (87), and of manoöl and the triterpenes (134), the diterpenic angular methyl group would appear to be β-oriented also. Comparison of the molecular rotations of CXVII and CXIX with that of *trans*-nordehydroabietane gave Δ (C=O) and Δ (C=C—C=O) values of +199° and +580°, respectively (180). The tentative conclusion that the C-12 methyl group of the diterpenic acids is related stereochemically to the A/B angular methyl group of the steroids is supported, therefore, by these large positive Δ values. Approaches to the confirmation by synthesis of the configurations of the C_{11} acid (CXXXI) and a C_{12} acid obtained from the degradation of abietic acid have been reported (124, 125). The remaining asymmetric center in abietic acid at C-13 is probably also in trans relationship to the C-12 methyl group. It would be anticipated that treatment with acidic reagents would provide more information about the configuration at this center.

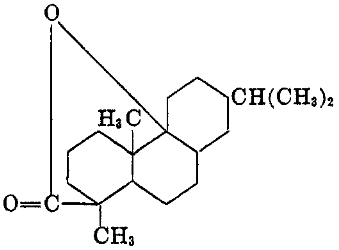


CXXXI

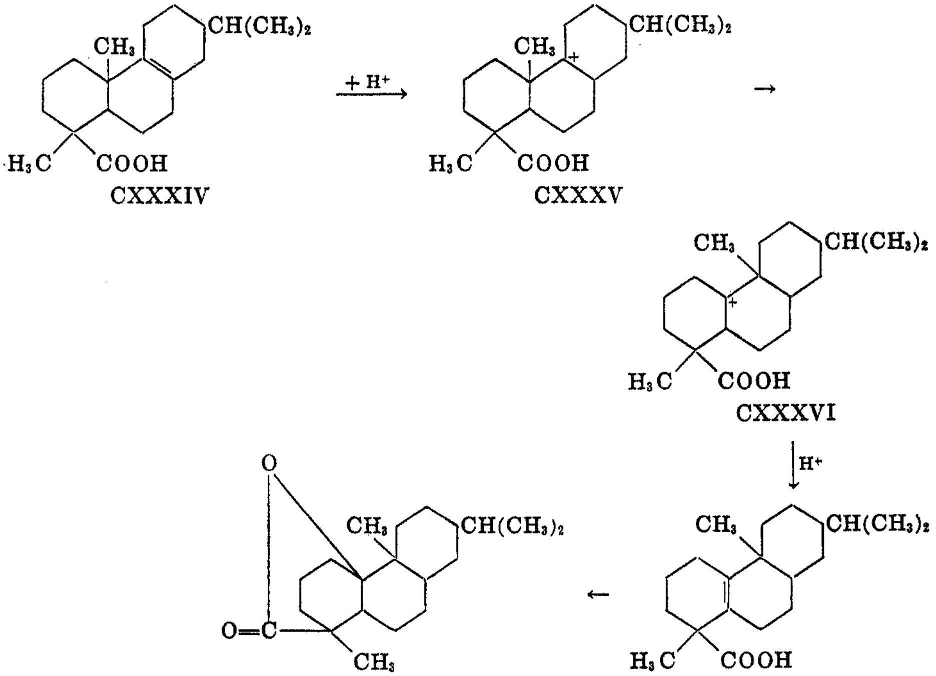


CXXXII

An isomeric saturated lactone, $C_{20}H_{32}O_2$, m.p. 130–131°C., $[\alpha]_D = \sim -2°$, obtained from various kinds (according to the position of the double bond) of dihydroabietic and dihydrolevopimaric acids, is usually shown with the lactone ring closure to the 13-position (CXXXIII). Barton (9) has suggested that such a strained relationship as that existing in CXXXIII is not probable and that ring closure would occur instead to the 12-position (CXXXVIII), since the A/B ring fusion in abietic acid is trans. A carbonium-ion rearrangement of dihydroabietic acid (CXXXIV) to CXXXVIII, involving a shift of the double bond from the 13,14-position to the 11,12-position (through intermediates CXXXV, CXXXVI, and CXXXVIII), was postulated to insure the necessary trans relationship of the carboxyl group at position 1 and the hydrogen at C-12. Recently 7,8-dihydroabietic acid (131) was prepared in a pure state from the di-*n*-amylamine salt of abietic acid by treatment with lithium in ether and liquid ammonia. Treatment of this acid with cold concentrated sulfuric acid led without any doubt to the formation of a mixture of the γ-lactone (CXXXVIII) and the δ-lactone (CXXXIII).



