RECENT PROGRESS IN THE MENTHONE CHEMISTRY

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INTRODUCTORY

Menthol, or "mint camphor," $C_{10}H_{20}O$, was first recognized as a crystalline principle in 1771 by the Dutch botanist Gambius, who termed it *camphora europaea menthæ piperitidis*. Its main source, the peppermint plant, which finds mention in the *Shin-J-Ho* (984) as *Megusa*, or eye herb, appears to have been cultivated in Japan for more than two thousand years. For several centuries English peppermint enjoyed a wide reputation: the oldest specimens of *Mentha piperita* now extant were collected by John Ray in 1696; they were grown in Hertfordshire, and are now in the British Museum. At the present day, although peppermint is still cultivated at Mitcham and elsewhere in England, the peppermint industry centers mainly in the United States and Japan. In America, two well-known varieties of the peppermint plant have been derived from the original English stock, namely, the black mint (*Mentha piperita vulgaris*) and the white mint (*Mentha piperita officinalis*); the former is favored for cultivation on account of its hardy nature and productivity. Japanese and Chinese peppermint oils are distilled from two varietal forms of an entirely distinct species, known respectively as *M. arvensis piperascens* and *M. arvensis glabrata* (1).

Until about 1920, only two primary substances had been used as points of departure in researches dealing with the structural chemistry and stereochemistry of the important group of homocyclic compounds centering around menthone: these substances,

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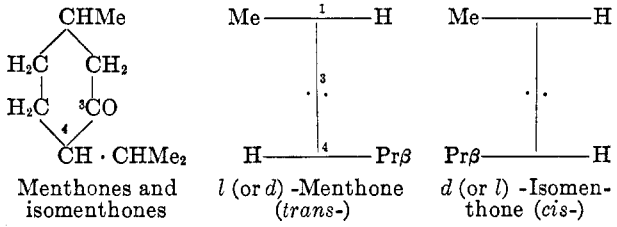
in order of chronology as well as of importance, are menthol and thymol.

The first reference in the voluminous literature of the menthone series contains an account of an oil, $C_{10}H_{18}O$, prepared at Tokyo in 1881 by Moriya (2), who treated menthol from Japanese peppermint oil with chromic acid in a sealed tube at 120°. Although made by the oxidation of levo-rotatory menthol, the oil was optically inactive. In a note added to the paper, Prof. Atkinson made the correct suggestion that "menthol is a secondary alcohol derived from a saturated closed chain hydrocarbon formed by the addition of six atoms of hydrogen to ordinary cymene, and that the oxidation product, $C_{10}H_{18}O$, obtained by Mr. Moriya, is the corresponding ketone." Andres and Andreef (3) first succeeded in isolating menthone from peppermint oil in 1892, although it should be noted that Moriya stated in his original paper that "it is not improbable that this substance, which holds the menthol (of peppermint oil) in solution, is the same body as that formed by the action of the chromic acid liquid upon the camphor."

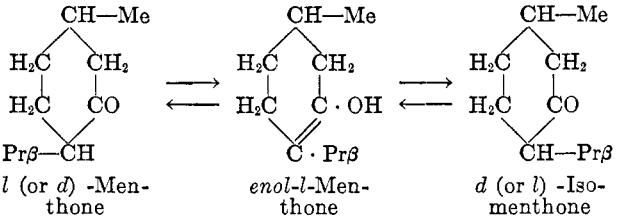
A certain confusion was introduced at the outset into the chemistry of menthone by Beckmann's discovery (4), in 1889, of the so-called "inversion" of the levo-rotatory ketone into a dextro-rotatory modification. *l*-Menthone, prepared by a carefully controlled oxidation of natural *l*-menthol with chromic acid mixture, had a maximum rotatory power of $[\alpha]_D$ −28.46°, and was found to be substantially identical with the levo-rotatory ketone occurring in peppermint oils. The ketone recovered from a solution in cold strong sulphuric acid showed a maximum value of $[\alpha]_D$ +28.14°, while treatment with acid or alkaline reagents, or the action of heat alone, yielded specimens with intermediate optical rotatory powers. The assumed conversion of the levo-rotatory ketone into its enantiomer, which has been repeatedly expressed or implied in the literature (5), was rendered untenable by Beckmann's further observation that the "inverted" ketone yielded an oily oxime possessing an optical rotation quite distinct from that of the crystalline and highly characteristic oxime of *l*-menthone.

The constitution (I) suggested for menthone by Semmler in 1892, and now generally accepted, indicates that the ketone should be capable of existing in *cis*- and *trans*-forms (II and III), each characterized by molecular enantiomorphism:



Menthones and isomenthones (I) — *l* (or *d*) -Menthone (*trans*-) (II) — *d* (or *l*) -Isomenthone (*cis*-) (III)

The constitution thus provides for two ketones, menthone and isomenthone, each of which should occur in *d*- and *l*-modifications. Further, the two ketones should be interconvertible through a process of enolization, which would enable a ketone of each type to pass through a common enol-form in which the asymmetry of carbon atom (4) is temporarily annulled; since, however, carbon atom (1) remains asymmetric throughout the tautomerization, the optical activity of the molecule does not vanish in the process. The observed change of sign in the rotatory power indicates that levo-rotatory menthone passes into dextro-rotatory isomenthone, and *vice versa*. An equilibrium may thus be pictured, of the form *l*-menthone $\rightleftarrows$ *d*-isomenthone, the proportions of the two stereoisomers being determined by the particular conditions:



l (or *d*) -Menthone (IV) — *enol-l*-Menthone (V) — *d* (or *l*) -Isomenthone (VI)

The value $[\alpha]_D$ +28.14°, observed by Beckmann, denotes therefore a definite mixture of *l*-menthone and *d*-isomenthone.

Originally there was a disposition to assign the *cis*-configuration

(III) to menthone; but according to recent observations by Zeitschel and Schmidt (6) this configuration should be allocated to isomenthone, in accordance with the Auwers-Skita rule that the higher density and refractive index are characteristic of the *cis*-isomer. A certain amount of support for this view is provided by Carter's measurements of parachors (7), the values for *d*- and *dl*-isomenthone being somewhat higher than for *l*- and *dl*-menthone. Nevertheless, the evidence is not wholly convincing, and the relative configurations of the two ketones here given can be regarded only as provisional until accurate physical determinations have been made for specimens of the active and inactive ketones of undoubted stereochemical homogeneity.

Prominent among the early derivatives of menthone to be discovered was *l*-menthylamine, first prepared by Andres and Andreef (3), in 1892, by the reduction of *l*-menthoneoxime. A similar method was used by Wallach (8), who also prepared a stereoisomeric "R-menthylamine" by heating *l*-menthone with solid ammonium formate; although dextro-rotatory, this base was shown to be distinct from the enantiomer of *l*-menthylamine. No other menthylamine was described until 1913, when Wallach (9) prepared a so-called "*i*-menthylamine" by reducing *dl*-menthoneoxime: this base has recently been shown to have been heterogeneous, owing presumably to the occurrence of "inversion" during the oximation of the optically inactive ketone.

In 1912, a considerable advance in the menthone chemistry was achieved by Pickard and Littlebury (10) as a result of their researches on menthols. When heated with phthalic anhydride, the menthols present in the complex mixture obtained in the catalytic hydrogenation of thymol yielded crystalline menthyl hydrogen phthalates. By a process of repeated fractional crystallization, followed by hydrolysis, it was possible to prepare from this product pure specimens of *dl*-menthol (m.p. 34°) and *dl*-neomenthol (m.p. 51°); moreover, by treatment with appropriate optically active alkaloids, *dl*-menthyl hydrogen phthalate and *dl*-neomenthyl hydrogen phthalate were resolved into optically active components, thus yielding *d*- and *l*-menthol

(m.p. 43°) and *d*- and *l*-neomenthol (oils). Since *l*-menthol and *d*-neomenthol are oxidized by chromic acid to *l*-menthone, and *d*-menthol and *l*-neomenthol to *d*-menthone, all these menthols must be regarded as derivatives of menthone (as distinct from isomenthone).

The earlier literature of this subject contains many disconnected and conflicting references to supposed derivatives of isomenthone. Among these, a publication by Beckmann (11) in 1909 proved later to be substantially correct. The crude liquid oxime of "inverted" *l*-menthone furnished a supposed *d*-isomenthylamine hydrochloride, having $[\alpha]_D$ +17.7° in dilute aqueous solution; this material reacted with nitrous acid to yield a dextro-rotatory isomenthol, which upon oxidation passed into a ketone having $[\alpha]_D$ +93.2°.

Thus, in brief, the researches based on *l*-menthol and thymol had succeeded in elucidating the main chemical relationships of *l*- and *dl*-menthone, of the derived *l*-, *d*- and *dl*-menthols and -neomenthols, and of *l*-menthylamine; but while important lacunæ still existed in the menthone series, the whole field of isomenthone and its derivatives awaited a systematic exploration. According to Meyer and Jacobson (12), "es wäre eine dankbare Aufgabe, die vier optisch aktiven und die beiden wahren racemischen Modificationen von krystallisirbaren Menthon-Derivaten darzustellen und unter besonderen Berücksichtigung der modernen, von van 't Hoff und Roozeboom vertretenen Anschauungen genau zu untersuchen, da dieser Fall von grundlegender Bedeutung für die Terpenchemie ist." The considerable expansion of the menthone chemistry which has occurred during the last few years is due almost entirely to the introduction into this field of work of the *Eucalyptus* ketone, piperitone.

PIPERITONE

History and occurrence

The genus *Eucalyptus*, as pointed out by R. T. Baker and H. G. Smith (13), is of immense scientific and economic importance, on account of its timbers, essential oils, exudations and dyes.

It comprises about three-quarters of the vegetation of Australia, and embraces some three hundred species, each possessing distinctive chemical characteristics. Since the examination by Cloëz (14), in 1870, of the essential oil of *E. globulus*, the presence of more than forty different components, consisting mainly of terpenes and their derivatives, has been established in *Eucalyptus* oils. The classical researches of Baker and Smith (13) have shown that the eucalypts fall broadly into three main groups, distinguished chemically by the composition of their leaf-oils and exudations (kinos) and morphologically by the leaf-venation,

TABLE 1

Characteristics of the three main groups of eucalypts

	GROUP I	GROUP II	GROUP III
Main components of leaf-oil	Pinene (bornyl acetate)	Pinene, cineole	*l*-α-Phellandrene (geranyl acetate, *l*-piperitone)
Leaf-venation	Obtuse, "feather" type	Acute, with marginal vein	Acute, "butterfly-wing" type; possibly two marginal veins
Yield of oil	To 0.5 per cent	Intermediate	To 4.5 per cent
Examples	*E. corymbosa*	*E. Smithii*, *E. globulus*	*E. amygdalina*, *E. dives*, *E. piperita*

the form and size of the cotyledons, etc. The more important characteristics which were elucidated in the course of these remarkable phytochemical researches are summarized in table 1 (15). According to Baker and Smith's evolutionary theory, the older species of the first group originated in N. W. Australia; while the third group, which predominates in S. E. Australia and Tasmania, contains the most recently evolved species.

Among the varied components of *Eucalyptus* oils, only one has been discovered which possesses ketonic properties. It imparts a strong peppermint odor to the oils of the so-called "peppermint"

eucalypts, a species of which attracted attention at Port Jackson (Sydney Harbor) soon after Governor Phillip's arrival in New South Wales, in 1788. The species is now known as *E. piperita*, or the Sydney peppermint, and the first *Eucalyptus* oil to be distilled was obtained from its leaves and used as a substitute for peppermint oil by Dr. White, Surgeon-General to the First Settlement. "The name Peppermint Tree has been given to this plant by Mr. White on account of the very great resemblance between the essential oil drawn from its leaves and that obtained from the Peppermint (*Mentha piperita*) which grows in England. This oil was found by Mr. White to be much more efficacious in removing all cholicky complaints than that of the English Peppermint, which he attributes to its being less pungent and more aromatic. A quart of the oil has been sent by him to Mr. Wilson" (16).

In 1900, the peppermint odor of this oil was shown by Smith (17) to be due to a ketone, which was not menthone as originally supposed (18); menthone, despite repeated statements to the contrary, has not been discovered in *Eucalyptus* oils. Subsequently, the new ketone, now diagnosed as $C_{10}H_{18}O$, was recognized as a new substance under the appropriate name of piperitone (13). Piperitone has since been found, apparently always in the levo-rotatory form, in twenty-three species of *Eucalyptus* (19), having the general characters indicated in the third group of table 1. The maximum amount is found in the oil of the broad-leaved peppermint (*E. dives*), which may contain from 40 to 50 per cent of the ketone, the chief remaining constituent being *l*-α-phellandrene. The yield of oil from the green leaves and twigs of *E. dives* reaches about 4 per cent, and since the regrowth from the felled or lopped trees is particularly rapid, piperitone could be produced in almost unlimited quantity upon waste land in suitable regions of Australia (as well as in other countries); it should be noted, however, that certain varietal forms of *E. dives* are practically worthless for the production of piperitone (20).

