SYNTHESIS OF KANUGIN AND RELATED COMPOUNDS

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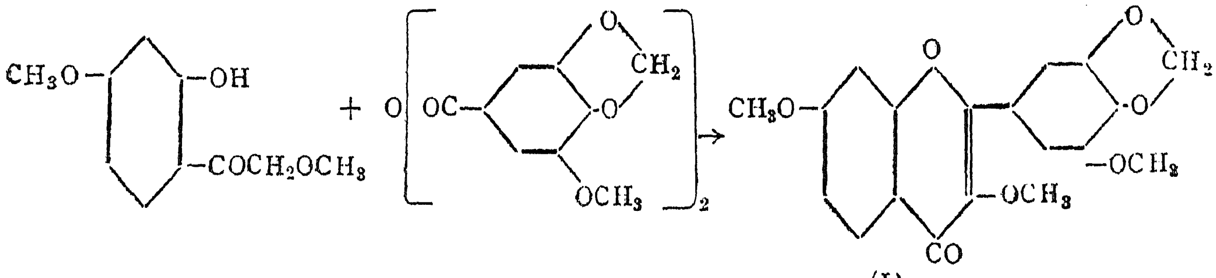
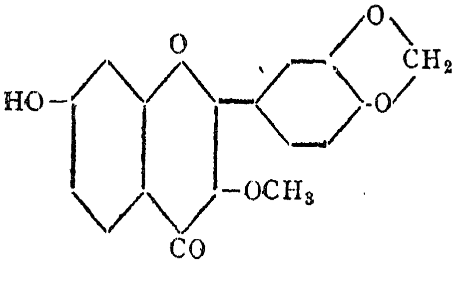
In an earlier communication[1] the determination of the constitution of kanugin (I) as 3:7:5′-trimethoxy-3′:4′-methylenedioxy-flavone was reported, based on a study of the compound and of its decomposition products. This constitution has now been confirmed by synthesising kanugin from ω:4-dimethoxy-2-hydroxy-acetophenone (fisetol dimethyl ether) and the anhydride and sodium salt of myristicic acid. The synthetic product is found to be identical with the natural one in all its properties and reactions and the mixed melting point is not depressed.



(I)



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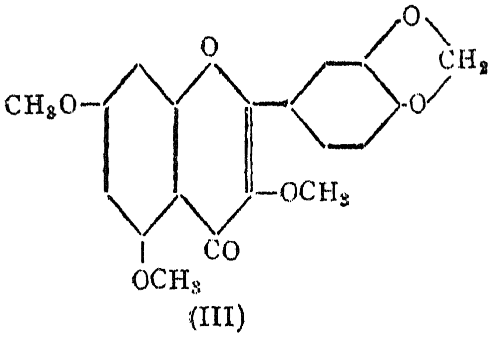

(III)

Since the Allan-Robinson condensation was not carried out previously with components containing methylenedioxy group and since myristicic acid is not easy to obtain, exploratory experiments have been done using first the anhydride and sodium salt of piperonylic acid. The condensation with ω-methoxy-resacetophenone proceeds smoothly to yield 7-hydroxy-3-methoxy-3′:4′-methylenedioxy-flavone (II). The best yields are obtained by limiting the heating to 2–3 hours. Incidentally the condensation has also been carried out with ω:4:6-trimethoxy-2-hydroxy-acetophenone to yield 3:5:7-trimethoxy-3′:4′-methylenedioxy-flavone (III) which is designated '*iso*-kanugin'. This compound differs from kanugin in that it has a methoxyl group in position 5 instead of in 5′. Unlike kanugin it does not exhibit fluorescence either in alcohol or in concentrated sulphuric acid. This seems to be another example of the influence of position 5, in suppressing the emission of fluorescence by anthoxanthins and related compounds.

Under the same conditions as those adopted for the preparation of the above compounds, kanugin could be obtained starting from myristicic acid. This acid was made in the past by the oxidation of isomyristicin prepared from oil of nutmeg.[2] A simplified procedure has now been adopted for obtaining it in good yield from the same source. It was first made synthetically by Baker[3] from 4 : 5-dihydroxy-3-methoxy benzaldehyde using methylene sulphate and aqueous potash but the yields reported by him (about 5%) were very poor. By a modification of the method of methylenation the yield could now be raised to 75%; 4 : 5-dihydroxy-3-methoxy benzaldehyde could be conveniently methylenated in anhydrous acetone solution using methylene sulphate and anhydrous potassium carbonate. The product comes directly pure without any difficulty.

