

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

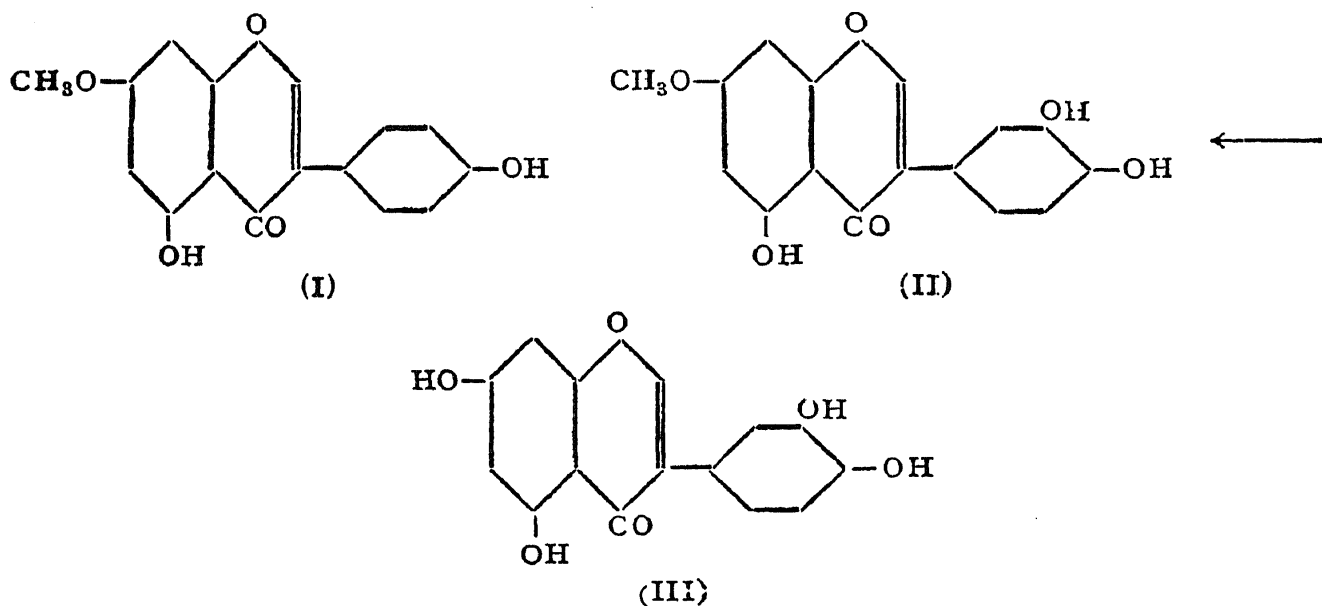
Part XIV. Synthesis of Santal

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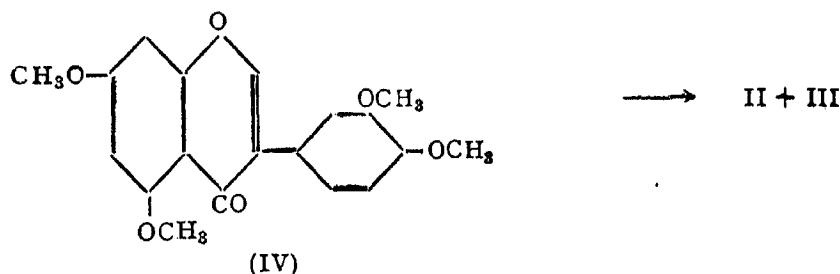
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IN Part XIII¹ of this series a synthesis of prunetin (I) was described. Santal is a similar isoflavone-7-methyl ether occurring in the wood of *Pterocarpus santalinus* and its constitution has been recently established as 7-methoxy-5:3':4'-trihydroxy isoflavone (II) by Robertson and coworkers.² The general method of synthesis involving direct methylation should therefore be applicable to this case also. It is now found to be so and santal has been obtained by the partial methylation of nor-santal (III) employing one mole of dimethyl sulphate. However, in the experiment the separation of the resulting mixture is not as simple as in the synthesis of prunetin because of the presence of more hydroxyl groups. The unreacted nor-santal could be removed by dissolution in sodium carbonate; but santal could not be so readily obtained pure by subsequent extraction with sodium hydroxide. It had to be subjected to fractional crystallisation and hence the yield was less.