In 1921, a detailed examination of piperitone was undertaken by Read and Smith, with the later collaboration of Bentivoglio,

Hughesdon and Earl (21). During these researches, *d*-piperitone was discovered by Simonsen (22) in the essential oil of *Andropogon Jwarancusa*, a Himalayan grass; apparently also, it is the dextro-modification which occurs in the oils of Japanese peppermint (23) and *Cymbopogon sennaarensis* (24). It is interesting, moreover, that the pulegone of *Mentha pulegium* is replaced in *M. pulegium* var. *hirsuta* by *l*-piperitone (25). The ketone is also

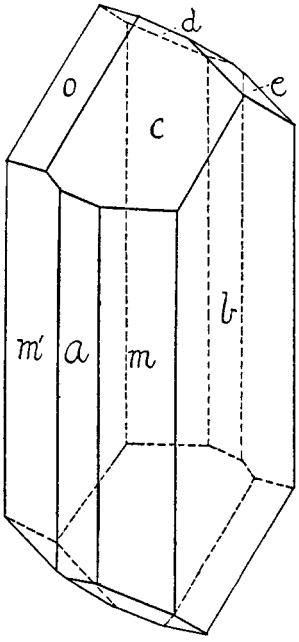


FIG. 1. *dl*-PIPERITONE-α-OXIME

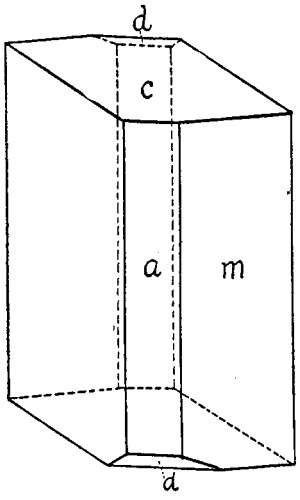


FIG. 2. *dl*-PIPERITONE-β-OXIME

said to occur in camphor oil, but the sense of the optical rotation is not stated (26).

Piperitone was ultimately diagnosed as Δ^1-menthenone-3. Owing to the discovery of its ready conversion to isomenthone, the new ketone provided a fresh and extremely effective point of departure for elucidating the chemical relationships of the menthones and their derivatives, its value for this purpose being enhanced by its availability in the *l*-, *d*- and *dl*-modifications.

Quite apart from the novel position of piperitone in the pure chemistry of the menthone series, its ready conversion to menthol and thymol (*vide infra*) lends it a pronounced economic interest: so that, altogether, this ketone may now be claimed as one of the most important of the alicyclic compounds. For this reason the chemistry of the substance calls for treatment in some detail.

Characterization

Piperitone gives rise to a number of crystalline derivatives of exceptional beauty and distinction, prominent among which are

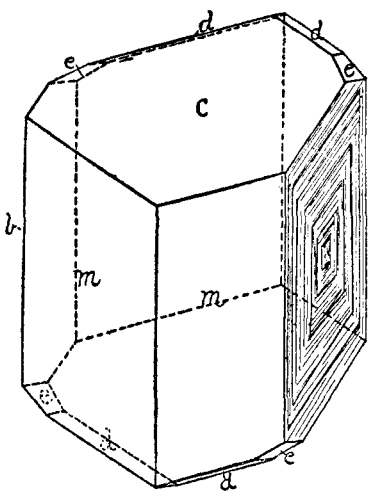


FIG. 3. BENZYLIDENE-*dl*-PIPERITONE, α-FORM

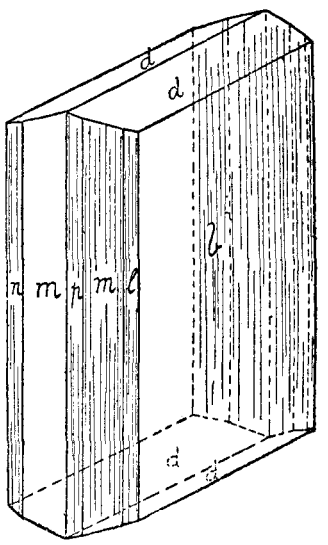


FIG. 4. BENZYLIDENE-*dl*-PIPERITONE, β-FORM

the α-oxime (m.p. 118–9°), the β-oxime (m.p. 88–9°) and the benzylidene derivative. Owing to the ease with which the active ketone racemizes, the derivatives are usually produced in the externally compensated form. The α-oxime (figure 1) and β-oxime (figure 2), which crystallize respectively in the triclinic and monoclinic systems (27), are regarded as *syn-* and *anti*-modifications. The α- and β-semicarbazones melt at 226–7° and 174–6°, respectively. The ketone also forms two hydroxylamino-oximes.

In the presence of alcoholic sodium ethoxide, piperitone condenses readily with aldehydes, giving rise to very characteristic derivatives. Benzylidene-*dl*-piperitone (28) provides a remarkable example of enantiotropic dimorphism: the monoclinic, pale yellow α-form (figure 3) melts at 59–61°, and the rhombic, deeper yellow β-form (figure 4) melts at 63–4°. The α-form is the stable modification at the ordinary temperature, but each form is readily procurable in a state of complete freedom from the other. For diagnostic purposes, the preparation of anisylidene-*dl*-piperi-

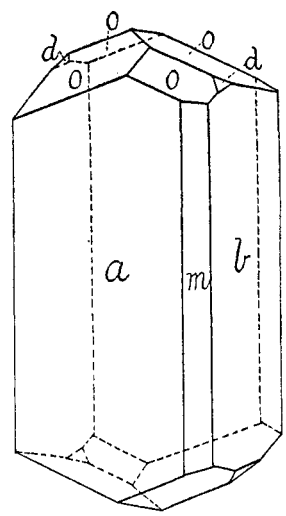


FIG. 5. ANISYLIDENE-*dl*-PIPERITONE

tone (m.p. 98°) is to be recommended (29); it forms pale yellow rhombic prisms (figure 5), and does not display dimorphism. It is also useful to note that the oximes are readily soluble in dilute mineral acids, from which they may be recovered by the addition of ammonia. This behavior differentiates piperitone from several closely related ketones.

Piperitone may be extracted from essential oils by means of hot aqueous solutions of sodium bisulfite or normal sulfite (30), but partial racemization invariably attends its liberation from the crystalline bisulfite compound. Racemization occurs also when

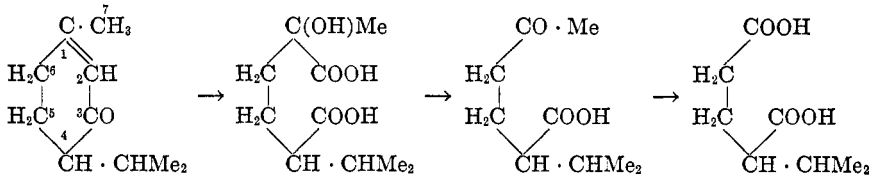
the active ketone is maintained at 200°, distilled under atmospheric pressure, or treated with alcoholic sodium ethoxide (31). Fractional distillation of a piperitone-bearing oil under ordinary pressure yields the optically inactive ketone. Thus the only method which can be used to isolate specimens possessing the maximum rotatory powers of about $[\alpha]_D^{20}$ ±50° is that of repeated fractional distillation under diminished pressure; products isolated in this way appear to contain some *dl*-piperitone (32), in addition to small quantities of other impurities (31). The active forms of the ketone are also difficult to characterize chemically: from *l*-piperitone a viscid oxime, having $[\alpha]_D$ +238° in benzene, has been prepared (31).

Pure *dl*-piperitone, prepared through the bisulfite compound and the α-semicarbazone, had the following physical constants (33): b.p. 113° at 18 mm., 232–233° at 768.6 mm., d_4^{20} 0.9331, n_D^{20} 1.4845, $[R_L]_D$ 46.70. The calculated molecular refractivity for a ketone, $C_{10}H_{16}O$, with one double bond is 45.82, so that the exaltation is 0.88 unit. It is interesting that the observed value is almost identical with the value (46.76) calculated for an enolic form.

Constitution

The chemical identity of the ketone from the various sources which have been enumerated was inferred from a study of the oximes and other characteristic derivatives. In this way, a complete goniometric correspondence was established (27) between specimens of the *dl*-α-oxime prepared from the oils of *E. dives* (Australia) and *A. Jwarancusa* (India). Since he was able to reduce piperitone to *dl*-menthol and oxidize it to thymol, Smith (13) recognized the substance as a menthenone-3. The disruptive oxidation of the ketone from Japanese peppermint oil (23) had yielded α-hydroxy-α-methyl-α′-isopropyladipic acid (VIII), γ-acetyl-α-isopropylbutyric acid (IX) and α-isopropylglutaric acid (X), and closely similar results were obtained by Simonsen (22), using the Indian ketone. Thus, assuming (*a*) the chemical identity of the ketone from the various sources, and (*b*)

the absence of molecular rearrangement prior to oxidation, piperitone would be Δ^1-menthenone-3 (VII), a ketone which had been synthesized from 1,3,4-trihydroxymenthane and briefly described by Wallach (34) in 1908:



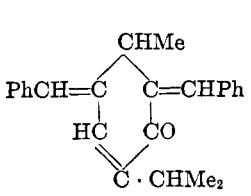
Piperitone

(VII) (VIII) (IX) (X)

This conclusion concerning the constitution of piperitone was confirmed by Read, Smith and Hughesdon (35), by means of a method which utilized only mild reagents at the ordinary temperature and avoided any disruption of the ring. If *dl*-piperitone has the constitution (VII), it is apparent that condensation with benzaldehyde cannot occur in position (2); whereas if the double bond is in any position except Δ^1, condensation will be confined to position (2). The latter condition will also apply to the ketone obtained upon hydrogenating *dl*-piperitone. The following two series of operations were accordingly carried out: (i) *dl*-piperitone → benzylidene-*dl*-piperitone → benzyl-*dl*-isomenthone; (ii) *dl*-piperitone → *dl*-isomenthone → 2-benzylidene-*dl*-isomenthone → 2-benzyl-*dl*-isomenthone. Since the two final products were distinct, piperitone is evidently the Δ^1-ketone.

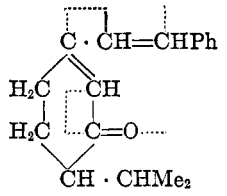
Simonsen (22), suggested that condensation with aldehydes occurs in position (6), owing to the activation exerted by the adjacent ethylenic linkage; a similar activation had indeed been observed by Wallach (36) in the case of Δ^4-menthenone-3, which forms a 2,6-dibenzylidene derivative (XI). Later, however, it was shown by Earl and Read (29) (37) that benzylidene-*dl*-piperitone yields α-isopropylglutaric acid (X), and not isopropylsuccinic acid, when oxidized with potassium permanganate in cold acetone. It may therefore be concluded that condensation with aldehydes occurs in the 7-position, the system C:C·CO,

curiously enough, exerting its maximum activating effect in the side-chain rather than in the ring:



2, 6-Dibenzylidene-Δ^4-menthenone-3

(XI)

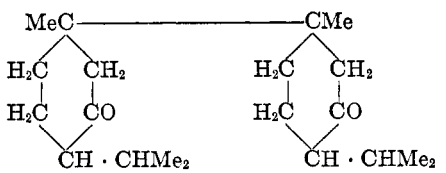


7-Benzylidene-piperitone

(XII)

In this instance there is no tendency to form a dibenzylidene derivative. It is of interest that the duplicated conjugation presented by the molecule of benzylidenepiperitone, and indicated in formula (XII), is often associated with dimorphism (38).

That piperitone is an $\alpha\beta$-unsaturated ketone is supported by the fact that its molecular refractivity displays the exaltation characteristic of menthenones of this type (39); moreover, it forms a hydroxylamino-oxime, and when reduced with sodium amalgam in aqueous alcohol gives rise to a so-called "bimolecular ketone" (13), characterized by Carter and Read (40) as 1,1'-bismenthone:

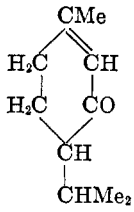


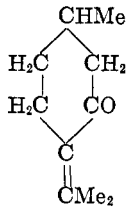
1, 1'-Bismenthone

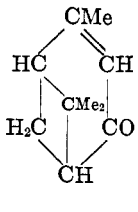
(XIII)

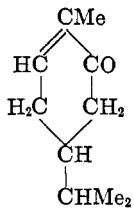
This derivative, the formation of which is very characteristic of piperitone, exists in two externally compensated forms, m.p. 166–7° and 135–6°.

