[CONTRIBUTION FROM THE UNITED STATES DEPARTMENT OF AGRICULTURE, AGRICULTURAL RESEARCH SERVICE, ENTOMOLOGY RESEARCH BRANCH]

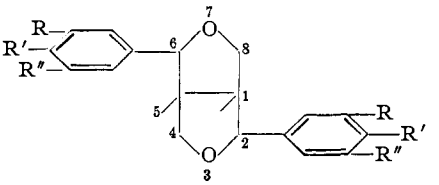
Epiasarinin, a Diastereoisomer of Sesamin and Asarinin. Stereochemistry of 2,6-Diaryl-*cis*-3,7-dioxabicyclo[3.3.0]octane

BY MORTON BEROZA

RECEIVED APRIL 9, 1956

A third diastereoisomer of sesamin and asarinin is theoretically possible. The *d*- and *l*-forms of this isomer were prepared by the isomerization of sesamin or asarinin with ethanolic hydrochloric acid. The structure of the compound was proved by isomerizing it with ethanolic hydrochloric acid to sesamin and asarinin. It is proposed that this isomer be named "epiasarinin." Seven derivatives of *d*- and *l*-epiasarinin were prepared. Stereochemical considerations indicate that the aryl groups of sesamin are *cis* to the bridge hydrogen atoms (at positions 1 and 5) of the central nucleus (IIb), whereas in epiasarinin the aryl groups are *trans* (IIc) to these hydrogen atoms. These findings should be useful in structure studies on the other lignans having the 2,6-diaryl-*cis*-3,7-dioxabicyclo[3.3.0]octane structure.

A number of naturally occurring lignans contain the 2,6-di-(substituted aryl)-*cis*-3,7-dioxabicyclo-[3.3.0]octane nucleus (formula I).



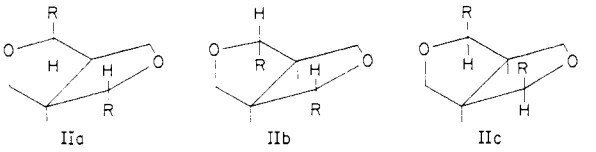
Ia, R and R′ = CH_2O_2, R″ = H
Ib, R = OCH_3, R′ = OH, R″ = H
Ic, R = R′ = OCH_3, R″ = H
Id, R = R″ = OCH_3, R′ = OH

The extensive literature on these compounds has been reviewed recently by Hearon and MacGregor.[1] Compounds containing this nucleus are *d*- and *l*-sesamin (Ia), *d*-asarinin (Ia, also called isosesamin), *l*-asarinin (Ia), pinoresinol (Ib), dimethyl pinoresinol (Ic), dimethyl epipinoresinol (Ic), eudesmin (Ic), epieudesmin (Ic), phillyrin, forsythin, phillygenol, gmelinol, symplocosin, symplocosigenol, syringaresinol (Id)[2] and sesamolin.[3-6] These compounds must have the bridge hydrogens of their central nucleus in a *cis* configuration since they may be reversibly isomerized by alcoholic hydrochloric acid (except sesamolin which splits off sesamol in the presence of acid). The sterically strained *trans*-3,7-dioxabicyclo[3.3.0]octane structure could not be part of a reversible system because of the inability of this fused ring structure to close again after opening.[4]

Of these lignans the diastereoisomers sesamin, asarinin and sesamolin have attained importance because of their activity as pyrethrum synergists.[7,8]

A third diastereoisomer of sesamin and asarinin, having a *cis* nucleus, should exist. These isomers, shown in formula II, differ only in the geometrical configurations at positions 2 and 6.

This conclusion is in harmony with the work on epipinoresinol (Ib) by Gripenberg,[9] who also implied the possibility of a third diastereoisomer. Gripenberg showed that upon bromination epipinoresinol gave two monobromo derivatives and pinoresinol only one. He therefore concluded that epipinoresinol has structure IIa (referred to as the unsymmetrical isomer; two monobromo compounds are possible depending upon whether the R at the 2- or 6-position is brominated) and pinoresinol either IIb or IIc (called symmetrical isomers, although actually not symmetrical molecules). Similarly Erdtman and Pelchowicz[6] have recently demonstrated that asarinin has structure IIa; therefore sesamin has either structure IIb or IIc.



