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Constitution of Resin Phenols and their Biogenetic Relations

XIX *. The Structure of Sesamolin, the Configuration of Sesamin ** and the Nature of Fagarol ***

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The constitution of sesamolin has been elucidated and found to be the acetal (I). Sesamin has been shown to possess a "symmetrical" configuration (VII a or VIII a). The optically inactive fagarol of Priess from *Fagara xanthoxyloides* (Lam.) was obviously *d,l*-sesamin. A renewed investigation of the constituents of the bark of this species showed that it contains *d*-sesamin together with some *l*-sesamin.

In many countries it is prescribed by law that sesame oil must be added to oils and fat employed in the manufacture of margarin and artificial cream. This is due to the fact that sesame oil gives a very characteristic colour reaction (Baudouin's reaction: a red colour with hydrogen chloride and furfural) which makes it easy to differentiate between natural butter and cream and their artificial substitutes.

Baudouin's reaction is due to the presence in the oil of a compound m. p. 94°, isolated by the Italian chemists Malagnini and Armanni [1]. Their analyses indicated a formula $C_{20}H_{18}O_7$ or $C_{17}H_{16}O_6$. Under the influence of acids this compound furnishes sesamol (4-hydroxy-1,2-methylenedioxybenzene [1-3]). It is this substance which reacts with furfural to give the red colour in Baudouin's reaction.

Adriani [3] called the compound m. p. 94° sesamolin and showed that it had the elementary composition $C_{20}H_{18}O_7$ and this has now been confirmed. Adriani also showed that sesamolin on acid cleavage gives in addition to sesamol a new compound called samin according to the equation $C_{20}H_{18}O_7 + H_2O = C_7H_6O_3$ (sesamol) + $C_{13}H_{14}O_5$ (samin). Both sesamolin and samin are dextrorotatory ($[\alpha]_D$ *ca.* +220°, and *ca.* +100°, respectively). This cleavage of

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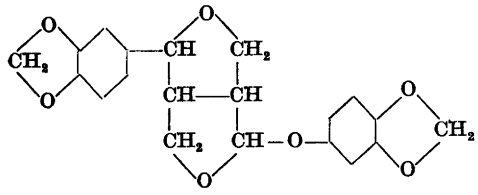
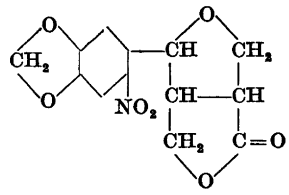
sesamolin indicates that the reaction is a simple hydrolysis and it has already been suggested by Böeseken, Cohen and Kip [4] that sesamolin might have a glycosidic structure.

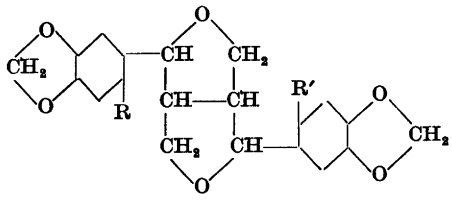
Sesame oil also contains another compound, sesamin (II) ($C_{20}H_{18}O_6$) differing from sesamolin only in possessing one oxygen atom less. Since both sesamolin and sesamin contain methylenedioxy groups the acetal structure (I) immediately suggests itself as the most probable structure for sesamolin.

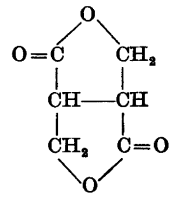


I



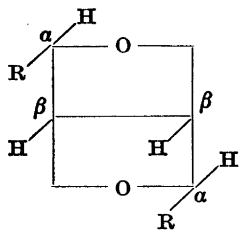
III



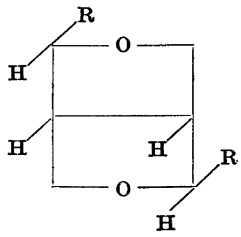


VI

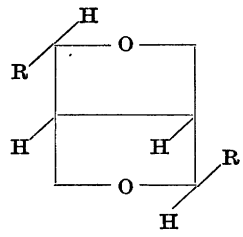
II R=R′=H
IV R=NO_2; R′=Br
V R=R′=Br
X R=NO_2; R′=H
XI R=Br; R′=H



VII a, b



VIII a, b



IX

VII a, VIII a: R=3,4-methylenedioxyphenyl

VII b, VIII b, IX: R=3-methoxy-4-hydroxyphenyl

The correctness of this assumption has been shown by converting both sesamolin and sesamin to the same nitrolactone $C_{13}H_{11}NO_7$ (III). This compound is obtained in excellent yield by cautious nitration of sesamolin and by the action of nitric acid on bromonitrosesamin (IV).