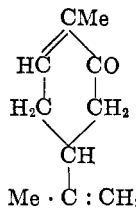
As an $\alpha\beta$-unsaturated ketone, piperitone resembles other important components of essential oils, including pulegone, verbenone, carvotanacetone and carvone:


Piperitone
(XIV)

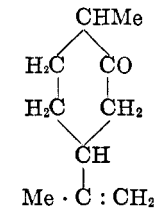

Pulegone
(XV)

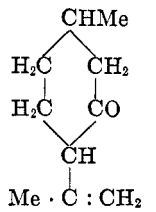

Verbenone
(XVI)

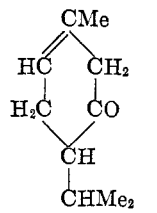

Carvotanacetone
(XVII)


Carvone
(XVIII)

Non-conjugated structures, such as those presented by isopulegone and dihydrocarvone, are also found in natural ketones of this class; but in such instances there is always a tendency towards isomerization into the more stable conjugated form. Although *Eucalyptus* piperitone is usually regarded as chemically homogeneous, recent work (41) has indicated the possibility of the presence in it of an intra-annular tautomeride of Δ^1-menthenone-3, such as the Δ^6-ketone; this would be related to the Δ^1-compound in much the same way as isopulegone to pulegone:

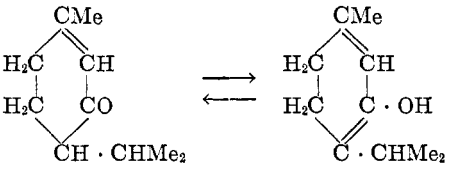

Dihydrocarvone
(XIX)


Isopulegone
(XX)


Δ^6-Menthenone-3
(XXI)

Racemization

As already stated, the optically active forms of piperitone readily undergo racemization when submitted to the action of heat or alkaline reagents; the racemizing action of acid reagents is less marked (31). This behavior has been attributed to enolization, since this process annuls the asymmetry of the molecule:



keto-Piperitone (XXII) ⟷ *enol*-Piperitone (XXIII)

It is evident that the racemization of piperitone is analogous to the "inversion" of *l*-menthone (formulae IV, V and VI); in the latter process, however, the molecule retains its optical activity owing to the undisturbed asymmetry of carbon atom (1), which in piperitone is symmetric.

Oxidation

The disruptive oxidation of piperitone has been reviewed in the discussion of its constitution; economically, however, the main interest centers around milder oxidative processes which leave the ring intact. Piperitone may be converted to thymol in various ways, notably by oxidation with ferric chloride in glacial acetic acid (42), by treatment with halogens (43), or by dehydrogenation (43). Oxidation with permanganate yields a small proportion of diosphenol (24), and the ketone reacts with hypochlorous acid to form a crystalline chlorohydrin, m.p. 101–2° (43).

Reduction

When reduced with sodium amalgam in moist ether or aqueous alcohol, piperitone affords a mixture of 1,1′-bismenthone, *dl*-isomenthol and *dl*-menthol (*vide infra*); the yield of menthol is increased by using absolute alcohol (24) (42). According to Smith and Penfold (42), the ketone is converted to *dl*-menthone when hydrogenated in the presence of nickel at 180°, but the product also contains *dl*-isomenthone (*vide infra*). Piperitone has been utilized successfully as a commercial source of *dl*-menthol and also of thymol.

During reduction by any of the above processes, optically active piperitone undergoes a preliminary racemization, and thus

gives rise to externally compensated menthones and menthols. In 1922, however, it was shown by Hughesdon, Smith and Read (44) that when hydrogenated according to Skita's method, *l*-piperitone yielded a highly dextro-rotatory product containing *d*-isomenthone. Most of the recent advances in the chemistry of the stereoisomeric menthones, menthols and menthylamines, which will now be discussed, followed from this discovery.

THE APPLICATION OF PIPERITONE IN THE MENTHONE CHEMISTRY

The menthones

In contact with an aqueous medium containing colloidal palladium, preferably at temperatures between 35° and 20°, *l*-piperitone readily absorbs a molecular proportion of hydrogen and gives rise to an optically active mixture of menthones of reversed and enhanced rotatory power. Thus, in the original experiments (45), a specimen of *l*-piperitone having $[\alpha]_D$ — 51.5° afforded a menthone with $[\alpha]_D$ + 65.1°. That this product was not *d*-menthone was apparent from its high rotatory power, the maximum value for *l*-menthone recorded by Beckmann (4) being $[\alpha]_D$ — 28.46°; since, in addition, the product showed a rapid decline in rotatory power when brought into contact with alkali, it was diagnosed as consisting essentially of *d*-isomenthone. This conclusion was confirmed by Read and Robertson (32), who showed that when submitted to the action of heat, alkaline reagents, etc., the hydrogenated product gave equilibrium mixtures of *d*-isomenthone and *l*-menthone closely similar to the mixtures afforded by *l*-menthone under similar conditions. The equilibrium proportions of *d*-isomenthone formed through the action of alcoholic sodium ethoxide, heat (200°) and melting 90 per cent sulphuric acid upon pure *l*-menthone were later found to be about 30, 37 and 46 per cent, respectively (46). By hydrogenating *d*-piperitone, from the oil of *Andropogon Jwarancusa*, a corresponding product composed mainly of *l*-isomenthone was obtained: this was converted by enolizing agents to mixtures of *l*-isomenthone and *d*-menthone. Thus, the "inversion" of *l*-menthone, originally observed by Beckmann (4),

represents one phase of a reversible process of the type: *l* (or *d*)-menthone $\rightleftarrows$ *d* (or *l*)-isomenthone.

In order to prepare optically pure *d*-isomenthone, hydrogenated *l*-piperitone was converted to *d*-isomenthol in the way described below; when carefully oxidized with chromic acid mixture, which was found to exercise only a slight "inverting" action under the conditions adopted, this substance yielded *d*-isomenthone having $[\alpha]_D^{15}$ + 91.7° (46). Since the highest value yet observed for *l*-menthone is $[\alpha]_D^{20}$ — 29.6° (32), Beckmann's "inverted" *l*-menthone, with the maximum value $[\alpha]_D$ + 28.14°, presumably contained about 52 per cent of *l*-menthone and 48 per cent of *d*-isomenthone. *l*-Menthone predominates in all the equilibrated mixtures yet examined, but so far a literal inversion of the rotatory power of *d*-isomenthone has not been observed. Specimens of optically pure isomenthones are difficult to prepare, owing to the sensitiveness of these substances to heat and other enolizing influences; the ketones are also difficult to characterize. *d*-Isomenthoneoxime is a colorless, viscid oil, having n_D^{17} 1.4830 and $[\alpha]_D^{15}$ + 45.1° in absolute alcohol; the most characteristic derivative yet prepared is the oxime hydrochloride, which forms large transparent prisms, m.p. 132°, $[\alpha]_D^{15}$ + 38.6° in chloroform (46). A study of the relationships existing between *l*-menthone and *d*-isomenthone indicates (*a*) that the optical rotatory effect of carbon atom (1) is less than that of (4), and (*b*) that the optical effects of these two centers of asymmetry are opposed in the active menthones and conjoined in the active isomenthones.

dl-Isomenthone contaminated with *dl*-menthone has been prepared by hydrogenating *dl*-piperitone and also by oxidizing the mixture of menthols obtained when *dl*-piperitone is reduced with sodium and alcohol (47); it yields a characteristic oxime, which forms anorthic crystals (figure 6), m.p. 99–100°. The α-semicarbazone melts at 219–20°. The pure ketone could obviously be prepared by oxidizing *dl*-isomenthol (*vide infra*), but this has not yet been done. The "inactive menthone" prepared by Wallach (36) by hydrogenating synthetic *dl*-Δ^1-menthenone-3 was evidently a mixture of *dl*-menthone and *dl*-isomenthone (47), and the same statement applies to the product formed in the

hydrogenation of piperitone in the presence of nickel at 180° (42). Thus, *l*-piperitone with $[\alpha]_D$ — 22.0°, when hydrogenated in this way, gave a product having $[\alpha]_D$ + 11.0° (1-dcm. tube), containing *dl*- and *d*-isomenthone and *dl*- and *l*-menthone (45).

It is interesting to note that neither *dl*-menthone nor *dl*-isomenthone can be obtained in any ordinary way by racemizing optically active menthones. In this respect the menthones differ markedly from the piperitones. Although the latter readily suffer racemization, once an optically active piperitone has been hydrogenated by Skita's method the optical activity cannot be

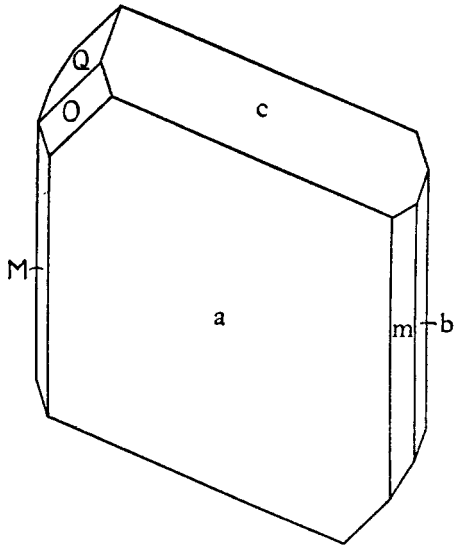


FIG. 6. *dl*-ISOMENTHONEOXIME

annulled. The exceptional value of piperitone in the menthone chemistry is largely bound up with the circumstance that it is available in the *l*-, *d*- and *dl*-forms, each of which leads directly to the corresponding forms of isomenthone and menthone.

Much interesting work remains to be carried out with stereochemically pure specimens of the active and externally compensated forms of menthone and isomenthone. Notably, the accurate determination of physical data for the various ketones should

aid materially in settling the question of their relative molecular configurations. Moreover, *d*-menthone, which has hitherto been a very rare substance, has lately been rendered accessible from *dl*-piperitone by way of *dl*-menthylamine and *d*-menthol, as described below.

Hydrogenation of menthenones

The striking effect of hydrogenating piperitone rendered it of interest to apply Skita's method to other optically active menthenones, particularly as Skita and Ritter (48) had stated that *d*-pulegone when treated in this way had yielded a "partly racemized *d*-menthone." Table 2 (32) contains a summary of the results obtained upon hydrogenating the purest available

TABLE 2

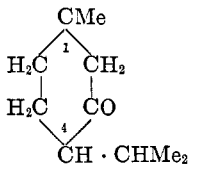
Results obtained by hydrogenation of some optically active menthenones

MENTHENONE	$[\alpha]_D^{15}$ OF MENTHENONE	$[\alpha]_D^{15}$ OF DERIVED MIXTURE OF MENTHONES	PERCENTAGE OF ISOMENTHONE
d-Pulegone	+23.6°	+33.5°	52
l-Δ^4-Menthenone-3	−78.4	+43.2	60
l-Piperitone	−53.9	+69.1	81–75
d-Piperitone	+62.5	−71.4	83–78

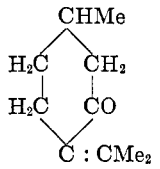
specimens of *d*-pulegone, *l*-Δ^4-menthenone-3, *l*-piperitone and *d*-piperitone. The second of these ketones was prepared from *l*-menthol through the methyl ester of *l*-menthylxanthic acid, by Tschugaev's method (49), and *d*-pulegone was isolated from French oil of pennyroyal (*Mentha pulegium*).

The results of equilibration experiments showed that the first two products consisted of mixtures of *d*-isomenthone and *l*-menthone. Hence it is clear that the spatial environment of the sole asymmetric carbon atom (1) of *d*-pulegone, as also of *l*-Δ^4-menthenone-3, is analogous to that of the corresponding asymmetric carbon atom (1) of *l*-menthone or *d*-isomenthone. This being so, the creation of the second asymmetric carbon atom (4), which occurs during the hydrogenation, leads necessarily to a mixture of *l*-menthone and *d*-isomenthone, i.e. to two substances

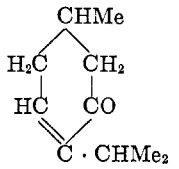
differing only in the asymmetry of carbon atom (4). In these instances, the qualitative composition of the products would not be affected by the occurrence of enolization during the hydrogenation. From the rotatory powers of the products from these two menthenones it is seen that they contain only a slight preponderance of *d*-isomenthone over *l*-menthone.