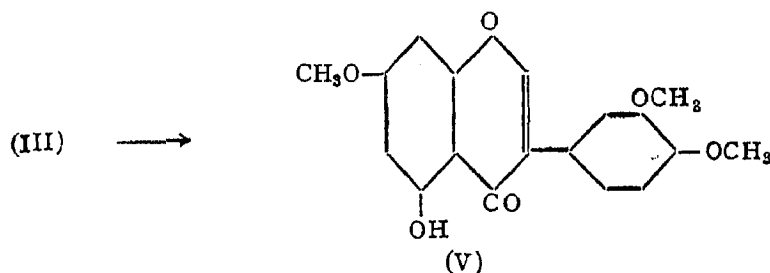


In the course of the preparation of nor-santal (III) synthetically an interesting observation has been made and this may be considered to constitute another synthesis of santal. 5:7:3':4'-Tetramethoxy isoflavone (IV)

was made by using a variation of the method described by Robertson *et al.*² quite similar to the one adopted by us for the preparation of genistein-trimethyl ether and it was subjected to demethylation by boiling with hydriodic acid for one hour. Instead of the expected nor-santal, a mixture was obtained from which santal (II) could be isolated by fractional crystallisation since it is comparatively less soluble. The separation was later made more quantitative by using sodium carbonate for dissolving nor-santal and the mixture was found to consist almost entirely of santal (II) and nor-santal (III). Complete demethylation to nor-santal could be effected by longer boiling with hydriodic acid (3 hours). The santal samples obtained by the two methods were identical and agreed in every respect with the description of natural santal.²



Besides santal, another partial methyl ether which is readily made from nor-santal is its trimethyl ether (santal dimethyl ether V). Raudnitz and Perlmann³ reported that by the methylation of santal using dimethyl sulphate and dilute aqueous alkali they obtained a dimethyl ether melting at 141°. We have now carried out the partial methylation of nor-santal using 3 moles of dimethyl sulphate and anhydrous potassium carbonate in dry acetone solution. The product is found to melt at 150–51° and has the properties required for the 5-hydroxy compound (V).



EXPERIMENTAL

3:4-Dimethoxy-benzyl cyanide

This was prepared earlier by Kaufmann and Muller⁴ by heating with acetic anhydride dimethoxy-phenyl-acetaldoxime. It has now been made by the more convenient method adopted by Baker and Robinson⁵ for the

preparation of 3:4:5-trimethoxy-benzyl cyanide. Starting from veratraldehyde, the first three stages, (1) the azlactone, (2) 3:4-dimethoxy-phenyl pyruvic acid and (3) its oxime have already been described by Kropp and Decker.⁶ But in regard to details we have followed the procedure of Baker and Robinson as more convenient. A dry sample of the oxime (10 g.) was heated with acetic anhydride (7 c.c.) on a steam-bath. After the vigorous reaction was over, water (50 c.c.) was added and the mixture cooled in ice; 3:4-dimethoxy-benzyl cyanide separated slowly in the form of colourless flakes. It was filtered, washed with aqueous bicarbonate and water and dried in a desiccator. It crystallised from light petroleum as colourless prisms and melted at 65–6°. Yield 7 g.

