

SYNTHETIC INVESTIGATIONS IN THE SESAMIN GROUP

Part I. Synthesis of Samin, a Degradation Product of Sesamolin

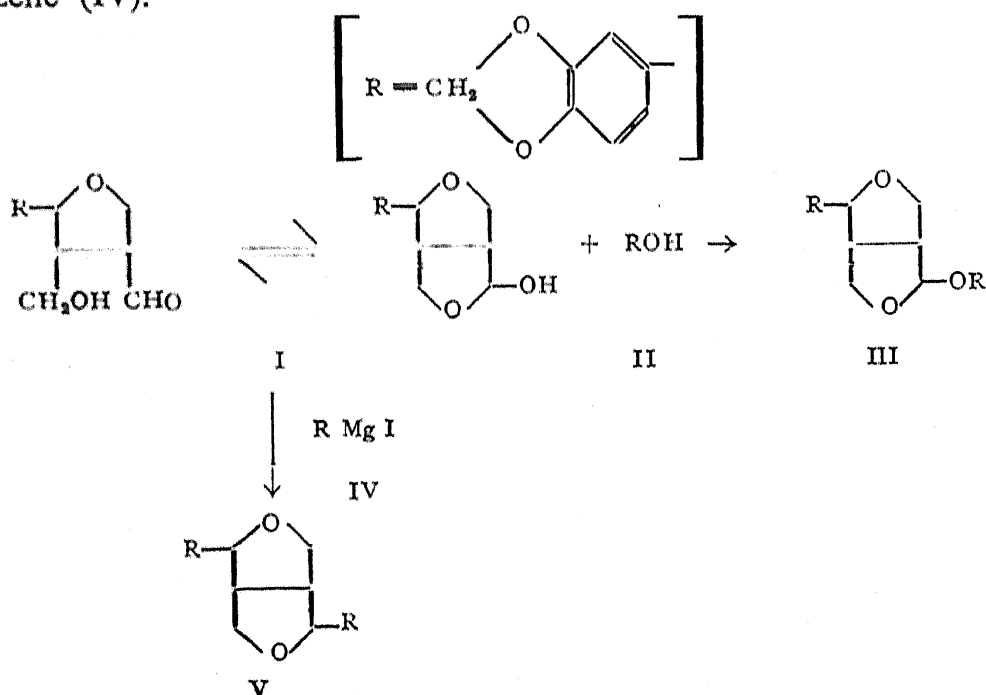
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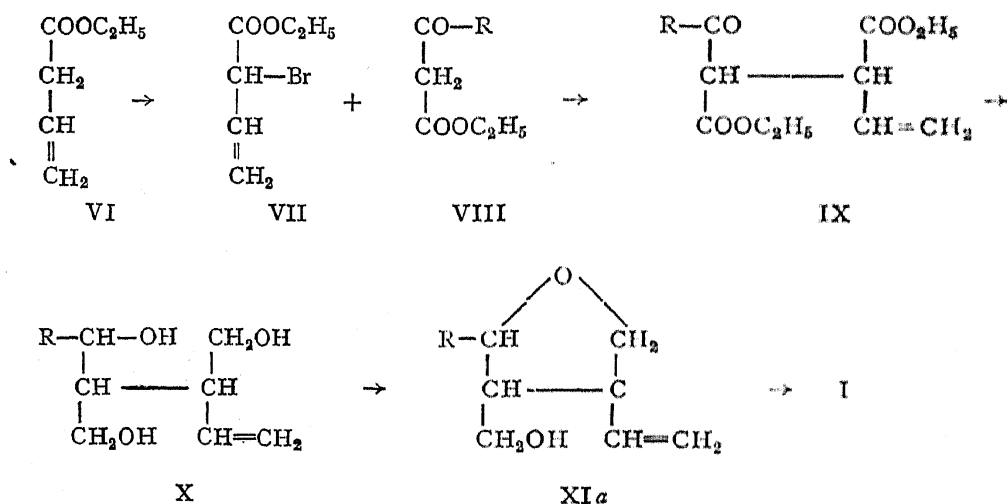
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THE discovery that the insecticidal potency of pyrethrins may be markedly synergised by sesame oil led Haller and coworkers¹ to investigate the principles responsible for this activity and it was found that sesamin¹ was one of these principles. Recently, sesamolin, another constituent of sesame oil, was reported² to be a more potent synergist, being about five times as active as sesamin.