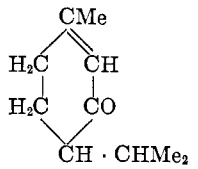
Menthone
(XXIV)



Pulegone
(XXV)



Δ^4-Menthenone-3
(XXVI)



Piperitone
(XXVII)

Similarly, the spatial environment of the sole asymmetric carbon atom (4) of *l*-piperitone is analogous to that of the corresponding asymmetric carbon atom (4) of *d*-isomenthone, which forms the main product of hydrogenation of the *Eucalyptus* ketone. The creation of the second asymmetric carbon atom (1) in the hydrogenation process should therefore lead to a mixture of *d*-isomenthone and *d*-menthone, since these two substances differ only in the asymmetry of carbon atom (1). The presence of *dl*-isomenthone in the hydrogenation product of *l*-piperitone (45) must be ascribed to the presence of *dl*-piperitone in the original ketone or to its partial racemization during the process of hydrogenation. In the latter event, simultaneous enolization of *d*-isomenthone would lead to the formation of some *l*-menthone. It is therefore likely that the hydrogenation product of *l*-piperitone contains *dl*-isomenthone, *dl*-menthone and *l*-menthone associated with the main product, *d*-isomenthone. The results of equilibration experiments (32) indicate that the contamination consists largely of *l*-menthone, produced by enolization during the hydrogenation. Assuming the product to consist wholly of *d*-isomenthone and *l*-menthone, the observed rotatory power corresponds to the presence of 81 per cent of the former substance; this proportion falls to 75 per cent if the product is considered

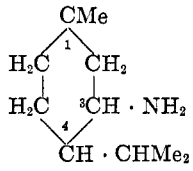
as a mixture of *d*-isomenthone with *dl*-isomenthone and *dl*-menthone. A slightly higher proportion of *l*-isomenthone was found in the hydrogenation product of *d*-piperitone, as shown in table 2.

On comparing the two types of hydrogenation, it is apparent that the stereochemical effect of asymmetric center (4) upon the additive process is much greater than that of asymmetric center (1). In practice, it was found that the hydrogenation occurred more rapidly with piperitone than with the other ketones. Of the four ketones under consideration, *d*-piperitone provides the only practical source of *d*-menthone by direct hydrogenation.

Upon treatment with alcoholic sodium ethoxide, the crude hydrogenation products of *l*-, *d*- and *dl*-piperitone yield mixtures containing a maximum proportion of about 70 per cent of *l*-, *d*- or *dl*-menthone, respectively, and this appears to be the highest proportion of menthone (as distinct from isomenthone) which piperitone can yield by a direct process. In no case has a pure isomenthone been obtained by the direct hydrogenation of a menthenone; the pure *d*-, *l*- and *dl*- forms of this ketone are at present accessible only by oxidizing the corresponding isomenthols, prepared as outlined below.

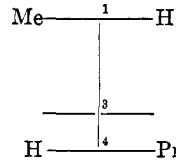
The menthylamines

The menthylamine constitution (XXVIII), since it includes three dissimilar asymmetric carbon atoms (1,3,4), demands the existence of eight optically active stereoisomers, together with four externally compensated forms. Two of these pairs of active forms will be derived from menthone (II above) and the remaining two pairs from isomenthone (III). Their nomenclature may be conveniently based upon the system devised by Aschan (50) and adopted by Pickard and Littlebury (10): the names are thus menthylamine, neomenthylamine, isomenthylamine and neoisomenthylamine. A corresponding nomenclature applies to the four pairs of optically active menthols (*vide infra*). The spatial relationships are appropriately represented by the use of projection formulas:



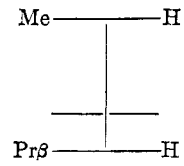
Menthylamines

(XXVIII)



Projection nucleus for menthylamines and menthols

(XXIX)

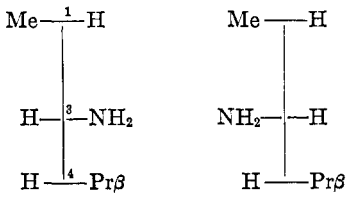


Projection nucleus for isomenthylamines and isomenthols

(XXX)

Prior to the work under review, only two of the twelve possible menthylamines had been prepared in a state of purity: these, as pointed out in the introductory section, were *l*-menthylamine, prepared by reducing *l*-menthoneoxime, and Wallach's "R-menthylamine" obtained (together with *l*-menthylamine) by heating *l*-menthone with ammonium formate (8). Although the second base is dextro-rotatory, it is not the enantiomer of *l*-menthylamine. Later, Wallach (51) showed that while *l*-menthylamine reacted with nitrous acid to yield *l*-menthol, the same reaction when applied to "R-menthylamine" furnished large quantities of a menthene having $[\alpha]_D$ + 55.44°. In the latter case the preliminary formation of a menthol was obviously followed by the elimination of water, and Wallach concluded that the groups —NH_2 (3) and —OH (4) occupy *cis*- and *trans*-configurative positions, respectively, in the molecules of "R-menthylamine" and *l*-menthylamine. From its mode of formation and its ready conversion to *l*-menthol, the latter substance is obviously derived from *l*-menthone; but whether "R-menthylamine" was to be regarded as a menthylamine or an isomenthylamine remained unsettled.

A fuller study of the reactions between these two bases and nitrous acid (32) (52) has shown that *l*-menthylamine yields *l*-menthol associated with a smaller amount of partly racemized *d*-Δ^3-menthene, and that although "R-menthylamine" furnishes the latter substance as the main product, a small proportion of *l*-menthol is also formed. It follows that these two bases are menthone derivatives, to which, accepting Wallach's conception, may be assigned the following relative molecular configurations:



l (or *d*)-Menthylamine (XXXI)

d (or *l*)-Neomenthylamine (XXXII)

"R-menthylamine" thus becomes *d*-neomenthylamine, and it may be prepared (through the crystalline formyl derivative) by heating *l*-menthone, *d*-isomenthone, or any mixture of these two ketones, with ammonium formate. Similarly, *l*-neomenthylamine (32) and *dl*-neomenthylamine (53) have been made from the hydrogenation products of *d*-piperitone and *dl*-piperitone, respectively. *l*-Neomenthylamine is more easily prepared by the optical resolution of *dl*-neomenthylamine with *d*-tartaric acid (54).

The neomenthylamines form hydrochlorides which melt below 200° and dissolve in light petroleum, and differ thereby from the other three families of menthylamines; in addition, they are distinguished by the beauty of their crystalline derivatives. The crystals of *dl*-neomenthylamine hydrochloride (figure 7) are monoclinic and show no resemblance to those of the *d*-component (figure 8), which are also monoclinic; the externally compensated substance is therefore truly racemic. Formyl-*dl*-neomenthylamine (figure 9) and formyl-*d*-neomenthylamine (figure 10) offer an exceptional crystallographic relationship: the crystals are orthorhombic and closely related; but while those of the *d*-component are holohedral, solutions of the *dl*-compound deposit right- and left-handed hemihedral crystals which display a faint optical activity in alcohol. In this interesting case the crystallographic differentiation of *d*- and *l*-forms appears to be facilitated by the presence in the solution of the opposite kind of molecule (55).

The oxime prepared from *l*-menthone in a faintly acid medium at the ordinary temperature is homogeneous, and when reduced it yields practically pure *l*-menthylamine (32). The best experi-

mental conditions for the production of pure *l*-menthylamine having been established under polarimetric control, similar processes were applied in preparing pure *dl*-menthylamine: the principle of preliminary exploration with the aid of the polarimeter, which is here manifest, was adopted repeatedly in the

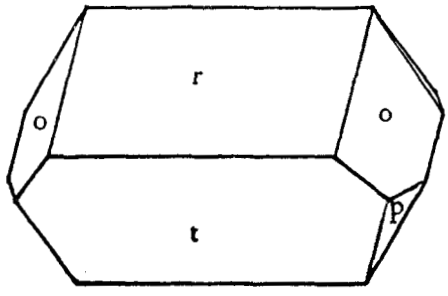


FIG. 7. *dl*-NEOMENTHYLAMINE HYDROCHLORIDE

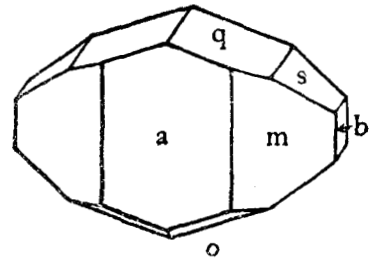


FIG. 8. *d*-NEOMENTHYLAMINE HYDROCHLORIDE

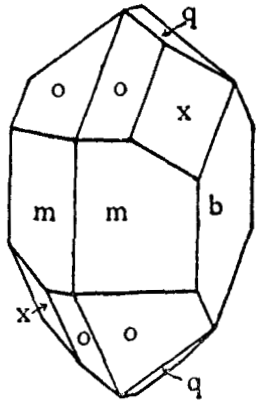


FIG. 9. FORMYL-*dl*-NEOMENTHYLAMINE

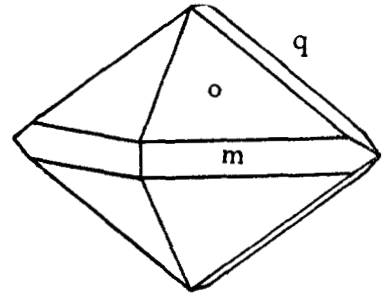


FIG. 10. FORMYL-*d*-NEOMENTHYLAMINE

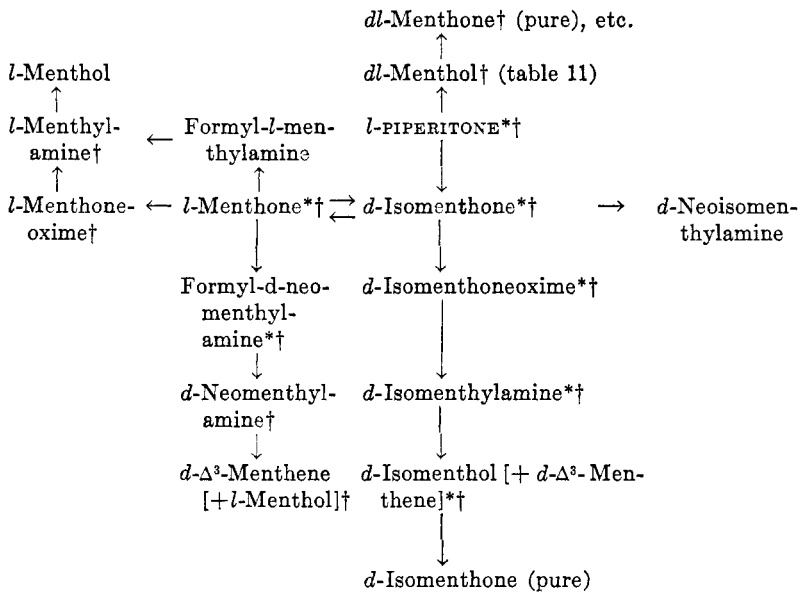
course of these investigations on menthones, menthols and menthylamines. *dl*-Menthylamine (table 3) is readily accessible from *dl*-menthol, through *dl*-menthone and *dl*-menthoneoxime; it reacts with nitrous acid to yield *dl*-menthol and some *dl*-Δ^3-menthene (53). It is apparent that *d*-menthylamine might be prepared from *d*-piperitone by way of *d*-menthone, but the best

practical approach to this valuable optically active base lies through *dl*-menthylamine: it has recently been shown that when *dl*-menthylamine is crystallized with *d*-tartaric acid the less soluble of the two diastereoisomeric acid salts is of the form *d*A*d*B. Pure *d*-menthylamine has therefore been prepared in this way (54).

The hydrogenation product of *l*-piperitone, consisting mainly of *d*-isomenthone, furnished a viscid liquid oxime, from which

TABLE 3

Preparation of certain stereoisomeric menthylamines, etc.



upon reduction with sodium and alcohol a new dextro-rotatory menthylamine was readily isolated (32). From the method of preparation, this base was regarded as *d*-isomenthylamine; its configurational resemblance to *l*-menthylamine was confirmed by the observation (46) that in reaction with nitrous acid it yielded *d*-isomenthol, together with partly racemized *d*-Δ^3-menthene, in the approximate ratio 2:1. By similar processes, *l*-

and *dl*-isomenthylamine were prepared from *d*- and *dl*-piperitone, respectively (32) (53).

The chief processes concerned in the preparation of the stereoisomeric menthylamines are summarized in table 3. The operations marked with an asterisk have been accomplished with both enantiomorphous forms of the substances concerned, and those in which the externally compensated substances also have been used are marked with a dagger.

