# ISOLATION OF 2,4,5-TRIMETHOXYALLYLBENZENE FROM CAESULIA AXILLARIES OIL

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#### Summary

The phenolic ether obtained from the essential oil of *Caesulia axillaries* has been shown to be 2,4,5-trimethoxyallylbenzene (I), on the basis of chemical and spectroscopic evidence. It has tentatively been named as  $\gamma$ -asarone.

Two trimethoxyallylbenzenes have been reported to occur in nature. Elemicin has been shown by Semmler<sup>1</sup> to be 3,4,5-trimethoxyallylbenzene and confirmed by syntheses.<sup>2,3</sup> Calamol<sup>4</sup> from the rhizomes of *Acorus calamus* (variety "Ghore Bacha") is believed to be 2,3,5- or 2,3,6-trimethoxyallylbenzene. A third isomer, 2,4,6trimethoxyallylbenzene, was synthesized by Holmes and co-workers.<sup>5</sup> The fourth isomer, 2,4,5-trimethoxyallylbenzene, was reported by Rao and Subramanian<sup>6</sup> but later the same authors showed it to be  $\beta$ -asarone,<sup>7</sup> a geometrical isomer of 2,4,5trimethoxypropenylbenzene. There seems to be no other reference in the literature pertaining to the isolation of 2,4,5-trimethoxyallylbenzene from a natural source. Scant physical data have been reported by Shulgin<sup>8</sup> on a synthetic by-product purported to be this trimethoxyallylbenzene, C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>, from the oil of *Caesulia axillaries*<sup>9</sup> in the pure form (gas and thin-layer chromatography) and present conclusive chemical and spectral evidence for the structure (I) of this product. We propose to name this compound as  $\gamma$ -asarone.<sup>‡</sup>

The compound has three methoxy groups (Zeisel determination). The molecular weight of  $\gamma$ -asarone as recorded by mass spectrometry was 208 (theoretical, 208). The i.r. spectrum of  $\gamma$ -asarone shows bands at 3030, 1818, 1626, 990, and 914 cm<sup>-1</sup>

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 $\ddagger$  Since the names  $\alpha$ - and  $\beta$ -asarone<sup>7</sup> have been given respectively to *trans* and *cis* isomers of 2,4,5-trimethoxypropenylbenzene, it would be better if 2,4,5-trimethoxyallylbenzene is designated as  $\gamma$ -asarone.

<sup>1</sup> Semmler, F. W., Ber. dt. chem. Ges., 1908, 41, 1768.

<sup>2</sup> Mauthner, F., Liebigs Ann., 1917, 414, 250.

<sup>3</sup> Hahn, G., and Wassmuth, A., Ber. dt. chem. Ges., 1934, 67, 696.

<sup>4</sup> Qudrat-i-Khuda, M., Mukherjee, A., and Ghosh, S. K., J. Indian chem. Soc., 1939, 16, 583.

<sup>5</sup> Holmes, P., White, D. E., and Wilson, I. H., J. chem. Soc., 1950, 2810.

<sup>6</sup> Sanjiva Rao, B., and Subramanian, K. S., Curr. Sci., 1935, 3, 552.

<sup>7</sup> Sanjiva Rao, B., and Subramanian, K. S., J. chem. Soc., 1937, 1938.

<sup>8</sup> Shulgin, A. T., Can. J. Chem., 1965, 43, 3437.

<sup>9</sup> Devgan, O. N., and Bokadia, M. M., Indian J. appl. Chem., 1967, 30, 166.

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for a vinylic double bond (-CH=CH<sub>2</sub>), bands at 1600, 1504, 862, 847, and 754 cm<sup>-1</sup> due to a 1,2,4,5-tetrasubstituted moiety and at 1220, 1193, and 1036 cm<sup>-1</sup> due to a phenolic ether. Hydrogenation of  $\gamma$ -asarone gave a dihydro derivative, C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> (II). The i.r. spectrum of the dihydro  $\gamma$ -asarone shows the absence of the bands at 3030, 1818, 1626, 990, and 914 cm<sup>-1</sup> indicating hydrogenation of the vinylic double bond. The double bond present in the side-chain is not in conjugation with the aromatic nucleus as it does not show any characteristic u.v. absorption ( $\lambda_{max} 228 \ m\mu$ , log  $\epsilon 3 \cdot 91$ ;  $\lambda_{max} 283 \ m\mu$ ; log  $\epsilon 3 \cdot 60$ ), whereas the i.r. spectrum of an authentic sample of  $\beta$ -asarone (III) shows bands at 1460 and 1389 cm<sup>-1</sup> due to the end-methyl grouping (C-CH<sub>3</sub>), 763, 862, 1534, 1608 cm<sup>-1</sup> due to the 1,2,4,5-tetrasubstituted benzene moiety, and 1036, 1202, 1220 cm<sup>-1</sup> due to the phenolic ether linkage.