Sesamolin has not so far been synthesised, although several syntheses³⁻⁶ of sesamin have been reported. It was considered that samin⁷ (I), a hydrolysis product of sesamolin, might serve as a suitable starting material for its synthesis, as it could lead to the formation of the mixed acetal grouping of sesamolin (III) by interacting with sesamol (II) in the presence of hydrogen chloride. Further, samin (I) can also be expected to furnish sesamin (V) on treatment with the Grignard reagent prepared from 4-iodomethylenedioxybenzene (IV).

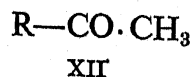


Because of the aforementioned considerations, the synthesis of samin (I) was undertaken according to the scheme outlined below:



Ethyl α -bromovinylacetate (VII) was prepared by treatment of ethyl vinylacetate^{8,9} (VI) with N-bromosuccinimide in the presence of benzoyl peroxide. It showed absorption peaks at 940 cm^{-1} and 980 cm^{-1} ($\text{CH}=\text{CH}_2$) and at 1724 cm^{-1} (ester $\text{C}=\text{O}$). Ethyl piperonylacetate (VIII), required for condensation with ethyl α -bromovinylacetate (VII), was at first prepared by the method of Bruchhausen and Gerhard,¹⁰ but better yield was obtained when the method of Perkin and Robinson¹¹ was followed later. The sodium salt of the β -keto ester (VIII) was condensed with the bromo ester (VII) in benzene to furnish a condensation product which on purification by short-path distillation separated into a solid (5%) and a liquid (25%) components.

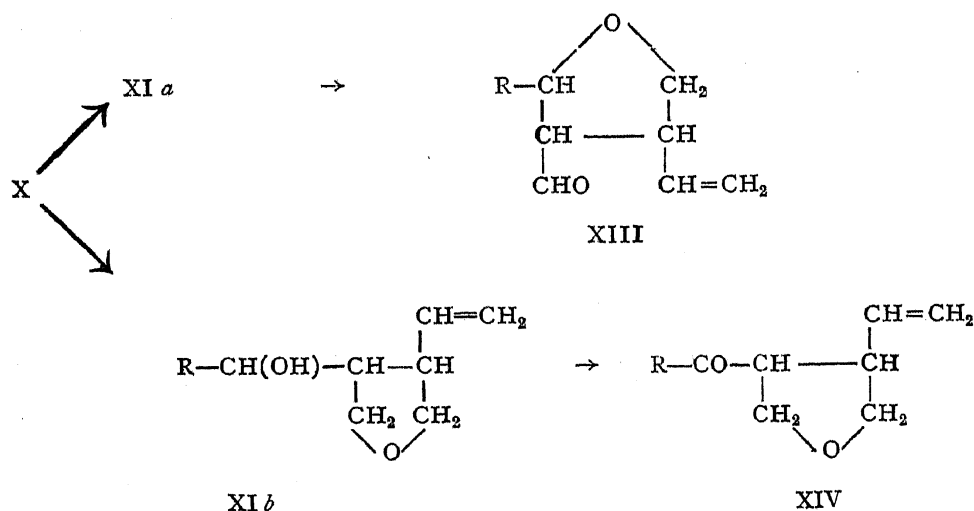
The solid product, m.p. 85–86°, which did not give any colour with alcoholic ferric chloride and whose infra-red spectrum revealed the absence of an ester carbonyl peak in 1735–1750 cm^{-1} region and the presence of a strong band at 1678 cm^{-1} (conjugated $\text{C}=\text{O}$) was identified as 4-aceto-methylenedioxybenzene (XII) through comparison of its infra-red spectrum with that of an authentic specimen and their mixture melting point determination.



The liquid component, which gave intense purple colour with alcoholic ferric chloride, was assigned the structure of the condensation product, diethyl α -vinyl- α' -piperonylsuccinate (IX), on the basis of spectral and analytical data. Later, the yield of the liquid component could be raised to 40% by

chromatography of the residue obtained following the removal of only the lower boiling solid product by distillation.