Sesamin belongs to the group of bis-furanoid lignans which can be divided into two subgroups, one containing methylenedioxy groups involving the oxygen atoms at 3,4,3′,4′ and another containing methoxyl groups (or hydroxyl groups) in these positions. The former includes sesamin, *iso*sesamin, *l*-sesamin and asarinin (*epi*-*l*-sesamin) and the latter pinoresinoldimethylether, *epi*pinoresinoldimethylether, eudesmin and *epi*eudesmin. Sesamin, *l*-sesamin, asarinin, pinoresinol and eudesmin have been isolated from natural sources. A β-glucoside of *epi*pinoresinolmonomethylether and a mono-β-glucoside of the optical antipode of *epi*pinoresinol (phillyrin (forsythin) and symplocosin, respectively) have also been encountered in nature. By elimination of the methylene groups followed by methylation, members of the former group have been transformed into compounds belonging to the latter group. (For references *cf.* Erdtman [5]).

Cohen [6] found that dibromosesamin (V) when treated with nitric acid furnished 4-bromo-5-nitromethylenedioxybenzene and Erdtman and Gripenberg [7] showed that dibromopinoresinoldimethylether similarly gives an excellent yield of 4-bromo-5-nitro-veratrol and the dextrorotatory bishydroxymethylsuccinic acid dilactone (VI). The same dextrorotatory dilactone has now been obtained from dibromosesamin. The optical activity of this dilactone shows that the hydrogen atoms at the β-carbon atoms in sesamin and pinoresinol are *cis* in concordance with the results obtained by v. Bruchhausen and Gerard [8] and by Haworth and Woodcock [9] by means of catalytic hydrogenation.

Sesamin (*d*-sesamin) and *l*-sesamin are optical antipodes and are converted into *d*-*iso*sesamin and *l*-*epi*sesamin (asarinin) under the influence of acids. This is due to inversion at one of the α-carbon atoms. Similarly pinoresinoldimethylether (*d*-pinoresinoldimethylether) and eudesmin (*l*-eudesmin) are optical antipodes and are converted into *d*-*epi*pinoresinol dimethylether and *l*-*epi*eudesmin by acids.

It has been shown by Erdtman [10] and by Gripenberg [11] that pinoresinol (and eudesmin) is "symmetrical" and hence can be described by one of the possible formulae (VII b) and (VIII b). Gripenberg [12] showed that *epi*pinoresinol lacks such "symmetry" and therefore has the formula (IX). Similarly we have now shown that mononitration of *d*-sesamin followed by bromination yields the same bromonitro-*d*-sesamin as that obtained by monobromination followed by nitration. Since no isomeric monosubstitution derivatives were found this shows that *d*-sesamin like pinoresinol is "symmetrical" (VII a) or (VIII a) (or their mirror images), and that these substances are structurally and configurationally analogous (as well as *l*-sesamin and *l*-eudesmin). These results invalidate the conclusions drawn by one of us [13] from the remarkable similarity in the changes in optical rotations on dinitration of *l*-asarinin and *l*-eudesmin.

