Properties.—The melting point of 50° has been confirmed by several investigators, among them Adams,[10] Mauthner,[11] and Goris and Canal.[12]

Eijkman, Bergema and Henrard [13] reported:

$$d^{81.2} \quad 1.1310$$
$$n_{\alpha}^{81.2} \quad 1.54322$$

Peonol is easily soluble in alcohol, ether, chloroform, carbon disulfide or benzol.

This phenolic ketone forms metallic complexes with a number of the heavy metals, viz., $(C_9H_9O_3)_2Ni$ from nickel salts; $(C_9H_9O_3)_2Cu$ from those of copper, according to Pfeiffer, Buchholz and Bauer.[14] Hein [15] reports the chromium salt ($C_{27}H_{27}O_9Cr \cdot O \cdot 25\ CHCl_3$) as melting at 270°–271° (uncorr.).

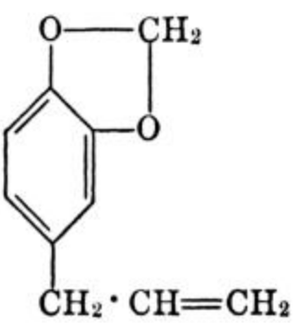
Use.—Peonol is used very little, if at all, in the perfume, soap, or flavor industries.

[1] *Compt. rend.* **202** (1936), 1351.
[2] *J. Am. Chem. Soc.* **41** (1919), 260.
[3] *J. Pharm. Soc. Japan* **56** (1936), 690. *Chem. Abstracts* **31** (1937), 2591.
[4] *J. Am. Chem. Soc.* **41** (1919), 261, 262.
[5] *Ibid.*, 260.
[6] *J. prakt. Chem.* **136** (1933), 208. See also *Math. naturw. Anz. ungar. Akad. Wiss.* **50** (1933), 468.
[7] *Compt. rend.* **202** (1936), 1351.
[8] *Ibid.*
[9] *Liebigs Ann.* **456** (1927), 304.
[10] *J. Am. Chem. Soc.* **41** (1919), 247.
[11] *J. prakt. Chem.* **136** (1933), 205. *Math. naturw. Anz. ungar. Akad. Wiss.* **50** (1933), 468.
[12] *Compt. rend.* **202** (1936), 1351.
[13] *Chem. Zentr.* I (1905), 815. *Chem. Weekblad* **2** (1905), 59, 79.
[14] *J. prakt. Chem.* **129** (1931), 163. See also Ephraim, *Ber.* **64B** (1931), 1210.
[15] *J. prakt. Chem.* **153** (1939), 172.

Safrole

$C_{10}H_{10}O_2$ Mol. Weight 162.18

1,2-Methylenedioxy-4-allylbenzene. Allylpyrocatecholmethylene ether



Occurrence.—Safrole is the main constituent of several important volatile oils—for example, American sassafras oil, Brazilian sassafras oil (*Ocotea pretiosa*?) and star anise oil (*Illicium verum*). Camphor oil contains considerable

quantities of safrole. This phenol ether also occurs as a minor constituent in numerous other volatile oils—for instance, in oil of nutmeg, American wormseed, cinnamon leaf, California laurel, probably ylang ylang, etc. According to Foote,[1] oil of *Illicium parviflorum* Michx. contains 90 per cent safrole, the highest safrole content of any volatile oil yet reported.

Isolation.—(1) By cooling the oil, or the safrole containing fraction of the oil, to at least −12° C (cf. Foote [2]).

(2) By fractional distillation, followed by cooling and crystallization. (Regarding distillation of safrole in mixtures consult Brauer.[3])

(3) Where safrole may be contaminated by oily constituents in an essential oil as in red camphor oil, the method of Ikeda and Takeda [4] may be employed advantageously to determine the safrole by preparation of the addition product with mercuric acetate and sodium chloride in dilute acetone. The precipitate so formed should be filtered in a gooch and weighed, and with a correction factor used to define the percentage of safrole in the sample.

This complex hydroxy chloride of safrole [$C_{10}H_{10}O_2(OH)HgCl$], according to Tsukamoto,[5] is readily decomposed to regenerate safrole either by hydrochloric acid, or sodium sulfide and zinc in potassium hydroxide. The oxychloride melts at 141°–142°, according to Fujita.[6]

Identification.—Safrole can be identified by several methods:

(1) By the preparation of derivatives:

(a) Tribromosafrole dibromide or "pentabromosafrole." Underwood, Baril and Toone [7] developed the following method:

Dissolve 0.41 g. of safrole in 3 cc. of alcohol and treat with 2 g. of bromine in the course of 8 min.; heat for 15 min. on a water bath, then cool. Recrystallize the solid from 7 cc. of benzene. Needles m. 169°–170°.