EXPERIMENTAL

Piperonylic anhydride.—Piperonylic acid (10 g.) (dried in an air oven at 110–20° for 2–3 hours) was mixed with dry carbon tetrachloride (20 c.c.) and the mixture treated with powdered phosphorous pentachloride (10 g.) in small amounts. It was warmed on a water-bath till no more fumes were evolved and all the solid went into solution (10 minutes). The solvent and the phosphorus oxychloride were then removed under reduced pressure on a water-bath when the acid chloride was left behind as a white crystalline solid. It was directly dissolved in anhydrous ether (100 c.c.) and dry pyridine (18 c.c.) slowly added while cooling in ice. After leaving in the ice-chest for 2½ hours, the mixture was treated with small bits of ice with vigorous stirring. In about 10 minutes a pale cream-coloured solid separated out in good yield. It was filtered, washed with ice-cold dilute hydrochloric acid and ice water and dried in a vacuum desiccator. Yield, 7 g. On crystallising from anhydrous benzene it came out as big colourless rectangular tablets melting at 153–4° (Found: C, 61·5; H, 2·9; $C_{16}H_{10}O_7$ requires C, 61·1; H, 3·2%). A small crystal of the compound when warmed with gallic acid and sulphuric acid formed a bright blue solution.

7-Hydroxy-3-methoxy-3′ : 4′-methylenedioxy-flavone (II).—ω-Methoxy-resacetophenone (1 g.) was fused with piperonylic anhydride (10 g.) and potassium piperonylate (3 g.) at 170–80° for 3 hours under reduced pressure. The product was boiled with alcoholic potash (80 c.c. of 10% solution) for 20 minutes. The solvent was then removed under reduced pressure, water (100 c.c.) was added and the clear brown solution saturated with carbon-dioxide when a brown solid (about 1 g.) separated out. It was filtered, washed and crystallised from alcohol. It came out as pale yellow rectangular plates melting at 265–67° (Found: C, 65·4; H, 3·8; $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·8%). The substance was soluble in aqueous alkali with a yellow colour and gave no characteristic colour with ferric chloride in alcoholic solution. With gallic acid and sulphuric acid it gave a beautiful emerald green colour which rapidly changed to pure blue.

3 : 5 : 7-*Trimethoxy*-3′ : 4′-*methylenedioxy-flavone* (*III*) (Iso-*kanugin*).—ω : 4 : 6-Trimethoxy-2-hydroxy-acetophenone (1 g.) was condensed with the anhydride (5 g.) and the potassium salt (2 g.) of piperonylic acid, under the conditions of the Allan-Robinson reaction. After hydrolysis with alcoholic potash and removal of the solvent under reduced pressure, water was added when a pale brown solid separated out. It was filtered and washed with water (Fraction A). On saturating the filtrate with carbon dioxide a yellowish brown solid separated out (Fraction B).

Fraction A (*iso*-kanugin) was crystallised from alcohol when it came out as colourless rectangular plates melting at 195–6° (Found: C, 64·0; H, 4·5; $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5). It was insoluble in aqueous alkali and gave no colour with alcoholic ferric chloride. But it gave an emerald green colour with gallic acid and sulphuric acid (test for the methylenedioxy group). Unlike kanugin it exhibited no fluorescence in alcohol and in concentrated sulphuric acid it formed a stable yellow colour. It could thus be easily distinguished from kanugin.

Fraction B was obtained in varying amounts in different experiments and when crystallised from alcohol it came out as a yellow crystalline solid melting indefinitely between 200 and 225°. It gave a marked olive green colour with ferric chloride, was sparingly soluble in aqueous alkali and was obviously having the 5-OH free. This should have arisen as the result of partial demethylation in the course of the Allan-Robinson condensation. It was not further examined.

Preparation of myristicic acid: (1) *from oil of nutmeg*.—The procedure followed for the preparation of myristicin was essentially that of Power and Salway[2] with a few modifications.

Oil of nutmeg was washed with 5% alkali to remove the phenolic and acidic components. It was subsequently washed with water and dried over sodium sulphate. The dry oil was first distilled under reduced pressure (60 mm.) when most of the terpenes passed over below 110°. Distillation was then effected under ordinary pressure up to a temperature of 240°. It was connected again to the pump and the distillation carried out at a pressure of 40 mm. Three fractions were collected: (1) below 160°, (2) 160–70° and (3) 170–75°. The last fraction corresponded to myristicin and its yield was 10 g. from 150 c.c. of the oil. It gave a positive test for the presence of the methylenedioxy group and the identity was further confirmed by the preparation of dibromomyristicin dibromide melting at 128–9°.