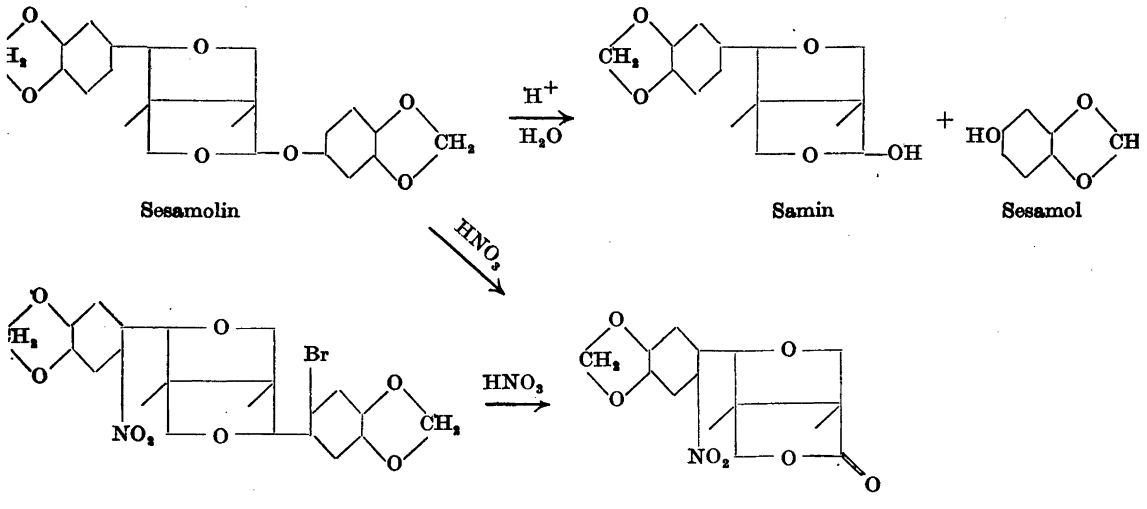
From the above chemical evidence the bisfuranoid keysubstances can be divided into two groups and this division is also confirmed by the molecular rotations.

The following chart, shows the relationships between the bisfuranoid keysubstances.

Group A, "symmetrical"		*Group B, "unsymmetrical"*
l-sesamin $[M]_D$ —234°	H^+	*l*-asarinin $[M]_D$ —422°
l-eudesmin $[M]_D$ —247°	H^+	*l-epi*eudesmin $[M]_D$ —560°
d-sesamin $[M]_D$ +242°	H^+	*d-iso*sesamin $[M]_D$ +422°
d-pinoresinoldimethylether $[M]_D$ +251°	H^+	*d-epi*pinoresinoldimethylether $[M]_D$ +545°

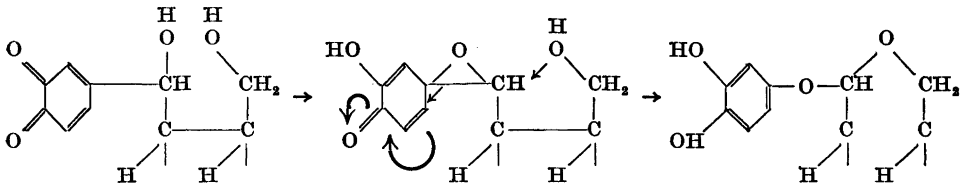
The only remaining configurational problem is the relative configurations at the α- and β-carbon atoms (*cf.* VII—IX). In group B the hydrogen atoms at the α-carbon atoms are *trans*. In group A they are *cis*, but it is not yet known whether they are *cis* or *trans* in relation to the hydrogen atoms at the β-carbon atoms.

As already mentioned, on treatment with nitric acid sesamolin gives a nitrolactone the composition of which is $C_{13}H_{11}NO_7$ and for which structure (III) was anticipated. When bromonitrosesamin is treated with nitric acid the brominated aromatic nucleus is extruded as 4-bromo-5-nitromethylene dioxybenzene and the lactone, $C_{13}H_{11}NO_7$, containing all the other carbon atoms of the sesamin molecule is formed. The yields of these fission products were almost quantitative and the reaction is directly analogous to the cleavage of 6,6′-dibromopinoresinoldimethylether or 6,6′-dibromosesamin (V). The lactones from sesamolin and from bromonitrosesamin were identical and this proves the structure of sesamolin and settles its configuration up to the limits set by our incomplete knowledge of the configuration of sesamin. The following formulae show the relationships between sesamin, sesamolin, samin and sesamol.



Sesamolin, obviously, is formed from sesamin or a nonmethylenated precursor by opening the molecule between one of the aromatic rings and the corresponding α-carbon atom.

The following formulae envisage a possible route but there are attractive alternatives including a rearrangement of a peroxide:



Among the lignans of unknown structure fagarol m. p. 127—128°, $C_{20}H_{18}O_6$, is unique in that it is optically inactive. It has been isolated from the root bark of *Fagara xanthoxyloides* Lam (Rutaceae), *cf.* Priess [14]. Östling [15] found a "sterol" $C_{27}H_{44}O$ m. p. 214° in the same material.