(b) Safrole picrate crystallizes from chloroform in the form of long orange-red blades m. 104°–105.5°, according to Baril and Megrdichian.[8]

(2) By oxidation:

Oxidizing safrole in acetone with aqueous potassium permanganate, Luff, Perkin and Robinson [9] obtained piperonylic acid m. 228°. Decker [10] found that a small quantity of piperonylacetic acid, m. 87°–88°, is formed as side reaction.

Foote [11] reported on the oxidation of safrole by the method of Fittig and Mielch [12] with alkaline potassium permanganate. The oxidation should be carefully controlled because of the variety of products obtainable. Foote suggested the following procedure:

Disperse 4 cc. of the sample in 240 cc. of a 1% sodium hydroxide solution contained in an 800-cc. flask. To this slowly add with agitation 200 cc. of a 5% potassium permanganate solution. Heat on a water bath for 1 hr. Filter hot and cool. Acidify the filtrate with sulfuric acid. The precipitated piperonylic acid is filtered off, washed with water, and recrystallized from hot alcohol. It melts at 228°.

On oxidation with potassium dichromate and dilute sulfuric acid, safrole yields piperonal (heliotropin) m. 35°, according to Power and Lees.[13]

Gildemeister and Hoffmann [14] reported that, on careful oxidation with permanganate, a glycol m. 82°–83° is formed first, and with further oxidation α-homopiperonylic acid m. 127°–128°.

(3) Note section on "Isolation" regarding mercury derivatives.

Quantitative Determination.—See Vol. I, Chapter 4, "Examination and Analysis of Essential Oils, Synthetics, and Isolates," p. 239.

Properties.—Safrole is a colorless liquid, which becomes yellow on standing. Its odor and flavor resemble sassafras. On cooling, safrole forms a crystalline mass.

The following properties have been reported by Gildemeister and Hoffmann,[15] Eijkman,[16] Waterman and Priester,[17] Perkin and Trikojus,[18] Priester,[19] and von Rechenberg: [20]

cong. pt.	11° [15,17,19]	d_4^{20}	1.100 [17]
m.	11° [19]	d_{12}	1.110 [16]
b.	234.5° [20] (corr.)	n_D^{20}	1.536–1.540 [15]
b_{759}	233° [15]		1.5383 [17]
b_{10-11}	100°–101.5° [18]		1.5381 [18]
b_4	91° [15]	n_D^{12}	1.5420 [16]

Crude isolates from natural sources are reported to melt at 7°–8°, according to Eijkman [21] and Foote.[22]

Safrole is insoluble in water, soluble in alcohol or ether. Volatile with steam.

Ciamician and Silber [23] found that safrole and isosafrole, when dissolved in concentrated sulfuric acid, develop an intense red color, while heating with phosphoric acid, according to Ono and Hirayama,[24] yields allylpyrocatechol.

On treatment with 1,3,5-trinitrobenzene, safrole yields a crystalline compound m. 51°, according to Sudborough and Beard.[25]

When heated with alkalies, safrole is converted to isosafrole. Sodium alcoholate decomposes the methylenedioxy group after rearrangement to isosafrole (cf. Ono and Imoto [26]).

Use.—Safrole is used widely for the flavoring of certain beverages, chewing gums, pharmaceuticals, oral preparations, tooth pastes, etc., and for the scenting of soaps. The principal use, however, is for the conversion to isosafrole and the manufacture of heliotropin.

[1] *J. Am. Pharm. Assocn.* **27** (1938), 574.
[2] *Ibid.*
[3] *Ber. Schimmel & Co., Jubiläums-Ausgabe* (1929), 153.
[4] *J. Chem. Soc. Japan* **57** (1936), 565. *Chem. Abstracts* **30** (1936), 7497. Cf. Matejika, *Ber.* **69B** (1936), 274; Huzita and Nakahara, *J. Chem. Soc. Japan* **62** (1941), 5. *Chem. Abstracts* **37** (1943), 3882.
[5] *J. Pharm. Soc. Japan* **50** (1930), 7. *Chem. Abstracts* **24** (1930), 1853.
[6] *J. Chem. Soc. Japan* **58** (1937), 1185. *Chem. Abstracts* **32** (1938), 3904. Cf. also Priester, *Rec. trav. chim.* **57** (1938), 811.
[7] *J. Am. Chem. Soc.* **52** (1930), 4090.
[8] *Ibid.* **58** (1936), 1415.
[9] *J. Chem. Soc.* **97** (1910), 1139.
[10] *Liebigs Ann.* **395** (1913), 295.
[11] *J. Am. Pharm. Assocn.* **27** (1938), 574.
[12] *Liebigs Ann.* **152** (1869), 40.
[13] *J. Chem. Soc.* **85** (1904), 638.
[14] "Die Ätherischen Öle," 3d. Ed., Vol. I, 614.
[15] *Ibid.*