CXXXIII



CXXXIV CXXXV CXXXVI CXXXVII CXXXVIII

The stereochemical difference between dextropimaric and isodextropimaric acids has been suggested to lie in isomerism at C-7 (75) or C-13 (167). Dihydrodextropimaric acid and dihydroisodextropimaric acid were converted by hydrogen chloride into their Δ^{13}-isomers, m.p. 181–183°C., $[\alpha]_D = +73.2°$ and m.p. 107–108°C., $[\alpha]_D = +76.7°$, respectively (59). The δ-lactones obtained by the treatment with concentrated sulfuric acid of dihydrodextropimaric and dihydroisodextropimaric acids are obviously different. These results clearly indicate that dextro- and isodextropimaric acids are epimeric at C-7 at least (64, 99). On the basis of surface tension and infrared measurements of the two acids, the vinyl groups are probably oriented quasi-equatorially and quasi-axially, respectively (32). The methyl groups at C-1:C-12:C-7 in dextro- and isodextropimaric acids are suggested to be cis:trans and cis:cis from the ratio of the amount of γ- and δ-lactones formed from the pimaric acids with concentrated sulfuric acid (168). Further evidence that dextro- and isodextropimaric acids are isomeric at C-13 was given by the cleavage of the double bonds of the two acids with osmic acid. The two *gem*-dimethyl acids obtained from such an oxidation were different, but could be converted into the same Δ^{13} acid (60).

The configurational relationship between lanostadienol (CXXXIX) and the diterpene manoöl (CXL) was demonstrated by degradation of both CXXXIX and CXL to a bicyclic C_{14} acid (CXLI) (97). *trans*-(+)-1-Methyl-1-carboxycyclohexyl-2-acetic acid (CXLIII) was obtained from the degradation of 3β,11α-diacetoxy-9α-hydroxy-7-oxo-22-ergostene (CXLII). CXLI and CXLIII can be used to establish the configuration of the combination points of rings A and B of the classical steroids, on the one hand, and of lanostadienol and the di- and triterpenes, on the other hand, on a purely experimental basis (79). Klyne has applied the method of molecular rotation differences to diterpene stereochemical problems (95). A part of his conclusions concerning the stereochemistry of the diterpene hydrocarbons is shown in the formulas for abietane (CXLIV) and pimarane (CXLV). Structures were proposed, in addition, for other diterpenoids.

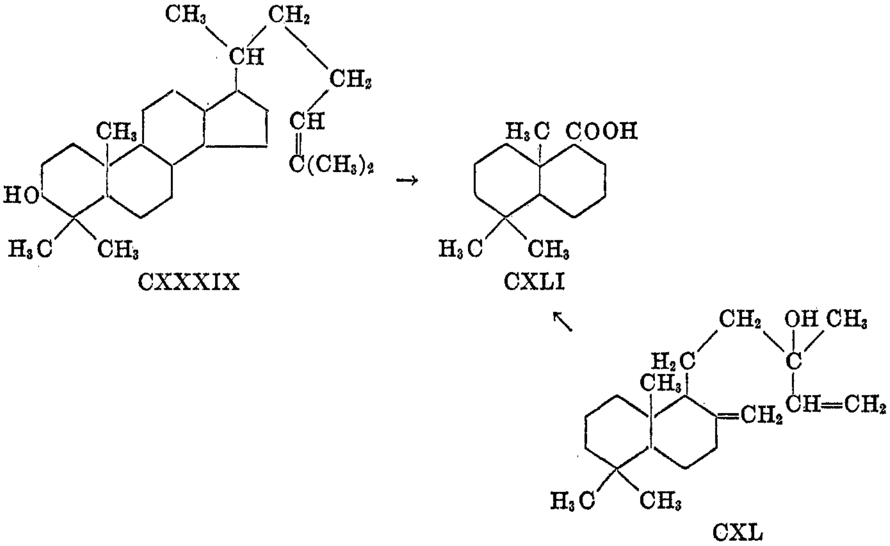
The orientation, however, at C-7 in many abietane, pimarane, and agathene

