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The Structure of Sesamolin and its Stereochemical Relationship to Sesamin, Asarinin and Pinoresinol

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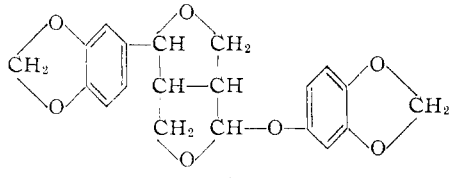
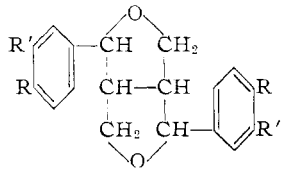
The chemical structure of sesamolin—2-(3,4-methylenedioxyphenoxy)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo-[3.3.0]octane—previously advanced has been supported by the isolation of the two additional degradation products, piperonylic acid and the *cis*-di-γ-lactone of α,β-bis-(hydroxymethyl)-succinic acid. The former compound confirms the existence of a second 3,4-methylenedioxyphenyl group in the compound and the latter proves the central nucleus of sesamolin to have a 3,7-dioxabicyclo[3.3.0]octane structure. This nucleus is believed to have a *cis* configuration. The possibility of sesamolin being 2-(3,4-methylenedioxyphenoxy)-4-(3,4-methylenedioxyphenyl)-*trans*-3,7-dioxabicyclo[3.3.0]octane is considered unlikely. Oxidation of sesamolin, sesamin and pinoresinol with nitric acid yields the same optically active dilactone whereas oxidation of asarinin yields the optical antipode of this dilactone. The central nuclei of sesamin and asarinin are, like that of pinoresinol, of the *cis* configuration.

In a recent study on pyrethrum synergists in sesame oil[1] the constituents sesamin and sesamolin were found to account for practically all the synergistic activity of the oil. Sesamolin, which had not been known previously to be synergistic, was about five times as active as sesamin. The chemical structure of this potent synergist was therefore of interest.

On the basis of chemical data formula I—2-(3,4-methylenedioxyphenoxy)-6-(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane—was advanced for the structure of sesamolin.[1] The similarity of this compound to sesamin (IIa) is apparent.



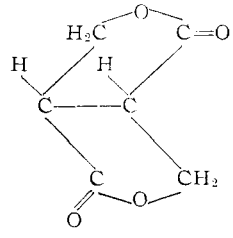
I



IIa, R,R′ = O_2CH_2 (methylenedioxy) for sesamin and arinin

b, R = R′ = OCH_3 for dimethyl ether of pinoresinol

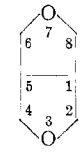
Additional evidence in favor of formula I has now been obtained from two additional degradation products isolated in further work on this problem, that is, piperonylic acid and the di-γ-lactone of α,β-bis-(hydroxymethyl)-succinic acid, the latter shown in formula III.



III

The presence of a 3,4-methylenedioxyphenoxy group in sesamolin is recognized because treatment of the compound with dilute mineral acids yields sesamol (3,4-methylenedioxyphenol). Permanganate oxidation yields piperonylic acid, which confirms the existence in the molecule of a second 3,4-methylenedioxyphenyl group, this group being attached to a carbon atom. This result confirms the previous inference from the ultraviolet spectra of sesamin and sesamolin, that the latter like the former contains two 3,4-methylenedioxyphenyl groups.

The remaining $C_6H_8O_2$ central nucleus is accounted for by the isolation of dilactone III from sesamolin by nitric acid oxidation. This optically active dilactone was isolated originally by Erdtman and Gripenberg[2] by degradation with concentrated nitric acid of the dimethyl ether of dibromopinoresinol (dibromo derivative of formula IIb). These workers also isolated the racemic form of dilactone III from *dl*-dibromoeudesamin. The isolation of the dilactone from sesamolin proves the sesamolin nucleus to have a 3,7-dioxabicyclo-[3.3.0]octane structure (formula IV). Furthermore,



IV

Erdtman and Gripenberg[2] have pointed out that the hydrogen atoms at positions 1 and 5 must be in the *cis* configuration, since a *trans* configuration of dilactone III would give a symmetrical molecule which could not exhibit optical activity.

