THE PREPARATION AND STEREOCHEMISTRY OF PINANE DERIVATIVES

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I. Introduction

Monoterpenes possessing the pinane skeleton (I) occur in the wood and leaf oils of many higher plants, particularly those of the order Coniferae and also in some algae and insects (84, 112), and can be readily converted into numerous non-naturally occurring bicyclo[3.1.1] heptane derivatives.

The chemistry of these compounds has been reviewed up to 1952 (97, 133), and more recently certain stereochemical aspects have been clarified (27, 28); but despite extensive study the details of the structure of certain compounds are in dispute and much of the recorded data are inconclusive or inconsistent. In work carried out before the last decade, gas–liquid chromatography (glc) was unavailable for isolation of pure samples and

for product analysis; physical methods were rarely used for the elucidation of structure; and the methods and rules now systematized as conformational analysis (53) were seldom applied to elucidate stereochemistry. Consequently, the use of synthetic routes of differing stereoselectivity, often using ill-defined reactants, resulted in ranges of values for the physical properties of nominally the same compound, as was inevitable in view of the prevalence of double-bond and skeletal rearrangements in these bicyclic structures.

This review, which covers the literature until December 1965, attempts: (i) to clarify the mass of confused data concerning pinane derivatives; (ii) to evaluate critically the stereochemistry and convenient stereoselective syntheses of the most important hydro-

carbons, alcohols, and carbonyl compounds with the pinane skeleton; and (iii) to record the most reliable values of certain physical properties of these compounds.

The elucidation of the structure of the pinane skeleton, the position of substituents, and the chemistry of the characteristic rearrangements of these compounds have been summarized elsewhere (20, 133). Few systematic investigations have been made on other classes of substituted pinanes, and only a few references to these will be made.

Weight has been given to modern studies using glc as a monitor of purity of reactants and products, but even here there is no guarantee that the final products were unique isomers. Most glc analysis has involved the use of one column under one set of operating conditions, and homogeneity of sample under such conditions is no absolute criterion of purity when mixtures of stereoisomers of unknown chromatographic properties are studied. Ideally, homogeneity should be shown on at least three different analytical-type glc columns, containing carefully chosen packings suitable for for the compound on hand and operated at the lowest practicable temperature (76, 99, 107, 157), before purity can be reasonably claimed. However, in the absence of this ideal situation, the glc criterion of purity is the best available. Thin-layer chromatography has been used for analysis on a more limited scale (155). Often, samples appearing chemically pure by these criteria are not optically pure. In such cases, the specific rotation corresponding to the use of optically pure precursors has been calculated on the assumption of no racemization during the interconversions, and this is denoted by $[\alpha]'_D$ (calcd) in the following sections. Although assuming (probably often unjustifiably) the use of chemically pure starting materials and the isolation of chemically pure products, this procedure does enable a comparison between the results of different workers to be made.

II. NOMENCLATURE

Numbering of the pinane skeleton (I) allows a systematic nomenclature to be developed, but trivial names are invariably used for most subclasses, and an alternative projection (as in II) is usually adopted. The parent hydrocarbon exists in two forms designated cis and trans (each of which exists as (+) and (−) isomers), depending on the relative orientations of the gem-dimethyl bridge and the C-10 methyl group: thus
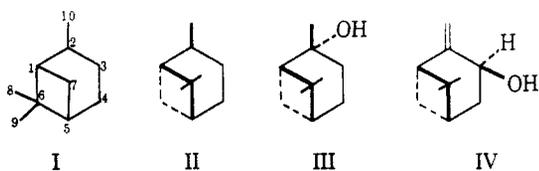
I   II   III   IV

II represents (+)-cis-pinane. Pinanes substituted at C-2 or C-10 are referred to these parents: thus III is

(+)-cis-2-pinanol. If C-2 is unsaturated, substitution at a ring atom gives cis or trans isomers according to the relationship between the bridge and the substituent: thus IV is (+)-cis-pinocarveol (here the trivial name is always employed; systematically, it is 2(10)-pinen-cis-3-ol). An alternative system of naming, adopted before the detailed stereochemistry was elucidated, designates the more and less stable isomers as normal and iso, or less usually α and β.

Substitution of the parent hydrocarbons at C-3, C-4, or C-7 yields four isomers in each case (two from cis- and two from trans-pinane, all of which exist in (+) and (−) forms), and these were named X, iso-X, neo-X, and neoiso-X, by analogy with the menthols, before their relative configurations were known. These names are still universally used.

III. STEREOCHEMISTRY

The absolute configurations of pinane derivatives follow from reference to parents which have in turn been degraded to absolute standards. Thus (−)-β-pinene (V) and (−)-cis-pinane (VI) are precursors of many derivatives and have the configurations $1S:5S$ and $1S:2R:5S$, respectively, as shown by their interconversion and multistep degradation to (+)-2-methylsuccinic acid (VII). Other degradative schemes are consistent with these assignments (23, 31, 103).

V   VI   VII
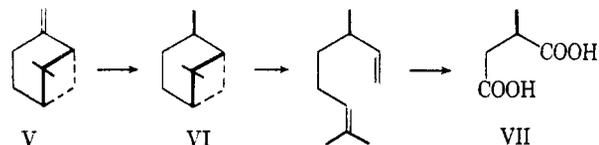
Increasing substitution of a cyclobutane ring increases its ease of formation and also presumably its stability once formed; it has been argued that the smaller ring of the pinane skeleton is less strained than that of cyclobutane. The strain of the four-membered ring in α-pinene can be calculated using thermal data to be about 11 kg cal mole^{-1} as compared with 24 kg cal mole^{-1} for cyclobutane itself (128); presumably the six-membered ring accommodates the bulk of the strain of the bicyclic system and departures from the unstrained cyclohexane ring must be considerable, whereas the smaller ring is of the normal puckered geometry. Certain substituents may, however, strain the C-4 ring: the infrared and ultraviolet absorptions due to the chromophore in VIII and IX indicate strain in the C-4 and C-6 rings, respectively (101).

VIII   IX   X
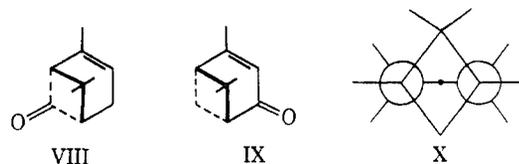
Little is known about the preferred conformations, although these have an important influence on reac-

tivities. The skeleton was originally considered to be a bridged chair (27), but this must be an oversimplification, for, while effectively staggering the hydrogen atoms and substituents on C-2, C-3, and C-4, this geometry would eclipse the hydrogen atoms on C-2 and C-4 with those on the bridgehead carbon atoms and cause interactions of the "bowsprit-flagpole" type (a bridged chair is also a bridged boat). Both these latter interactions could be relieved by flattening part of the six-membered ring to give a Y-shaped molecule, shown in Newman projection in X, but this would in turn completely eclipse hydrogens and substituents on C-2, C-3, and C-4. Recently, the nmr spectrum of iso-

XI   XII   XIII
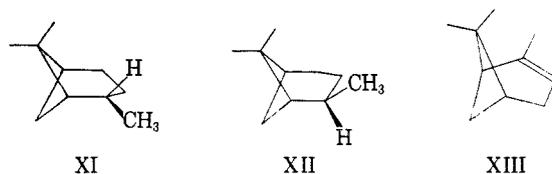
pinocampheol has been shown to be consistent with such a flattened skeleton, although the results have not been fully analyzed (158).

The most stable conformation probably lies between the extremes of the two bridged chairs and the Y-shaped molecule, X, although since the bulk of the strain resides in the six-membered ring, the Y-shaped molecule may be slightly favored. In any particular case the favored conformation will be influenced by the presence of substituents and by the environment, and a dynamic equilibrium with less favored orientations will occur.

Models and calculations of steric compressions suggest that *trans*-pinane takes up a conformation, XI, in which C-3 is slightly displaced toward the methylene bridge away from the plane of C-1, C-2, C-4, and C-5, and the epimeric *cis* compound probably puckers in the opposite direction to form XII, such that the 2-methyl group becomes pseudo-equatorial in both cases, and so minimizes its interactions with the *gem*-dimethyl bridge.

Chemical and physical evidence for these geometries is sparse. The more and less stable isomers of 3-pinanone have been assigned structures similar to XI and XII, respectively, on the basis of the relative rates of oximation and bromination (22, 119). The ketone corresponding to XII would possess a carbonyl group screened by the *gem*-dimethyl groups, but was considered to be more readily enolized (and hence brominated) than its epimer. The nmr spectra of these ketones are very similar, and it has been proposed that in the neat liquid both isomers existed in a conformation similar to XI, but such spectra are complex and none have been fully analyzed (9, 54, 57, 158). The optical rotary dispersion curves of pinane derivatives of known configuration are also difficult to rationalize

on the basis of the Octant rule (61), and so this technique cannot be applied to settle conformational problems. A study of the interactions in the endocyclic pinenes suggests that the conformation is probably close to a bridged half-chair, giving a Y-shaped molecule in which five carbon atoms are nearly planar (XIII). This structure is supported by electron diffraction studies: similar studies applied to saturated derivatives have been incomplete and do not specify the position of C-3 (11, 12).

The methods of conformational analysis applicable to unstrained cyclohexanes (21) have been widely used to assign the relative configurations discussed in sections IV to IX, and such extrapolation to bicyclics usually seems to be justified (27) in terms of pseudo-orientations based on the skeletons XI and XII. The following well-established principles will be applied without comment to specific structures and reactions in subsequent sections.

(i) The von Auwers–Skita rule, that the *trans* form of a pair of stereoisomers has the lower density, boiling point, and refractive index.

(ii) Equilibration of ketones or alcohols with base yields the most stable isomer; *i.e.*, that with the most possible large equatorial substituents. Thus, alkaline reduction of a ketone leads to this isomer of the product alcohol.

(iii) Kinetically controlled products of Meerwein–Ponndorf–Verley reduction of ketones are often the less stable isomers, but these revert to thermodynamically controlled products on prolonged reaction.