Recently Paris and Moyse-Mignon [16] reported the isolation of fagarol from *Fagara xanthoxyloides* and they comment upon certain discrepancies in the older literature and point out that they are probably due to confusion as regards the botanical identity of the (closely similar) *Fagara* species. Paris and Moyse-Mignon[17] have also isolated fagarol from the root bark of *Fagara viridis* A. Chev. Both species are West African (Senegal, Ivory Coast, Gold Coast, Togo).

Mameli [18], without adducing any new evidence, assumed that fagarol is *d,l*-cubebin ($C_{20}H_{20}O_6$) which, however, is not in agreement with the analyses. In view of the fact that the genera *Fagara* and *Xanthoxylum (Zanthoxylum)* are very closely related and that asarinin occurs in several *Xanthoxylum* species it appeared likely that fagarol might be identical with *d,l*-asarinin, m. p. 135—136°, or perhaps more likely with *d,l*-sesamin, m. p. 129—130°.

Through the good offices of Sir John Simonsen, London, we have been able to investigate bark from a tree identified by experts in London as *Fagara xanthoxyloides* and kindly provided by Dr. F. E. Hughes, Chief Conservator of Forests, Accra, Gold Coast. Extraction with light petroleum yielded an oil from which a compound m. p. 121—122° possessing the empirical composition $C_{20}H_{18}O_6$ and another compound m. p. 215°. Analysis showed the latter compound to have the formula $C_{30}H_{50}O$. It was obviously identical with Östling's "sterol" since it had the same optical rotation and also yielded an acetate with properties agreeing with those reported by Östling [15]. (Östling gives m. p. 119° instead of 219° obviously due to a misprint). The compound was identified (B. Thomas) as lupeol by direct comparison with an authentic sample kindly provided by Professor E. R. H. Jones, Manchester. Lupeol has been isolated from several *Fagara* and *Xanthoxylum* species [19,20].

The compound m. p. 121—122° was identical with *d*-sesamin. From the mother liquors of the sesamin, fractions were obtained which possessed the same or slightly higher melting points (123—124°) but lower rotations (about +50°). They did not depress the melting point of *d*-sesamin or *d,l*-sesamin and

obviously consisted of mixtures of *d*- and *l*-sesamin the *d*-form preponderating. According to Kaku and Ri [21] *d,l*-sesamin is a pseudoracemate ("Mischkristallisat") which is in agreement with our findings.

A specimen of "fagarol" ($[\alpha]_D$ +26° in chloroform) kindly provided by Professor Paris showed no depression on admixture with our sesamin preparations, but a large depression when mixed with *d,l*-asarinin. The IR absorption spectra of our sesamins (both that of *d*-sesamin and *d,l*-sesamin and the product of low optical rotation from *F. xanthoxyloides* and of the "fagarol" specimen of the French authors were identical. Hence Priess fagarol is certainly *d,l*-sesamin. The species *Fagara xanthoxyloides* is able to synthesise *d*-sesamin as well as *l*-sesamin although the relative amounts may perhaps vary from specimen to specimen. Alternatively there may be various strains of *Fagara xanthoxyloides* or hybrids between closely related species. It is possible that Priess recrystallised his fagarol until it consisted exclusively of *d,l*-sesamin, which has a higher melting point than the pure antipodes.

EXPERIMENTAL

Isolation of sesamolin and sesamin from sesame oil. Sesame oil was continuously extracted with methanol until the Baudouin reaction was negative or very faint. The methanol was evaporated and the residual oil treated with light petroleum (40–60°) and left in the refrigerator for 24 hours to crystallise. The crystalline material, judging by the rotation ($[\alpha]_D$ +115 ± 5°) was a mixture of sesamin and sesamolin in the approximate proportion of 5:1. By leaching with hot methanol the mixture was almost freed from sesamolin and the remaining sesamin was crystallised from ethanol giving pure sesamin, long rodlike needles, m. p. 122–122.5°, $[\alpha]_D^{20}$ +67.9°. The sesamolin was crystallised from methanol giving small leaflets m. p. 94–94.5°, $[\alpha]_D^{20}$ +212° (*c* 1.13 in chloroform). (Found: C 64.64; H 5.09. Calc. for $C_{20}H_{18}O_7$ (370.3): C 64.86; H 4.90).