The substituted phenyl groups of pinoresinol and eudesamin were confirmed to be at positions 2 and 6 (or 4 and 8) of formula IV because dilactone III was isolated from the nitric acid oxidation of these compounds.[2] Using the same method, Freudenberg and Dietrich[3] showed that it was possible to obtain the dilactone directly from unbrominated pinoresinol, although in lesser yield. These workers also synthesized syringaresinol enzymatically and proved, by isolation of racemic dilactone III, that the nucleus of their compound had a *cis*-3,7-dioxabicyclo[3.3.0]octane structure; furthermore, the points of attachment of the substituted phenyl

(1) M. Beroza, *J. Am. Oil Chemists' Soc.*, **31**, 302 (1954).

(2) H. Erdtman and J. Gripenberg, *Acta Chim. Scand.*, **1**, 71 (1947).

(3) K. Freudenberg and H. Dietrich, *Chem. Ber.*, **86**, 4 (1953).

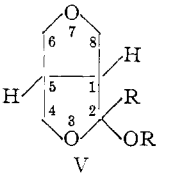
groups were established at positions 2 and 6 (or 4 and 8).

The same optically active (+)dilactone III also now has been obtained from sesamin and dibromosesamin, and incidentally by simpler means. The (−)antipode of the dilactone was obtained from asarinin. Sesamin and asarinin as well as pinoresinol, eudesamin and syringaresinol are compounds of established structure known to have the central nucleus shown in formula IV with substituted phenyl groups at positions 2 and 6 (or 4 and 8). In every case the carbonyl groups of the dilactones resulting from nitric acid oxidation formed only at the point of attachment of the phenyl groups.

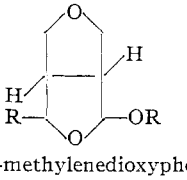
Inasmuch as the *cis*-dilactone III now has been isolated from sesamolin, it appears that the aromatic groups in sesamolin likewise are attached at positions 2 and 6 (or 4 and 8) and the nucleus is in the *cis* configuration.

Infrared data give further confirmation of the sesamolin structure. A model compound, that is, 2-(3,4-methylenedioxyphenoxy)-tetrahydropyran,[4] contains an acetal grouping similar to the one present in sesamolin. In the 8–9 μ region where ethers are known to absorb, the compound has a peak at 7.90 μ, an intense peak (doublet) at about 8.50 μ and a peak at 8.92 μ. These peaks are present in the spectrum of sesamolin[1]; thus the spectrum of sesamolin contains a shoulder at 7.87 μ and an intense peak at 8.50 μ, not present in the sesamin spectrum.[1] Sesamin and sesamolin both exhibit peaks at 8.90 μ, but the one in the spectrum of the latter compound is much more intense.

On the basis that sesamolin may exist in the *trans* form, two other structures for this compound, shown in formulas V and VI, have been suggested.



V



VI, R = 3,4-methylenedioxyphenyl

Molecular models of the bicyclo[3.3.0]octane structure indicate that the *cis* configuration is practically strainless whereas the *trans* form is under great strain. Hückel[5] has calculated on a tetrahedral basis that the strain of the *trans* system would be nearly equal to that of camphor. Although *trans*-bicyclo[3.3.0]octane has been synthesized,[6] we could find no example of a compound containing a *trans*-3,7-dioxabicyclo[3.3.0]octane system such as might be present in sesamolin. Indeed, Erdtman and Gripenberg[2] considered such a *trans* nucleus for pinoresinol sterically improbable. Michael and Ross[7] who originally synthesized the *dl-cis* form of dilactone III were unable to prepare its *trans* analog. Heating of the *dl-cis*-dilactone III with alkali caused racemization and gave two forms of the disodium salt which were separated. On treatment with acid, one form closed to give the original *dl-cis*-dilactone, whereas the other salt formed a monolactone in which the remaining carboxyl and methylol groups would not lactonize. The attempt to force lactonization by means of a dehydrating agent resulted instead in the loss of a molecule of water and the formation of an unsaturated lactonic acid. The authors state that in the monolactone the carboxyl and methylol groups are not in the same plane but are widely separated (*trans*).

It is apparent from the foregoing discussion that should the nucleus of sesamolin exist in the *trans* form, it will not close again to a *trans* structure once is is opened (with acid).