(iv) Catalytic hydrogenation of double bonds or carbonyl groups in ethanol or acetic acid as solvents (53), reduction of the former with diimide (138), and also hydroboronation (158) are all highly stereospecific *cis* additions to the side of the skeleton remote from the *gem*-dimethyl bridge, although prolonged reduction in the presence of a metal catalyst may lead to isomerization of the initial product. Oxidation of the hydroboronation complex and hydrolysis to an alcohol proceeds with retention of configuration (158).

(v) Base-catalyzed elimination from halides or tosylates and acid-promoted dehydration of alcohols both require a transition state with the leaving groups *anti*-periplanar. Pyrolytic elimination from xanthates requires a *syn*-clinal or *syn*-periplanar orientation, with an axial–equatorial relationship of the leaving groups.

(vi) The formation and saponification of esters are more rapid with equatorial alcohols than with axial.

IV. PINENES AND PINANES

(+)-XIV; (+)-α-pinene   (+)-XV; (+)-β-pinene

R₁
.R₂
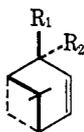
(+)-XVIa, R₁ = CH₃, R₂ = H; (+)-cis-δ-pinene
(−)-XVIb, R₁ = H, R₂ = CH₃; (−)-trans-δ-pinene

A. α-PINENE

XIV and XV are the parents of most synthetic pinane derivatives, the former being the most widely distributed natural monoterpene (87a), and both occur as major components of turpentine oil. The commercial product consists of extracts from different species and typical analyses of wood and gum oils vary widely (92): in oil from 14 national sources, XIV comprised 35-94% with $[\alpha]_D$ varying from -47 to $+48°$, and XV comprised 2-65% with $[\alpha]_D$ in the range -21.3 to $-21.8°$ (45). (In these as in many other data, the temperature of the measurements was not recorded.) Allepo oil contains (+)-XIV, $[\alpha]_D$ $+49.2°$, in excellent yield and Bordeaux oil consists mainly of (−)-XIV, $[\alpha]_D$ $-45.8°$ (100). The most popular commercially grown pines mainly produce (+)-XIV although contamination with fir wood containing the (−) isomer frequently lowers the optical purity of commercial blends (151). However, many other pine species give oils containing up to 90% of (−)-XIV of good optical purity (112). XIV is easily purified by distillation, bp 155.9 ● 0.1°, n^{25}_D 1.4631, d_{25} 0.8539 (62), or by glc, although other methods are required to obtain optically pure specimens; but addition of 0.001% pyrogallol is necessary to prevent rapid autoxidation (98). The material of highest recorded specific rotation, $[\alpha]^{25}_D$ $+52.4°$, is obtained after purification through a silver complex (42), but specimens of high optical purity, $[\alpha]^{20}_D$ $+51.1°$, can be obtained by fractional recrystallization of the nitrosochloride (141), or by either refluxing the naturally occurring highly optically pure (−)-XV with rosin acid (86) or by treating with palladium saturated with hydrogen at 20°, when (−)-XIV results (102, 151). Optically pure material rarely occurs naturally, the best, $[\alpha]^{25}_D$ $+51.5°$, is probably that from a New Zealand pine species (32).

B. β-PINENE

In contrast to XIV, this widely occurs in nature as the almost optically pure (−) isomer; only a few species synthesize the (+) form (87, 112). Conversion of (−)-XV into (−)-XIV and into (−)-cis-pinane proves the absolute configuration, and the regular occurrence of (+)-XIV and (−)-XV (i.e., with skeletons of different absolute configuration) in the same species suggests that biosynthesis occurs from different immediate precursors. The highest recorded specific rotations are of samples purified by fractionation of turpentine, $[\alpha]^{25}_D$ $-22.4°$, bp 166.0 ± 0.1°, n^{25}_D 1.4768, d_{25} 0.8667(47, 62),

and by the silver complex method; $[\alpha]^{25}_D$ $-22.7°(42)$. In the former method the temperature must be kept below 100° to prevent any rosin acid present in the crude oil catalyzing conversion into XIV and ring-opening. XIV is more stable than XV, contrary to a recent assertion (149), as is shown by the heats of combustion (63), the ready interconversions already discussed, and the equilibrium mixtures formed on treatment of XV with titanic acid or phenol under mild conditions (105, 106).

C. δ-PINENE

These isomers do not occur naturally. γ-Pinene (1-pinene) is unknown; its existence would contravene Bredts' rule, by putting a carbon double bond at a bridgehead.

Mixtures of XIV and XVI were first obtained by elimination from 3-pinanonium salts (in reactions showing anti-Hofmann orientation) and xanthates (40, 111), but the first pure samples were of $[\alpha]_D$ $-107.7°$, bp 157-158°, n^{20}_D 1.4671, d_{20} 0.863, and $[\alpha]_D$ $+58.8°$, bp 159-161°, n^{20}_D 1.4696, d_{20} 0.867, formed, respectively, by the base-promoted decomposition of the tosylate of (+)-pinocampheol and by the pyrolysis of the methyl xanthate of (+)-verbanol (124). The von Auwers–Skita rule indicated these to be trans and cis isomers, and this was confirmed by reduction to (+)-trans- and (+)-cis-pinanes, the specific rotations of which revealed the original olefins to be probably almost optically pure. The absolute configurations follow from these reductions and from the methods of preparation. It has been claimed that XVI can be purified by treatment with hydrochloric acid thereby converting contaminating XIV into easily separable camphene hydrochloride, and by this means (−)-XVIb, $[\alpha]^{20}_D$ $-90.1°$, was prepared (144).

D. PINANES

R₁
.R₂
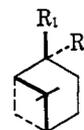
(+)-XVIIa, R₁ = CH₃, R₂ = H; (+)-cis-pinane
(+)-XVIIb, R₁ = H, R₂ = CH₃; (+)-trans-pinane

Early attempts to reduce pinenes to form the parent hydrocarbon were confused both by rearrangements due to the acidic reagents used, which led to products contaminated with p-menthane, and by an inappreciation of the existence of geometrical isomerism. Reduction of (+)-α-pinene and (+)-cis- and (−)-trans-δ-pinenes over nickel or platinum oxide largely eliminated rearrangement and led to the isolation of (+)-XVIIb, $[\alpha]_D$ $+23.8°$, bp 165-166°, n^{20}_D 1.4618, d_{20} 0.8558, and (+)-XVIIa, $[\alpha]_D$ $+30.9°$, bp 167-168°, n^{20}_D 1.4633, d_{20} 0.8590 (82, 124). These assignments were made using the von Auwers–Skita rule and were later con-

firmed by conformational arguments based on the interconversions of pinanes, δ-pinenes, and pinocampheols. It was pointed out that XVIIb would be the more stable, as it could adopt a conformation with an equatorial methyl group (27, 124). These preparations are probably impure, as recent glc analysis of products from similar reductions indicate up to 17% of the minor epimer (15), and careful fractionation of a product mixture from (−)-β-pinene gave (−)-XVIIa, [α]$_D$ (calcd) −24.2° (58). Consistently, hydroboronation and subsequent hydrolysis using the same substrate gave the same product, [α]^{20}D −24.3°, in over 90% yield, although an accompanying preparation of (+)-XVIIa from (+)-α-pinene by the same method gave (+)-XVIIa, [α]^{20}D (calcd) +27.6°, n^{20}D 1.4614 (158). This latter discrepancy is puzzling, as the products were all claimed to be greater than 98% chemically pure by glc, and so contamination by the epimer formed from any lack of stereospecific backside addition seems unlikely. Hydroboronation of (−)-β-pinene, thermal equilibration to the more stable trans-boron complex, and acidolysis gave (−)-XVIIb, [α]^{20}D (calcd) −18.3°, n^{20}D 1.4610

(−)-XV   (−)-XVIIb
(90% over-all)
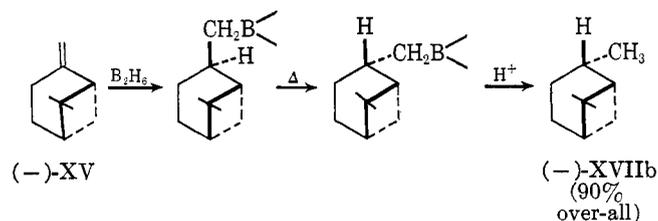
(30, 158), of nearly identical optical purity as that ([α]$_D$ (calcd) −17.7°) obtained by hydrolysis of the complex of the same substrate with lithium aluminum hydride (81). A convenient method of preparation of XVIIa (yield 97–99%, no optical data reported) is the reduction of α- or β-pinene with diimide (138).

V. DERIVATIVES WITH SUBSTITUENTS AT C-2

A. 3-PINEN-2-OLS
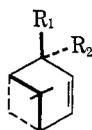
(−)-XVIIIa, R₁ = CH₃, R₂ = H;   (−)-cis-3-pinen-2-ol
(−)-XVIIIb, R₁ = H, R₂ = CH₃;   (−)-trans-3-pinen-2-ol

Few studies have been made on these compounds. (−)-XVIIIa can be synthesized from (−)-verbenene, [α]^{20}D −114°, obtained from autoxidation of (+)-α-pinene, and this determines the absolute configuration. Addition of hydrogen chloride formed cis-3-pinene-2-chloride which gave the unrearranged alcohol in 46% over-all yield on treatment with base; [α]^{20}D −96° (c 3.2, chloroform), mp 47–49°, bp 86° (10 mm) (17, 89). (+)-XVIIIa and (+)-XVIIIb, [α]^{20}D +99.2° (c 2.5, chloroform), mp 47–49°, and [α]^{20}D +45.3° (c 2.6,

chloroform), mp 44°, respectively) were formed from autoxidation of (−)-α-pinene; and (−)-XVIIIa, of unspecified rotation, was generated on hydrolysis of the ester produced by treatment of (+)-α-pinene with lead tetraacetate (89, 150). The configurations of (−)-XVIIIa, (+)-XVIIIa, and (+)-XVIIIb have been determined by reduction to the known (+)-cis-, (−)-cis-, and (−)-trans-2-pinanols, but as the specific rotations of optically pure pinanols are uncertain, and as details concerning the optical purity of the starting materials in these syntheses are unavailable, the optical purity of the pinenols is not known. Nevertheless, the specific rotations of the linalools that are formed on reduction and pyrolysis (89) indicate that it is probably greater than 90%.