IIa IIb IIc

R = substituted aryl

An investigation to prepare this third diastereoisomer was undertaken. *d*-Sesamin was refluxed with alcoholic hydrochloric acid, a treatment known to bring about a Walden inversion of the aryl groups at positions 2 and 6. By a process of chromatography and fractional crystallization, a compound melting at 168–171° could be isolated from the equilibrium mixture. Because of the 3° melting range, doubts of its purity were entertained. However, chromatographic studies on the compound indicated it was pure.

The formula of epiasarinin is $C_{20}H_{18}O_6$, and it is therefore isomeric with sesamin. An ethoxyl determination and a qualitative test for chlorine were both negative. Because the ultraviolet spectrum was practically identical with similar spectra of sesamin and asarinin, it was concluded that the two 3,4-methylenedioxyphenyl groups were intact. Finally, the infrared spectrum (Fig. 1) showed no carbonyl or hydroxyl groups, nor were any bands present that were not compatible with a sesamin or asarinin stereoisomer.

Proof that the compound was the third stereoisomer was obtained by isomerizing a small quantity with alcoholic hydrochloric acid and chromatographing the product. Only two zones were obtained in appreciable amounts, and the compounds in these zones were identified as *d*-asarinin and

(1) W. M. Hearon and W. S. MacGregor, *Chem. Revs.*, **55**, 991 (1955).
(2) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 4 (1953).
(3) M Beroza, *J. Am. Oil Chemists' Soc.*, **31**, 302 (1954).
(4) M. Beroza, THIS JOURNAL, **77**, 3332 (1955).
(5) E. Haslam and R. D. Haworth, *J. Chem. Soc.*, 827 (1955).
(6) H. Erdtman and Z. Pelchowicz, *Chemistry & Industry*, 567 (1955).
(7) H. L. Haller, F. B. LaForge and W. N. Sullivan, *J. Org. Chem.*, **7**, 185 (1942).
(8) W. A. Gersdorff, N. Mitlin and M. Beroza, *J. Econ. Entomol.*, **47**, 839 (1954).
(9) J. Gripenberg, *Acta Chem. Scand.*, **2**, 82 (1948).

d-sesamin. It is proposed that this compound be named *d*-epiasarinin, $[\alpha]^{26}D$ +385°.

The entire procedure was repeated with asarinin as the starting material, and the enantiomorph, *l*-epiasarinin, was obtained, m.p. 168–171°, $[\alpha]^{26}D$ 380°. *dl*-Epiasarinin melted 145–147°.

DERIVATIVES OF EPIASARININ

	M.p., °C.	$[\alpha]^{26}D$		M.p., °C.	$[\alpha]^{26}D$
Dibromo-*d*-	216–218	+295°	Dinitro-*l*-	285 dec.	−100°
Dinitro-*d*-	288 dec.	+ 97	Dibromo-*dl*-	191–193	...
Dibromo-*l*-	216–218	−290	Dinitro-*dl*-	300 dec.	...

An examination of models shows that of the three possibilities, IIc shows the most steric interference between the two aryl groups (large groups in close proximity), and accordingly this structure has been assigned to epiasarinin, the least stable of the three isomers. Formula IIb has therefore been assigned to sesamin. Pinoresinal must also have this formula (IIb).

All other lignans and their derivatives having the 2,6-disubstituted-*cis*-3,7-dioxabicyclo[3.3.0]octane nucleus may be expected to have a third diastereoisomer in addition to the two that have been described for each.

Experimental[10]

d-Sesamin (7 g.) was refluxed 16 hr. with 325 g. of a 10% (w./w.) solution of hydrogen chloride in absolute ethanol. On cooling, the product was seeded with *d*-asarinin (isosesamin) and 2.2 g. of crystals, m.p. 116–118°, were deposited, which upon recrystallization (ethanol) gave 2.05 g. of practically pure *d*-asarinin, m.p. 120–121°, undepressed by an authentic sample. The combined mother liquors, seeded with *d*-asarinin and *d*-sesamin, were held at 4° for several days and yielded 2.1 g. of crystals, m.p. 105–113°. (By fractional crystallization or chromatography *d*-asarinin and *d*-sesamin could be separated from these crystals.) The mother liquor was diluted with 600 ml. of water and extracted once with 100-ml. and twice with 50-ml. portions of chloroform. The aqueous layer contained none of the sesamin isomers (practically no absorbance at 288 mμ) and was discarded. The combined chloroform extracts were dried over sodium sulfate and evaporated to dryness. The residue, taken up in 50 ml. of hot alcohol and allowed to remain at 4° for several days, yielded crystals weighing 1.3 g. This fraction contained *d*-episarinin, and its separation by chromatography is described in the next section.