As required by previously reported data on sesamolin,[1] structures V and VI each contains one acetal (acid hydrolysis) and one benzyl ether group (hydrogenolysis). Upon treatment of either structure with nitric acid, sesamol should split off and the ring containing the acetal should open. Formula V requires two additional assumptions. The first is that carbon atoms 2 and 4 are oxidized to carboxyl groups by the nitric acid at room temperature; and second, that the other ring then will open to permit rotation about positions 1–5, followed by ring closure to give dilactone III. Since the product (III) is known to have a *cis* configuration,[2] structure V presumes that the nucleus of sesamolin exists originally in the *trans* form.

In regard to the first assumption the oxidation of carbon 2 to a carboxyl group is expected, but such an oxidation also should take place at carbons 6 and 8 as well as at carbon 4. However, only one pure product was obtained in this degradation. Furthermore, Freudenberg and Dietrich[3] obtained 40 and 63% yields of dilactone from pinoresinol and dibromopinoresinol dimethyl ether even though these compounds were oxidized with concentrated nitric acid at 100°. If this dilactone survives these drastic conditions without being further oxidized to the anhydride or dianhydride, it is unreasonable to assume that such an oxidation will take place at room temperature.

In regard to the second assumption that the tetrahydrofuran rings will open, the high yields of dilactone obtained by Freudenberg and Dietrich again are pertinent. If the tetrahydrofuran rings were opened under their conditions (100°), which are known to oxidize methylol groups, one cannot account for the high yields of dilactone. It is more reasonable to conclude that the rings were not opened. With the much milder treatment of sesamolin (at room temperature) such ring scission would appear to be remote.

Formula VI likewise requires the opening of the second tetrahydrofuran ring and rotation about the 1–5 positions and, for the reasons presented above, is considered unlikely although more likely than formula V.

The fact that a *trans* nucleus would not close again in the *trans* form suggests a means of proving the structure of sesamolin. Samin, the hemiacetal of sesamolin, prepared by hydrolytic scission of sesamol from sesamolin with dilute hydrochloric acid,[8] has the formula (whether sesamolin is structure I or VI but not V)

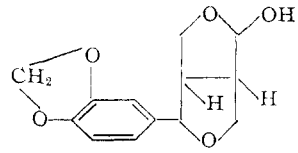
(4) Synthesis to be reported.

(5) W. Hückel, "Theoretische Grundlagen der Organischen Chemie," Vol. I, 63 (1934).

(6) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934); J. W. Barrett and R. P. Linstead, *ibid.*, 436 (1935).

(7) A. Michael and J. Ross, THIS JOURNAL, **55**, 3693 (1933).

(8) W. Adriani, *Z. Untersuch. Lebensm.*, **56**, 187 (1928).



Preparation of samin from a *trans* nucleus would involve rotation about positions 1–5 followed by ring closure. Treatment of samin with excess sesamol in the presence of hydrochloric acid should regenerate sesamolin only if sesamolin existed originally in the *cis* form. Unfortunately the author thus far has been unable to prepare this compound.

Inasmuch as the isolation of the optical antipode of dilactone III had not been reported, this dilactone was isolated from asarinin, a diastereoisomer of sesamin. Its properties were identical with those of the dilactone from sesamin and sesamolin except for its optical rotation, which was negative by an approximately equal amount. Since the dilactones derived from sesamin and asarinin, like that from pinoresinol, are optically active, their nuclei also must have the *cis* configuration.

The *dl*-dilactone prepared by mixing equal weights of the optically active dilactones derived from sesamolin and asarinin melted at 137–138°. Michael and Ross, who first synthesized this compound, reported a m.p. of 138° for their product.[7]

Experimental

Permanganate Oxidation of Sesamolin.—0.92 gram of sesamolin, dissolved in 25 ml. of acetone, was heated under reflux for 8 hours while 3.3 g. of potassium permanganate was added in small portions, each portion being decolorized prior to the next addition. After standing overnight, the acetone solution was filtered from the manganese dioxide and evaporated. The manganese dioxide was not discarded. The residue was taken up in water plus some 1 *N* potassium hydroxide. The ether extract of this solution yielded 600 mg. of unchanged sesamolin after evaporation and crystallization. The extracted alkaline solution was concentrated and then acidified with hydrochloric acid. An amorphous material and a small quantity of crystals were deposited, but these products were not readily characterizable.