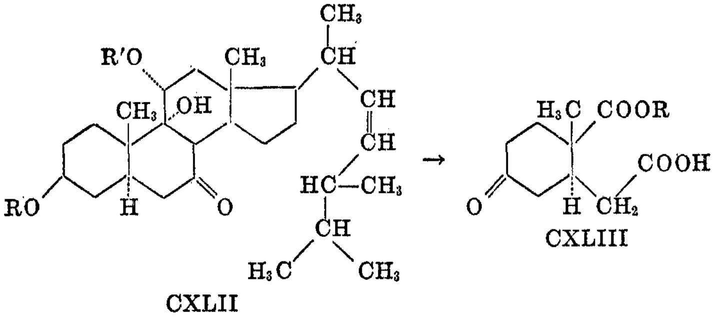
TABLE 2

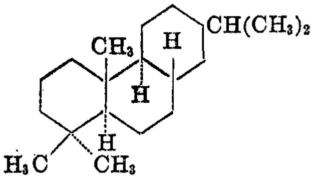
Stereochemistry of the diterpenes

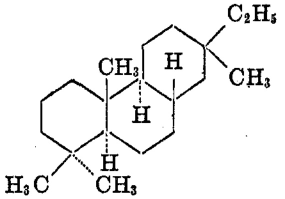
Compound	C-1(COOH):C-11(H)	C-11(H):C-12(CH_3)	C-12(CH_3):C-13(H)
Abietic acid	cis	trans	trans
Neoabietic acid	cis	trans	cis ?
Dextropimaric acid	cis	trans	trans ?
Levopimaric acid	cis	trans	trans ?
Podocarpic acid	trans	trans	trans
Cativic acid	—	trans	—
Eperuic acid	—	trans*	—
Labdanolic acid	—	trans	—
Vinhaticoic acid	cis	trans	?
Vouacapenic acid	trans†	trans	—
Cassaic acid	—	trans	—
Rimuene (totarene)	cis	trans	trans ?
Cafestol	—	trans‡	—
Manoöl	—	trans	—
Marrubiin	cis ?	trans	—

* α-CH_3.
† β-COOH.
‡ α(?)-CH_3.






CXLIV


CXLV

derivatives, and at C-13 and C-14 in many pimarane and 7,8-seco derivatives, is still unknown. Petru and Galik (120) have suggested that sandaracopimaric acid probably differs from either dextro- or isodextropimaric acid at C-1, having the opposite configuration at this center. Wenkert (167) suggested that the diterpenes of the abietane type are derived biogenetically by the concerted rearrangement of pimaradienes (e.g., rimuene) having a quasi-axial methyl and quasi-equatorial vinyl function. He suggested that only pimaradienes (and diterpenes derived from them) epimeric at C-7 to rimuene will be found in nature. The A/B ring juncture in the phyllocladene group, including the *Garrya* alkaloids, was claimed to be antipodal to that of the other polyterpenes and steroids. The stereochemistry of cafestol and phyllocladene, suggested from the study of rotatory dispersion curves (see Section III, pages 1042 and 1045), lends uncertainty to the suggested configuration of the C-12 angular methyl group of pimaradiene and to the biogenetically concerted mechanism of pimaradiene rearrangement (51, 52). The present knowledge of the stereochemistry of the diterpenes is summarized in table 2.

This review is dedicated to the memory of Shotaro Arakawa, late president of the Arakawa Forestry Chemicals Company, Osaka, Japan, and one of the founders of the Japanese pine resin industry.