In searching for the remaining group of neoisomenthylamines, it appeared that since *l*-menthone and *d*-isomenthone undergo

TABLE 4

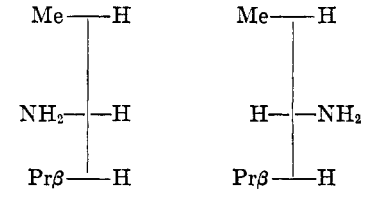
Important derivatives of four menthylamines

DERIVATIVE		MENTHYLAMINES			
		l-	*d*-Neo-	*d*-Iso-	*d*-Neoiso-
Hydrochloride	m. p.	>280°	189°	>250°	>250°
	$[\alpha]_D$	−36.6°	+21.5°	+23.6°	+20.9°
Formyl	m. p.	102–103	117–118	45–46	Liquid
	$[\alpha]_D$	−83.8	+53.8	+31.3	−3.9
Acetyl	m. p.	145	169–170	77–79	99–100
	$[\alpha]_D$	−81.7	+53.0	+30.7	−2.6
Benzoyl	m. p.	157	121.5	97–98	151
	$[\alpha]_D$	−62.8	+22.7	+18.3	−10.4
Benzylidene	m. p.	69–70	45–46	67–68	68–69
	$[\alpha]_D$	−132.5	+61.7	+90.7	−34.2
Salicylidene	m. p.	57–58	99–100	122	99–100
	$[\alpha]_D$	−119.2	+30.0	+77.6	−17.9

"inversion" when heated with ammonium formate, the product should contain the iso-analogues of *l*-menthylamine and *d*-neomenthylamine. A study of the derivatives of *l*-, *d*-neo- and *d*-iso-menthylamine eventually led to an investigation of the mixture of salicylidene derivatives furnished by this product. *d*-Neoisomenthylamine, which was isolated as an outcome of this work (52), is a feebly dextro-rotatory base; but its derivatives, apart from the salts, are mainly levo-rotatory. The *l*-form of this base could be prepared from *d*-piperitone, but the isolation of the *dl*-base has so far proved impracticable owing to the lack of polarimetric guidance in this case (38).

Table 4 summarizes some of the more important derivatives of the four optically active bases under discussion, and indicates their striking similarity in certain respects. The rotatory powers were observed in water for the hydrochlorides and in chloroform for the other derivatives.

Configurationally, *d*-neoisomenthylamine is closely analogous to *d*-neomenthylamine, since it yields partly racemized *d*-Δ^3-menthene, and apparently a little *d*-isomenthol, when brought into reaction with nitrous acid. The following relative molecular configurations have accordingly been assigned to the isomenthylamines (52):



d (or *l*)-Isomenthylamine (XXXIII)

d (or *l*)-Neoisomenthylamine (XXXIV)

The circumstance that all four bases yield partly racemized *d*-Δ^3-menthene, in varying amounts, when treated with nitrous acid, affords a proof of the similar spatial disposition throughout the series of the groups about carbon atom (1), which is the sole asymmetric center in Δ^3-menthene. It will be noted that Δ^3-menthene appears to be always formed, in lieu of neomenthol or neoisomenthol, in these reactions. In the arguments which have been advanced, "the configurations which have been assigned to these substances are based largely upon the assumption that the stereoisomeride which passes most readily into a particular menthol when treated with nitrous acid is configurationally similar to that menthol. . . . . Thus, *l*-menthylamine and *d*-isomenthylamine yield the largest proportions of *l*-menthol and *d*-isomenthol, respectively, when treated with this reagent. Accepting these processes as the normal ones, the simultaneous formation of partly racemized *d*-Δ^3-menthene takes place through a Walden inversion, leading to the intermediate production of

d-neomenthol and an optically active neoisomenthol, respectively; these alcohols, since they possess a hydrogen atom (4) in the *cis*-configurative position to the hydroxyl group (3), then undergo dehydration. The formation of partly racemized *d*-Δ^3-menthene as the main product in the remaining instances of *d*-neomenthylamine and *d*-neoisomenthylamine is accordingly regarded as the normal procedure" (52). Recent investigations (56) have shown that *d*-neomenthylamine reacts much more rapidly than *l*-menthylamine with acetic anhydride, propionic anhydride, benzaldehyde and anisaldehyde: additional support is thus lent to the relative configurations which have been deduced from the reactions with nitrous acid.

All the menthylamines are liquids with a characteristic basic odor. Their physical constants, which have lately been determined (56), are closely similar. They absorb carbon dioxide readily, forming solid carbonates. Three out of the four hydrochlorides included in table 4 display almost identical rotatory powers in aqueous solution. In general, the properties of the stereoisomeric menthylamines are so alike as to prevent the separation of mixtures of these bases formed in the reduction of piperitoneoxime, etc. (53).

The optical resolution of externally compensated menthylamines presents peculiar difficulties, which appear to be associated with the abnormal molecular rotatory powers exhibited in dilute aqueous solution by the salts of the optically active bases with strong optically active acids (54). Further light upon this interesting problem may be anticipated from a study of *N*-alkylated menthylamines and quaternary menthylammonium compounds (38).

A comparison of the ten salicylidenementhylamines which are now known has shown that the derivatives of the menthylamines and isomenthylamines are phototropic, while those of the neo- and neoiso-menthylamines are not (52). The reversible color-change is shown most distinctly by salicylidene-*l*- and -*d*-menthylamine, which are deep orange in bright light and pale yellow in subdued light. No other example of a phototropic distinction between stereoisomers appears to have been observed (57).

From the data summarized in table 4, it is seen that the derivatives of menthone (*trans*) possess greater rotatory powers than those of isomenthone (*cis*). The optical relationships are more

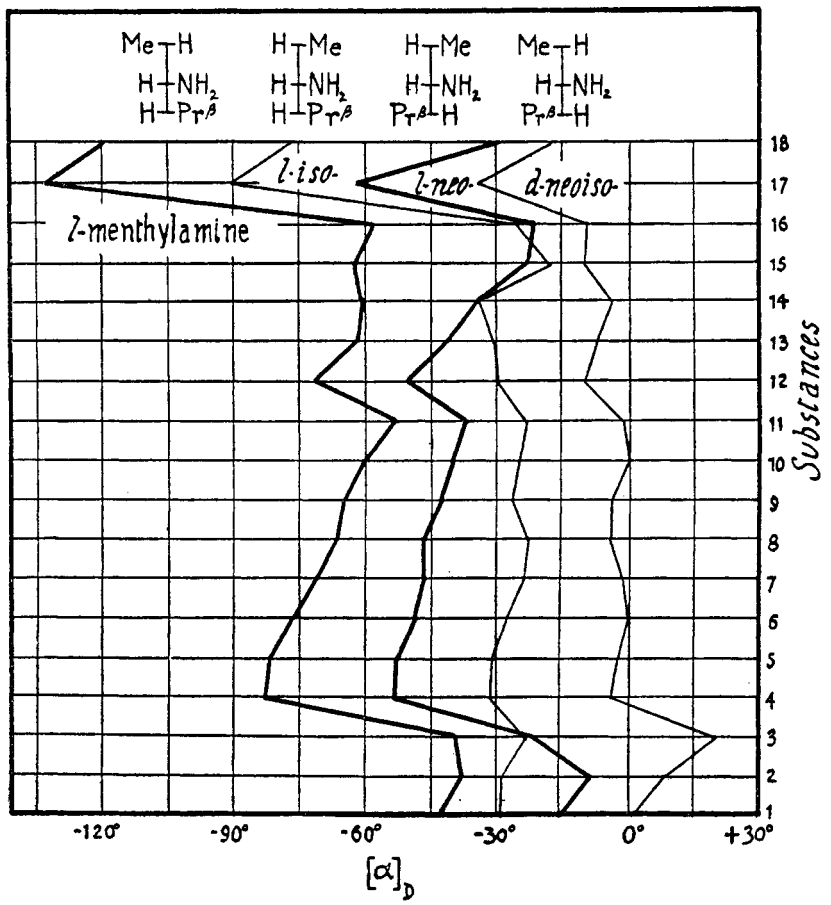


FIG. 11. GRAPHICAL REPRESENTATION OF THE SPECIFIC ROTATORY POWERS OF THE FOUR SERIES OF STEREOISOMERIC MENTHYLAMINES AND CERTAIN OF THEIR DERIVATIVES (SEE TABLE 5)

fully evident from the graphical representation of figure 11, in which observations of specific rotatory power (56) are summarized for each base, without solvent (No. 1) and dissolved in chloro-

form (No. 2); for the respective hydrochlorides, dissolved in water (No. 3); and for 15 other derivatives of each base (enumerated in table 5), dissolved in chloroform (c = 1.0, approximately). In order to simplify the representation, the values of $[\alpha]_D$ observed for *d*-neo- and *d*-iso-menthylamine have been changed from positive to negative, so that the values in figure 11 refer to *l*-, *l*-neo-, *l*-iso- and *d*-neoiso-menthylamine, respectively. The following are among the more important general conclusions to be drawn from the diagram:

(i) A generic relationship is shown by the four curves.

(ii) The two bases derived from menthone (indicated by thicker lines) display a marked family likeness, and so do the two bases derived from isomenthone.

(iii) *d*-Neoisomenthylamine, in spite of the dextro-rotation shown by the free base and its hydrochloride, belongs to the *l*-series, and the dextro-rotation in question is in keeping with the general trend of the diagram.

(iv) The bases of the *l*-series are characterized by the presence of the configurational unit, $H|NH_2$.

(v) Apart from the anomaly created by the intrusion of *d*-neoisomenthylamine and its hydrochloride into the dextro-rotatory zone, reversal of the asymmetry of carbon atom (3), carrying the characteristic amino group, changes the sign of the optical rotation; on the other hand, reversal of the asymmetry of carbon atom (1) or (4) leaves the sense of the rotation unaltered.

(vi) There is an increasing change in the magnitude of the optical rotation upon passing from *l*-menthylamine in succession to *l*-neo-, *l*-iso- and *d*-neoiso-menthylamine: that is to say, in this sequence an increasing optical disturbance is created by reversing the asymmetry of carbon atoms (1) and (4) together; carbon atom (1) alone; carbon atom (4) alone; and carbon atom (3) alone.

(vii) The curve of *d*-neomenthylamine forms a somewhat distorted reflection of the curve of *l*-menthylamine, and the distortion increases upon passing in succession to *d*-iso- and *l*-neoiso-menthylamine.

(viii) The lowest rotatory powers are given by iso- and neoiso-

menthylamine and their derivatives: the corresponding molecular configurations display, respectively, the greatest symmetry of distribution of like (H) and similar (Me and Prβ) groups.

An inspection of the optical rotatory powers of the acetyl derivatives of *l*-, *d*-neo-, *d*-iso- and *d*-neoiso-menthylamine (table 4) shows that the sum of any two of the values is approximately equal in magnitude and opposite in sign to the sum of the other two. The additional observations summarized in table 5 indicate

TABLE 5

Values of $[\alpha]_D$ *for menthylamines and derivatives (in chloroform, unless otherwise indicated)*

REFERENCE NUMBER AND NAME OF DERIVATIVE	*l*-	*d*-Neo-	*d*-Iso-	*d*-Neoiso-	*l*- + *d*-Neo-	*d*-Iso- + *d*-Neoiso-
1. Base (no solvent).....	−43.2°	+15.1°	+28.8°	+0.28°	−28.1°	+29.1°
2. Base.....	−38.3	+8.7	+28.1	+8.7	−29.6	+36.8
3. Hydrochloride (water).	−36.6	+21.5	+23.6	+20.9	−15.1	+44.5
4. Formyl.....	−83.8	+53.8	+31.3	−3.9	−30.0	+27.4
5. Acetyl.....	−81.7	+53.0	+30.7	−2.6	−28.7	+28.1
6. Propionyl.....	−76.6	+48.3	+27.7	0.0	−28.3	+27.7
7. Butyryl.....	−70.9	+46.8	+23.9	−1.0	−24.1	+22.9
8. Isobutyryl.....	−66.5	+47.5	+22.8	−3.7	−19.0	+19.1
9. Valeryl.....	−64.7	+42.8	+27.0	−4.1	−21.9	+22.9
10. Caproyl.....	−60.0	+40.0	+24.9	0.0	−20.0	+24.9
11. Capryl.....	−53.2	+36.7	+23.3	−1.2	−16.5	+22.1
12. Chloroacetyl.....	−71.9	+50.7	+30.0	−9.8	−21.2	+20.2
13. Bromoacetyl.....	−61.6	+40.9	+30.3	−7.5	−20.7	+22.8
14. Phenylacetyl.....	−60.4	+34.5	+33.3	−3.4	−25.9	+29.9
15. Benzoyl.....	−62.8	+22.7	+18.3	−10.4	−40.1	+7.9
16. Anisoyl.....	−57.7	+21.1	+25.3	−9.5	−36.6	+14.8
17. Benzylidene.....	−132.5	+61.7	+90.7	−34.2	−70.8	+56.5
18. Salicylidene.....	−119.2	+30.0	+77.6	−17.9	−89.2	+59.7

that this curious relationship holds generally for derivatives of the type $R \cdot CH_2 \cdot CO \cdot NH \cdot R'$, and for the free bases; it obtains, moreover, for $[\alpha]_{5461}$, as well as for $[\alpha]_D$. When R is phenyl and the adjacent methylene group is simultaneously eliminated, the relationship fails; also, it is not evident in derivatives of the type $R \cdot CH{:}NR'$. Thus, with derivatives of the type $R \cdot CH_2 \cdot CO \cdot NHR'$, if three of the values of $[\alpha]_D$ are known, the fourth value can be calculated empirically with a close approach to

accuracy. The result suggests the operation of a principle of optical superposition among these stereoisomeric series of derivatives, and this matter may now be discussed.