2:4:6-Trihydroxy-phenyl-3':4'-dimethoxy-benzyl ketone

A solution of phloroglucinol (10 g.) and 3:4-dimethoxy-benzyl cyanide (13 g.) in ether (100 c.c.) was treated with zinc chloride (2 g.), was saturated with dry hydrogen chloride for 4 hours and left in the ice chest overnight. The pale yellow ketimine hydrochloride was separated and washed with ether, dissolved in water (100 c.c.) and heated on a boiling water-bath for 2 hours. Even from the hot solution the ketone crystallised out. After cooling it was filtered and recrystallised from dilute methyl alcohol from which it separated in the form of colourless prisms. It melted at 208–10° after losing water at 100°. It gave a purplish red colour with ferric chloride. (Found in a sample dried at 120° for 4 hours: C, 62.8; H, 5.5; $C_{16}H_{18}O_6$ requires C, 63.2; H, 5.3%).

2-Hydroxy-4:6-dimethoxy-phenyl-3':4'-dimethoxy-benzyl ketone

The above trihydroxy-dimethoxy ketone (6 g.) was dissolved in dry acetone (200 c.c.), dimethyl sulphate (4 c.c.) and anhydrous potassium carbonate (8 g.) added and the mixture refluxed for 10 hours. Acetone was then distilled off, the residue treated with water and extracted with ether. The ether solution was thrice extracted with aqueous sodium hydroxide (5%) and the combined alkali extract cooled and acidified. The colourless solid that separated out, crystallised from methyl alcohol as colourless needles and rectangular rods melting at 120–21°. It gave a reddish brown colour with ferric chloride and a blue colour with concentrated nitric acid. It agreed in all its properties with the description of Robertson *et al.*²

Demethylation

(1) *Santal and Nor-santal*.—5:7:3':4'-Tetramethoxy isoflavone (1 g.) was dissolved in acetic anhydride (5 c.c.) and treated with cooling with hydriodic acid (12 c.c., d. 1.7). The solution was heated in an oil-bath at 140°

for 1 hour. It was then cooled, decolourised with sulphurous acid and left in the refrigerator overnight. The pale yellow solid that separated was filtered and washed well with water. The crude product (A) melted indefinitely between 230° and 240°. It was then crystallised from excess of ethyl acetate. The first fraction that separated on cooling the ethyl acetate solution melted between 210° and 215° and was insoluble in aqueous sodium carbonate. A second crystallisation raised the melting point to 220–22° and further crystallisations did not affect it. The product gave an intense brownish red colour with ferric chloride. From the mother liquor, ethyl acetate was completely removed and the residue macerated with cold sodium carbonate when a part of it was left undissolved. This was filtered, washed with water and crystallised from ethyl acetate when it appeared as colourless rectangular plates and prisms melting at 220–22° and was identical with the above sample. In bulk the solid had a very pale yellow colour. It agreed in all its properties with santal. Total yield 0.2 g. (Found; OCH₃, 10.1; C₁₅H₉O₅ (OCH₃), H₂O requires OCH₃, 9.8%; loss on drying 6.0; C₁₆H₁₂O₆, H₂O requires loss 5.7%).

The carbonate solution was acidified; the pale brownish yellow solid that separated crystallised from dilute acetic acid in the form of pale yellow globular clusters of minute prisms and needles melting at 269–71°. It gave a green colour changing to a purplish brown with ferric chloride. With concentrated sulphuric acid it developed a yellowish solution becoming blood red on addition of a few drops of concentrated nitric acid. It agreed in its properties with the description of nor-santal (Robertson *et al.*²). Yield 0.4 g.

In a repetition of the above demethylation the crude product (A) was directly extracted with aqueous sodium carbonate; the insoluble portion consisting of santal (0.2 g.) crystallised from ethyl acetate as colourless rectangular plates and prisms and melted at 220–2°. The carbonate soluble portion (0.4 g.) consisting of nor-santal crystallised from dilute acetic acid as globular clusters of minute prisms and needles melting at 269–71°.