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VIII. REFERENCES

(1) ARAKAWA, M., AND ZEISS, H. H.: Private communication.
(2) BAKER, R. T., AND SMITH, H. G.: *The Pines of Australia*, p. 419. Technological Museum, Sidney, New South Wales (1910).
(3) BARLTROP, J. A., BIGLEY, D. B., AND ROGERS, N. A. J.: Chem. & Ind. (London) **1959,** 400.
(4) BARLTROP, J. A., AND DAY, A. C.: J. Chem. Soc. **1959,** 671.
(5) BARLTROP, J. A., AND ROGERS, N. A. J.: Chem. & Ind. (London) **1957,** 20.
(6) BARLTROP, J. A., AND ROGERS, N. A. J.: Chem. & Ind. (London) **1957,** 397.
(7) BARTLETT, M. F.: Ph.D. Thesis, University of New Brunswick (1954).
(8) BARTLETT, M. F., AND WIESNER, K.: Chem. & Ind. (London) **1954,** 542.
(9) BARTON, D. H. R.: Chem. & Ind. (London) **1948,** 638.
(10) BARTON, D. H. R., BRUUN, T., AND SORENSEN, N. A.: Acta Chem. Scand. **5,** 1356 (1951).
(11) BARTON, D. H. R., AND ELAD, D.: J. Chem. Soc. **1956,** 2085.
(12) BARTON, D. H. R., AND SCHMEIDLER, G. A.: J. Chem. Soc. **1948,** 1197.
(13) BEATH, G. B.: J. Soc. Chem. Ind. **52,** 338T (1933).
(14) BEER, R. J. S., DUTTON, B. G., JAQUISS, D. B., ROBERTSON, A., AND SAVIGE, W. E.: J. Chem. Soc. **1956,** 4850.
(15) BENDAS, H., AND DJERASSI, C.: Chem. & Ind. (London) **1955,** 1481.
(16) BENGIS, R. O., AND ANDERSON, R. J.: J. Biol. Chem. **97,** 99 (1932).
(17) BHATTACHARYYA, B. K.: J. Indian Chem. Soc. **22,** 165 (1945).
(18) BIGLEY, D. B., ROGERS, N. A. J., AND BARLTROP, J. A.: Chem. & Ind. (London) **1958,** 558.
(19) BIRCH, J., RICKARDS, R. W., SMITH, H., HARRIS, A., AND WHALLEY, W. B.: Proc. Chem. Soc. **1958,** 223.
(20) BOTTOMLEY, W., COLE, A. R. H., AND WHITE, D. E.: J. Chem. Soc. **1955,** 2624.
(21) BRANDT, C. W.: New Zealand J. Sci. Technol. **20B,** 8 (1938); Chem. Abstracts **33,** 551 (1939).
(22) BRANDT, C. W.: New Zealand J. Sci. Technol. **34B,** 46 (1952); Chem. Abstracts **47,** 10506 (1953).
(23) BRANDT, C. W., AND THOMAS, B. R.: New Zealand J. Sci. Technol. **33B,** No. 1, 30 (1951); Chem. Abstracts **46,** 6618 (1952).
(24) BREDENBERG, J. B.: Acta Chem. Scand. **11,** 927 (1957).
(25) BRIDEL, M., AND LAVIEILLE, R.: Compt. rend. **192,** 1123 (1931).
(26) BRIGGS, L. H., CAIN, B. F., AND WILMSHURST, J. K.: Chem. & Ind. (London) **1958,** 599.
(27) BRIGGS, L. H., CAWLEY, R. W., LOE, J. A., AND TAYLOR, W. I.: J. Chem. Soc. **1950,** 955.