The above myristicin fraction (10 g.) was dissolved in alcoholic potash (alcohol 30 c.c. and potash 8 g.) and the solution refluxed on a water-bath for 24 hours. The solvent was then distilled off, the residue treated with excess of water and extracted with ether. The crude isomyristicin left after evaporating the ether was directly used for the oxidation.

Isomyristicin (8 g.) was made into an emulsion with water (500 c.c.). An aqueous solution of potassium permanganate (22 g. in 500 c.c.) was slowly added, keeping the mixture at 80° and stirring, during the course of an hour and a half. It was kept stirred for another 30 minutes by which time all the permanganate was reduced. Sufficient 10 % aqueous potash was then added in order to make the mixture alkaline and the manganese dioxide formed was filtered while hot and washed with hot water. From the filtrate myristicic aldehyde crystallised out on cooling. This was filtered off and the solution extracted twice with ether to remove the aldehyde completely. When the alkaline solution was acidified with concentrated hydrochloric acid, myristicic acid separated out. It was filtered, washed with a little water and crystallised from methyl alcohol when it came out as big rectangular prisms with a tendency to taper at the ends and melting at 212–14°. Yield, 5 g.

The residual manganese dioxide was suspended in water and brought into solution by passing a current of sulphur dioxide. On extracting the solution with ether some more of the myristicic aldehyde could be obtained.

The total yield of the myristicic aldehyde was crystallised from water when it appeared as thin colourless rectangular plates melting at 131–32°. Yield, 1·5 g. The 2:4-dinitrophenylhydrazone was obtained as dark red needles melting at 230–32°.

(ii) *By Synthesis.*—A solution of 3-methoxy-4:5-dihydroxy benzaldehyde (2 g.) and methylene sulphate (2 g.) in anhydrous acetone (30 c.c.) was treated with freshly ignited potassium carbonate (10 g.). The mixture was then refluxed on a water-bath for 6 hours. During the course of the reaction vigorous effervescence followed by the evolution of formaldehyde and deposition of a white solid in the cooler parts of the condenser were noticed. The potassium salts were finally filtered off and the residue washed thoroughly with acetone. The filtrate was distilled to remove the solvent when a crystalline solid was obtained. It was almost pure myristicic aldehyde and was further purified by crystallisation from water when it separated as thin colourless rectangular plates melting at 131–2°. Mixed melting point with the sample of myristicic aldehyde from oil of nutmeg was not depressed. Yield, 1·5 g.

Myristicic anhydride.—The anhydride was prepared in just the same way as piperonylic anhydride starting from the dry acid (4 g.), phosphorous pentachloride (5 g.) and anhydrous pyridine (8 c.c.). The crude product was obtained as a white solid; yield, 2·5 g. When crystallised from anhydrous benzene it came out as stout rhombic prisms melting at 172–3° (Found: C, 58·1; H, 4·1; $C_{18}H_{14}O_9$ requires C, 57·8, H, 3·7%).

3 : 7 : 5′-*Trimethoxy*-3′ : 4′-*methylenedioxy-flavone* (I) (*kanugin*).—An intimate mixture of ω : 4-dimethoxy-2-hydroxy acetophenone (0·8 g.), myristicic anhydride (2 g.) and the sodium salt of myristicic acid (0·5 g.) was heated under vacuum at 170 80° for 3 hours. The product was cooled, powdered and boiled with alcoholic potash (30 c.c. of 10% solution) for 15 minutes. The solvent was then distilled off under reduced pressure, the residue treated with water (100 c.c.) and the pale brown solid that separated out was filtered and washed. It was purified by crystallisation from alcohol when it came out as colourless rectangular plates melting at 204–05°. Yield, 0·8 g. Mixed melting point with a pure sample of natural kanugin was not depressed (Found: C, 64·4; H, 4·4; $C_{19}H_{16}O_7$ requires C, 64·0; H, 4·5).

An alcoholic solution of the compound gave a blue fluorescence. In concentrated sulphuric acid it dissolved to a bright yellow solution which changed through orange to red with green fluorescence just like the natural sample. With gallic acid and sulphuric acid it developed a beautiful emerald green colour.

SUMMARY

The synthesis of 3-methoxy-7-hydroxy-3′ : 4′-methylenedioxyflavone, kanugin and *iso*-kanugin has been effected. Myristicic acid required for the synthesis of kanugin is prepared from oil of nutmeg by a simplified procedure and an improved method for its synthetic preparation worked out. There is marked difference in properties between kanugin and *iso*-kanugin (3 : 5 : 7-trimethoxy-3′ : 4′-methylene-dioxyflavone).

REFERENCES

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3. Baker .. *ibid.*, 1932, 1283.