(2) *Nor-santal*.—The above demethylation using the tetramethoxy isoflavone (1 g.) was done for 3 hours the temperature being maintained between 140° and 150°. The product was worked up as usual. It dissolved completely in cold aqueous sodium carbonate. On crystallising from dilute acetic acid it was obtained in the form of pale yellow globular clusters of tiny prisms and needles and melted at 269–71°. It agreed in its properties and colour reactions with the description of nor-santal. Its acetate, prepared by heating it with acetic anhydride and pyridine, crystallised from ethyl acetate as fine colourless needles melting at 209–10°.

O-Triacetyl santal.—Santal obtained in the above demethylation experiment (0.2 g.) was acetylated by boiling with acetic anhydride (5 c.c.) and a few drops of pyridine for 1 hour. The acetate crystallised from ethyl acetate in the form of clusters of colourless needles melting at 168–70° with sintering at 165°. It agreed in its properties with the description of santal triacetate given by Robertson and coworkers.²

O-Triethyl santal.—Santal (0.2 g.) was refluxed in acetone solution with excess of ethyl iodide and potassium carbonate for 20 hours. On filtering and distilling off acetone, the product separated as a viscous oil which solidified to a colourless solid on cooling. It crystallised from alcohol as colourless elongated rectangular prisms melting at 111–12°. It was insoluble in aqueous sodium hydroxide and gave no colour with ferric chloride. It agreed in its properties with the description of *O*-triethyl santal by Robertson *et al.*² (Found: C, 68.6; H, 6.6; $C_{22}H_{24}O_6$ requires C, 68.8; H, 6.3%).

Partial methylation of nor-santal

(1) *Santal*.—To a solution of nor-santal (1 g.) in acetone (100 c.c.) dimethyl sulphate (0.3 c.c.) and anhydrous potassium carbonate (1 g.) were added and the mixture refluxed on a water-bath for 4 hours. Acetone was then distilled off and the residue treated with water. The solid that separated was filtered from the carbonate solution, washed once with aqueous sodium carbonate and with water. It was then crystallised from excess of ethyl acetate. The first crop obtained on cooling the solution was found to melt between 180° and 190°. It dissolved partly in sodium hydroxide and gave an intense reddish brown colour with ferric chloride. It was evidently a mixture but it was too small in quantity for further separation. The ethyl acetate mother liquor on further concentration deposited colourless plates. When this was recrystallised from ethyl acetate, it melted at 220–2°. It gave all the colour reactions of santal and a mixed melting point with the sample obtained by the demethylation method was undepressed. Yield 0.1 g.

The carbonate solution on acidification gave nor-santal (0.3 g.) which after crystallisation melted at 269–71°.

(2) *Santal dimethyl ether (5-Hydroxy-7:3':4'-trimethoxy isoflavone)*.—Nor-santal (0.50 g.) was refluxed in acetone solution with dimethyl sulphate (0.55 c.c.) and anhydrous potassium carbonate (1 g.) for 10 hours. On filtering and distilling off acetone from the filtrate, a pale brown solid was left behind. It crystallised from ethyl acetate as colourless needles melting at 150–51°. It gave a deep red colour with ferric chloride and was sparingly

soluble in aqueous sodium hydroxide. (Found; C, 65.4; H, 4.7; $C_{18}H_{16}O_6$ requires C, 65.9; H, 4.9%).

SUMMARY

Santal has been synthesised by methylating 5:7:3':4'-tetrahydroxy isoflavone with one mole of dimethyl sulphate. When three moles of dimethyl sulphate are employed santal dimethyl ether is obtained. An interesting observation has been made that demethylation of santal trimethyl ether under restricted conditions with hydriodic acid leads to the formation of a mixture of santal and nor-santal. They have been separated using aqueous sodium carbonate.

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3. Raudnitz and Perlmann .. *Ber.*, 1935, 68, 1862.
4. Kaufmann and Muller .. *Ibid.*, 1918, 51, 127.
5. Baker and Robinson .. *J. C. S.*, 1929, 157.
6. Kropp and Decker .. *Ber.*, 1909, 42, 1186.