(28) Briggs, L. H., and Sutherland, M. D.: J. Org. Chem. **13,** 4 (1948).
(29) Britt, J. J., and Arigoni, D.: Proc. Chem. Soc. **1958,** 224.
(30) Brossi, A., Gutmann, H., and Jeger, O.: Helv. Chim. Acta **33,** 1730 (1950).
(31) Brossi, A., and Jeger, O.: Helv. Chim. Acta **33,** 722 (1950).
(32) Bruun, H. H.: Acta Acad. Aboensis. Math. et Phys. Rept. No. 75, **19,** 7 (1954); Chem. Abstracts **48,** 7390 (1954).
(33) Bruun, H. H.: Acta Chem. Scand. **11,** 907 (1957).
(34) Buchi, G., and Pappas, J. J.: J. Am. Chem. Soc. **76,** 2963 (1954).
(35) Burn, D., and Rigby, W.: Chem. & Ind. (London) **1955,** 386.
(36) Burn, D., and Rigby, W.: J. Chem. Soc. **1957,** 2964.
(37) Cocker, J. D., and Halsall, T. G.: J. Chem. Soc. **1956,** 4262.
(38) Cocker, J. D., and Halsall, T. G.: Abstracts, Symposium on Recent Advances in the Chemistry of Terpenoid Compounds, Glasgow, Scotland, July, 1957.
(39) Cocker, J. D., Halsall, T. G., and Bowers, A.: J. Chem. Soc. **1956,** 4259.
(40) Cocker, W., Cross, B. E., Duff, S. R., Edward, J. T., and Holley, T. F.: J. Chem. Soc. **1953,** 2540.
(41) Cocker, W., Cross, B. E., Duff, S. R., and Holley, T. F.: Chem. & Ind. (London) **1952,** 827.
(42) Cocker, W., Edward, J. T., and Holley, T. F.: Chem. & Ind. (London) **1953,** 1227.
(43) Cocker, W., Edward, J. T., and Holley, T. F.: Chem. & Ind. (London) **1955,** 772.
(44) Considine, W. J., and Zeiss, H. H.: J. Org. Chem. **24,** 253 (1959).
(45) Corey, E. J., Slomp, G., Dev, S., Tobinaga, S., and Glazier, E. R.: J. Am. Chem. Soc. **80,** 1204 (1958).
(46) Cross, B. E., Grove, J. F., MacMillan, J., and Mulholland, T. P. C.: Chem. & Ind. (London) **1956,** 954.
(47) Cross, B. E., Grove, J. F., MacMillan, J., and Mulholland, T. P. C.: Abstracts of Papers Presented at the 132nd Meeting of the American Chemical Society, New York City, New York, September, 1957, p. 35-C. (A copy of this symposium paper was kindly made available to the writers of this review.)
(48) Curtis, P. J., and Cross, B. E.: Chem. & Ind. (London) **1954,** 1066.
(49) Dalma, G.: Helv. Chim. Acta **22,** 1497 (1939).
(50) Djerassi, C., Bendas, H., and Sengupta, P.: J. Org. Chem. **20,** 1046 (1955).
(51) Djerassi, C., Cais, M., and Mitscher, L. A.: J. Am. Chem. Soc. **80,** 247 (1958).
(52) Djerassi, C., Riniker, R., and Riniker, B.: J. Am. Chem. Soc. **78,** 6362 (1956).
(53) Djerassi, C., Smith, C. R., Lippman, A. E., Figdor, S. K., and Herran, J.: J. Am. Chem. Soc. **77,** 4801 (1955).
(54) Djerassi, C., Smith, C. R., Lippman, A. E., Figdor, S. K., and Herran, J.: J. Am. Chem. Soc. **77,** 6633 (1955).
(55) Djerassi, C., Wilfred, E., Visco, L., and Lemin, A. J.: J. Org. Chem. **18,** 1449 (1953).
(56) Drake, A. E.: U. S. patent 2,434,643 (January 20, 1948); Chem. Abstracts **42,** 2786 (1948).
(57) Dvornik, D., and Edwards, O. E.: Chem. & Ind. (London) **1958,** 623.
(58) Edwards, O. E., and Howe, R.: Can. J. Chem. **37,** 760 (1959).
(59) Edwards, O. E., and Howe, R.: Chem. & Ind. (London) **1958,** 629.
(60) Edwards, O. E., and Howe, R.: Chem. & Ind. (London) **1959,** 537.
(61) Feist, K., Rintelen, P., and Kuntz, E.: Ann. **517,** 119 (1935).
(62) Fieser, L. F., and Fieser, M.: *Natural Products Related to Phenanthrene,* American Chemical Society Monograph No. 70, p. 50. Reinhold Publishing Corporation, New York (1949).
(63) Grant, F. W., Jr., and Zeiss, H. H.: J. Am. Chem. Soc. **76,** 5001 (1954).
(64) Green, B., Harris, A., and Whalley, W. B.: Chem. & Ind. (London) **1958,** 1084.
(65) Green, B., Harris, A., Whalley, W. B., and Smith, H.: Chem. & Ind. (London) **1958,** 1369.

(66) Gupta, R. C., and Muthana, M. S.: J. Indian Inst. Sci. **36A,** 76 (1954); Chem. Abstracts **48,** 7852 (1954).

(67) Gupta, R. C., and Muthana, M. S.: J. Indian Inst. Sci. **36A,** 122 (1954); Chem. Abstracts **49,** 6186 (1955).

(68) Halsall, T. G. H.: Ann. Repts. on Progr. Chem. (Chem. Soc. London) **54,** 223 (1957).

(69) Hampton, B. L.: J. Org. Chem. **21,** 918 (1956).

(70) Hansen, E. S., and Zeiss, H. H.: J. Am. Chem. Soc. **77,** 1643 (1955).

(71) Hardy, D. G., and Rigby, W.: Chem. & Ind. (London) **1953,** 1150.

(72) Harris, A., Robertson, A., and Whalley, W. B.: J. Chem. Soc. **1958,** 1799.

(73) Harris, A., Robertson, A., and Whalley, W. B.: J. Chem. Soc. **1958,** 1807.

(74) Harris, G. C., and Sanderson, T. F.: J. Am. Chem. Soc. **70,** 2081 (1948).

(75) Harris, G. C., and Sanderson, T. F.: J. Am. Chem. Soc. **74,** 3072 (1953).

(76) Haworth, R. D., and Johnstone, R. A. W.: J. Chem. Soc. **1957,** 1492.

(77) Haworth, R. D., Jubb, A. H., and McKenna, J.: J. Chem. Soc. **1955,** 1983.

(78) Haworth, R. D., and Moor, B. P.: J. Chem. Soc. **1946,** 633.

(79) Heusser, H., Beriger, E., Anliker, R., Jeger, O., and Ruzicka, L.: Helv. Chim. Acta **36,** 1918 (1953).

(80) Hollis, F., Richards, J. H., and Robertson, A.: Nature **143,** 604 (1939).