The condensation product (IX) on reduction with lithium aluminium hydride yielded 2-vinyl-3-(3', 4'-methylenedioxyphenyl)-hydroxymethyl-tetramethylene-1, 4-glycol (X). Cyclisation of the triol (X) with 1% ethanolic hydrogen chloride gave 2-(3', 4'-methylenedioxyphenyl)-3-hydroxymethyl-4-vinyltetrahydrofuran (XI *a*). Depending upon the alcoholic groups involved, the aforementioned cyclisation might also have given rise to the structural isomer 3-(3', 4'-methylenedioxyphenylhydroxymethyl)-4-vinyltetrahydrofuran (XI *b*). Oppenauer oxidation of the cyclised product, using aluminium



t-butoxide and acetone in refluxing benzene, furnished an aldehyde (XIII) which responded to Tollen's and Schiff's reagents, and this proved the structure of the cyclised product to be XI *a*, as the alternative structure (XI *b*) would have formed the ketone (XIV).

The cyclised compound (XI) was ozonolysed and the resulting crude ozonide, on treatment with zinc and acetic acid, afforded samīn (I) in 20% yield, m.p. 139–140°, which gave an intense pink colour with Schiff's reagent. The infra-red spectrum, which showed absorption bands at 3448 cm.⁻¹ (OH), 2780 cm.⁻¹ (shoulder, aldehyde C—H), 1718 cm.⁻¹ (aldehyde C=O), 1099 and 1042 cm.⁻¹ (tetrahydrofuran), was consistent with the structure of samīn (I).

Samin, which was first claimed to have been obtained in 1928 by Adriani,⁷ was reported to melt at 103° and have specific rotation, $[\alpha]_D^{20} + 103$ (CHCl₃). But Haworth¹² and Beroza¹³ failed to repeat the hydrolysis experiment of Adriani to obtain samīn, and we could not obtain a sample of samīn derived from sesamolin for direct comparison with our synthetic sample.

EXPERIMENTAL*

Ethyl Vinylacetate (VI).—This was prepared by modification of the method of Mannich.⁹

A solution of 30 g. vinylacetic acid⁸ in 300 ml. of dry ethanol and 200 ml. of carbon tetrachloride was refluxed with a small quantity of *p*-toluenesulphonic acid in a flask attached to a water separator,¹⁴ till no more water separated. Most of the solvent was removed and the residue was taken in ether. The ethereal solution was washed with 5% sodium bicarbonate solution and water and dried (MgSO_4). The residue obtained after removal of the solvent was distilled to give 23 g. (75%) of ethyl vinylacetate (VI), b.p. 115–118° (recorded b.p. 119°); n_D^{25} 1.4250.

Ethyl α -Bromovinylacetate (VII).—A mixture of 14 g. of ethyl vinylacetate (VI), 30 g. of N-bromosuccinimide, and 50 mg. of benzoyl peroxide in 200 ml. of carbon tetrachloride was refluxed for 5 hours. The reaction mixture was cooled and filtered from succinimide. The filtrate was washed with water and dried (MgSO_4). The solvent was removed and the residue distilled to give 12 g. (51%) of ethyl α -bromovinylacetate (VII), b.p. 72–75°/1 mm.; n_D^{20} 1.4985; ν (liquid film) 1724 cm^{-1} , 940 cm^{-1} , 980 cm^{-1} (Found: Br, 40.94%. Calc. for $\text{C}_6\text{H}_9\text{BrO}_2$: Br, 41.43%).