B. NOPINONE AND NOPINOLS

(−)-XIX;   (−)-nopinone   (+)-XXa, R₁ = OH, R₂ = H; (+)-α-nopinol
(+)-XXb, R₁ = H, R₂ = OH; (+)-β-nopinol

The alcohols (XX) do not occur naturally, but their derivatives are of especial interest as undergoing mechanistically complex skeletal rearrangements, involving both classical and nonclassical ions (115, 153). (+)-XIX ([α]^{25}D (calcd) +18.4 or 18.9°, bp 77–78° (8 mm), n^{25}D 1.4769, d_{24} 0.9818 (83, 117, 154), or +13.3° (c 8, benzene), +45.2° (c 8, ether) (65)) is formed by ozonolysis or permanganate oxidation of (−)-nopinene, as (−)-β-pinene was archaically named. Lithium aluminum hydride reduction of this ketone gives (−)-XXa ([α]^{23}D (calcd) −6.0° (c 10, ether), mp 102°) whereas Meerwein–Ponndorf–Verley reduction gives predominantly (−)-XXb ([α]^{23}D (calcd) −21.5° (c 12.2, ether), mp 37°) (154). These configurations were assigned by conformational reasoning based on preparative methods, rates of oxidation, and rates of saponification of various esters (117). Earlier studies had given essentially similar results (77, 148). The stable conformations are probably those in which the hydroxyl group is pseudo-equatorial, and this is consistent with the grossly different reaction routes of the two isomers and particularly of their esters on solvolysis (153).

C. 2-PINANOLS
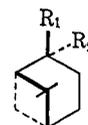
(+)-XXc, R₁ = CH₃, R₂ = OH; (+)-cis-2-pinanol or pinene hydrate
(+)-XXd, R₁ = OH, R₂ = CH₃; (+)-trans-2-pinanol or methylnopinol

Crystalline samples of the isomeric XXc and d have been prepared from starting materials of unspecified purity and, as their specific rotations have been measured under a variety of different conditions, it is not possible to compare directly the optical purity of different samples. The best preparations of (+)- and (−)-XXc, $[\alpha]^{20}$D +28.4 and −29.7° (c 2.15, chloroform), mp 77–78°, are probably those from the reduction of the 3-pinen-2-ols (89), but a more convenient route (which also verifies the configuration of the starting material) is the reduction of (−)-β-pinene oxide with lithium aluminum hydride to give (−)-XXc ($[\alpha]^{20}$D −22.6° (c 2.2, ethanol), mp 77.5–78°, bp 90–91° (11 mm)) in 80% yield together with 20% of (−)-XXd (59, 65, 146). Permanganate oxidation of (−)-cis-pinane gives a small yield of (−)-XXc (82), but thermal decomposition of the pinane hydroperoxide (formed from autoxidation) gives a much better yield ($[\alpha]$D −19.1° (c 8, hexane), mp 78–79°) that is improved when pyridine is present to remove any adventitious acid that could cause ring opening (58, 116).

The reduction of (+)-trans-3-pinen-2-ol gives (−)-XXd, $[\alpha]^{20}$D −8.8° (c 2, chloroform), mp 58–59° (89), but a more convenient method is the addition of methylmagnesium iodide to (+)-nopinone to give a product, $[\alpha]^{20}$D −5.3° (c 6.3, ether), −3.6° (c 2.2, ethanol) (59, 65, 146).

The configuration at C-2 in these compounds follows from conformational analysis of the preparative methods and is confirmed by an elegant product study (35). On heating with acetic anhydride, XXc and d readily isomerized to isobornyl (XXIII) and isofenchyl acetate

XXd   XXI   XXII
XXc   XXIII   + XXII
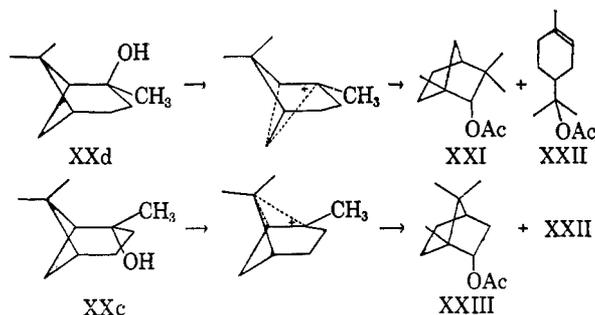
(XXI), respectively, together with some α-terpenyl acetate (XXII). These reactions almost certainly proceed through nonclassical ions, and are stereospecific because of the necessity for these ions (and the products) to be formed with inversion at the ionizing center from the configurations and conformations shown. Such conformations are favored by the preference for the C-2 methyl group to be equatorial. The great differences in routes and products of sovolysis for derivatives of nopinols and pinanols are a direct consequence of the conformational fixing of the hydroxyl groups as equatorial or axial, respectively, in these two classes.

VI. DERIVATIVES WITH SUBSTITUENTS AT C-3

A. PINOCARVONE
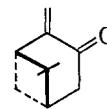
(−)-XXIV; (−)-pinocarvone

XXIV can be isolated from Spanish eucalyptus oil and purified specimens have $[\alpha]$D −69.8 or −62°, bp 84–85° (4 mm), n^{20}D 1.4950, d_{15} 0.9875 (122, 125,137). On boiling at atmospheric pressure it readily polymerizes (145).

Early synthetic specimens were actually samples of myrtenal and XXIV was named "carvopinol" and assigned an incorrect structure. This error originated from an unsuspected allylic rearrangement during deamination of a pinylamine and much confused the literature before 1941 (120).
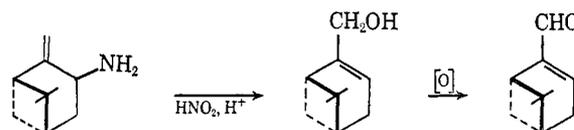
(+)-XXIV is conveniently synthesized by oxidation of (−)-β-pinene with selenium dioxide to give products, $[\alpha]^{30}$D (calcd) +63.6°, bp 82–84° (3 mm), n^{30}D 1.4910, d_{30} 0.973, or $[\alpha]^{24}$D +61.6° (c 3, ethanol), or $[\alpha]^{20}$D (calcd) +49.9° (c 1.02, benzene), n^{25}D 1.4940 (60, 104, 135). The last was probably an almost optically pure specimen, the low specific rotation resulting from the nonpolar solvent causing association of solute

B. PINOCARVEOLS
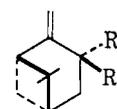
(+)-XXVa, R_1 = OH, R_2 = H; (+)-cis-pinocarveol
(−)-XXVb, R_1 = H, R_2 = OH; (−)-trans-pinocarveol

Early, believed pure, preparations of (−)-XXVb contained myrtenol, but an authentic specimen ($[\alpha]^{20}$D −73.3° (c 5, ethanol), mp 5°, bp 209–210°, n^{20}D 1.5005, $d^0{}_{20}$ 0.981) was purified from Spanish eucalyptus and other oils (122, 131), and an epimer ($[\alpha]^{20}$D +55.9° (c 5, ethanol), mp 51°, bp 217–218°, n^{20}D 1.5057, $d^0{}_{20}$ 1.004) was obtained by Meerwein–Ponndorf–Verley reduction of pinocarvone or debromination with zinc of the purified bromine adduct of this substrate, and many derivatives were prepared (122). These alcohols were assigned trans and cis, respectively, by the von Auwers–Skita rule, and oxidation of either gave (−)-pinocarvone to fix the absolute configuration. These assignments have been disputed on conformational grounds (27), based on studies of dehydration, acid-catalyzed addition of water, and rates of esterification (123), but recent

completely conclusive assignments of the derived pino-campheols vindicate the original structural views (158). The failure of conformational arguments to give the correct configuration is probably due to an inappreciation of the importance of the hydroxyl group in controlling the stable conformation in the absence of the more powerfully controlling 2-methyl group. XXVa is probably best represented as XXVI, but XXVb by XXVII; i.e., the hydroxyl group is pseudo-equatorial in the stable conformation of either compound. XXVI is dehydrated by dilute acid, whereas XXVII is hy-

XXVI   XXVII
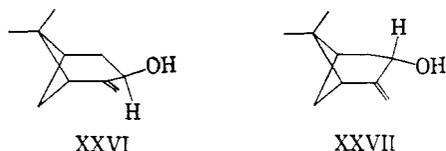
drated under similar conditions, attack on the double bond being apparently hindered in the former. There is some evidence for these preferred conformations from analysis of the mechanisms of skeletal rearrangement that can be induced by hydrogen bromide in acetic acid (60).

Acetate of XXVI →   Acetate of XXVII →
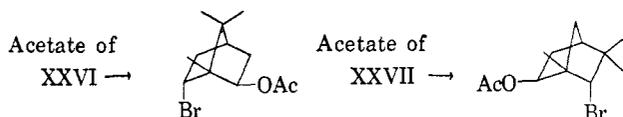
Several recent synthetic routes to the pinocarveols are available. Oxidation of (−)-β-pinene with lead tetraacetate and hydrolysis of the resulting ester gives XXVb, $[\alpha]^{20}$D (calcd) +68.4° (c 0.9, benzene), n^{20}D 1.4992 (60), which has also been produced with $[\alpha]^{20}$D (calcd) −72.6°, mp 2°, bp 208–209°, n^{20}D 1.4989, d_{20} 0.976, by photosensitized (114) or selenium dioxide oxidation (96) of (+)-α-pinene. All these reactions give yields of 70% or greater, but in the last-mentioned the quantity of oxidant must be carefully controlled to prevent further oxidation to pinocarvone and subsequent polymerization. The configuration of XXVb is verified by its formation in good yield on reduction of α-pinene oxide (39, 80), which predominantly exists as the isomer with the cis-pinane skeleton.