(81) Hosking, J. R., and Brandt, C. W.: Ber. **68,** 1311 (1935).

(82) Huebner, C. F., and Jacobs, W. A.: J. Biol. Chem. **174,** 1001 (1948).

(83) Humber, L. G., and Taylor, W. I.: J. Chem. Soc. **1955,** 1044.

(84) Ito, S., and Humber, L. G.: Chem. & Ind. (London) **1957,** 397.

(85) Iwasa, J., Kumasawa, Z., and Nakajima, M.: Abstracts, Symposium on Natural Products, Japan, p. 143, October 1958, and private communication.

(86) Jacobs, W. A.: J. Org. Chem. **16,** 1593 (1951).

(87) Jeger, O., Durst, O., and Buchi, G.: Helv. Chim. Acta **30,** 1853 (1947).

(88) Kalman, N. V.: J. Am. Chem. Soc. **60,** 1423 (1938).

(89) King, F. E., Godson, D. H., and King, T. J.: J. Chem. Soc. **1955,** 1117.

(90) King, F. E., and Jones, G.: J. Chem. Soc. **1955,** 658.

(91) King, F. E., King, T. J., and Neill, K. G.: J. Chem. Soc. **1953,** 1055.

(92) King, F. E., King, T. J., and Topliss, J. G.: Chem. & Ind. (London) **1954,** 108.

(93) King, F. E., King, T. J., and Topliss, J. G.: Chem. & Ind. (London) **1956,** 113.

(94) King, F. E., King, T. J., and Uprichard, J. M.: J. Chem. Soc. **1958,** 3428.

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

(96) Kubo, M. O.: Arch. exptl. Pathol. Pharmakol. **67,** 111 (1912); Chem. Abstracts **6,** 2136 (1912).

(97) Kyburz, E., Riniker, B., Schenk, H. R., Heusser, H., and Jeger, O.: Helv. Chim. Acta **36,** 1891 (1953).

(98) Lederer, E., Marx, F., Mercier, D., and Perot, G.: Helv. Chim. Acta **29,** 1354 (1946).

(99) Le-Van-Thoi, M.: Compt. rend. **1958,** 1343.

(100) Locke, D. M., and Pelletier, S. W.: J. Am. Chem. Soc. **80,** 2588 (1958).

(101) Loeblich, V. M., Baldwin, D. E., and Lawrence, R. V.: J. Am. Chem. Soc. **77,** 2823 (1957).

(102) Lombard, R., and Frey, J.-M.: Bull. soc. chim. France **1954,** 35.

(103) Malevskaya, S. S., and Kayeeva, E. V.: Zhur. Priklad. Khim. (J. Applied Chem.) **21,** 854 (1948); Chem. Abstracts **43,** 6185 (1949).

(104) Manske, R. H. F., and Holmes, H. L., Editors.: *The Alkaloids. Chemistry and Physiology,* Vol. IV. Academic Press, Inc., New York (1954).

(105) Mayo, P. de: *The Chemistry of Natural Products.* Vol. III. *The Higher Terpenoids.* Interscience Publishers, New York (1959).

(106) Mercier, L. J., and Mercier, F.: Compt. rend. **195,** 1102 (1932).

(107) Moore, R. N., and Lawrence, R. V.: J. Am. Chem. Soc. **81,** 458 (1959).

(108) Mosettig, E., and Nes, W. R.: J. Org. Chem. **20,** 884 (1955).

(109) Nakazima, M., and Iwasa, Z.: Botyu Kagaku No. **13,** 11 (Summary in English) (1949); Chem. Abstracts **44,** 1090 (1950).

(110) Nakazima, M., and Miyazima, S.: Botyu Kagaku No. **15,** 28 (Summary in English) (1950); Chem. Abstracts **44,** 7811 (1950).

(111) Nakazima, M., Miyazima, S., Suga, T., and Iwasa, Z.: Botyu Kagaku No. **15,** 30 (Summary in English) (1950); Chem. Abstracts **44,** 7811 (1950).

(112) Nasipuri, D.: Chem. & Ind. (London) **1957,** 425.

(113) Nazarow, I. N., Zavyalov, S. I., Burmistrova, M. S., Gurvich, I. A., and Shmonina, L. I.: J. Gen. Chem. U.S.S.R. **26,** 465 (1956); Chem. Abstracts **51,** 2679 (1957).

(114) Ohta, M., and Ohmori, L.: Pharm. Bull. (Tokyo) **5,** 96 (1957); Chem. Abstracts **51,** 16390 (1957).