Ethyl Piperonylacetate.—This was at first prepared by the method of Bruchhausen¹⁰ in 40% yield, but later by the method** of Perkin and Robinson¹¹ in better yields (55%). One half the volume of a solution of sodium ethoxide, prepared from 2.3 g. of sodium and 26 ml. of dry ethanol, was added to a stirred and cooled (ice and salt) solution of 6.5 g. of ethyl acetoacetate in 10 ml. of ethanol, followed by the addition of half the volume of a solution of 9.2 g. of piperonyl chloride in 50 ml. of dry ether. Later, rest of the ethanolic sodium ethoxide and ethereal piperonyl chloride were alternately added in small equivalent volumes and the reaction mixture was left overnight. The precipitated sodio-salt was filtered and heated on a water-bath for 15 minutes with 100 ml. of water, 15 ml. of 10% aqueous ammonia, and 3.5 g. of ammonium chloride. The cooled reaction mixture was extracted with ether and the extract dried (Na_2SO_4). After removal of the solvent, the residue was purified by short-path distillation, 140–145°/2 mm.; yield 6.5 g.

* All melting points are uncorrected. The U.V. absorption spectra were taken in Beckmann spectrophotometer, Model DU. The I.R. spectra were taken in Perkin-Elmer Infracord, Model 137.

Diethyl α -Vinyl- α' -Piperonylsuccinate (IX).—The sodium derivative of ethyl piperonylacetate (VIII) was prepared by stirring a solution of 8.3 g. of the β -keto ester (VIII) with 0.81 g. of sodium dust in 200 ml. of dry benzene for 8 hours followed by refluxing for 2 hours. Freshly distilled ethyl α -bromovinylacetate (8 g.) was added dropwise to it with stirring, and the reaction mixture was refluxed for 1 hour. After cooling, ice-cold water was added to it, the benzene layer was separated, and the aqueous layer was extracted with ether. The combined benzene-ether solution was washed well with water and dried (MgSO_4). Purification of the residue obtained after removal of the solvent by short-path distillation afforded two fractions:

(i) This fraction (0.5 g.), b.p. 130–140°/0.2 mm., solidified on standing and was crystallised from aqueous methanol, m.p. 86–87°, and it did not give any colour with alcoholic ferric chloride; ν (CHCl_3), 1678 cm^{-1} (Found: C, 65.31; H, 4.81%. Calc. for $\text{C}_9\text{H}_8\text{O}_3$: C, 65.86; H, 4.88%). On admixture of a sample of this substance with an authentic specimen of acetopiperone (XII), prepared by the method of Mauthner,¹⁵ the melting point remained undepressed. The I.R. spectra of the two were also identical.

The 2, 4-dinitrophenylhydrazone on crystallisation from methanol melted at 255–257° (Found: N, 16.46%. Calc. for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_6$: N, 16.27%). This on admixture with the 2, 4-dinitrophenylhydrazone prepared from authentic acetopiperone, the melting point remained undepressed.

(ii) The second fraction (2.5 g, 25%) was an oil, b.p. 140–145°/0.2 mm., which gave a purple colour with alcoholic ferric chloride; ν (CHCl_3), 1667 cm^{-1} (conjugated C=O), 1724 cm^{-1} (ester C=O), 935 cm^{-1} and 980–985 cm^{-1} ($\text{CH}=\text{CH}_2$) (Found: C, 61.87; H, 5.55%. Calc. for $\text{C}_{13}\text{H}_{20}\text{O}_7$: C, 62.08, H, 5.7%).

In another experiment, starting with 10.4 g. piperonylacetate, 1 g. of sodium, and 10 g. of ethyl α -bromovinylacetate, there was obtained 10 g. of a viscous residue after removal of the lower boiling solid material (1 g.) by short-path distillation. The aforementioned residue was chromatographed on activated (140°/35 mm.) Brockmann alumina (300 g.). On elution with benzene (1 L.), 6.55 g. (40%) of diethyl α -vinyl- α' -piperonylsuccinate (IX) was obtained.