Selecting a suitable derivative, e.g. the acetyl derivative, and superposing the four configurations in question (XXXI, XXXII, XXXIII and XXXIV), it is seen from table 5 that the algebraic sum of the four values of $[\alpha]_D$ approximates to zero. In the process of superposition, the optical effects of the asymmetric groups (3) and (4) would appear to undergo a mutual neutralization, owing to the opposed spatial dispositions of these groups in the various molecules. The possibility of such an annulment is not immediately obvious, however, for the asymmetric group (1), which has the same spatial disposition (i.e. Me|H) in all four configurations. Unless the approach to a zero value is purely fortuitous, which appears improbable, a simple explanation may be sought in the assumption that the asymmetric group (1) exerts a numerically constant rotational effect in all four configurations, the positive or negative sense of which is determined by the nature of the attached complex group (*vide infra*). If, in two of the four instances, the effect is negative, and in the other two positive, the origin of the zero value is explained.

By taking the mean optical rotation of the *l*- and *d*-iso-acetyl derivatives, the rotational effect of the asymmetric group (1) is evaluated at 25.5 units, and the mean optical rotation of the *l*-neo- and *l*-neoiso-acetyl derivatives gives the almost identical result, 25.2 units; the average value is thus 25.4 units. Similarly, the average value for the combined rotational effect of the remaining asymmetric centres, (3) and (4), is 56.2 units for *cis*-H and 27.8 units for *trans*-H. By adding −25.4 units to −56.2 and +56.2 units, respectively, the values of $[\alpha]_D$ for the *l*- and *d*-iso-acetyl derivatives are regained; correspondingly, the values for the *l*-neo- and *l*-neoiso-acetyl derivatives are regained by adding −25.4 units to −27.8 and +27.8 units, respectively.

Proceeding now to a generalization, it seems that in each of the eight stereoisomeric acetylmenthylamines the asymmetric group (1) has a constant value of 25.4 units of specific rotational power (in chloroform solution, for sodium light). When the configura-

tion Me|H is attached to H|NHAc or to NHAc|H it exerts a
H|Prβ Prβ|H
levo-rotatory effect; but when the same configuration is attached to H|NHAc or to NHAc|H its effect, although equal in magni-
Prβ|H H|Prβ
tude, is dextro-rotatory. Further, the complex asymmetric groups H|NHAc and H|NHAc have respective constant values of
H|Prβ Prβ|H
−56.2 and −27.8 units of specific rotational power. From the three constants, 25.4, 56.2 and 27.8, it is possible to calculate

TABLE 6

Specific rotational values ($[\alpha]_D$ in chloroform, unless otherwise indicated) for asymmetric groups in the menthylamines and some of their derivatives

REFERENCE NUMBER AND NAME OF DERIVATIVE	Me|H	H|NHR / H|Prβ	H|NHR / Prβ|H	H|NHR	H|Prβ
1. Base (no solvent)	±7.5	−36.0	−7.4	−21.7	−14.3
4. Formyl	25.6	−57.6	−28.9	−43.3	−14.4
5. Acetyl	25.4	−56.2	−27.8	−42.0	−14.2
6. Propionyl	24.3	−52.2	−24.2	−38.2	−14.0
7. Butyryl	23.2	−47.4	−23.9	−35.7	−11.8
8. Isobutyryl	21.9	−44.7	−25.6	−35.2	−9.6
9. Valeryl	19.1	−45.9	−23.5	−34.7	−11.2
10. Caproyl	18.8	−42.5	−20.0	−31.3	−11.3
11. Capryl	16.4	−38.3	−19.0	−28.7	−9.7
12. Chloroacetyl	20.7	−51.0	−30.3	−40.7	−10.4
13. Bromoacetyl	16.2	−46.0	−24.2	−35.1	−10.9
14. Phenylacetyl	14.6	−46.9	−19.0	−33.0	−14.0

the value of $[\alpha]_D$ for any acetylmenthylamine whose relative molecular configuration is known. A similar statement applies to any menthylamine derivative of the type $R \cdot CH_2 \cdot CO \cdot NHR'$ which has been examined up to the present (see table 6). As an illustrative example, the configuration of acetyl-*d*-menthylamine may be selected: H|Me The complex configurational unit
NHAc|H .
Prβ|H
NHAc|H has the value +56.2; Me|H attached to it has the value
Prβ|H
−25.4, so that obviously the value for H|Me is +25.4. Thus,

$[\alpha]_D$ for acetyl-*d*-menthylamine is $56.2 + 25.4 = +81.6$. Table 6 (first three columns) summarizes these three constants for the free bases and for various derivatives of the type $R \cdot CH_2 \cdot CO \cdot NHR'$.

It appears, further, that the magnitude of the optical effect of any one of the three asymmetric groups is retained throughout the various stereoisomeric forms, independently of the other two asymmetric groups which are present: provided always that the configuration Me|H is made negative when the group (1) is attached to the *cis*-H configuration and positive when it is attached to the *trans*-H configuration of the combined groups (3)

TABLE 7

Values of $[\alpha]_D$ *for menthylamines and menthols*

	l-	*d*-Neo-	*d*-Iso-	*d*-Neoiso-
Menthylamine (no solvent)	−43.2°	+15.1°	+28.8°	+0.3°
Menthol (no solvent)	−49.9	+19.6	—	
(in alcohol)	−49.1	—	+27.0	?

TABLE 8

Specific rotational values for asymmetric groups in the menthols ($[\alpha]_D$ *in alcohol*)

Me|H	H|OH	H|Prβ
±11.1	−23.3	−14.8
Corresponding values for the menthylamines (table 6; no solvent)		
Me|H	H|NH_2	H|Prβ
±7.5	−21.7	−14.3

and (4). That is to say, the perturbation caused by rotating one of the groups (3) or (4) through 180° is compensated for by changing the sign of the rotational value of Me | H. The following constant mean specific rotational values may then be calculated for the individual asymmetric groups (3) and (4) of the acetylmenthylamines (in chloroform): H | NHAc −42.0; H | Prβ −14.2. Thus, for example, the calculated value of $[\alpha]_D$ for acetyl-*d*-menthylamine may now be obtained in the following simplified manner, as the algebraic sum of the three individual asymmetric groups: $+25.4 + 42.0 + 14.2 = +81.6$. Table 6

(last two columns) contains a list of rotational values for the individual groups (3) and (4).

Further studies of this kind may be expected to throw a good deal of new light upon the so-called principle of optical superposition. The main obstacle to such work lies in the great difficulty of gaining access to complete stereoisomeric series of suitable substances. It will be of particular interest to conduct similar investigations with the menthols and their derivatives, when the complete series eventually becomes accessible. Meanwhile, a close parallelism is discernible between the optical rotations of the menthylamines and the corresponding menthols, so far as the latter are known (see table 10). The comparison shown in table 7 is instructive. Unfortunately, the specific rotatory powers of the neomenthols appear not to have been observed in alcohol (10); but from the data available for *l*-menthol [(5), p. 469], the value may be accepted provisionally as being practically identical with

TABLE 9

Optical rotational influence exerted by the three asymmetric groups

	l-	*d*-Neo-	*d*-Iso-	*d*-Neoiso-
Group (1)	−	+	−	+
Group (3)	−	+	+	−
Group (4)	−	−	+	+

that of the liquid substance. Applying then to the specific rotatory powers of the three known series of menthols processes similar to those developed above for the analogous menthylamines, the specific rotational values shown in table 8 are calculable for the three fundamental asymmetric groups. The prediction may now be made that the value of $[\alpha]_D$ for the unknown *d*-neoisomenthol (configuration XXXVIII below) will be $+11.1 - 23.3 + 14.8 = +2.6°$.

From a consideration of these relationships, it appears that upon turning group (1) through an angle of 180°, the consequent change in optical rotation is expressed by reversing the sign of the rotational value of this group only. Also upon turning groups (3) and (4) together through 180°, the change is expressed by reversing the signs of the rotational values of these groups

only. Briefly, in each of these two cases the molecule behaves as a system of two asymmetric centers; that is, groups (3) and (4) act as a composite center when their mutual configurational relationship undergoes no change.

But when one only of the groups (3) and (4) is turned through 180°, two adjustments have to be made, because the asymmetry of the turned group is reversed with respect to both of the other asymmetric groups. Thus, the rotational value of group (1), as well as that of the turned group, has to be reversed, since the molecule behaves in this instance as a system of three distinct asymmetric groups.

These conclusions are closely bound up with the circumstance that there is no alteration in the immediate environment of group (1), or in that of the composite group (3) and (4), when either of these two configurational units is turned through 180°.

TABLE 10

Physical characteristics of the known menthols

	MENTHOLS			NEOMENTHOLS			ISOMENTHOLS		
	d-	*l-*	*dl-*	*d-*	*l-*	*dl-*	*d-*	*l-*	*dl-*
m. p.	43°	43°	34°	oil	oil	51°	81.5°	80.5°	53.5°
$[\alpha]_D$	+49°	−49°		+19.6°	−19.6°		+27.0°	−24.1°	
	(in alcohol)			(no solvent)			(in alcohol)		

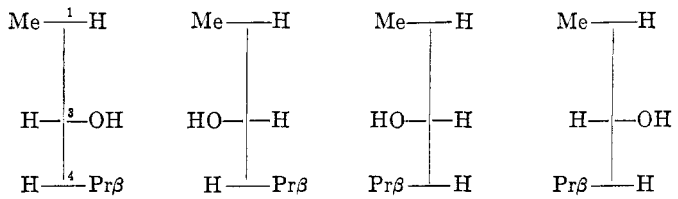
The sense of the optical rotational influence exerted by each of the three asymmetric groups in the molecular configurations of the substances which have been discussed may be summarized as in table 9.

The menthols

As already indicated, the three stereoisomeric forms of ordinary menthol were first made available through the work of Pickard and Littlebury (10), and it has been shown in the preceding section that *d-*, *l-* and *dl*-isomenthol may be prepared from *l-*, *d-* and *dl*-piperitone, respectively, through the corresponding isomenthylamines (table 3). The physical characteristics of the known menthols are summarized in table 10.

From their apparent relationship to the menthylamines, out-

lined above, the menthols have been provisionally assigned the following relative molecular configurations (58):



l (or *d*)-Menthol (XXXV) | *d* (or *l*)-Neomenthol (XXXVI) | *d* (or *l*)-Isomenthol (XXXVII) | *d* (or *l*)-Neoisomenthols (XXXVIII)

Vavon and Couderc (59) consider —OH(3) to be in the *trans*-position to —H(4) in neomenthol, since this alcohol esterifies more slowly than menthol. Zeitschel and Schmidt (6), however, found that neomenthol is dehydrated much more readily than menthol, forming Δ^3-menthene. The balance of the evidence thus appears to favor the configurations given above. The externally compensated forms of menthols and isomenthols have lower melting points than their active components, but in the neo-series this relationship is reversed; possibly, therefore, *dl*-neoisomenthol will prove to possess a higher melting point than its active components. The melting-point curve of mixtures of *d*- and *l*-isomenthol is typical of a conglomerate (46). Various unsubstantiated references to racemic menthols and menthones have been made by Bedos (60), Fleury and Seel (61) and others, but up to the present the neoisomenthols appear not to have been prepared.