The manganese dioxide was washed with hot water and the alkaline filtrate acidified with hydrochloric acid. After standing overnight crystals formed. The solution and crystals were extracted several times with ether; the ether layer was extracted twice with 1 *N* potassium hydroxide and the resulting aqueous layer acidified with hydrochloric acid. After several extractions of the acidified solution with ether, the ether layer was dried over sodium sulfate and evaporated. The residue was taken up in a small amount of methanol, and water was added until a slightly turbid solution formed when the mixture was heated in hot water. After standing overnight, crystals melting at 227° were obtained. The melting point of a mixture of these crystals with authentic piperonylic acid, m.p. 228°, was not depressed; neut. equiv. 168, theory for piperonylic acid 166. The ultraviolet spectrum from 225–315 mμ agreed with that of piperonylic acid.

Dilactone from Sesamolin.—One gram of sesamolin was rubbed up in a mortar with 18 ml. of concentrated nitric acid. The sesamolin reacted rapidly with the liberation of oxides of nitrogen. The clear solution was allowed to remain overnight and then evaporated *in vacuo* (water-pump) on an 80° water-bath until the residue was a froth. After the addition of about 50 ml. of water, a precipitate formed which was filtered off and discarded. The solution was neutralized to *p*H 5–6 and again filtered. The filtrate then was extracted once with about 5 ml. of chloroform (discarded) and eight times with 60-ml. portions of chloroform. After drying over sodium sulfate, the combined chloroform extracts were completely evaporated. The residue (120 mg.) was taken up in hot benzene and after being filtered, concentrated and cooled, crystals appeared. These crystals were filtered off and washed with dry ether; yield 85 mg. (22%), $[\alpha]^{36}D$ +210° (*c* 1.01) in water, m.p. 160–161°, sapon. equiv. 73 (theory 71).

Anal. Calcd. for $C_6H_6O_4$: C, 50.7; H, 4.3. Found: C, 51.00; H, 4.33.

The melting point of the dilactone was undepressed in admixture with that obtained from dibromosesamin by following the procedure of Erdtman and Gripenberg[2] with the dimethyl ether of dibromopinoresinol.

Dilactone from Sesamin.—By following the procedure used for sesamolin, the same dilactone was obtained from sesamin.

Dilactone from Asarinin.—The procedure for sesamolin was used to obtain the dilactone from asarinin except that the reaction mixture was heated on a steam-bath for one hour after the asarinin had been rubbed up with the nitric acid. Only 17 mg. of the dilactone was obtained from 1 g. of asarinin, m.p. 160–161°, $[\alpha]^{30}D$ −204 (*c* 0.49), sapon. equiv. 73 (theory 71).

***dl*-Dilactone.**—Equal weights of the dilactones from sesamolin and asarinin were dissolved in hot benzene. After slow evaporation of the solvent the crystals melted at 137–138°.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

The Synthesis of 1,3,4,5-Tetrahydrobenz[cd]indole

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5-Nitrotetralin (I) has been treated with ethyl oxalate to yield 8-nitro-1,2,3,4-tetrahydro-1-naphthalenglyoxylic acid (II) which, on reduction with ferrous hydroxide, has afforded 2-carboxy-1,3,4,5-tetrahydrobenz[cd]indole (III). The tricyclic derivative III lost carbon dioxide in acid solution to give 1,3,4,5-tetrahydrobenz[cd]indole (IV) which was obtained, as well, by cyclization of N-formyl-1,2,3,4-tetrahydro-5-naphthylamine in the presence of potassium *t*-butoxide.

Among the natural products which fall into the classification of indole derivatives, the sole representative of a polynuclear system characterized by cyclization into the 4-position remains lysergic acid, the complex amino acid obtained by hydrolytic cleavage of the ergot alkaloids. One of the major problems encountered in attempts to construct the ergoline skeleton of lysergic acid derives from the difficulty of elaboration of this unique 3,4-trimethyleneindole mode of ring fusion for which there was no precedent in the earlier development of heterocyclic chemistry. The relatively indifferent nature of the 4-position in indole itself, as well as the frequent inaccessibility of appropriate 1,2,3-trisubstituted benzene derivatives desired as intermediates, has limited rather markedly the number of approaches practicable for extended synthetic work.