Repetition of the original synthesis of XXVa from pinocarvone dibromide has given a probably nearly optically pure sample; $[\alpha]$D −41° (c 1.04, benzene), mp 50–50.5°, bp 64–65° (15 mm) (60).

C. PINOCAMPHONES
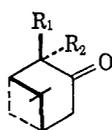
(+)-XXVIIIa, R_1 = H, R_2 = CH₃; (+)-pinocamphone
(+)-XXVIIIb, R_1 = CH₃, R_2 = H; (+)-isopinocamphone

(−)-XXVIIIa can be isolated from oil of hyssop in 45% yield; $[\alpha]$D −19.7°, bp 208–209° (745 mm),

n^{17}D 1.4743 (64). The (+) isomer rarely occurs naturally but can be readily prepared by oxidation of (+)-pinocampheol as an oil; $[\alpha]^{20}$D +24.9°, bp 211°, n^{20}D 1.4728, d_{15} 0.9643 (123). Oxidation of (−)-iso-pinocampheol gives XXVIIIb, $[\alpha]^{20}$D +10.8°, bp 213°, n^{20}D 1.4749, d_{15} 0.9690, or $[\alpha]^{20}$D +10.4, +11.3, or +18.8° (c 5, ethanol), according to various workers (38, 44, 123, 158), and hydroboronation of (+)-α-pinene and treatment of the boron complex with chromic acid give the same product. The last method gives "several per cent" of XXVIIIa (34) and so the hydroborations–oxidation technique for the synthesis of alcohol from olefins may not be as stereospecific as is claimed (158).

Treatment of either ketone with base (158) leads to an equilibrium mixture containing 81% XXVIIIa, which was originally believed to exist in conformation XXVIIIc, whereas the epimer existed as XXVIIId.

XXVIIIc   XXVIIId   XXVIIIe
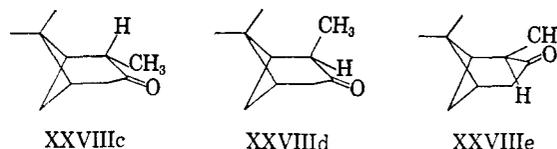
The expected energy difference between these structures is much larger than that observed, however (22). A half-chair structure would reduce this difference but would not explain the chemical evidence that the carbonyl group of isopinocamphone is more hindered than that of pinocamphone. On this basis structure XXVIIIe has been proposed for isopinocamphone (22). The energy gain of an equatorial methyl group is probably sufficient to balance the repulsion between the gem-dimethyl group and the carbonyl group, but in any case the latter interaction would be greatly reduced as the molecule approached the Y-shaped conformation. Spectroscopic data, however, favor structure XXVIIId (54) so the problem must remain open.

The absolute configurations follow from the relationship to the pinocampheols, and ultimately to α-pinene. Thus (+)-XXVIIIa and b are both formed from the iron-catalyzed thermal decomposition of the epoxide of (+)-α-pinene, but under milder conditions only the latter is obtained (38, 72).

D. PINOCAMPHEOLS
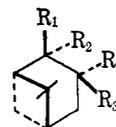
(+)-XXIXa; R_1 = H, R_2 = CH₃, R_3 = OH, R_4 = H;
 (+)-pinocampheol
(−)-XXIXb; R_1 = H, R_2 = CH₃, R_3 = H, R_4 = OH;
 (−)-neopinocampheol
(+)-XXIXc; R_1 = CH₃, R_2 = H, R_3 = OH, R_4 = H;
 (+)-neoisopinocampheol
(−)-XXIXd; R_1 = CH₃, R_2 = H, R_3 = H, R_4 = OH;
 (−)-isopinocampheol

(−)-XXIXd ([α]D −45.3° (no solvent specified), mp 56–57°, n^{20}D 1.4888, d_{20} 0.9501) of higher negative rotation than any reported synthetic sample but probably impure, has been isolated from oil of hyssop (109), but the other isomers rarely occur naturally and are usually synthesized by reduction of appropriate ketones. Reduction of (+)-pinocamphone with sodium and ethanol gives a good yield of (+)-XXIXa, [α]^{20}D +72° (c 10 benzene), mp 67°, bp 217°, n^{20}D 1.4877, d^{25}_{20} 0.9725; and over metal catalysts at 130–200° it forms mainly XXIXb, [α]^{20}D −17° (c 10, benzene), mp 27°, bp 215°, n^{20}D 1.4882, d^{15}_{20} 0.9735. Similar catalytic reduction of (−)-trans-pinocarveol gives (−)-XXIXd, [α]^{20}D −32° (c 10, benzene), mp 57°, bp 219°, n^{29}D 1.4865, d^{15}_{20} 0.9720, and of (+)- cis-pinocarveol forms XXIXc, [α]^{20}D +36° (c 10, benzene), mp 48°, bp 217°, n^{20}D 1.4920, d^{15}_{20} 0.9770 (123). A good method for the last-mentioned isomer is the reduction of isopinocamphone by lithium trimethoxy-aluminum hydride (158) to form 80% product; [α]^{20}D (calcd) +39.6° (c 3, in benzene), mp 45–47°. All these samples are probably essentially chemically and optically pure, although recent hydroboronation-oxidation of (+)-α-pinene has given (−)-XXIXd; [α]^{20}D (calcd) −36° (c 10, benzene), mp 55–57° (158).

After equilibration with base, XXIXa was found to be the most stable of the four isomers, as was implied in its manner of preparation, and the configurations XXIXa to d were assigned on the basis of the von Auwers–Skita rule, although such assignments were tentative in view of the small differences in physical constants (123). Many derivatives were also prepared, including the amines corresponding to XXIXa and d (29).

Conformational arguments based on an incorrect assignment to the pinocarveols have led to different configurations for isopinocampheol and neoisopinocampheol (27, 66), but the controversy has now been decisively settled in favor of the original assignments, and in so doing the structures of the pinocarveols have been deduced (36, 158). The stereoselective routes shown lead to chemically and optically pure products, with configurations consistent with nmr studies (38, 158). The 2-methyl group of isopinocamphone is
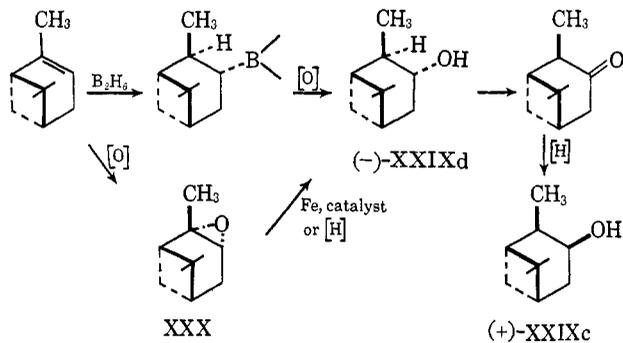
known to be cis to the gem-dimethyl bridge and α-pinene oxide (XXX) is known to largely exist as the isomer with a cis-pinane skeleton (72).

Pinocampheol and its neo, iso, and neoiso isomers very probably adopt the ground-state conformations XXXIa, b, d, and c, such that the methyl group is equatorial in all cases. On consideration of the respective steric interactions, the order of stability should be a > b > d > c. These assignments are consistent

XXXIa, R₁ = OH, R₂ = H   XXXIc, R₁ = OH, R₂ = H
XXXIb, R₁ = H, R₂ = OH   XXXId, R₁ = H, R₂ = OH

with several sets of observations.

(i) Kinetic evidence of acetylation and saponification on the orientations of the hydroxyl groups (27), which, however, can only be tentatively interpreted as it is based on analogy with cyclohexanes; the observations could be the result of eclipsing of the hydroxyl group by a cis-methyl in a Y-shaped molecule. Also it is not clear from the above conformations why neoisopinocamphyl acetate is saponified more rapidly than the neo isomer.

(ii) The ease, neo- > neoiso- > iso- > pinocampheol, of base-promoted and solvolytic elimination from tosylate esters (123, 124).

(iii) The formation of largely α-pinene in the pyrolysis of isopinocamphyl methylxanthate (123).

VII. DERIVATIVES WITH SUBSTITUENTS AT C-4

A. VERBENONE
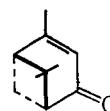
(+)-XXXII; (+)-verbenone

XXXII occurs in small amounts in verbena and various other species. The purest specimen is probably that ([α]D (calcd) +282°, bp 100° (11 mm)) obtained from the oxidation of carefully purified verbenol that in turn had been formed (together with verbenone and myrtenal) by selenium dioxide oxidation of (+)-α-pinene in the presence of a cobalt catalyst (48, 100). Oxidation in the absence of the catalyst gives almost entirely myrtenal, and the cobalt ion probably promotes radical oxidation at the C-4 position. Cobalt salts of resin acids are highly efficient catalysts, and it is possible that metal salts of these acids catalyze the oxidation in vivo. Other pure samples ([α]D +273°, mp 9.8°, bp 101–102° (15 mm), n^{20}D 1.4965, d_{20} 0.9754, and [α]^{25}D −254°, n^{20}D 1.4961, d_{20} 0.9731) are obtained from autoxidation of (+)- and (−)-α-pinenes of unspecified

XXX   (+)-XXIXc

optical purity (85, 132), or from chromic acid oxidation of (+)-α-pinene as [α]D +253°, bp 101–102° (15 mm) (70). The pure ketone rapidly discolors on exposure to air.

