

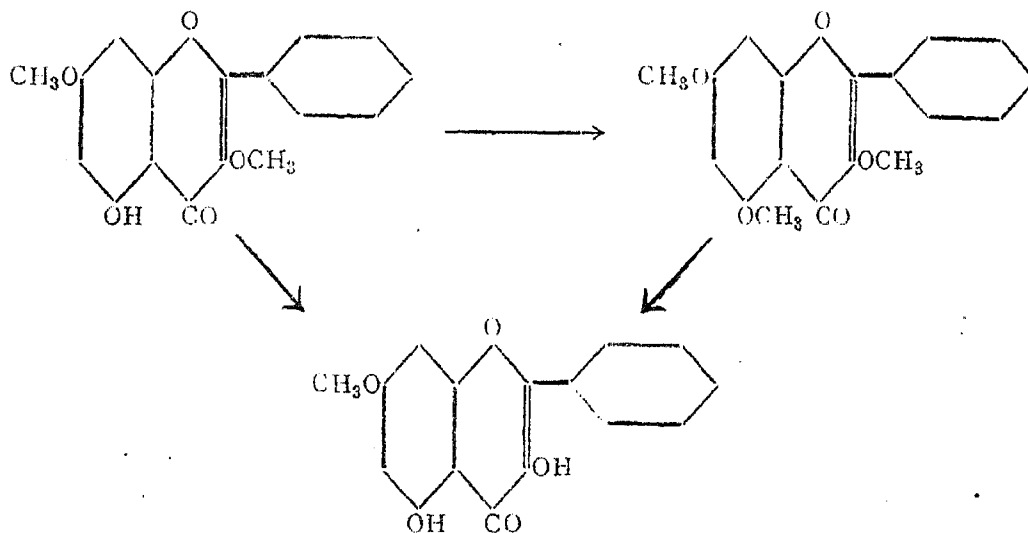
SYNTHESIS OF IZALPININ

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Received October 27, 1945

IZALPININ was isolated from the seeds of *Alpinea japonica* by Kimura and Hoshi¹ and its constitution was based on the following considerations. It has the molecular formula $C_{16}H_{12}O_5$ and contains one methoxyl group. On demethylation it yields nor-izalpinin identical with galangin and on methylation forms galangin-trimethyl ether. It contains a hydroxyl group resistant to methylation and it is different from the 3-methyl ether of galangin. It was, therefore, concluded to be galangin 7-methyl ether, *i.e.*, 7-methoxy-3:5-dihydroxy-flavone. Excepting the preparation of 3:5:7-trimethoxy flavone which was shown to be identical with the dimethyl ether of izalpinin no further synthetic proof was advanced by the above authors. Since no method is available for the direct synthesis of izalpinin, it has now been obtained by the partial demethylation of the di- and tri-methyl ethers of galangin by means of anhydrous aluminium chloride and bromide.



Partial demethylation with aluminium chloride was investigated in the past using several methoxy-flavones and it was established that the reagent affects the 5-methoxyl group alone. Employing this, tectochrysin,² genkwanin,³ 8-methyl ether of primetin,⁴ primetin⁵ and wogonin⁶ have been prepared. The use of this reagent was extended to the field of methylated flavonols by Krishnaswamy and Seshadri.⁷ Their experiments showed that like the 5-methoxyl, the 3-methoxy-group also underwent demethylation preferentially.

The action of aluminium bromide as a demethylating agent has not been studied so far in the flavone and flavonol series. Its higher solubility and greater reactivity as compared with the chloride are advantages in its favour. Consequently experiments have now been carried out on the methyl ethers of galangin using this reagent also.

Tasaki⁸ who first reported the preparation of the trimethyl ether of galangin gave the melting point as 165–66°. But, later, Kimura and Hoshi¹ who prepared it by condensing ω :4:6-trimethoxy-2-hydroxyacetophenone (obtained by the fission of hexamethyl myricetin) with benzoic anhydride and sodium benzoate described it as light brown hexahedral prisms melting at 195–96°. On repeating the experiment of Kimura and Hoshi using a synthetic sample of the above ketone, the product obtained was not the expected 3:5:7-trimethoxy-flavone. It was yellow, gave a greenish brown colour with ferric chloride in alcoholic solution and melted at 144–46° thus agreeing with 3:7-dimethoxy-5-hydroxy-flavone obtained by methylating galangin with methyl iodide. The presence of the 5-hydroxyl was confirmed by the preparation of the acetate and also by further methylation to 3:5:7-trimethoxy-flavone. This trimethyl ether has now been obtained as colourless hexahedral prisms melting at 199–200°. It is, therefore, evident that during the above Allan-Robinson condensation demethylation has taken place. Similar cases were noted in the flavone series by Wesseley and Moser⁹ and by Baker *et al.*¹⁰ Such demethylation does not seem to be taking place as a rule though the possibility exists definitely. Our observation recorded above appears to be the first example in the flavonol series. More cases have been met with in the course of similar work in these laboratories.

