

The Structure of Alpinone

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The seeds of *Alpinia japonica* Miq. contain alpinone and its 3-acetate. The former has been shown to be identical with pinobanksin-7-methylether (V). 3-Hydroxy-5,7-dimethoxy-2-methylflavanone has been synthesised.

In 1936 Kimura and Hoshi¹ advanced the formula (I) for alpinone, a constituent of the seeds of *Alpinia japonica* Miq. The evidence they cited in support of this structure was, however, not very convincing. In particular the very easy loss of the methyl group in position 2, when alpinone was treated with alkali, appears to be extremely improbable. A reinvestigation of the structure of alpinone became even more necessary, when it could be shown that one of the key compounds in Kimura and Hoshi's arguments, namely the so called "apoalpinonemonomethylether" was wrongly formulated².

Two different approaches towards the solution of this problem were used. The first was to synthesise a compound with the structure (I) and compare it with alpinone, and the second was a reinvestigation of authentic alpinone. The second approach eventually led to a solution of the problem and the synthetic route was therefore left uncompleted, but the results obtained in the synthesis up to this time are reported in this paper.

When the seeds of *Alpinia japonica* were extracted with light petroleum two crystalline substances were obtained. They could be separated from one another by virtue of their different solubilities in toluene. The less soluble compound had m. p. 179-180°, $[\alpha]_D^{20} + 91^\circ$ (pyridine), -12° (chloroform) and gave a benzoate of m. p. 208-210°. Kimura and Hoshi¹ report for alpinone m. p. 178°; $[\alpha]_D^{20} + 79.11$ (pyridine), and for its dibenzoate m. p. 208-209°. It is thus evident that this compound is identical with the alpinone of Kimura and Hoshi¹. Its analysis agrees, however, far better with $C_{16}H_{14}O_5$ than with $C_{17}H_{16}O_5$, as proposed by the Japanese authors. They converted alpinone with alkali into the so called apoalpinone, which upon methylation gave a dimethylether. This was identical with the methylether of a compound which Kimura and Hoshi synthesised and believed to be 3-hydroxy-5,7-dimethoxyflavanone (II)¹. It has, however, recently been shown that this compound is 2-benzyl-2-hydroxy-4,6-dimethoxycoumaran-3-one (III)², from which it follows that "apoalpinone" must be (IV). The formation of (IV) from alpinone under alkaline conditions together with the analytical results mentio-

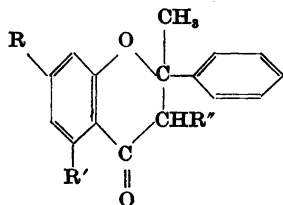
ned above, strongly suggest that alpinone is 3,5-dihydroxy-7-methoxyflavone (V). It should thus be either identical with pinobanksin-7-methylether³ or a stereoisomer of this compound. The following comparison clearly establishes that the two compounds are identical, as has been previously reported in a preliminary note⁴.

	m. p.	$[\alpha]_D^{20}$ in pyridine	$[\alpha]_D^{20}$ in chloroform	m. p. of dibenzoate
Alpinone	179–180°	+ 91°	– 12°	208–210°
Pinobanksin-7-methylether	181–182° ³	+ 92°	– 19° ³	208–210°

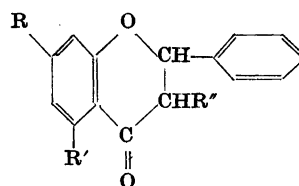
No depression of m.p.s was observed on mixing either the compounds themselves or their dibenzoates.

The same conclusion regarding the structure of alpinone has also been reached by Kotake, Sakan and Kubota⁵.

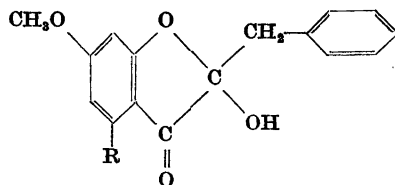
As mentioned above, the extraction of the seeds of *Alpinia japonica* gave in addition to alpinone a second compound, more soluble in toluene. This has m. p. 135°; $[\alpha]_D^{20}$ + 17° (pyridine) and corresponds to the formula $C_{17}H_{13}O_5$ (OCH_3). It gave the same colour reactions with ferric chloride and with magnesium and zinc and hydrochloric acid as alpinone and its U.V.-spectrum is almost indistinguishable from that of alpinone (λ_{max} 292 m μ ; log ϵ 4.28). On hydrolysis with strong acids it gave alpinone and acetic acid. It must thus be a monoacetate of alpinone and its positive colour reaction with ferric chloride places the acetyl group on the hydroxyl in position 3, enabling it to be formulated as (VI). When alpinone was acetylated with acetic anhydride and pyridine the same acetate was obtained. This is, as far as the present authors are aware, the first instance, that a 3-hydroxyflavanone has been found in Nature as its acetate. This compound occurs in an amount about equal to that of alpinone and it is difficult to see why Kimura and Hoshi were unable to isolate it.