The u.v. and i.r. spectra of the dihydro derivatives of  $\gamma$ -asarone and  $\beta$ -asarone are identical. On oxidation with neutral potassium permanganate  $\gamma$ -asarone gives 2,4,5-trimethoxybenzoic acid, which shows no depression in melting point with an authentic sample obtained by the oxidation of  $\beta$ -asarone. The volatile product of ozonolysis of  $\gamma$ -asarone was identified as formaldehyde through its dimedone derivative. The non-volatile product of ozonolysis was identified as 2,4,5-trimethoxyphenylacetaldehyde by analysis and i.r. spectrum which shows bands at 2703 and 1718 cm<sup>-1</sup> due to an aldehydic function; 1605, 1515, 862, 847, and 754 cm<sup>-1</sup> due to the 1,2,4,5-tetrasubstituted benzene moiety. On refluxing with alcoholic potassium hydroxide solution,  $\gamma$ -asarone is isomerized to  $\beta$ -asarone. The u.v. absorption ( $\lambda_{max}$ 247.5 m $\mu$ , log  $\epsilon$  4.24,  $\lambda_{max}$  295.5 m $\mu$ , log  $\epsilon$  3.62) and i.r. absorption of the isomerized product were identical with that of the authentic sample of  $\beta$ -asarone.

The n.m.r. spectrum of  $\gamma$ -asarone shows signals at  $3 \cdot 24$  and  $3 \cdot 42 \tau$  (due to aromatic protons), multiplets centered at  $3 \cdot 98$  and  $4 \cdot 92 \tau$  respectively due to sidechain protons (-CH=CH<sub>2</sub>); two singlets centered at  $6 \cdot 19 \tau$  (due to -OCH<sub>3</sub> protons) and a doublet at  $6 \cdot 67 \tau$  (due to benzylic protons). The n.m.r. of  $\beta$ -asarone is considerably different and shows the presence of an end-methyl group and two separate methine protons in the side-chain. It shows multiplets centered at  $3 \cdot 1$  and  $3 \cdot 46 \tau$ (due to two aromatic protons along with the unsaturated proton Y); a multiplet for proton X centred at  $4 \cdot 24 \tau$ ; a broad singlet centred at  $6 \cdot 1 \tau$  (due to the protons of -OCH<sub>3</sub> groups); a quartet at  $8 \cdot 0 \tau$  (due to -CH<sub>3</sub> protons).

#### EXPERIMENTAL

Infrared and gas chromatographic analysis were carried out in the Essential Oil Division, National Chemical Laboratory, Poona-8, and nuclear magnetic resonance spectra were recorded in the Tata Institute of Fundamental Research, Colaba, Bombay. The i.r. spectra were taken as

liquid films on a Perkin–Elmer 137B Infracord spectrometer. Gas chromatographic analysis were carried out on a Griffin–George instrument on a polyester column using hydrogen as the carrier gas. The n.m.r. spectra were recorded on a Varian spectrometer operating at 56.445 Mc/s. Anhydrous magnesium sulphate was used for all drying purposes. All melting points and boiling points are uncorrected.