[16] *Rec. trav. chim.* **4** (1885), 32. *Ber.* **23** (1890), 862.
[17] *Rec. trav. chim.* **47** (1928), 849.
[18] *J. Chem. Soc.* (1927), 1663.
[19] *Rec. trav. chim.* **57** (1938), 811.
[20] "Einfache und fraktionierte Destillation," 2 Aufl. (Miltitz 1923), 218.
[21] See Gildemeister and Hoffmann, "Die Ätherischen Öle," 3d Ed., Vol. I, 614.
[22] *J. Am. Pharm. Assocn.* **27** (1938), 574.
[23] *Ber.* **23** (1890), 1160.
[24] *J. Chem. Soc. Japan* **58** (1937), 926. *Chem. Abstracts* **32** (1938), 528.
[25] *J. Chem. Soc.* **99** (1911), 214.
[26] *J. Chem. Soc. Japan* **59** (1938), 359. *Chem. Abstracts* **32** (1938), 9060.

Suggested Additional Literature

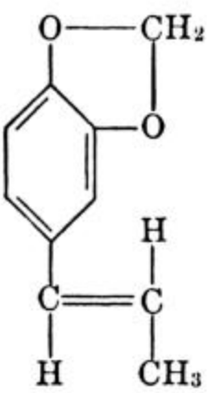
L. Bert, "Synthesis of Allyl and Propenyl Essential Oils. General Method," *Compt. rend.* **213** (1941), 873. *Chem. Abstracts* **37** (1943), 4060.

Yasuji Fujita and Takeo Yamashita, "Determination of Safrole in Essential Oils," *J. Chem. Soc. Japan* **63** (1942), 410. *Chem. Abstracts* **41** (1947), 3259.

Isosafrole

$C_{10}H_{10}O_2$ Mol. Weight 162.18

1,2-Methylenedioxy-4-propenylbenzene. Propenylpyrocatecholmethylene ether



Theoretically, isosafrole can exist in the form of two geometrical isomers. In fact, years ago Hoering and Baum [1] identified in technical isosafrole two isomeric forms which they named α- and β-isosafrole. The latter largely predominates in the commercial product. According to Nagai,[2] the relationship of the isosafroles is a case of *cis-trans-* isomerism, the labile *cis-* form on warming being converted into the stable *trans-* form. Waterman and Priester [3] came to the conclusion that the *cis-* or α-isosafrole reported in earlier literature is a mixture of safrole and *trans*-isosafrole, and that only the *trans-* or β-isosafrole isolate is homogeneous.

Occurrence.—Isosafrole is not as widely distributed in nature as safrole. It occurs probably in oil of ylang ylang.

Isolation.—By fractional distillation, and purification through the picrate.

Identification.—Isosafrole can be characterized by several methods. The variant melting points reported for several of these compounds may be due in part to the fact that the products retained a small percentage of unstable geometric isomers.

(1) By the preparation of derivatives:

(a) Bromoisosafrole dibromide. Underwood, Baril and Toone [4] suggested the following method:

Add 2.03 g. of bromine dropwise in the course of 15 min. to 0.41 g. of isosafrole dissolved in 2 cc. of carbon disulfide, and allow to stand for 24 hr. Grind the solid mass in a mortar with 3 cc. of cold alcohol and recrystallize from 5 cc. of petroleum ether. Needles m. 109°. Ciamician and Silber [5] reported m. 109°–110°, Pond, Erb and Ford [6] m. 110°–111°.

(b) Isosafrole picrate m. 74°–75° dark, red thick needles when crystallized from chloroform or alcohol, according to Baril and Megrdichian.[7] Nagai [8] recorded 73.5°–74° for the *trans*- isomer and 68.5° for the *cis*- isomer.

(2) By oxidation:

Oxidizing 5 g. of isosafrole with 25 g. of potassium bichromate and 8 g. of sulfuric acid in 80 cc. of water, Ciamician and Silber [9] obtained about 4 g. of heliotropin (piperonal), as isolated through its sodium bisulfite addition compound.

Oxidation of isosafrole with potassium permanganate yields piperonylic acid. Imoto [10] described the following method:

Add 15 g. of isosafrole to 135 cc. of water, stir vigorously, and treat at 80°–90° with a 4% aqueous solution of potassium permanganate (69 g.) added dropwise during an hour. After the passage of another 30 min., filter and steam distill the unreacted products, and precipitate the organic acid with hydrochloric acid. The yield will be 11.9 g., or 79.5%, of piperonylic acid m. 226°–227.5°.