Isolation of *d*-Episarinin by Chromatography.—The 1.3-g. sample was dissolved in several milliliters of chloroform and added to a column, 5.5 cm. in diameter, prepared from a slurry of 400 g. of silicic acid (Merck) in isoöctane. The sample was washed in with several portions of 1:4 by volume chloroform–isoöctane followed by 200 ml. of isoöctane. The column was developed with 2.7% ethyl acetate in isooctane. The elution of compounds was followed by determination of the absorbance of effluent at 288 mμ. Between 2800 and 4600 ml. a zone containing mostly *d*-asarinin was eluted and separated into three equal fractions. From the second and third fractions the *d*-epiasarinin was isolated. The solvent from these fractions was removed, and each residue in a test-tube was dissolved in a minimum of hot alcohol and set aside to crystallize. When the product was heated in an 80° bath, the light needle-like crystals of *d*-asarinin dissolved readily and left a small amount of heavy insoluble crystals. By means of a pipet the hot mother liquor was quickly withdrawn. The heavy crystals were taken up in chloroform and filtered. The residue, after removal of the chloroform, crystallized from about 1 ml. of ethanol; wt. 140 mg. (2% yield), m.p. 168–171°, $[\alpha]^{26}D$ +385° (*c* 1.0 chloroform). The compound gave negative tests for chlorine and ethoxyl.

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.8; H, 5.12; mol. wt., 354. Found: C, 67.57; H, 5.12; mol. wt. (Rast), 370.

(10) Melting points are corrected and were determined with the Hershberg apparatus unless otherwise specified.

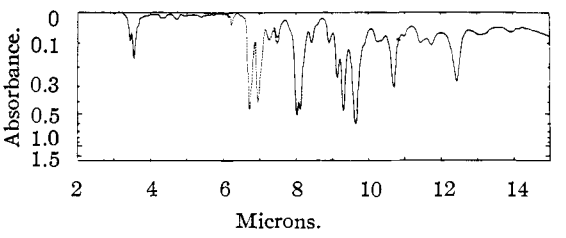


Fig. 1.—Infrared spectrum of epiasarinin in carbon disulfide (solid line) and in chloroform (dotted line), 10 mg./ml.

The *d*-epiasarinin was rechromatographed as above on a column, 2.5 cm. in diameter, containing 100 g. of adsorbent. Only one zone was obtained. The residues from the first and last tenths of the zone gave identical infrared spectra.

Isolation of *l*-Epiasarinin.—This compound was prepared by isomerizing 2 g. of *l*-asarinin with ethanolic hydrochloric acid in the same manner as described for *d*-sesamin. The product was diluted with water and extracted with chloroform, and the residue after evaporation was taken up in ethanol. The *l*-asarinin and *l*-sesamin were crystallized out and again isomerized, the mother liquor being held aside. This process was repeated three times. The residue obtained by evaporating the combined mother liquors was chromatographed and worked up as described above. In spite of this more tedious procedure, the yield was still only about 2%; wt. 37 mg., m.p. 168–171°, $[\alpha]^{26}D$ −380° (*c* 1.0 chloroform).

Anal. Calcd. for $C_{20}H_{18}O_6$: C, 67.8; H, 5.12. Found: C, 67.76; H, 5.10.

Isomerization and Chromatography of *d*-Epiasarinin.—*d*-Epiasarinin (38 mg.) was refluxed with 5 ml. of 10% ethanolic hydrochloric acid for 16 hr. as described above. The product was diluted with 10 ml. of water and extracted three times with 10-ml. portions of chloroform. The chloroform layer was washed with water, dried over sodium sulfate, concentrated to a few milliliters, and chromatographed on a 100-g. silicic acid column as described above, with 2% ethyl acetate in isoöctane until the first zone (1100–1800 ml.) was eluted, and 3% ethyl acetate in isoöctane until the second zone (2000–2450 ml.) was eluted. The residue from the evaporation of the first zone gave crystals melting at 118.5–119.5°, which after one recrystallization melted at 120–121°; wt. 12 mg. (31.5%). In admixture with *d*-asarinin it gave no depression; its infrared spectrum was identical with that of *d*-asarinin. The second zone yielded 9 mg. (24%) of crystals (alcohol) melting (without recrystallization) at 121.5–122.5°, undepressed in admixture with *d*-sesamin; its infrared spectrum was identical with that of *d*-sesamin. Additional material could be obtained by concentrating the mother liquors from both zones.