The demethylation of 3:7-dimethoxy-5-hydroxy-flavone and 3:5:7-trimethoxy flavone has now been effected in nitrobenzene solution at 100° with aluminium chloride; izalpinin is obtained in good yield in both cases. The action of aluminium bromide has been investigated under two different conditions (1) at 100° for 1 hour and (2) at the laboratory temperature for 12 hours using again nitrobenzene as the solvent and the compounds mentioned below; the same products are obtained under both conditions. 5:7-Dihydroxy-3-methoxy flavone yields galangin, 3:7-dimethoxy-5-hydroxy-flavone and 3:5:7-trimethoxyflavone yield izalpinin. It has been the practice to remove the solvent by steam distillation but this leads to considerable decomposition yielding resinous products. A simpler and more convenient method has now been adopted. It involves the use of petroleum ether which dissolves and removes nitrobenzene leaving behind the aluminium halide complex which can be conveniently decomposed later on.

Izalpinin obtained synthetically by the above methods has all the properties attributed to the natural sample. One property which has now been observed and which distinguishes it from galangin is its insolubility in aqueous sodium carbonate. Galangin is soluble in this reagent. This observation will be useful for separating a mixture of the two when occurring in nature. The acetate of izalpinin has also been prepared and described.

EXPERIMENTAL

3:7-Dimethoxy-5-hydroxy-flavone:— ω :4:6-Trimethoxy-2-hydroxy-acetophenone was prepared according to the method of Row and Seshadri,¹¹ effecting partial methylation of ω -methoxy phloracetophenone.

An intimate mixture of this ketone (2 g.), benzoic anhydride (8 g.) and sodium benzoate (2 g.) was heated under vacuum at 170–80° for 4–5 hours. It was then cooled and the product boiled with alcoholic potash (40 c.c. of 10% solution) for 20 min. The alcohol was then removed under reduced pressure and the residue treated with water (100 c.c.). The yellowish brown solid was filtered and washed with water (fraction I). The filtrate, on saturation with carbon dioxide, yielded a brown solid which was also filtered and washed with water (fraction II).

Fraction I was crystallised from acetic acid when a yellow shining crystalline solid (needles) melting at 142–45° was obtained. A second crystallisation from alcohol gave a product melting sharp at 145–46°. Fraction II was similarly crystallised. It was also obtained as yellow needles melting at 145–46° (m.p. of galangin dimethyl ether reported by Perkin and Everest,¹² 142°). It was found to be identical with fraction I and the mixed melting point was not depressed. (Found: C, 68.0; H, 4.5; $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.7%.) The flavone was sparingly soluble in aqueous alkali. In alcoholic solution it gave an olive brown colour with ferric chloride. Yield, 1.5 g.

A search was made for the trimethyl ether in the mother-liquors obtained from the crystallisation of fraction I. On evaporation to dryness a dark brown residue was obtained. When crystallised from alcohol twice a very small quantity of a yellow solid melting indefinitely between 130–60° was obtained. It also gave a brown colour with ferric chloride. The quantity was too small to enable further study. It appeared that there was no significant amount of the trimethyl ether.

3:7-Dimethoxy-5-acetoxy flavone:—3:7-Dimethoxy-5-hydroxy flavone (0.1 g.) was acetylated by boiling with acetic anhydride (3 c.c.) and sodium acetate (0.5 g.) for 2 hours. The white solid obtained on pouring the

reaction mixture into ice-water was filtered, washed and crystallised twice from alcohol. It came out in the form of fine colourless silky needles melting at 175–76°. It gave no colour with ferric chloride. (Found: C, 66.7; H, 4.5; $C_{19}H_{16}O_6$ requires C, 67.0; H, 4.7%.)

3:5:7-Trimethoxy-flavone: I Method:—A solution of 3:7-dimethoxy-5-hydroxy-flavone (0.5 g.) in anhydrous acetone (50 c.c.) was treated with dimethyl sulphate (0.5 c.c.) and freshly ignited potassium carbonate (3 g.). After refluxing for 12 hours, the potassium salts were filtered off and the filtrate evaporated when the trimethyl ether was left behind as a crystalline solid. It was purified by crystallising twice from alcohol when it came out as big colourless hexahedral prisms melting at 199–200°. It was insoluble in aqueous alkali and gave no colour with alcoholic ferric chloride. (Found: C, 69.2; H, 4.8; $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%.) Yield, 0.5 g.

II Method:—5:7-Dihydroxy-3-methoxy flavone (1.5 g.) (prepared according to Kalff and Robinson¹³) was methylated in anhydrous acetone solution (200 c.c.) with dimethyl sulphate (2 c.c.) and anhydrous potassium carbonate (10 g.). The trimethyl ether was purified by crystallisation from alcohol. Yield, 1.4 g. It was identical with the sample obtained by the first method and the mixed melting point was undepressed.