B. VERBENOLS
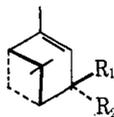
(+)-XXXIIIa, R_1 = OH, R_2 = H; (+)-cis-verbenol
(+)-XXXIIIb, R_1 = H, R_2 = OH; (+)-trans-verbenol

Mixtures of (+)-verbenone and (+)-XXXIII occur in various plant oils, but reasonably pure samples of the latter were first obtained by oxidation of oil of turpentine with a cobalt catalyst, and by Meerwein–Ponndorf–Verley reduction of (+)-verbenone and recrystallization via the p-nitrobenzoate esters (126). The assignments were made by the von Auwers–Skita rule: XXXIIIb, [α]D (calcd) +164°, mp 20.6°, bp 92° (10 mm), n^{20}D 1.4916, d_{25} 0.9697; XXXIIIa, [α]D (calcd) +72°, mp 15.5°, bp 90° (10 mm), n^{20}D 1.4932, d_{25} 0.9724. Both gave (+)-verbenone on oxidation, the rotation of which allows the theoretical maximum specific rotations to be calculated. A later study (132) gave XXXIIIb, [α]D (calcd) +175°, mp 24°, bp 92° (10 mm), n^{25}D 1.4908, d_{25} 0.9657, and XXXIIIa, [α]D (calcd) +68.2°, mp 15.5°, bp 90° (10 mm), n^{25}D 1.4912, d_{25} 0.9684. The latter isomer was considered to be only about 90% pure owing to dehydration during purification, perhaps caused by steric acceleration of formation of an allylic ion occurring uniquely in this isomer by interaction of the gem-dimethyl bridge and the bulky cis-ester group.

(+)-XXXIIIb ([α]D (calcd) +124 (c 2, benzene) and +127.6°) has been prepared from hydrolysis of the product of lead tetraacetate oxidation of (+)-α-pinene (38, 150), and unspecified (+)-verbenols, almost certainly XXXIIIa ([α]D (calcd) +92 and +79.2°), have been prepared (26, 100) from autoxidation and selenum dioxide oxidation of the same substrate. The situation has recently become confused by the isolation of claimed XXXIIIa, characterized by conversions to verbanols and oxidations to verbenone, having [α]D −3°, mp 62–64 or 64°, from sodium borohydride or lithium aluminum hydride reduction of (+)-verbenone (38, 93, 100). Further studies, monitored by glc, are urgently needed to elucidate these discrepancies concerning the cis isomer.

C. VERBANONES
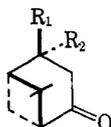
(+)-XXXIVa, R_1 = CH₃, R_2 = H; (+)-cis-or isoverbanone
(+)-XXXIVb, R_1 = H, R_2 = CH₃; (+)-trans-verbanone

These isomers have not been extensively studied. (+)-XXXIVb ([α]D (calcd) +54.2°, bp 223–224° (749 mm), n^{20}D 1.4754, d_{20} 0.9642) can easily be prepared by chromic acid oxidation of (+)-verbanols or catalytic reduction of (+)-verbenols or (+)-verbenone of uncertain optical purities, and the configuration at C-2 which is indicated by the latter preparative method was confirmed by Wolff–Kishner reduction to what is now recognized as (+)-trans-pinane (24, 152).

A sample ([α]D (calcd) +73.9°) prepared by hydrogenation of (+)-verbenone over platinum black under more forcing conditions was characterized as impure XXXIVa by its relationships to the derived isoverbanols and ultimately to cis-pinane (28, 70), and more recent preparations from oxidations of (+)-verbanols and reduction of (+)-verbanone over Raney nickel give samples of [α]D +59°, bp 84° (8 mm), n^{20}D 1.4779, d_{20} 0.9644, and [α]D (calcd) +62°, respectively (13, 132). Equilibration studies are lacking but presumably XXXIVb is the more stable.

D. VERBANOLS
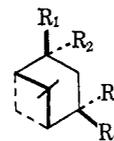
(+)-XXXVa, R_1 = CH₃, R_2 = H, R_3 = OH, R_4 = H;
  (+)-neoisoverbanol
(+)-XXXVb, R_1 = CH₃, R_2 = H, R_3 = H, R_4 = OH;
  (+)-isoverbanol
(?)-XXXVc, R_1 = H, R_2 = CH₃, R_3 = OH, R_4 = H;
  (?)-neoverbanol
(+)-XXXVd, R_1 = H, R_2 = CH₃, R_3 = H, R_4 = OH;
  (+)-verbanol
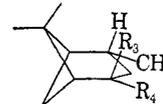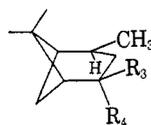
XXXVa, R_3 = OH, R_4 = H   XXXVc, R_3 = OH, R_4 = H
XXXVb, R_3 = H, R_4 = OH   XXXVd, R_3 = H, R_4 = OH

The nomenclature of these follows that of the pinocampheols and menthols, although much of the earlier literature discusses cis and trans isomers with no attempt to specify the complete configuration. The presently accepted configurations and probable stable conformations are as shown, and energy calculations and the limited experimental data suggest the order of stability to be XXXVd > a > c > b.

Reduction of (+)-verbenol or (+)-verbanone of unspecified optical purity with sodium and alcohol gave XXXVd, [α]D +1.3° (c 10, ethanol), bp 218°, mp 58°, in about 60% yield (24, 152). Similar treatment of (+)-isoverbanone gave mainly an uncharacterized alcohol, almost certainly a mixture of XXXVb and XXXVd (70), the latter resulting both from verbanone in the original impure substrate and formed (via base-

catalyzed enolization) during reduction; but hydrogenation over platinum black gave a product [α]D +5.2°, mp 74.5°) which later work indicates to have been essentially pure XXXVa. Kinetically or thermodynamically controlled hydrogenation would have been expected to lead to this.

XXXVa ([α]D +5.5° (in benzene), mp 73–74°), which was confirmed to be the same isomer as the above preparation by the identity of the hydrogen phthalate esters, was prepared by catalytic reduction of *cis*-verbenol, while *trans*-verbenol led to XXXVb ([α]D +15.5° (in benzene), mp 75–76°) (132). These configurations were assigned on the basis that each gave (+)-isoverbanone ([α]D +59°) on oxidation, but the doubt about the maximum rotation of this product prevents optical purities of these isomers being calculated. Recent infrared studies (93) have proported to confirm the existence of equatorial and axial hydroxyl groups in XXXVa and XXXVb, respectively, but the validity of extrapolating spectroscopic data applicable to cyclohexanes to these bicyclic systems seems questionable. A recent preparation (38) of (−)-XXXVa from lithium aluminum hydride reduction of (−)-isoverbanone gave a product (85% yield), [α]D (calcd) −6.2°.

XXXVc has not been characterized, although a hydrogen phthalate, which has been isolated from the reaction mixture after hydrogenation of verbenol and does not correspond to the derivatives from known isomers, may be derived from this compound (28).

VIII. DERIVATIVES WITH SUBSTITUENTS AT C-10

A. MYRTENAL
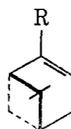
(+)-XXXVI, R = CHO; (+)-myrtenal
(+)-XXXVII, R = CH₂OH; (+)-myrtenol

(+)-XXXVI occurs in eucalyptus and other plant oils (41, 134) and was much confused with (+)-pinocarvone in the early literature. Complicated chemical separations were necessary to remove co-occurring monocyclic aldehydes, and a specimen ([α]D +13.6°, bp 89–92° (11 mm), n^{20}D 1.5061, d^{20} 0.9859) was probably the purest obtained (120). Synthetically, preparations of typical properties, [α]²⁰D (calcd) +16.9°, −18.6°, bp 91.7–92° (12.5 mm), n^{20}D (12.5 mm), 1.5038, d_{20} 0.9898, are obtained by oxidation of myrtenol (38, 108) or (+)-α- or (−)-β-pinene (4, 135) in reactions which determine the absolute configuration. A recent repetition of the last reaction led to almost racemic XXXVI (104), and the reactions involved are obscure.

B. MYRTENOL

Both (+)- and (−)-XXXVIII have been isolated from myrtle and eucalyptus oils ([α]D +49.7, +46.5, −46.0, −47.0° (in ethanol), bp 221–222°, n^{20}D 1.4968, d_{20} 0.980 (41, 108, 118, 121, 136)), especially using a convenient separation of their crystalline hydrogen phthalates, and many derivatives have been prepared (71, 88, 108, 142). Good preparative routes are by controlled oxidation of (+)-α-pinene to give a typical product, [α]D +44.1° (50, 51), or of (−)-α-pinene (product [α]²⁵D (calcd) −53.7°, bp 106–107° (15 mm), n^{25}D 1.4950, d_{25} 0.979 (4)) by stereoselective photosensitized oxidation (in 82% yield) of (−)-β-pinene (product [α]²⁰D (calcd) −47.8°, bp 62° (0.4 mm), n^{20}D 1.4960, d_{20} 0.990 (114)) or, as the acetate ester, by lead tetraacetate treatment of (−)-β-pinene, when *trans*-pinocarvyl acetate is the initial product (60).

C. MYRTANAL AND MYRTANOLS
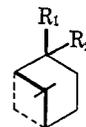
(+)-XXXVIIIa, R₁ = H, R₂ = CHO; (+)-*trans*-myrtanal
(−)-XXXVIIIb, R₁ = CHO, R₂ = H; (−)-*cis*- or isomyrtanal
(+)-XXXIXa, R₁ = H, R₂ = CH₂OH; (+)-*trans*-myrtanol
(+)-XXXIXb, R₁ = CH₂OH, R₂ = H; (+)-*cis*- or isomyrtanol

The isomers XXXVIII have rarely been prepared (56, 95), but a reasonably pure specimen, [α]¹⁶₅₇₈ +55.1°, bp 89.5–91° (12 mm), n^{16}D 1.4847, d_{20} 0.9821, has been obtained by distillation of (−)-β-pinene oxide over alumina (75). This is probably largely (+)-XXXVIIIb, for the substrate almost certainly was predominantly the isomer with the *cis*-pinane skeleton. Electrolytic oxidation of XXXIX has also been explored (127). XXXIX, of unspecified optical properties, has only been isolated from a few obscure shrubs and is invariably obtained synthetically (69, 129, 130). Early studies, not self-consistent as regards optical purities of reactants and products, gave an isomer, [α]D −26.1°, bp 126–127° (22 mm), n^{20}D 1.4898, d^0_0 0.9858, from sodium and ethanol reduction of (−)-myrtenol and another, [α]D −24.5 or +20.7°, bp 122° (20 mm), n^{21}D 1.4925, d_{20} 0.9803, from catalytic reduction of (−)-myrtenol or (+)-myrtenal over platinum (49). The methods of preparation and the Raman spectra allowed assignment as XXXIXa and b, respectively. The absolute configurations are also consistent with the good yield of (−)-XXXIXb resulting from nickel reduction of (−)-β-pinene oxide (73).