***d*-Dibromoepiasarinin.**—*d*-Epiasarinin (22.5 mg.) was dissolved in about 0.25 ml. of hot acetic acid and cooled quickly by swirling in a 20° bath. Immediately 0.3 ml. of 20% (w./v.) bromine in acetic acid was added dropwise over a 5-minute period. At the end of the addition crystals were deposited, which were filtered off and washed with ethanol; wt. 15.2 mg. The crystals were recrystallized by dissolving in chloroform, evaporating to dryness and adding ethanol to the residue; wt. 14 mg., m.p. 216–218°, $[\alpha]^{26}D$ +295° (*c* 0.433 chloroform).

Anal. Calcd. for $C_{20}H_{16}O_6Br_2$: Br, 31.2. Found: Br, 31.28.

Several milligrams of impure material, m.p. 205–213°, was obtained from the mother liquor.

***l*-Dibromoepiasarinin.**—From 12.4 mg. of *l*-epiasarinin there was obtained 9.8 mg. of *l*-dibromoepiasarinin in the same manner as described above, m.p. 216–218°, $[\alpha]^{26}D$ −290° (*c* 0.59 chloroform).

Anal. Calcd. for $C_{20}H_{16}O_6Br_2$: Br, 31.2. Found: Br, 31.10.

Here also an additional precipitate was obtained from the mother liquor.

***d*-Dinitroepiasarinin.**—A test-tube containing 20.7 mg. of *d*-epiasarinin dissolved in 0.12 ml. of hot acetic acid was swirled in a 40° bath while about 0.15 ml. of 2:3 by volume concentrated nitric–acetic acids was added dropwise over a 2-minute period. After another 5 minutes the test-tube

was removed. Yellow crystals soon appeared, and were filtered off and washed with ethanol. Attempts to dissolve the crystals with chloroform or acetone were unsuccessful, so that the product was not recrystallized; wt. 11.5 mg. $[\alpha]^{26}D$ +97° (*c* 0.25 pyridine). When placed on a hot-stage at 270° and the temperature was raised at 5°/minute, the compound darkened at 284°, became black and melted suddenly at 288° dec.

Anal. Calcd. for $C_{20}H_{16}O_{10}N_2$: N, 6.30. Found: N, 6.11.

l-**Dinitroepiasarinin.**—In the same manner as described above 9.8 mg. of *l*-epiasarinin yielded yellow crystals of *l*-dinitroepiasarinin weighing 7.4 mg. Its melting point, when determined in the same way as that of its racemate, darkened at 281°, blackened and melted at 283–285° dec., $[\alpha]^{26}D$ −100° (*c* 0.25 pyridine).

Anal. Calcd. for $C_{20}H_{16}O_{10}N_2$: N, 6.30. Found: N, 6.19.

dl-**Epiasarinin.**—Equal weights of the racemates were heated in ethanol and permitted to crystallize, m.p. 145–147°. Recrystallization did not change the melting point.

dl-**Dibromoepiasarinin.**—Equal weights of the enantiomorphs were dissolved in a small amount of chloroform. Ethanol was added and the solution was evaporated to a small volume. Small needles came out of solution, m.p. 191–193°. The melting point remained unchanged on recrystallization from ethanol.

dl-**Dinitroepiasarinin.**—Equal weights of the racemates were dissolved in hot chloroform and concentrated to a small volume. A small amount of ethanol was added and crystals appeared. The compound was recrystallized and its melting point was determined in the same way as that of its constituent racemates. The crystals started to darken gradually above 288°, were quite dark at 296°, but were still unmelted at 300°.

BELTSVILLE, MD.