Mononitrosesamin (X). Sesamin (2 g) was dissolved in a mixture of glacial acetic acid (15 ml) and acetic anhydride (5 ml). The solution was cooled to −10° and a cold solution of nitric acid (0.35 ml, d = 1.40) in acetic anhydride (3 ml) was added. After one hour water was added until the solution became cloudy and the dinitrosesamin which subsequently precipitated was collected (0.18 g) and crystallised from ethylacetate. Yellow-greenish needles, m. p. 240–241°, $[\alpha]_D^{20}$ +37° (*c* 1.10 in chloroform). When more water was added to the mother liquor an oil separated which solidified after a few hours. Fractional crystallisation from ethanol gave mononitrosesamin (0.85 g) as slightly yellow needles m. p. 142–143°, $[\alpha]_D^{20}$ −68.9° (*c* 1.42 in chloroform). (Found: N 3.86. Calc. for $C_{20}H_{17}NO_8$ (399.3): N 3.51). From the mother liquors sesamin (0.6 g) was recovered.

Monobromosesamin (XI). To a solution of sesamin (5 g) in pyridine (5 ml) and glacial acetic acid (50 ml) a solution of bromine (0.75 ml) in glacial acetic acid (30 ml) was added at room temperature and after 3/4 of an hour water was added until the solution became cloudy. Dibromosesamin (0.7 g) separated and was collected. Thin needles from ethanol, M. p. 180.5–181°, $[\alpha]_D^{20}$ −13.2° (*c* 1.01 in chloroform). Addition of more water to the mother liquor gave an oil which yielded monobromosesamin (1.72 g) and unreacted sesamin (0.5 g) on fractional crystallisation from methanol. The monobromosesamin crystallised in needles m. p. 85–85.5, $[\alpha]_D^{20}$ +29° (*c* 1.87 in chloroform). (Found: Br 18.98. Calc. for $C_{20}H_{17}BrO_6$ (433.3): Br 18.45).

Bromonitrosesamin (IV). A. Mononitrosesamin (0.5 g) dissolved in glacial acetic acid (8 ml) containing a few drops of pyridine was treated with bromine (0.06 ml) in glacial acetic acid (4 ml) at room temperature. After 15 minutes the product was precipitated in almost quantitative yield by the addition of water. The bromonitrosesamin crystallised from chloroform-ethanol in threadlike yellow needles, m. p. 201.5–202.5°

(softening at 186—187°), $[\alpha]_D^{20}$ −35° (*c* 1.35 in chloroform). (Found: Br 16.35. Calc. for $C_{20}H_{16}BeNO_8$ (478.3): Br 16.71).

B. Monobromosesamin (0.25 g) dissolved in a mixture of glacial acetic acid (1 ml) and acetic anhydride (1 ml) was nitrated at −15° with nitric acid (0.05 ml, d = 1.40) in acetic anhydride (1 ml). After a few minutes water was added to precipitate the product (0.21 g) which on crystallisation from chloroform-ethanol melted at 186—186.5°, $[\alpha]_D^{20}$ −34.5° (*c*. 1.34 in chloroform). When seeded with the higher melting bromonitrosesamin the melting point was raised to 201.5—202.5° and a mixed m. p. of preparations A and B showed no depression.

Degradation of dibromosesamin with nitric acid. Dibromosesamin (2 g) was added in small portions to nitric acid (30 ml, d = 1.40) at room temperature. A very faint reaction was noticed and a yellow crystalline precipitate was formed immediately and identified as 4-bromo-5-nitromethylenedioxybenzene (1.2 g). Yellow plates, m. p. 89° from ethanol. Addition of water to the nitration mixture gave another crop (0.27 g) of this compound. The mixture was then neutralised with bicarbonate, the water evaporated, and the dried residue continuously extracted with ether for 24 hours. The ether extract was evaporated and the residue dissolved in water, filtered and again evaporated to dryness. The product (0.25 g) was crystallised from benzene containing a few drops of ether. M. p. 162.5—163°, $[\alpha]_D^{20}$ +219° (*c* 0.89 in water). Erdtman and Gripenberg [7] found for the dilactone of bishydroxymethylsuccinic acid, m. p. 160—161°, $[\alpha]_D$ +206° (*c* 1.06 in water). Mixed m. p. of the two samples 160—162°.