(115) Oneto, J. F.: J. Am. Pharm. Assoc. **35,** 204 (1946).

(116) Parham, W. E., Wheeler, E. L., and Dodson, R. M.: J. Am. Chem. Soc. **77,** 1166 (1955).

(117) Pelletier, S. W.: Chem. & Ind. (London) **1958,** 1116.

(118) Pelletier, S. W., and Jacobs, W. A.: Chem. & Ind. (London) **1955,** 1385.

(119) Pelletier, S. W., and Jacobs, W. A.: J. Am. Chem. Soc. **76,** 4496 (1954).

(120) Petru, F., and Galik, V.: Collection Czechoslov. Chem. Communs. **18,** 717 (1953); Chem. Abstracts **49,** 240 (1955).

(121) Prelog, V., and Acklin, W.: Helv. Chim. Acta **39,** 748 (1956).

(122) Pudles, J., Diara, A., and Lederer, E.: Compt. rend. **244,** 472 (1957).

(123) Raman, K., and Rao, P. N.: Experientia **12,** 472 (1956).

(124) Rao, P. N., and Bagchi, P.: J. Org. Chem. **23,** 169 (1958).

(125) Rao, P. N., and Bagchi, P.: Science and Culture (India) **19,** 507 (1954); Chem. Abstracts **49,** 10235 (1955).

(126) Rao, P. N., and Raman, K.: Tetrahedron **4,** 294 (1958).

(127) Ritchie, P., Sanderson, T., and McBurney, L.: J. Am. Chem. Soc. **75,** 2610 (1953).

(128) Ritchie, P., Sanderson, T., and McBurney, L. F.: J. Am. Chem. Soc. **76,** 723 (1954).

(129) Roberts, E. M., and Lawrence, R. V.: Abstracts of Papers Presented at the 131st Meeting of the American Chemical Society, Miami, Florida, April, 1957, p. 21-O.

(130) Robertson, A., Smithies, W. R., and Tittensor, E.: J. Chem. Soc. **1949,** 879.

(131) Royals, E. E., Bailey, W. C., and Kennedy, R. W.: J. Org. Chem. **23,** 151 (1958).

(132) Ruzicka, L., and Balas, F.: Helv. Chim. Acta **6,** 677 (1923).

(133) Ruzicka, L., and Dalma, G.: Helv. Chim. Acta **23,** 753 (1940).

(134) Ruzicka, L., Dürst, O., and Jeger, O.: Helv. Chim. Acta **30,** 353 (1947).

(135) Ruzicka, L., Engel, B. G., Ronco, A., and Berse, K.: Helv. Chim. Acta **28,** 1038 (1945).

(136) Ruzicka, L., Graaff, G. B. R. de, and Müller, H. J.: Helv. Chim. Acta **15,** 1300 (1932).

(137) Ruzicka, L., and Hosking, J. R.: Helv. Chim. Acta **13,** 1413 (1930).

(138) Ruzicka, L., and Hosking, J. R.: Helv. Chim. Acta **14,** 203 (1931).

(139) Ruzicka, L., and Lardon, F.: Helv. Chim. Acta **29,** 912 (1946).

(140) Ruzicka, L., Seidel, C. F., and Engel, L. L.: Helv. Chim. Acta **25,** 621 (1942).

(141) Ruzicka, L., Sternbach, L., and Jeger, O.: Helv. Chim. Acta **24,** 504 (1941).

(142) Schuller, W. H., Moore, R. H., and Lawrence, R. V.: Paper presented before the Meeting-in-Miniature of the Florida Section of the American Chemical Society, St. Petersburg, Florida, May 8–9, 1959.

(143) Short, W. F., and Wang, H.: J. Chem. Soc. **1950,** 991.

(144) Simonsen, J., and Barton, D. H. R.: *The Terpenes.* Vol. III. *The Sesquiterpenes, Diterpenes and their Derivatives.* The University Press, Cambridge (1952).

(145) Slotta, K. H., and Neisser, K.: Ber. **71,** 1991 (1938).

(146) Slotta, K. H., and Neisser, K.: Ber. **71,** 2342 (1938).