More recently the same methods applied to (−)-myrtenal (derived from (−)-α-pinene) have given specimens of XXXIXa ([α]D (calcd) −32.1°, bp 117–119° (15 mm), n^{25}D 1.4870, d_{25} 0.966) and XXXIXb ([α]D (calcd) −26.8°, bp 118° (15 mm), n^{25}D 1.4883, d_{25} 0.972) in greater than 90% yields (4, 52), and (−)-

XXXIXa has been claimed to result from treatment of (−)-β-pinene with lithium aluminum hydride, followed by oxidation of the complex and hydrolysis (36% yield) (81, 156). At higher temperatures a similar process using diisobutyl aluminium hydride led to 55% (−)-XXXIXa and 45% (−)-XXXIXb (139).

Hydroboronation–oxidation of (−)-β-pinene leads to pure (−)-XXXIXa, pure (−)-XXXIXb, or mixtures depending on the reaction temperature, in overall yields of greater than 80% (30, 46, 158). On heating, the initially formed boron complex XLa can equilibrate to its more stable epimer XLb. In this way
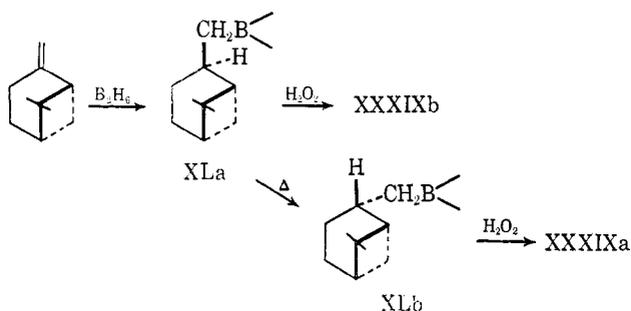
glc-pure XXXIXa, $[\alpha]^{20}$D (calcd) −30.1°, and XXIXb, $[\alpha]^{20}$D (calcd) −22.5° (both c 4, chloroform), were obtained (159). Heating the complex from (+)-α-pinene causes migration of the boron group without skeletal rearrangement to give (+)-XXXIXa in excellent yield (5, 33, 158) after oxidation.

IX. MISCELLANEOUS DERIVATIVES

A. NOPOL

(+)-XLI; (+)-nopol   (−)-XLII; (−)-verbenone

(−)-XLIII;   XLIV;   (?)-XLV;
(−)-chrysanthenone   homopinenes   (?)-apopinene
                     (R = alkyl)
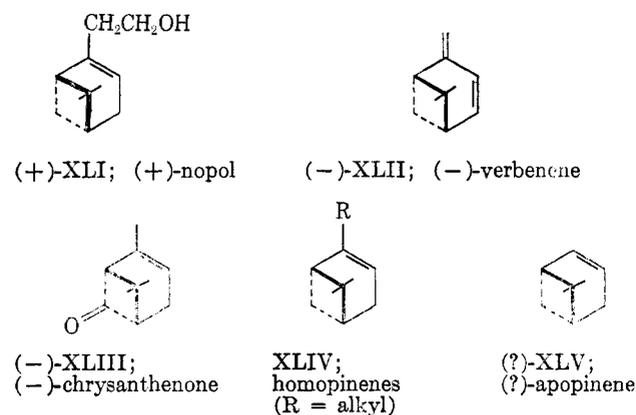
(−)-XLI, a useful synthetic solvent ($[\alpha]$D (calcd) −37.8°, bp 117.5° (16 mm), n^{20}D 1.4945, d_{20} 0.9679) results from condensation of (−)-β-pinene with formaldehyde (2, 14, 16, 19), and it is readily reduced over Adams catalyst to the saturated alcohol, $[\alpha]^{25}$D (calcd) −29.5°, bp 108–110° (2 mm), n^{25}D 1.4872 (3, 52). Saturated homologs cannot be prepared via Grignard addition to nopinone owing to preferential dehydration and ring opening, but under special conditions such 1,4 addition to pinocarvone and its derivatives can be

achieved (3, 4, 143, 144). Dehydration products and other derivatives of XLI have been reported (88, 110).

B. VERBENENE

(−)-XLII ($[\alpha]$D −100.7°, bp 159–160° (758 mm), n^{20}D 1.4985, d_{20} 0.8822, after purification through the dibromide) was first prepared by treatment of (+)-verbenol of uncertain optical purity with acetic anhydride (25). Similar treatment with zinc chloride or phosphorus pentoxide caused aromatization to p-cymene. The originally proposed formula contained C-2–C-3 and C-4–C-5 double bonds, but this contravenes Bredt's rule and the generally accepted structure, formed by rearrangement during dehydration, was suggested (111). Specimens of (+)-XLII have been prepared from products of autoxidation of (−)-α-pinene (85, 90), but the purest sample obtained to date is probably that of $[\alpha]^{20}$D −114°, obtained in an adaption of the original synthesis by pyrolyzing (+)-trans-verbenyl acetate (89). This is one of the few examples of rearrangement occurring during this type of elimination. It is not known whether XLII is formed directly, presumably in an E1 reaction, or whether the very unstable endocyclic diene is transiently produced; the latter could possibly be trapped as a Diels–Alder adduct.

C. CHRYSANTHENONE

(+)-XLIII ($[\alpha]^{22}$D +13.1° (c 2.95, chloroform), bp 104–106° (36 mm)) was first characterized from the blossoms of chrysanthenum species (79, 140), although the earlier reported car-3-ene 5,6-epoxide from another species (67, 91) appears identical. A good synthetic route which reveals the absolute configuration is by ultraviolet irradiation of (+)-verbenone (67). The product ($[\alpha]$D (calcd) +47.1° (c 2.1, chloroform), bp 88–89° (12 mm), n^{22}D 1.4720) probably has a lower optical purity than the starting materials for ring opening, and recycling to form a racemate almost certainly competes with direct valence-bond rearrangement. On reduction with lithium aluminum hydride the corresponding alcohol, bp 89–90° (8 mm), is formed (79), presumably the isomer with the gem-dimethyl bridge and the hydroxyl group cis predominating.

D. HOMO- AND APOPINENES

Homopinenes are readily prepared by substitution of myrtenyl bromide with alkyl Grignard reagents (7, 108), a reaction characteristic of allyl bromides. More is known concerning apo derivatives of the pinane skeleton. XLV (of unspecified rotation) (bp 47–48° (30 mm) n^{20}D 1.4687, d^{20} 0.8710) may be prepared in 60% yield by decarbonation of myrtenal on prolonged heating with a palladium–barium catalyst and can be reduced over nickel to apopinane, bp 149°, n^{20}D 1.4616

(55). The latter also results from Wolff–Krishner reduction of nopinone (68).

A previously claimed preparation of apopinene by dehydration of nopinol with potassium bisulfate (78) gave a product of very similar properties (in so far as they were recorded), but is probably an isomer, for it has recently been demonstrated that the nopinyl skeleton very readily rearranges in carbonium ion reactions. Thus, solvolyses of nopinyl esters give less than 3% of products of retained skeleton, and dehydration of each nopinol isomer with acid gives no product that is un-rearranged (115, 153).

Hydroboronation of apopinene followed by oxidation gives a mixture of *trans*-nopinol and XLVI. The latter has been oxidized to isonopinone, bp 85° (10 mm), which can be reduced back to give a 80–20% mixture of *cis*-isonopinol and XLVI (37).

E. PINENE OXIDES
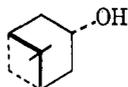
(?)-XLVI; (?)-*trans*-isonopinol

(+)-XLVII;
(+)-*cis*-α-pinene oxide
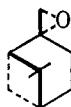
(−)-XLVIII;
(−)-*cis*-β-pinene oxide

XLVII and XLVIII are of interest both as intermediates in synthetic routes and by reason of showing characteristic skeletal rearrangements catalyzed by Lewis acids (20). Each should exist in (+) and (−) pairs based on each of the *cis*- and *trans*-pinane skeletons, but it is not clear which isomers have been isolated, and the somewhat scattered values of the reported physical constants suggest that mixtures of *cis* and *trans* isomers have generally been prepared. This is reasonable, as the synthetic routes used are unlikely to be very highly stereospecific.

XLVII, of typical and fairly consistent properties, bp 71–71.5° (12 mm), n^{15}D 1.4715, d_{20} 0.961, has usually been prepared from treatment of (+)- or (−)-α-pinene with peracids in excellent (90%) yields. A range of specific rotations, $[\alpha]^{20}$D +50.2, +76.9, −92, −38.5°, has been recorded (from (+)- and (−)-α-pinenes, respectively) (6, 10, 43, 72, 94). A convenient larger scale synthesis (yield 25%) is the autoxidation of α-pinene at 50°, but a difficult separation from several other products is required (18).

Samples of XLVIII with a range of specific rotations, $[\alpha]^{20}$D +10.3 or +3.3 (calcd), +7.8°, $[\alpha]_{578}$ +2.1° (c 10, chloroform), have been prepared from (−)-β-pinene by peracid oxidation (1, 56, 65, 73, 74, 95, 147).

Again, the other physical properties, although measured at various temperatures, are fairly self-consistent. A typical preparation had bp 79–81° (12 mm), n^{20}D 1.4770, d^{22}_{20} 0.9702.