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH BRANCH, AGRICULTURAL RESEARCH SERVICE, UNITED STATES DEPARTMENT OF AGRICULTURE]

Pellitorine Isomers. III. The Synthesis of N-Isobutyl-*trans*-4-*trans*-6-decadienamide and the Structure of Spilanthol[1]

BY MARTIN JACOBSON

RECEIVED MAY 2, 1956

The accepted structure of spilanthol, the pungent, insecticidal constituent of the flower heads of several species of *Spilanthes*, has been N-isobutyl-4,6-decadienamide (geometrical configuration unknown). The *trans,trans* form of this compound has now been synthesized by a stereospecific procedure and found to have different properties from those of the natural material. These properties and several discrepancies in the spectral data and degradative behavior reported for spilanthol cast doubt on the correctness of the gross structure assigned to the latter. An attempt to isolate spilanthol from an American species of *Spilanthes* was unsuccessful. N-Isobutyl-*trans*-2-*trans*-4-octadienamide, related to pellitorine, has been prepared and found to be a powerful sialogog with limited insecticidal activity.

The flower heads of several species of *Spilanthes* (family *Compositae*) contain a pungent principle which has been used medicinally. It was first obtained in the crude state from *S. oleracea* Jacq. by Gerber,[2] who designated it "spilanthol." The same crude material was obtained by Asahina and Asano[3] as a reddish-brown sirup which could not be distilled without decomposition. Hydrolysis gave isobutylamine and polymerized acidic material, while hydrogenation yielded N-isobutylcapramide, b.p. 171° (6 mm.), m.p. 37–38°. Asano and Kanematsu[4] claimed the isolation of pure spilanthol from the flower heads of *S. acmella* L. as a pale yellow, pungent liquid boiling at 165° at 1 mm., which analyzed for $C_{14}H_{25}NO$ and absorbed 2 moles of hydrogen to give N-isobutylcapramide. Ozonization of the liquid resulted in formic and succinic acids and a compound thought to be valeric acid. On the basis of these results, Asano and Kanematsu postulated an allenic structure (I) for spilanthol.

$$CH_3CH_2CH_2CH_2CH{=}C{=}CHCH_2CH_2CONHCH_2CH(CH_3)_2 \quad (I)$$

After further investigation of the ozonization products, these investigators[5] claimed the isolation of formic, succinic and butyric acids (based on Duclaux values), and reported the formation, in very poor yield, of a spilanthol–maleic anhydride adduct, m.p. 167–168°. They accordingly discarded structure I and assigned structure II (N-isobutyl-4,6-decadienamide) to spilanthol.

$$CH_3CH_2CH_2CH{=}CHCH{=}CHCH_2CH_2CONHCH_2CH(CH_3)_2 \quad (II)$$

In 1945, Gokhale and Bhide[6] obtained spilanthol from an Indian variety of *S. acmella* as a pale yellow liquid, b.p. 220–225° (20 mm.); this material formed a maleic anhydride adduct, m.p. 168–169°, in undisclosed yield, and yielded succinic acid on permanganate oxidation in acetone. According to Aihara,[7] natural spilanthol absorbs in the ultraviolet at 220 mμ (undisclosed intensity). Nothing has been reported concerning the geometrical configuration of this compound.

Spilanthol has been reported to be effective against the larvae of *Anopheles*[8] and *Culex* mosquitoes.[9] This was of interest in view of the insecticidal activity of a number of other natural, unsaturated sialogogs,[10] particularly those isolated from the *Compositae*, and prompted an investigation into the possible synthesis of spilanthol.

There are four possible stereoisomers of the diene II. The facile distillation of natural spilanthol

(1) Part I, M. Jacobson, THIS JOURNAL, **72**, 1489 (1950); part II, **75**, 2584 (1953).

(2) E. Gerber, *Arch. Pharm.*, **241**, 270 (1903).

(3) Y. Asahina and M. Asano, *J. Pharm. Soc. Japan*, **40**, 503 (1920); **42**, 85 (1922).

(4) M. Asano and T. Kanematsu, *ibid.*, **47**, 521 (1927).

(5) M. Asano and T. Kanematsu, *Ber.*, **65B**, 1602 (1932).

(6) V. G. Gokhale and B. V. Bhide, *J. Indian Chem. Soc.*, **22**, 250 (1945).

(7) T. Aihara, *J. Pharm. Soc. Japan*, **70**, 43 (1950).

(8) G. S. Pendse, *et al.*, *Current Sci. (India)*, **14**, 37 (1945); *J. Univ. Bombay*, **15A**, New Ser. Pt. 3, No. 20, 26 (1946).

(9) T. Aihara and T. Suzuki, *J. Pharm. Soc. Japan*, **71**, 1323 (1951).

(10) See L. Feinstein and M. Jacobson, *Fortschr. Chem. Org. Naturstoffe*, **10**, 423 (1953), for a review of the subject.