Degradation of sesamolin with nitric acid. When sesamolin (0.3 g) was added to nitric acid (7 ml, d = 1.40 at room temperature it immediately dissolved with evolution of heat and nitrous fumes. After a few minutes water was added until the solution became cloudy and the mixture after leaving for some hours, deposited a yellow solid (0.16 g) which was crystallised from ligroin containing a little acetone. Thin yellow needles, m. p. 155.5—156.5°, $[\alpha]_D^{20}$ ±0° (*c* 0.68 in chloroform), +23.5° (*c* 0.53 in pyridine) (Found: C 53.14; H 3.87; N 5.11. Calc. for $C_{13}H_{11}O_7$ (293.2): C 53.24; H 3.78; N 4.78.)

Degradation of bromonitrosesamin with nitric acid. Bromonitrosesamin (0.6 g) was added to nitric acid (15 ml, d = 1.40) at room temperature. After 15 minutes the mixture was filtered from bromonitromethylenedioxybenzene (0.1 g) and then water was added until no more material was precipitated. The precipitate (0.44 g) was collected after standing some hours in the refrigerator and was found to be a mixture of bromonitromethylenedioxybenzene and another substance (0.27 g) which was crystallised from ligroin. M. p. 156—157°, undepressed on mixing with the degradation product from sesamolin.

Isolation of sesamin and lupeol from Fagara *bark.* The ground trunk or root bark of *Fagara xanthoxyloides* (Lam) was continuously extracted with light petroleum (40—60°) for 5 days. The residual oil after evaporation of the solvent was mixed with methanol. On standing crystals deposited. The first crops (A) were recrystallised from ethanol and further crops (B) from acetic acid. From A a relatively small amount of pure *d*-sesamin was obtained. M. p. 121—122°, $[\alpha]_D^{20}$ +65.2° (*c* 1.6 in chloroform). (Found: C 67.88; H 5.20. Calc. for $C_{20}H_{18}O_6$ (354.3): C 67.79; H 5.12). From the mother liquors fractions were obtained which showed a lower rotation but a slightly higher melting point, *e. g.* m. p. 123—124°, $[\alpha]_D^{20}$ + 49.8° (*c* 1.09 in chloroform). The melting points of these fractions were always between that of *d*-sesamin and *d,l*-sesamin. From all these sesamin fractions dibromo-*d*-sesamin was obtained m. p. 174—175°, $[\alpha]_D^{20}$ −14.3° (*c* 1.7 in chloroform), mixed m. p. with authentic dibromo-*d*-sesamin, $[\alpha]_D^{20}$ −15.0° (*c* 0.88 in chloroform), 175—176°. Cohen [6] gives $[\alpha]_D$ −9.6° (in chloroform) and Kaku and Ri [21] give $[\alpha]_D$ +16.2° (*c* 0.86 in chloroform) for dibromo-*l*-sesamin.

From B a colourless product was obtained by recrystallisation from acetic acid. M. p. 215—216°, undepressed by an authentic specimen of lupeol, $[\alpha]_D^{20}$ +25° (*c* 1.2 in chloroform). The acetate was prepared using acetic anhydride in pyridine and crystallised from chloroform-alcohol. M. p. and mixed m. p. 218—219°, $[\alpha]_D^{20}$ +30°. (*c* 1.2 in chloroform). (Found: C 81.86; H 11.23; Calc. for $C_{32}H_{52}O_2$ (468.7): C 81.99; H 11.18).

We are indebted to *Statens Tekniska Forskningsråd* and to the *Scientific Department, Israeli Ministry of Defence*, for financial support and to *Margarinbolaget*, Stockholm, for a generous gift of sesame oil.

Added in proof: The structure of sesamolin has recently been proved independently by M. Beroza (*J. Am. Oil Chemists' Soc.* **77** (1955) 3332) and by E. Haslam and R. D. Haworth (*J. Chem. Soc.* **1955** 827).

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