2-Vinyl-3-(3', 4'-Methylenedioxyphenyl)-hydroxymethyltetramethyleneglycol (1, 4) (X).—A solution of 6 g. of diethyl α -vinyl- α' -piperonylsuccinate (IX)

** We are grateful to Sir Robert Robinson for furnishing the details of the method and permitting us to publish it.

in 100 ml. of dry ether was added dropwise to a slurry of 2 g. of lithium aluminium hydride in 200 ml. of dry ether over a period of 45 minutes, taking care that the reaction did not become too vigorous. The reaction mixture was refluxed for 3 hours and left overnight at room temperature. It was cooled to 0° and then poured into 100 ml. of 5% ice-cold sulphuric acid. The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solution was washed with 5% sodium bicarbonate solution and water and then dried (Na_2SO_4). After removal of the solvent, the crude product was purified by short-path distillation, b.p. 150–155°/0.6 mm., yield 3.8 g. (83%); ν (CHCl_3), 3700 cm^{-1} and 3509 cm^{-1} (free and associated OH), 938 cm^{-1} and 980 cm^{-1} ($\text{CH}=\text{CH}_2$) (Found: C, 63.37; H, 6.58%. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_5$: C, 63.16; H, 6.77%).

2-(3', 4'-Methylenedioxyphenyl)-3-hydroxymethyl-4-vinyltetrahydrofuran (XI a).—A solution of 3.8 g. of the triol (X) in 40 ml. of 1% ethanolic hydrogen chloride was refluxed for 1 hour. The solvent was removed and the residue was taken up in ether. The ethereal solution was washed well with water and dried (MgSO_4). The residue (3.5 g.), obtained after removal of the solvent, was chromatographed over 35 g. of alumina. Elution with benzene furnished 2.95 g. (83%) of the tetrahydrofuran derivative (XI a) as a thick gum (Found: C, 67.92; H, 6.29%. Calc. for $\text{C}_{14}\text{H}_{16}\text{O}_4$: C, 67.68; H, 6.45%).

2-(3', 4'-Methylenedioxyphenyl)-3-aldehyde-4-vinyltetrahydrofuran (XIII).—A solution of 200 mg. of the cyclised product (XI a) in a mixture of 100 ml. of dry benzene and 20 ml. of dry acetone was added to a refluxing solution of 2 g. of aluminium *t*-butoxide in 50 ml. of dry benzene and the refluxing continued for 8 hours. The reaction mixture was cooled and poured into 100 ml. of 5% ice-cold sulphuric acid. The ethereal layer was separated and the aqueous layer extracted with ether. The combined ethereal solution was washed thoroughly with water and dried (Na_2SO_4). After removal of the solvent, the residue (150 mg.) was chromatographed over 4.5 g. of alumina. The product (32 mg., 16%) eluted with chloroform gave intense pink colour with Schiff's reagent (Found: C, 68.23; H, 5.72%. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_4$: C, 68.3; H, 5.69%).

Samin (I).—Ozonised oxygen was passed through a solution of 3 g. of 2-(3', 4'-methylenedioxyphenyl)-3-hydroxymethyl-4-vinyltetrahydrofuran (XI a) in 75 ml. of ethyl acetate at 0° for 1 hour. The solution was allowed to attain the room temperature and then treated with 10 ml. of acetic acid and 4 g. of zinc dust, and the mixture was allowed to stand overnight. It was then filtered and the residue washed with 10 ml. of ethyl acetate. The com-

bined filtrate and the washings were washed free from acetic acid and dried (MgSO_4). The solvent was removed and the residue was crystallised from ether-pet. ether (40–60°) mixture to furnish 0.6 g. (20%) of samin (I), m.p. 139–140°. This gave intense pink colour with Schiff's reagent and silver mirror with Tollen's reagent (Found: C, 62.26; H, 5.55%. Calc. for $\text{C}_{13}\text{H}_{14}\text{O}_5$: C, 62.40; H, 5.60%).

The 2, 4-dinitrophenylhydrazone crystallised from ethanol, m.p. 205–206° (Found: N, 13.18%. Calc. for $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_8$: N, 13.02%).

SUMMARY

Ethyl α -bromovinylacetate (VII) was condensed with the sodio derivative of ethyl piperonylacetate (VIII) to give diethyl α -vinyl- α' -piperonylsuccinate (IX). The latter on reduction with lithium aluminium hydride furnished the triol (X), which underwent smooth cyclisation with 1% ethanolic hydrogen chloride to 2-(3', 4'-methylenedioxyphenyl)-hydroxymethyl-4-vinyltetrahydrofuran (XI a). The structure of XI a was established by Oppenauer oxidation to an aldehyde. Ozonolysis of XI a afforded samin (I).

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