The general opinion is that XLVII largely exists as the isomer with a *cis*-pinane skeleton; *i.e.*, the stereochemistry of epoxidation is similar to that of hydroboronation. This is consistent with previously quoted examples and with the reduction of XLVII over nickel to isopinocampheol and by lithium aluminium hydride to *trans*-pinocarveol in over 60% yields (8, 39, 80). The yield in the latter reaction is highly dependent on the solvent and much skeletally rearranged product is also formed. Apopinene oxide is similarly reduced by lithium aluminium hydride to a *trans* alcohol (39). Although nmr measurements and electron diffraction studies have been interpreted as indicating a *trans*-pinane skeleton, with the 10-methyl group almost equatorial and with little strain in the six-membered ring (9, 12), more refined studies on pure isomers are necessary before the chemical evidence can be discounted.

Chemical evidence indicates that XLVIII, as typically prepared, exists in about an 80:20 proportion of isomers with the *cis*- and *trans*-pinane skeletons. Reduction of one preparation with sodium and moist ether, or with lithium aluminium hydride under a variety of conditions, gave these approximate proportions of pinene hydrate and methylnopinol (65, 113), and treatment with hydrogen over Raney nickel gave an 85% yield of *cis*-myrtanol (73).

X. REFERENCES

(1) Abraham, N. A., *Ann. Chim.* (Paris), **15**, 961 (1960).
(2) Allard, J., and Berge, R., *Bull. Soc. Chim. France*, 1399 (1958).
(3) Allard, J., and Berge, R., *Bull. Soc. Chim. France*, 1787 (1956).
(4) Allard, J., Vignalou, C., and Lacombe, M., *Bull. Soc. Chim. France*, 196 (1958).
(5) Anlt, H. G., Sheers, E. H., and Chamberlain, R. J., *Chem. Ind.* (London), 1409 (1961).
(6) Arbuzov, B., *Ber.*, **68**, 1430 (1935).
(7) Arbuzov, B. A., and Frinovskaya, P., *Dokl. Akad. Nauk SSSR*, **112**, 427 (1957).
(8) Arbuzov, B. A., and Isaeva, Z. G., *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1049 (1959).
(9) Arbuzov, B. A., Isaeva, Z. G., and Samitov, Y. Y., *Dokl. Akad. Nauk SSSR*, **137**, 589 (1961).
(10) Arbuzov, B. A., and Michailow, B. M., *J. Prakt. Chem.*, **127**, 1 (1930).
(11) Arbuzov, B. A., and Naumov, V. A., *Dokl. Akad. Nauk SSSR*, **158**, 376 (1964).
(12) Arbuzov, B. A., Naumov, V. A., and Alekseev, N. V., *Dokl. Akad. Nauk SSSR*, **155**, 592 (1964).
(13) Badoche, M., *Bull. Soc. Chim. France*, 1065 (1964).
(14) Bain, J. P., *J. Am. Chem. Soc.*, **68**, 638 (1946).
(15) Bain, J. P., French Patent, 1,349,980 (1956); *Chem. Abstr.*, **61**, 1902d (1964).
(16) Bain, J. P., Best, A. H., Hampton, B. L., Hawkins, G. A., and Kitchen, L. J., *J. Am. Chem. Soc.*, **72**, 3124 (1950).

(17) Bain, J. P., and Gary, W. Y., U. S. Patent, 2,818,427 (1957); *Chem. Abstr.*, **52**, 6729e (1958).

(18) Bain, J. P., and Gary, W. Y., U. S. Patent, 2,911,442 (1959); *Chem. Abstr.*, **55**, 608a (1961).

(19) Bain, J. P., and Webb, R. L., *J. Am. Chem. Soc.*, **74**, 4292 (1952).

(20) Banthorpe, D. V., and Whittaker, D., *Quart. Rev.* (London), in press.

(21) Barton, D. H. R., and Cookson. R. C., *Quart. Rev.* (London), **10**, 44 (1956).

(22) Bhatt, M. V., *Chem. Ind.* (London), 1452 (1959).

(23) Birch, A. J., *Ann. Rept. Progr. Chem.* (Chem. Soc. London), **47**, 190 (1950).

(24) Blumann, A., and Zeitschel, O., *Ber.*, **46**, 1178 (1913).

(25) Blumann, A., and Zeitschel, O., *Ber.*, **54**, 887 (1912).

(26) Boake-Roberts, A., and Co., Belgian Patent, 616,032 (1962); *Chem. Abstr.*, **58**, 1500d (1962).

(27) Bose, A. K., *J. Org. Chem.*, **20**, 1003 (1955).

(28) Bose, A. K., *J. Org. Chem.*, **20**, 1010 (1955).

(29) Bose. A. K., Harrison, S., and Farber, L., *J. Org. Chem.*, **28**, 1223 (1963).

(30) Braun, J. C., and Fisher, G. S., *Tetrahedron Letters*, **No. 21**, 9 (1960).

(31) Brewster, J. H., *J. Am. Chem. Soc.*, **81**, 5491 (1959).

(32) Briggs, L. H., and Taylor, W. I., *J. Org. Chem.*, **12**, 551 (1947).

(33) Brown, H. C., and Bhatt, M. V., *J. Am. Chem. Soc.*, **82**, 2074 (1960).

(34) Brown, H. C., and Jarg, C. P., *J. Am. Chem. Soc.*, **83**, 2951 (1961).

(35) Burrows, W. D., and Eastman, R. H., *J. Am. Chem. Soc.*, **81**, 245 (1959).

(36) Chloupek, F. J., and Zweifel, G., *J. Org. Chem.*, **29**, 2092 (1964).

(37) Chretien-Bessiere, Y., *Compt. Rend.*, **255**, 943 (1962).

(38) Chretien-Bessiere, Y., *Bull. Soc. Chim. France*, 2182 (1964).

(39) Chretien-Bessiere, Y., Desalbres, H., and Montheard, J. P., *Bull. Soc. Chim. France*, 2546 (1963).

(40) Chugaev, L. A., *J. Russ. Phys. Chem. Soc.*, **39**, 1330 (1907).

(41) Couchman, F. M., Pinder, A. R., and Bromham, N. H., *Tetrahedron*, **20**, 2037 (1964).

(42) Comyms, A. E., and Lucas, H. J., *J. Am. Chem. Soc.*, **79**, 4339 (1957).

(43) Delaby, R., and Billuart, A., *Bull. Soc. Chim. France*, 567 (1943).

(44) Delepine, M., and Badoche, M., *Ann. Chim.* (Paris), **3**, 585 (1948).

(45) Dudley, Sully, B., *Chem. Ind.* (London), 264 (1964).

(46) Duluo, R., and Chretien-Bessiere, Y., *Bull. Soc. Chim. France*, 1362 (1959).

(47) Dupont, G., *Ann. Chim.*, [X] **1**, 184 (1924).

(48) Dupont, G., and Zacharewicz, W., *Compt. Rend.*, **198**, 1699 (1934).

(49) Dupont, G., and Zacharewicz, W., *Compt. Rend.*, **199**, 365 (1934).

(50) Dupont, G., and Zacharewicz, W., *Bull. Soc. Chim. France*, 533 (1935).

(51) Dupont, G., and Zacharewicz, W., *Compt. Rend.*, **200**, 759 (1935).

(52) Eigenmann, G. W., and Arnold, R. T., *J. Am. Chem. Soc.*, **81**, 3440 (1959).

(53) Eliel, E. L., "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, Chapter 8.

(54) Erskine, R. L., and Knight, S. A., *Chem. Ind.* (London), 1160 (1960).

(55) Eschinazi, H. E., and Pines, H., *J. Org. Chem.*, **24**, 1369 (1959).

(56) Faidutti, M., *Compt. Rend.*, **189**, 854 (1929).

(57) Finnegan, R. A., and McNees, R. S., *J. Org. Chem.*, **29**, 3241 (1964).

(58) Fisher, G. S., Stinson, J. S., and Goldblatt, L. A., *J. Am. Chem. Soc.*, **75**, 3675 (1953).

(59) Hanack, M., *Ber.*, **93**, 844 (1960).

(60) Hartshorn, M. P., and Wallis, A. F. A., *J. Chem. Soc.*, 5254 (1964).

(61) Hartshorn, M. P., and Wallis, A. F. A., *Tetrahedron*, **21**, 273 (1965).

(62) Hawkins, J. E., and Armstrong, G. T., *J. Am. Chem. Soc.*, **76**, 3756 (1954).

(63) Hawkins, J. E., and Eriksen, W. T., *J. Am. Chem. Soc.*, **76**, 2669 (1954).

(64) Hope, A. J. N., and Mitchell, S., *J. Chem. Soc.*, 4217 (1954).

(65) Hückel, W., and Gelchsheimer, E., *Ann.*, **625**, 12 (1959).

(66) Hückel, W., and Nag, D. S., *Ann.*, **645**, 101 (1961).

(67) Hurst, J. J., and Whitham, G., *J. Chem. Soc.*, 2864 (1960).

(68) Ipatief, V. N., Czajkouski, G. C., and Pines, H., *J. Am. Chem. Soc.*, **73**, 4098 (1951).

(69) Kafuku, P., and Ichikawa, M., *Bull. Chem. Soc. Japan*, **8**, 371 (1933).

(70) Kahneman, M., and Vavon, M., *Bull. Soc. Chim. France*, 1167 (1933).

(71) Kergomard, A., *Ann. Chim.* (Paris), **8**, 153 (1953).

(72) Kergomard, A., and Geneix, M. Th., *Bull. Soc. Chim. France*, 394 (1958).

(73) Kergomard, A., and Geneix, M. Th., *Bull. Soc. Chim. France*, 397 (1958).

(74) Kergomard, A., and Philibert-Bigou, M. J., *Bull. Soc. Chim. France*, 393 (1958).

(75) Kergomard, A., and Philibert, P., *Bull. Soc. Chim. France*, 1381 (1959).

(76) Klouwen, M. H., and ter-Heide, R., *J. Chromatog.*, **7**, 297 (1962).

(77) Komppa, G., and Hasselström, T., *Ann. Acad. Sci. Fennicae*, **A30**, 14 (1929).