Preparation of Izalpinin:

Demethylation of (1) galangin-dimethyl-ether: (a) Aluminium chloride method:—A solution of 3:7-dimethoxy-5-hydroxy-flavone (0.5 g.) in dry nitrobenzene (10 c.c.) was treated with a solution of anhydrous aluminium chloride (1 g.) in the same solvent (5 c.c.) with cooling. The dark coloured solution was kept on a boiling water-bath for 45 minutes and cooled. Ice-cold hydrochloric acid (20 c.c. of 1:1 acid) was then added with cooling and the nitrobenzene removed by steam distillation. The dark brown residue was crystallised from alcohol when a yellowish brown solid was obtained which melted at 185–90° with sintering at 178°. A second crystallisation raised the melting point to 190–93°, with slight sintering at 188°. After a third crystallisation from alcohol izalpinin came out as pale yellow lance-shaped plates melting at 194–95°. The yield of the pure product was 0.15 g. It was easily soluble in aqueous alkali to a bright yellow coloured solution and it gave a brown colour with ferric chloride in alcoholic solution.

(b) Aluminium bromide method:—A solution of 3:7-dimethoxy-5-hydroxy flavone (0.3 g.) in dry nitrobenzene (8 c.c.) was treated with anhydrous aluminium bromide (0.5 g.); the solution was kept at 100° for 1 hour and then cooled. Excess of petroleum ether was added, the contents

were shaken well and allowed to stand for 5 minutes. The clear upper layer of liquid was decanted off from the brown semi-solid of the aluminium bromide complex. The latter was washed thrice again with petroleum ether and was then decomposed by adding small pieces of ice and hydrochloric acid (20 c.c. of 1:1 acid). After keeping for 2-3 hours the yellow solid was filtered and washed with water and a little petroleum ether. On crystallisation from alcohol it came out as yellow short lance-shaped plates melting at 190-93°. A second crystallisation gave the pure product melting at 194-95°. It was identical with the sample obtained above. Yield, 0.22 g.

(2) *Galangin-trimethyl ether*: (a) *Aluminium chloride method*:—A solution of 3:5:7-trimethoxy-flavone (0.5 g.) in dry nitrobenzene (10 c.c.) was treated with aluminium chloride (1 g.) in the same solvent. The mixture was kept at 100° for one hour and then cooled. The solvent was then removed by means of petroleum ether and the residue treated with water and concentrated hydrochloric acid. The final decomposition of the product was effected by heating the mixture on the water-bath for 10 minutes. The resulting yellow solid was filtered, washed with water and crystallised from ethyl acetate. Izalpinin came out in the form of yellow rectangular prisms melting at 194-95°. Yield, 0.4 g.

(b) *Aluminium bromide method*:—3:5:7-Trimethoxy-flavone (0.5 g.) was treated with aluminium bromide (1 g.) in dry nitrobenzene (15 c.c.) and the solution kept at the laboratory temperature for 12 hours. The solvent was then removed with the help of petroleum ether and the complex decomposed in the manner described above. The product, on crystallisation successively from alcohol and dilute acetic acid, came out as glistening lance-shaped plates melting at 194-95°. It was identical with the samples obtained by the above methods. Yield 0.4 g.

The above experiment was repeated using a temperature of 100° for 45 minutes for the demethylation: the yield and purity of izalpinin were just the same. (Found: C, 67.9; H, 4.3, OCH₃ 10.9, 11.1; C₁₆H₁₂O₅ requires C, 67.6; H, 4.3; OCH₃; 10.9%.)

Izalpinin acetate:—Izalpinin (0.4 g.) was boiled for 2 hours with acetic anhydride (5 c.c.) and anhydrous pyridine (2 drops). The solid that separated out on pouring the reaction mixture into ice-water, was extracted with ether and the ether solution shaken with cold aqueous sodium bicarbonate to remove acetic acid. The solvent was evaporated and the colourless residue was first crystallised from alcohol and subsequently from benzene-petroleum ether mixture. The acetate was thus obtained as colourless, long rectangular prisms melting at 172-73°. The yield was almost quantitative.

The mixed melting point with 3:7-dimethoxy-5-acetoxy flavone was considerably depressed (150-55°). (Found: C, 65.4; H, 4.6; $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%.)

A solution of izalpinin acetate (0.25 g.) in alcohol (10 c.c.) was treated with concentrated hydrochloric acid (2 c.c.) and the solution kept boiling for 10 minutes. The yellow crystalline solid that separated out was filtered, washed with water and recrystallised from alcohol when it came out as yellow lance-shaped plates melting at 194-95°. It was identical with the original sample of izalpinin and the mixed melting point was undepressed.

SUMMARY

Izalpinin (7-methyl ether of galangin) has been obtained by the demethylation of galangin di- and trimethyl ethers using both aluminium chloride and aluminium bromide. The synthetic sample has all the properties recorded for the naturally occurring substance. The condensation of ω :4:6-trimethoxy-phloroacetophenone with benzoic anhydride and sodium benzoate yields mainly 3:7-dimethyl ether of galangin.

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