#### Isolation of $\gamma$ -Asarone

The oil was obtained from the plant Caesulia axillaries as described.<sup>9</sup> It was fractionally distilled and the fraction boiling at 130–140°/4 mm was collected. The fraction (5 g) was chromatographed on alumina (grade II, 250 g) and eluted successively with light petroleum and light petroleum-benzene (I : 1). The light petroleum-benzene (1 : 1) elution yielded  $\gamma$ -asarone (4·7 g) in the pure form (gas and thin-layer chromatography). It showed the following properties: b.p. 96–97°/1·5 mm;  $n_{23}^{\text{D}}$  1·5295;  $d_{28}^{28}$  1·0796 (Found: C, 69·4; H, 7·7; OCH<sub>3</sub>, 43·15. C<sub>12</sub>H<sub>16</sub>O<sub>3</sub> requires C, 69·2; H, 7·7; OCH<sub>3</sub>, 44·2%). I.r. bands at 3030, 2899, 2778, 1818, 1626, 1600, 1504, 1451, 1431, 1387, 1307, 1220, 1193, 1117, 1036, 990, 914, 862, 847, 815, and 754 cm<sup>-1</sup>.

#### Dihydro- $\gamma$ -asarone (II)

 $\gamma$ -Asarone (0.26 g) in alcohol (80 ml) was hydrogenated using palladium-charcoal (0.08 g) as catalyst. The hydrogenation practically stopped at 24.1 ml (24°/706 mm). The catalyst was filtered off and the alcohol removed under suction. The residue was chromatographed over neutral alumina (grade III, 15 g) and eluted with petroleum (40–60°). The first two fractions 25 ml each, gave *dihydro-\gamma-asarone* (0.203 g), b.p. 140–142° (bath)/4 mm;  $n_D^{30}$  1.5108 (Found: C, 68.75; H, 8.7. C<sub>12</sub>H<sub>18</sub>O<sub>3</sub> requires C, 68.6; H, 8.6%). Its i.r. spectrum has absorption bands at 2941, 1600, 1504, 1449, 1389, 1307, 1220, 1198, 1117, 1036, 975, 860, and 784 cm<sup>-1</sup>.

#### Potassium Permanganate Oxidation of y-Asarone

 $\gamma$ -Asarone (0.7 g) in acetone (40 ml) was gently refluxed on a water-bath and to it was added potassium permanganate (9 g) in small portions. Excess of potassium permanganate was destroyed with sulphur dioxide. The contents were filtered under suction and the acetone solution was concentrated whereupon a white powder separated. On crystallization from hot water it yielded colourless needles of 2,4,5-trimethoxybenzoic acid, m.p. and mixed m.p. with an authentic sample obtained by the KMnO<sub>4</sub> oxidation of  $\beta$ -asarone, 144.5°.

#### Ozonolysis of y-Asarone

 $\gamma$ -Asarone (0.5 g) was dissolved in dry benzene (50 ml) and ozone was passed at the rate of 60 mg/hr for 4 hr at 0°. The solvent was removed at 40° under suction and the ozonide decomposed by adding water and heating on a water-bath (3 hr). The volatile product was passed through a saturated solution of dimedone in alcohol. The methylene-bisdimedone formed was crystallized from dilute alcohol, m.p. and mixed m.p. 188°. The non-volatile portion was cooled and extracted with ether, washed first with sodium bicarbonate solution and then with water till neutral, and dried. The removal of the solvent yielded a liquid product (0.35 g) which was chromatographed over alumina (grade III, 10 g). The light petroleum-benzene elutions yielded the aldehydic component 2,4,5-trimethoxyphenylacetaldehyde which was distilled under reduced pressure (b.p. 150–152°/7 mm) (Found: C, 62·9; H, 6·5. C<sub>11</sub>H<sub>14</sub>O<sub>4</sub> requires C, 62·9; H, 6·7%). Its i.r. spectrum has absorption bands at 2941, 2703, 1718, 1605, 1515, 1460, 1439, 1370, 1316, 1227, 1205, 1121, 1042, 862, 847, 918, and 754 cm<sup>-1</sup>.

## Isomerization of $\gamma$ -Asarone to $\beta$ -Asarone

 $\gamma$ -Asarone (0.5 g) was added to a solution of potassium hydroxide (1 g) in alcohol (20 ml) and the contents refluxed for 7 hr. Alcohol was removed under suction, the residue cooled, diluted with water (25 ml), and extracted with ether. The extract was washed with water and dried. On removing ether a liquid residue (0.4 g) was left which distilled at 148–149°/8 mm (Found: C, 69.5; H, 7.8. Calc. for C<sub>12</sub>H<sub>16</sub>O<sub>3</sub>: C, 69.2; H, 7.7%). Its i.r. and u.v. spectra are identical with those of an authentic sample of  $\beta$ -asarone.