(3) The pseudonitrosite m. 133°, according to Monti and Dinelli,[11] prepared by the method of Angeli.[12]

Hudson and Robinson [13] reported that the reaction of 13 g. of isosafrole, 10 g. of maleic anhydride and 40 cc. of xylene refluxed 3 hr. gives 10 g. of adduct. Extract this derivative with chloroform, discarding the insoluble portion. The chloroform extract, as well as the xylene mother liquors, yields a naphthalenedicarboxylic acid anhydride m. 142°–143°; the phenylimide derived from the anhydride by heating with aniline melts at 243°.

Properties.—Isosafrole is a liquid with an anise-like odor.

As mentioned, Waterman and Priester [14] found that the *cis*- (or α-) isosafrole reported in the literature is a mixture of safrole and *trans*-isosafrole and that only the *trans*- (or β-) isosafrole is known with certainty.

The following properties have been reported by Waterman and Priester,[15] Nagai,[16] Eijkman,[17] and Gildemeister and Hoffmann [18] for the stable *trans*- and the labile *cis*-isosafrole:

	Trans-	*Cis*-
m.	6.7°–6.8° [15]	
b.	247°–248° [16]	242°–243° [16]
b_4	105°–106° [18]	
d_4^{20}	1.122 [15]	
d_4^{15}	1.1230–1.1235 [16]	
$d_{11.5}$	1.126 [17]	
n_D^{20}	1.5782 [15]	
n_D^{15}		1.5630–1.5632 [16]

Conclusions relative to the configuration should not be drawn in terms of the von Auwers-Skita [19] rule, which ordinarily requires the *cis-* compounds to be of higher specific gravity and refractive index, but of smaller molecular refractions. It has been shown that this rule cannot be applied to members of the styrene series. As regards isosafrole, the data on the *cis-* form are still too meager for conclusions to be drawn.

Isosafrole is soluble in organic solvents, alcohol, ether, benzene, etc. It is volatile with steam, and polymerizes under the influence of acids.

Use.—Isosafrole is used mainly for the manufacture of heliotropin.

[1] *Ber.* **42** (1909), 3076.
[2] *J. Coll. Eng. Tokyo Imp. Univ.* **11** (1921), 83.
[3] *Rec. trav. chim.* **47** (1928), 851.
[4] *J. Am. Chem. Soc.* **52** (1930), 4090.
[5] *Ber.* **23** (1890), 1164.
[6] *J. Am. Chem. Soc.* **24** (1902), 341.
[7] *Ibid.* **58** (1936), 1415.
[8] *J. Coll. Eng. Tokyo Imp. Univ.* **11** (1921), 108. *Chem. Abstracts* **16** (1922), 418.
[9] *Ber.* **23** (1890), 1160.
[10] *J. Soc. Chem. Ind. Japan* **37,** Suppl. (1934), 26.
[11] *Gazz. chim. ital.* **62** (1932), 370. Cf. Wallach and Mueller, *Liebigs Ann.* **332** (1904), 331.
[12] *Gazz. chim. ital.* **22,** II (1892), 335.
[13] *J. Chem. Soc.* (1941), 715.
[14] *Rec. trav. chim.* **47** (1928), 851, 1036; **48** (1929), 1272.
[15] *Ibid.* **47** (1928), 851, 1033; **48** (1929), 1272.
[16] *J. Coll. Eng. Tokyo Imp. Univ.* **11** (1921), 108. *Chem. Abstracts* **16** (1922), 418.
[17] *Ber.* **23** (1890), 859.
[18] "Die Ätherischen Öle," 3d Ed., Vol. I, 615.
[19] *Liebigs Ann.* **420** (1920), 91. *Ber.* **53** (1920), 1792; **68** (1935), 1346.

Suggested Additional Literature

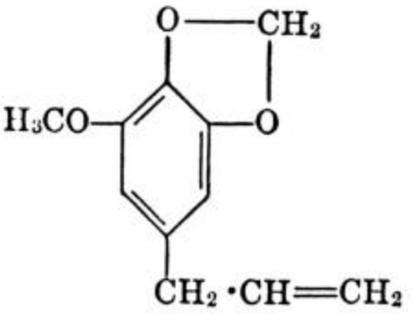
Matsuji Takebayashi, "Reaction of Isosafrole with Hydrogen Halides. Consideration of the Dimerization of Isosafrole," *J. Chem. Soc. Japan* **64** (1943), 1363. *Chem. Abstracts* **41** (1947), 3774.

Matsuji Takebayashi, "Polymerization of Isosafrole. Synthesis of Diisosafrole with Metallic Salts," *J. Chem. Soc. Japan* **65** (1944), 582. *Chem. Abstracts* **41** (1947), 3774.

Myristicin

$C_{11}H_{12}O_3$ Mol. Weight 192.21

1,2-Methylenedioxy-6-methoxy-4-allylbenzene.



Occurrence.—Myristicin occurs in oils of nutmeg and mace, also in French parsley and dill oil. This phenol ether must not be confused with the deposit