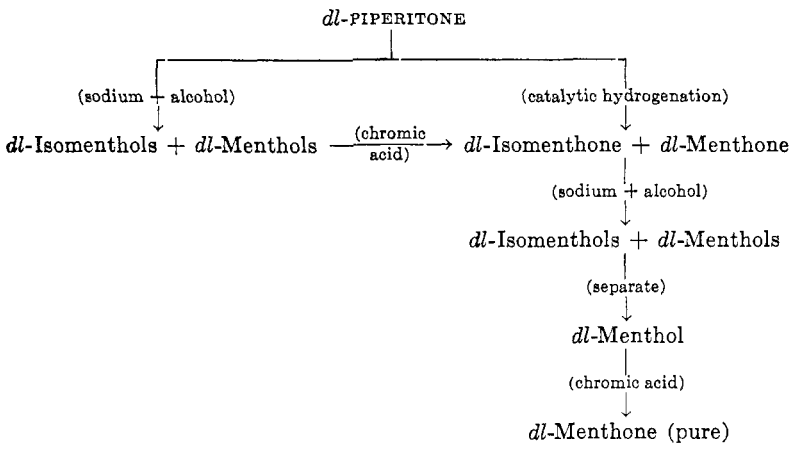
The main approach yet discovered from optically active piperitone to optically active menthol is by the route: *l* (or *d*)-piperitone → *l* (or *d*)-menthone → *l* (or *d*)-menthoneoxime → *l* (or *d*)-menthylamine → *l* (or *d*)-menthol (table 3); alternatively, the menthone may be reduced with sodium and alcohol. The practical value of these processes is seriously impaired by the circumstance that *l* (or *d*)-menthone prepared in this way is associated with *d* (or *l*)-isomenthone. *dl*-Menthol, however, may be prepared from piperitone by direct reduction (*vide infra*); and

since *dl*-menthol is also available from other primary sources, such as *m*-cresol and thymol, the most satisfactory method at present apparent for the production of *d*-menthol departs from *dl*-menthol and proceeds by way of *dl*-menthone, *dl*-menthone-oxime, *dl*-menthylamine and *d*-menthylamine (*vide supra*). The preparation of *d*-menthol in quantity by the direct optical resolution of *dl*-menthyl hydrogen phthalates (10) is impracticable.[2]

Piperitone may be reduced electrolytically to isomenthone (62), and no doubt the reduction might be intensified to yield menthols. When active or externally compensated piperitone is reduced with

TABLE 11

The conversion of dl-piperitone into dl-menthone



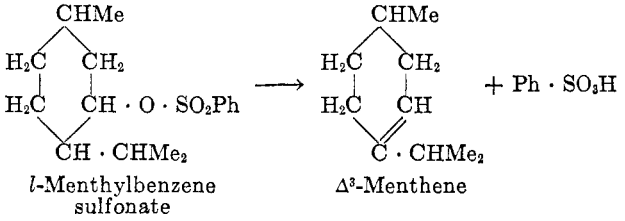
sodium and alcohol it yields a mixture of inactive menthols consisting chiefly of isomenthols (47), but containing a little *dl*-menthol (46). The yield of *dl*-menthol may be improved by oxidizing the product and reducing the equilibrated mixture of *dl*-menthone and *dl*-isomenthone; alternatively, the last-named mixture may be prepared by the catalytic hydrogenation and electrolytic reduction of *dl*-piperitone. By separating and oxidizing the crystalline *dl*-menthol, it is thus possible to pass from *dl*-

[2] A novel method for the preparation of *d*-menthol from *dl*-menthol, in useful quantities, has recently been devised in the S. Andrews laboratories (38).

piperitone to pure *dl*-menthone. The main operations are summarized in table 11.

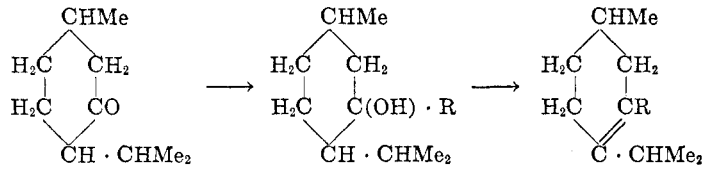
Menthenes, menthadienes and menthenols

Since *d*-Δ^3-menthene is formed by the action of nitrous acid on *l*-, *d*-neo-, *d*-iso- or *d*-neoiso-menthylamine, the enantiomers of these bases would yield *l*-Δ^3-menthene. In all these instances the hydrocarbon is partly racemized, e.g. the product from *d*-neomenthylamine (52), having $[\alpha]_D$ + 58.6° (in ether), contains almost 80 per cent of *d*-Δ^3-menthene, assuming that the value +106.6° of a specimen prepared by Tschugaev's xanthic ester method (32) is characteristic of the optically pure substance. Partly racemized Δ^3-menthenes are produced also by the action of thionyl chloride, phosphorus chlorides and other dehydrating agents upon menthols (6) (63); thus, *l*-menthol when treated with phosphorus trichloride yielded *d*-Δ^3-menthene with $[\alpha]_D$ +22.3° (64). Wallach prepared a specimen having $[\alpha]_D$ +89.3° by distilling *l*-menthyltrimethylammonium hydroxide (51); more recently, Patterson and McAlpine (65) have shown that feebly dextro-rotatory Δ^3-menthene is produced by distilling *l*-menthylbenzene sulfonate under diminished pressure:



l-Menthylbenzene sulfonate (XXXIX) — Δ^3-Menthene (XL)

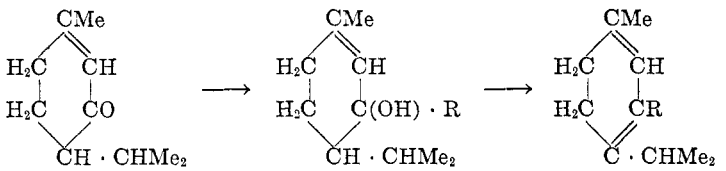
The action upon *l*-menthone of magnesium methyl iodide has been examined by Wanin (66) and also by Zelinsky (67); and Murat (68) applied magnesium phenyl bromide to the same ketone. Recent work in this field (43) has shown that both *l*-menthone and *d*-isomenthone react with magnesium methyl, ethyl and phenyl halides to form 3-substituted menthan-3-ols; these tertiary alcohols, when heated with anhydrous oxalic acid, undergo dehydration to produce 3-substituted Δ^3- menthenes:



Menthones (XLI) → 3-Homologues of menthanol-3 (XLII) → 3-Homologues of Δ^3-menthene (XLIII)

From the data summarized in table 12, it is seen that the two ketones give rise to distinct products; these, however, cannot be regarded as stereochemically homogeneous. The alcohol in each case is probably a mixture of four of the eight possible optically active modifications of constitution (XLII), and the hydrocarbons (especially those from *d*-isomenthone) appear to be partly racemized homologous menthenes (XLIII).

Piperitone, in reaction with Grignard reagents, was found to yield 3-alkyl-1,3-terpinenes directly, the intervening menthenols not being isolable. This result points to the interesting conclusion that a ready elimination of water occurs from these homologues of piperitol (XLV), owing to the activation of the tertiary hydroxyl group by the adjacent ethylene linking:



Piperitone (XLIV) → Hypothetical intermediate menthenols (XLV) → 3-Homologues of 1, 3-terpinene (XLVI)

In no case was any action observed to occur between magnesium isopropyl iodide and piperitone or menthones, possibly owing to steric hindrance.

Hydrogenation of the above unsaturated hydrocarbons would lead to 3-substituted menthanes. In addition, evidence is forthcoming (38) which indicates that isomeric series of substituted menthanols, menthenes and menthadienes may be rendered acces-

sible by applying Grignard reagents to tetrahydrocarvone, dihydrocarvone, carvotanacetone, pulegone, etc. Moreover, from carvone it may prove possible to pass to 2-substituted homologues of *p*-cymene, by isomerizing unsaturated hydrocarbons formed by Grignardizing the ketone.

BIOGENETIC RELATIONSHIPS

Close structural relationships are often observed to exist between the individual components of a particular essential oil; moreover, striking parallels may be discerned in many instances between groups of substances occurring in two or more oils from

TABLE 12

Menthanols and menthenes derived from l-menthone and d-isomenthone

KETONE	SUBSTITUENT	$[\alpha]_D$ OF SUBSTITUTED MENTHANOL (1-DCM. TUBE)	$[\alpha]_D$ OF SUBSTITUTED MENTHENE
l-Menthone, $[\alpha]_D$ −25.7°	Me	−6.5°	+62.8°
	Et	+1.5	+39.2
	n-Pr	−0.7	+35.9
	Ph	−22.9	+43.5
d-Isomenthone (from *l*-piperitone) $[\alpha]_D$ +69.9°	Me	+27.0	+17.9
	Et	+22.0	+6.8
	Ph	+0.4	+16.3

related species. The consideration of analogies of these two general types leads invariably to the idea of a common mechanism of formation, i.e. to the derivation in the plant of related substances from common chemical ancestors. Thus, Kremers (69), in 1922, suggested the tentative scheme shown in table 13 to account for the biogenesis[3] of the two distinctive but closely related groups of substances found in the oils of American black mint (*Mentha piperita vulgaris*) and spearmint (*Mentha spicata*).

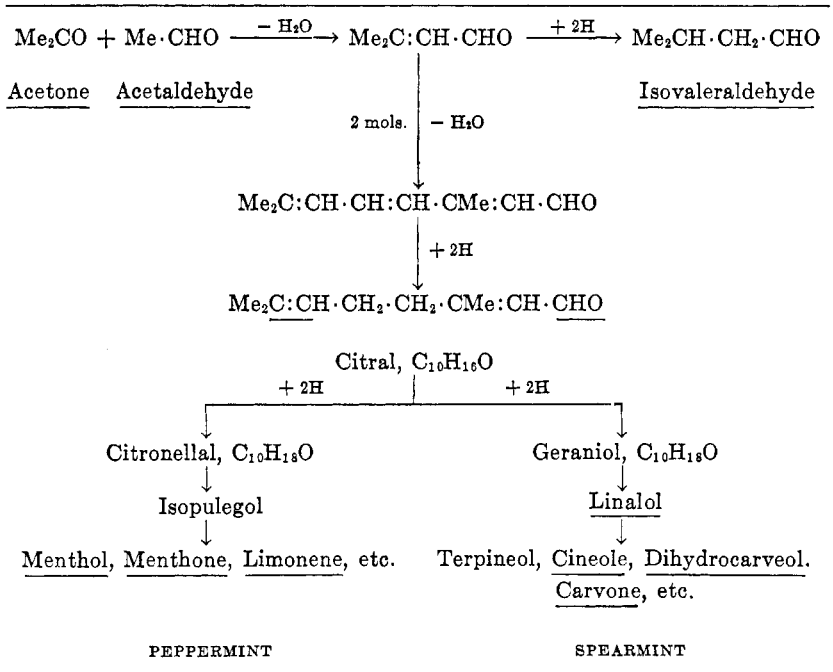
The immediate common ancestor of the two series of substances shown in this scheme is citral. According to Kremers, the biochemical conditions which in spearmint bring about the reduction of the aldehyde group are modified in peppermint so as to cause the reduction of an ethylene linkage. Thus (i) the carvone group

[3] That is, the chemical origin *in vivo*, or biological synthesis.

of substances is formed in spearmint and (ii) the menthone group in peppermint. The differential reduction of citral may be accomplished in the laboratory by using (i) sodium amalgam and acetic acid, and (ii) hydrogen in the presence of colloidal palladium; but it is interesting to reflect that in the cross-breeding of closely related species of plants such biochemical divergencies may possibly be due to the operation of Mendelian factors.

TABLE 13

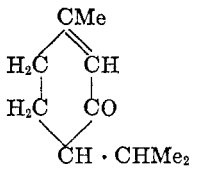
The biogenesis of the two groups of substances found in the oils of American black mint and spearmint



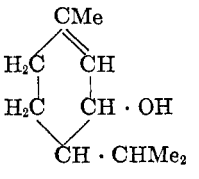
The names of substances actually found in the oils are underlined, as are also the two reducible groups in the citral molecule.

From the fact that most of the components of essential oils contain molecular systems of five, ten or fifteen carbon atoms, Astengo (70) regards isovaleraldehyde as their common ancestor and suggests a sequence of the following kind: isovaleraldehyde → isocitronellal → rhodinal, citronellal, geraniol → rhodinol, citronellol, linalol, menthone, isopulegol, citral.