(78) Komppa, G., and Hasselström, T., *Ann. Acad. Sci. Fennicae*, **A30**, 6 (1930).

(79) Kotake, M., and Nonaka, H., *Ann.*, **607**, 153 (1957).

(80) Kuczynski, H., and Chadbudzinskivi, Z., *Roczniki Chem.*, **30**, 773 (1956); *Chem. Abstr.*, **51**, 14623d (1957).

(81) Lalande, R., and Ducasse, Y., *Compt. Rend.*, **252**, 2114 (1961).

(82) Lipp, A., *Ber.*, **56**, 2089 (1923).

(83) Meinwald, J., and Gassmann, P. C., *J. Am. Chem. Soc.*, **82**, 5445 (1960).

(84) Moore, J. M., *J. Insect Physiol.*, **10**, 371 (1964).

(85) Moore, R. N., and Fisher, G. S., *J. Am. Chem. Soc.*, **78**, 4362 (1956).

(86) Moore, R. N., Golumbic, C., and Fisher, G. S., *J. Am. Chem. Soc.*, **78**, 1173 (1956).

(87) Nelson, E. K., *J. Am. Chem. Soc.*, **55**, 3400 (1933).

(87a) Nicholas, H. J., in "Biogenesis of Natural Compounds," P. H. W. Bernfeld, Ed., Pergamon, Oxford, 1963, p 653.

(88) Ohloff, G., Farnow, H., and Schade, G., *Chem. Ber.*, **89**, 1549 (1956).

(89) Ohloff, G., and Klein, E., *Tetrahedron*, **18**, 37 (1962).

(90) Pacquot, C., *Compt. Rend.*, **209**, 171 (1939).

(91) Penfold, A. R., Ramage, G. R., and Simonsen, J. L., *J. Chem. Soc.*, 1496 (1939).

(92) Pigulevskii, G. V., *Vestn. Leningr. Univ.*, 24 (1947); *Chem. Abstr.*, **41**, 6928f (1947).

(93) Poddubnaya, S. S., Cherkaev, V. G., and Rudolfi, T. A., *Chem. Abstr.*, **62**, 11855h (1965).

(94) Prileschajew, N., *Ber.*, **42**, 4811 (1909).

(95) Prileschajew, N., and Prokoptschuk, N., *Zh. Obshch. Khim.*, **3**, 865 (1933).

(96) Quinn, J. M., *J. Chem. Eng. Data*, **9**, 389 (1964).

(97) Raphael, R. A., "Chemistry of Carbon Compounds," Vol. IIA, E. Rodd, Ed., Elsevier, Amsterdam, 1953, p 314.

(98) Rau, M. G., *Indian Forest Records*, **11**, 199 (1924); quoted in ref 133.

(99) Renney, R. L., and Fisher, G. S., *J. Gas Chromatog.*, **1**, 19 (1963).

(100) Retamar, J. A., *Rec. Fac. Ing. Quim., Univ. Nacl. Litoral, Santa Fe, Arg.*, **29**, 45 (1960); *Chem. Abstr.*, **57**, 16772b (1962).

(101) Retamar, J. A., and Ricciardi, A. I. A., *Rec. Fac. Ing. Quim., Univ. Nacl. Litoral, Santa Fe Arg.*, **30**, 17 (1961); *Chem. Abstr.*, **58**, 13300b (1963).

(102) Richter, F., and Wolff, W., *Ber.*, **59**, 1733 (1926).

(103) Rienäcker, R., and Ohloff, G., *Angew. Chem.*, **73**, 240 (1961).

(104) Rothman, E. S., and Day, A. R., *J. Am. Chem. Soc.*, **76**, 111 (1954).

(105) Rudakov, G. A., and Shestaeva, M. M., *Zh. Obshch. Khim.*, **25**, 597 (1955).

(106) Rudakov, G. A., and Shestaeva, M. M., *Zh. Obshch. Khim.*, **26**, 2357 (1956).

(107) von Rudloff, E., *Can. J. Chem.*, **39**, 1190 (1961).

(108) Rüpe, H., and Heritier, A., *Ann.*, **459**, 171 (1927).

(109) Rutovskii, V. M., and Vinagradova, P., *Trans. Sci.-Chem.-Pharm. Inst.* (Moscow), **10**, 22 (1924); quoted in ref 133.

(110) Rutkovsky, G. N., and Alferova, J., *Zh. Prikl. Khim.*, **24**, 583 (1951).

(111) Ruzicka, L., and Trebler, H., *Helv. Chim. Acta*, **7**, 489 (1924).

(112) Sandermann, W., in "Comparative Biochemistry," Vol. III, M. Florkin and H. S. Mason, Ed., Academic Press Inc., New York, N. Y., 1962, p 507.

(113) Sauers, R. R., and Landesberg, J. M., *J. Org. Chem.*, **26**, 964 (1961).

(114) Schenck, G. O., Eggert, H., and Denk, W., *Ann.*, **584**, 177 (1953).

(115) Schleyer, P. von R., Watts, W. E., and Cupas, C., *J. Am. Chem. Soc.*, **86**, 2722 (1964).

(116) Schmidt, G. A., and Fisher, G. S., *J. Am. Chem. Soc.*, **81**, 445 (1959).

(117) Schmidt, H., *Z. Angew. Chem.*, **42**, 126 (1929).

(118) Schmidt, H., *Ber. Schimmel & Co. Akt.-Ges.*, 20 (1941); *Chem. Zentr.*, **112**, 2531 (1942).

(119) Schmidt, H., *Ber. Schimmel & Co. Akt.-Ges.*, 50 (1941); *Chem. Abstr.*, **37**, 4380 (1943).

(120) Schmidt, H., *Ber. Schimmel & Co. Akt.-Ges.*, 56 (1941); *Chem. Abstr.*, **37**, 4714 (1943).

(121) Schmidt, H., *Ber. Schimmel & Co. Akt.-Ges.*, 70 (1941); *Chem. Abstr.*, **37**, 4715 (1943).

(122) Schmidt, H., *Ber.*, **77**, 167 (1944).

(123) Schmidt, H., *Ber.*, **77**, 544 (1944).

(124) Schmidt, H., *Ber.*, **80**, 520 (1947).

(125) Schmidt, H., *Ber.*, **80**, 528 (1947).

(126) Schmidt, H., Schulz, L., and Doll, W., *Ber. Schimmel & Co. Akt.-Ges.*, 38 (1940); *Chem. Abstr.*, **37**, 361 (1943).

(127) Schwabe, K., and Berg, H., *Z. Elektrochem.*, **56**, 952 (1952).

(128) Seubold, F. H., *Chem. Ind.* (London), 1389 (1954).

(129) Sebe, Y., *Bull. Chem. Soc. Japan*, **59**, 1285 (1938).

(130) Sebe, Y., *Bull. Chem. Soc. Japan*, **62**, 22 (1941).

(131) Sharma, M. L., Nigam, M. C., and Hande, K. L., *Perfumery Essent. Oil Record*, **54**, 579 (1963).

(132) Shulz, L., and Doll, W., *Ber. Schimmel & Co. Akt.-Ges.*, 50 (1942-3); *Chem. Abstr.*, **41**, 739a (1947).

(133) Simonsen, J. L., "The Terpenes," Vol. III, 2nd ed, Cambridge University Press, London, 1949, p 100.

(134) Reference 133, p 223.

(135) Stallcup, W., and Hawkins, J. E., *J. Am. Chem. Soc.*, **63**, 3339 (1941).

(136) Stoll, A., Seebeck, E., and Stauffacher, D., *Helv. Chim. Acta*, **40**, 1205 (1957).

(137) Takenot, T., and Nakajura, N., *J. Pharm. Soc. Japan*, **75**, 1036 (1955).

(138) van Tamelen, E. E., and Timmons, R. J., *J. Am. Chem. Soc.*, **84**, 1067 (1962).

(139) Teisseire, T., and Plattier, M., *Recherches* (Paris), **24** (1963); *Chem. Abstr.*, **60**, 15915g (1964).

(140) Teresa, J. de P., Sanchez Bellido, H., and Bellido, I. S., *Anales Real Soc. Espan. Fis. Quim.* (Madrid), **58B**, 339 (1962).

(141) Thurber, F. H., and Thielke, R. C., *J. Am. Chem. Soc.*, **53**, 1030 (1931).

(142) Tischenko, D., *Zh. Obshch. Khim.*, **22**, 7981 (1952).

(143) Treibs, W., *Ber.*, **77**, 572 (1944).

(144) Treibs, W., *Ann.*, **558**, 136 (1947).

(145) Treibs, W., and Schmidt, H., *Ber.*, **82**, 218 (1949).

(146) Vilkas, M., Dupont, G., and Duluo, R., *Compt. Rend.*, **242**, 1329 (1956).

(147) Vilkas, M., *Bull. Soc. Chim. France*, 1401 (1959).

(148) Wallach, O., *Ann.*, **356**, 227 (1907).

(149) Wheeler, O. H., *Chem. Ind.* (London), 1020 (1954).

(150) Whitham, G., *J. Chem. Soc.*, 2232 (1961).

(151) Widmark, G., *Acta Chem. Scand.*, **9**, 938 (1955).

(152) Wienhaus, H., and Schumm, P., *Ann.*, **439**, 20 (1924).

(153) Winstein, S., and Friedrich, E. C., *J. Am. Chem. Soc.*, **86**, 2721 (1964).

(154) Winstein, S., and Holness, N. J., *J. Am. Chem. Soc.*, **77**, 3054 (1955).

(155) Wolford, R. W., Attaway, J. A., and Barabas, L. J., *Anal. Chem.*, **37**, 1289 (1965).

(156) Ziegler, K., Krupp, F., and Zosel, K., *Ann.*, **629**, 241 (1960).

(157) Zubyk, W., and Conner, A. Z., *Anal. Chem.*, **32**, 912 (1960).

(158) Zweifel, G., and Brown, H. C., *J. Am. Chem. Soc.*, **86**, 393 (1964).