(147) Šorm, F., Suchý, M., Vonášek, F., Plíva, J., and Herout, V.: Collection Czechoslov. Chem. Communs. **16**, 268 (1951); Chem. Abstracts **47**, 9944 (1953).
(148) Spoelstra, D. B.: Rec. trav. chim. **49**, 226 (1930).
(149) Stodola, F. H., Nelson, G. E. N., and Spence, D. J.: Arch. Biochem. Biophys. **66**, 438 (1957).
(150) Stork, G., and Burgstahler, A.: J. Am. Chem. Soc. **73**, 3544 (1951).
(151) Stork, G., and Schulenberg, J. W.: J. Am. Chem. Soc. **78**, 250 (1956).
(152) Takei, S., and Miyajima, S.: J. Agr. Chem. Soc. Japan **10**, 1098 (1934); Chem. Abstracts **29**, 1133 (1935).
(153) Takemoto, T.: Paper presented before the meeting of the Pharmaceutical Society, Kinki Section, Japan, March, 1958.
(154) Takemoto, T., and Nakajima, N.: Paper presented before the meeting of the Pharmaceutical Society, Kinki Section, Japan, February, 1956.
(155) Takemoto, T., and Nakajima, N.: J. Pharm. Soc. Japan **73**, 1021 (1953).
(156) Tallent, W. H., Riethof, M. L., and Horning, E. C.: J. Am. Chem. Soc. **79**, 4548 (1957).
(157) Tishchenko, D., Komshilov, N., Kissel, K., and Malevskaya, S. S.: J. Gen. Chem. U.S.S.R. **20**, 1225 (1950); Chem. Abstracts **45**, 1546 (1951).
(158) Todd, A. R.: *Perspectives in Organic Chemistry.* Interscience Publishers, New York (1956).
(159) Tsutsui, M.: J. Chem. Soc. Japan, Pure Chem. Sect. **70**, 203 (1949).
(160) Tsutsui, M.: Paper presented before the meeting of the Chemical Society of Japan, Kyoto, Japan, April, 1950.
(161) Turner, R. B., Herzog, E. G., Morin, R. B., and Riebel, A.: Tetrahedron Letters No. **2**, 7 (1959).
(162) Ukita, C.: Private communication.
(163) Ukita, C., and Tsumita, T.: J. Pharm. Soc. Japan **72**, 1324 (1952); Chem. Abstracts **47**, 4862 (1953).
(164) Ukita, C., Tsumita, T., and Utsugi, N.: Pharm. Bull. (Tokyo) **3**, 441 (1955); Chem. Abstracts **50**, 14651 (1956).
(165) Vesterberg, A.: Ber. **36**, 4200 (1903).
(166) Voser, W., White, D. E., Heuser, H., Jeger, O., and Ruzicka, L.: Helv. Chim. Acta **35**, 830 (1952).
(167) Wenkert, E.: Chem. & Ind. (London) **1955**, 282.
(168) Wenkert, E., and Chamberlin, J. W.: J. Am. Chem. Soc. **80**, 2912 (1958).
(169) Wenkert, E., and Chamberlin, J. W.: J. Am. Chem. Soc. **81**, 688 (1959).
(170) Wenkert, E., and Stevens, T. E.: J. Am. Chem. Soc. **78**, 5627 (1956).
(171) Wessely, F., Dinjaski, K., Isemann, W., and Singer, G.: Monatsh. Chem. **66**, 87 (1935).
(172) Wettstein, A., Hunziker, F., and Miescher, K.: Helv. Chim. Acta **26**, 1197 (1943).
(173) Wiesner, K., Armstrong, R., Bartlett, M. F., and Edwards, J. A.: Chem. & Ind. (London) **1954**, 132.
(174) Wiesner, K., Armstrong, R., Bartlett, M. F., and Edwards, J. A.: J. Am. Chem. Soc. **76**, 6068 (1954).
(175) Wiesner, K., and Edwards, J. A.: Experientia **11**, 255 (1955).
(176) Wiesner, K., Taylor, W. I., Figdor, S. K., Bartlett, M. F., Armstrong, J. R., and Edwards, J. A.: Ber. **86**, 800 (1953).
(177) Wood, H. B., Jr., and Fletcher, H. G., Jr.: J. Am. Chem. Soc. **78**, 207 (1956).
(178) Yabuta, T., and Hayashi, T.: J. Agr. Chem. Soc. Japan **15**, 257 (1939); Chem. Abstracts **33**, 8238 (1939).
(179) Yabuta, T., Sumiki, Y., and Asô, K.: J. Agr. Chem. Soc. Japan **25**, 159 (1951); Chem. Abstracts **46**, 5143 (1952).
(180) Zeiss, H. H., and Martin, W. B., Jr.: J. Am. Chem. Soc. **75**, 5935 (1953).
(181) Zeiss, H. H., and Tsutsui, M.: J. Am. Chem. Soc. **77**, 6707 (1955).