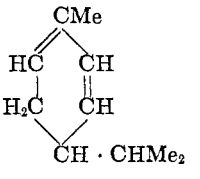
Some of the most arresting biogenetic relationships in the menthone series centre around piperitone. An inspection of the appended formulas shows at once that structurally *l*-piperitone is closely related to *l*-piperitol and *l*-α-phellandrene, with which substances it is associated in the oils of *E. dives*, *E. radiata* and other *Eucalyptus* species:



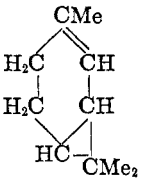
Piperitone
(XLVII)



Piperitol
(XLVIII)



α-Phellandrene
(XLIX)

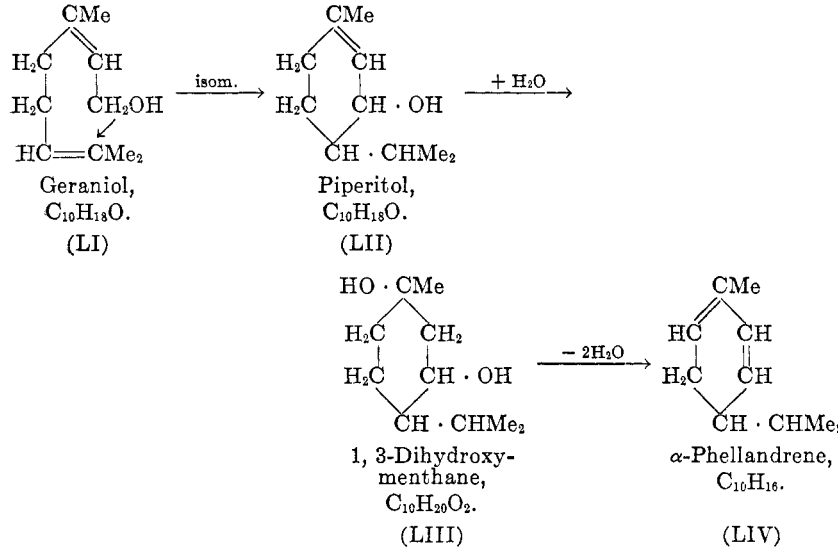


Δ⁴-Carene
(L)

The relationship of *d*-piperitone to *d*-Δ⁴-carene (L), which it accompanies in the oil of *Andropogon Jwarancusa* (22), is not so apparent; but it is extremely significant that the occurrence of *d*-piperitol with *d*-Δ⁴-carene has also been established by Simonsen (71) in the oil of a new species of *Andropogon* growing in the United Provinces. In endeavoring to trace a genetic relationship between Δ⁴-carene and piperitol, Simonsen (71) has pointed out that of the four possible active stereoisomeric forms of piperitol two might be expected to yield α-terpinene upon dehydration, while the other two should give rise to Δ⁴-carene; hence piperitol might conceivably function as the immediate precursor of Δ⁴-carene in these Indian oils. Laboratory experiments showed that *d*-piperitol when dehydrated with magnesium methyl iodide actually yielded α-terpinene, thus behaving similarly to its synthetic homologues (XLV) mentioned in the foregoing section.

It appears to the writer (72) that the clue to the biogenetic relationships of the substances under discussion is to be found in the circumstance that piperitone appears to be invariably associated in *Eucalyptus* oils with a small proportion of geranyl acetate, and it is hoped in due course to submit the ideas derived from this circumstance to experimental investigation, as far as artificial conditions may permit. According to Baker and Smith (13),

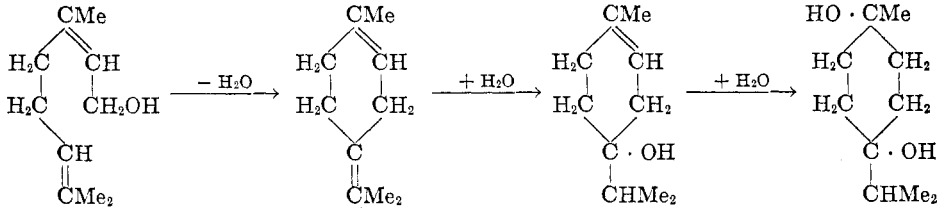
geranyl acetate "passed into *Eucalyptus* through *Angophora*, and as it occurs also in the oils of many of the 'Peppermints' it probably runs through the whole genus *Eucalyptus*, although in some of the oils the amount is very small" (p. 366). An exceptional species, *E. Macarthuri*, yields an oil containing as much as 77 per cent of geranyl acetate, together with a small proportion of free geraniol. Thus, in *E. Macarthuri* the particular chain of biochemical processes is arrested at the formation of geraniol; while in other species the geraniol, under the different conditions prevailing in the plant, may be presumed to undergo further transformations and to function as the precursor of piperitol, piperitone, α-phellandrene and other substances. In the case of *E. dives* the following mechanism may be postulated:



According to this scheme, the initial product of the isomerization of geraniol, i.e. piperitol, yields (i) α-phellandrene by successive hydration and dehydration, and (ii) piperitone by oxidation. It may be noted that *d*-α-phellandrene occurs with geraniol in gingergrass oil.

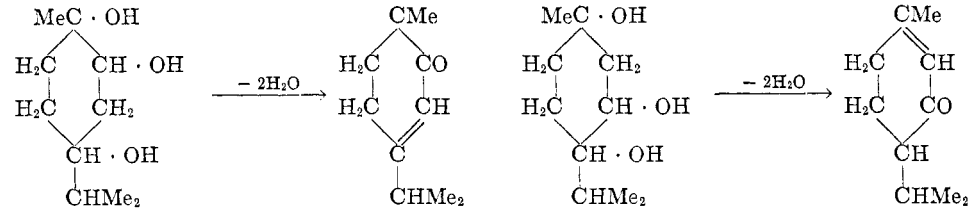
The formation from geraniol of 4-terpineol, which has recently been found in certain specimens of the oil of *E. dives*, and its

subsequent hydration to 1,4-terpin, may also be readily explained in terms of the above scheme; in this instance terpinolene is possibly, although not necessarily, an intermediate product in the series of changes:



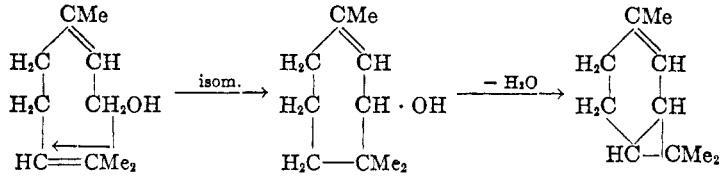
Geraniol. (LV) — Terpinolene. (LVI) — 4-Terpineol. (LVII) — 1,4-Terpin. (LVIII)

No members of the carvone series have been discovered in *Eucalyptus* oils. It is therefore of particular interest that a passage from *Eucalyptus* components to this series is provided by the observation (73) that 1,2,4-trihydroxymenthane (m.p. 113–5°), obtained from 4-terpineol by the action of cold permanganate, may be dehydrated to carvenone by a reaction which is reminiscent of Wallach's synthesis of piperitone (34) from 1,3,4-trihydroxymenthane (m.p. 120°):



1, 2, 4-Trihydroxymenthane. (LIX) — Carvenone. (LX) — 1, 3, 4-Trihydroxymenthane. (LXI) — Piperitone. (LXII)

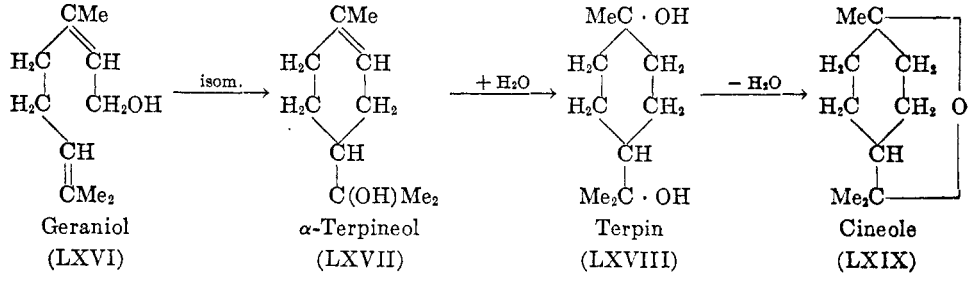
Possibly the most interesting biogenetic association of piperitone and piperitol is with Δ^4-carene, and here geraniol may be regarded as the immediate precursor not only of the alcohol and ketone, as already shown, but also of the bridged hydrocarbon:



Geraniol, $C_{10}H_{18}O$. (LXIII) — Intermediate compound, $C_{10}H_{18}O$. (LXIV) — Δ^4-Carene, $C_{10}H_{16}$. (LXV)

The simple mechanism indicated in the above representation demands only the transference of a hydrogen atom to form an unstable 7-carbon ring-compound, which would then be readily dehydrated to Δ^4-carene. In the light of this idea, it should be of interest to search systematically for Δ^4-carene in geraniol oils.

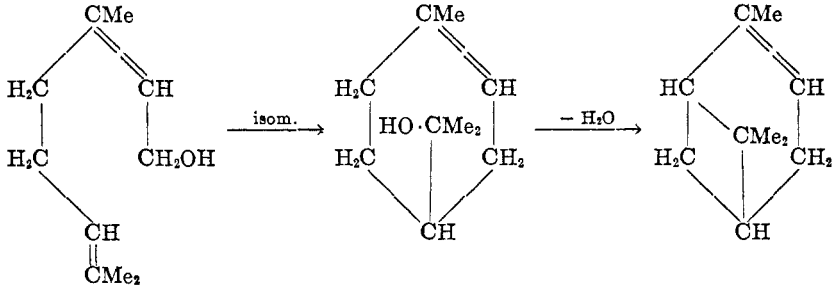
The mechanisms which have been outlined could obviously be extended to the production of menthone and menthol from geraniol, and although these substances have not been found in *Eucalyptus* oils they are associated with piperitone in Japanese peppermint oil (23). It seems possible also that cineole, another of the main components of *Eucalyptus* oils, may be derived from geraniol, by way of α-terpineol and terpin:



Geraniol (LXVI) — α-Terpineol (LXVII) — Terpin (LXVIII) — Cineole (LXIX)

The remaining constituent of *Eucalyptus* oils of the first importance is pinene (table 1). Whether this *meta*-bridged hydrocarbon may be correlated biogenetically with geraniol is problematical. It may be pointed out, however, that the 6-methylene group of α-terpineol may be regarded as activated by the $\alpha\beta$-ethylenic linkage, as in piperitone and Δ^4-menthenone (*vide supra*); further, according to Thorpe and Ingold's modification of Baeyer's

strain theory, the grouping $>CMe_2$ confers stability upon a 4-carbon ring-system, and hence presumably facilitates its formation. Thus, although it has not proved possible to proceed from α-terpineol to pinene *in vitro*, it may well be that *in vivo* some such scheme as the following may take place:



Geraniol (LXX) — α-Terpineol (LXXI) — Pinene (LXXII)

To sum up, it is evident that geraniol (or, possibly, its geometrical isomer, nerol) possesses strong claims to be regarded as the immediate precursor of piperitol, piperitone, Δ^4-carene and other substances which occur in this association in essential oils. All these substances may be readily depicted as transformation products obtained by applying simple processes of isomerization, hydration, dehydration, oxidation and reduction to the parent compound. The latter, in turn, may originate, in accordance with the conceptions of Kremers, Astengo and others, from such simple units as isovaleraldehyde: from this point of view it is interesting that isoamyl alcohol, valeraldehyde and esters of valeric acid have all been found in *Eucalyptus* oils (13).

In conclusion, the implied aptitude of geraniol to function in nature as a precursor of so many other substances may be attributed largely to the unusual conformation of its molecule, which possesses a structure (A), $\cdot CMe{:}CH\cdot CH_2OH$, consisting of a primary alcohol group activated by an $\alpha\beta$-ethylenic linkage and situated in spatial proximity to a second active grouping (B), $\cdot CH{:}CMe_2$, containing another double bond. Migration of a hydrogen atom, in the 'nascent' molecule of geraniol, from the primary alcohol group of (A) to one side of the double bond of

(B) leads to piperitol, piperitone and α-phellandrene; migration of the same hydrogen atom to the other side of the double bond leads to Δ^4-carene. Thus, while the migration in *Eucalyptus* species is limited to one direction, in *Andropogon* species it occurs simultaneously in both directions. Even in the migration common to both families, an exceedingly refined distinction is still apparent, since from the symmetric molecule of geraniol the Australian trees produce the left-handed variety of piperitol and of piperitone, while the Indian grasses give rise to the right-handed forms of these asymmetrically constituted substances. The excessively delicate control of molecular transformation which is here implied appears to be a prerogative of the living organism. The organic chemist is powerless to effect such subtle differentiations by artificial means. At the present stage of our knowledge, the finer manifestations of organic synthesis appear to be inseparably associated with the life-processes.

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