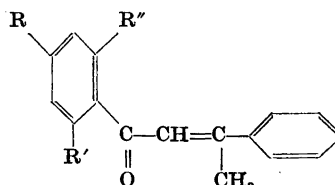
- I R = OCH_3 ; R' = R'' = OH
 IX R = R' = OH; R'' = H
 X R = R' = OCH_3 ; R'' = H
 XI R = R' = OCH_3 ; R'' = OH



- II R = R' = OCH_3 ; R'' = OH
 V R = OCH_3 ; R' = R'' = OH
 VI R = OCH_3 ; R' = OH; R'' = $OCOCH_3$



- III R = OCH_3
 IV R = OH



- VII R = R' = R'' = OCH_3
 VIII R = R' = OCH_3 ; R'' = OH

Of the methods available for the synthesis of 3-hydroxyflavanones, the two methods due to Oyamada ^{6,7} appeared to be most promising for the synthesis of (I). In the first of these ⁶ bromine is added to the double bond of the acetate of the corresponding chalcone. The dibromide is then treated with silver acetate and the diacetoxydihydrochalcone is submitted to acid hydrolysis giving the 3-hydroxyflavanone. The starting material was in this case 2',4',6'-trimethoxy- β -methylchalcone (VII) obtainable from phloroglucinoltrimethyl ether and β -methylcinnamoyl chloride under Friedel-Crafts conditions. This was partially demethylated to (VIII) using aluminium bromide in benzene. Addition of bromine to the acetate of (VIII) was, however, unsuccessful. Only intractable tars were obtained.

The second method involves oxidation of the corresponding flavanone with lead tetra-acetate, followed by hydrolysis of the thus formed 3-hydroxyflavanone acetate. The flavanone (IX) has been prepared, although in low yield, by Lindstedt and Misiorny ⁷ and by Kotake ⁸. Because the hydroxyl groups have to be protected during the lead tetra-acetate oxidation it was found more convenient to synthesise its dimethylether (X) from the corresponding chalcone (VIII). The lead tetra-acetate oxidation of (X) gave a very low yield of (IX). For reasons given above, no attempt was made to improve the yield in this step or to carry out the reaction on a larger scale in order to obtain sufficient material for carrying the synthesis to completion.

EXPERIMENTAL

Isolation of alpinone and its 3-acetate. The finely ground seeds of *Alpinia japonica* were extracted in a Soxhlet apparatus with light petroleum for 6 hours. The solvent was distilled off and the residue was steam distilled in order to remove volatile components. The dried residue was boiled with toluene, leaving a green amorphous mass undissolved. Fractional crystallisation of the toluene soluble part gave, as a less soluble component alpinone, m. p. 179–180°, $[\alpha]_D^{20} + 91^\circ$ (c 3.46 in pyridine); -12° (c 2.64 in chloroform). (Found: C 66.50; H 4.82. $C_{16}H_{14}O_5$ requires C 67.12; H 4.93). The dibenzoate was prepared with benzoyl chloride and pyridine on a water bath; m. p. 208–210°.

The more soluble component was alpinone-3-acetate, m. p. 135°, $[\alpha]_D^{20} + 17^\circ$ (c 4.7 in pyridine). (Found: C 66.12; H 4.97; OCH_3 9.60. $C_{17}H_{18}O_6(OCH_3)$ requires C 65.85; H 4.91; OCH_3 9.46).

Alpinone and its 3-acetate have widely different R_F -values (0.42 and 0.76, respectively, in ligroin:water:methanol (100:50:1)).

Hydrolysis of alpinone-3-acetate. Alpinone-3-acetate (330 mg) was boiled in a nitrogen atmosphere for one hour with a solution of hydriodic acid (9 ml) in abs. ethanol (1.5 ml). Water was then added and the precipitate recrystallised from methanol, m. p. 181–182°, undepressed when mixed with alpinone. (Found: C 67.21; H 4.94; OCH_3 10.94. $C_{15}H_{11}O_4(OCH_3)$ requires C 67.12; H 4.93; OCH_3 10.84). The same result was also obtained by using conc. hydrochloric acid or 42 % sulphuric acid. In the last case the volatile acid formed in the reaction was distilled off and its half distillation value (determined according to Virtanen and Pulkki ¹⁰) was found to be 37, which is the value given for acetic acid ¹⁰.

Synthesis of alpinone-3-acetate. Pinobanksin-7-methylether ³ (30 mg) was dissolved in acetic anhydride and one drop of pyridine was added. After standing overnight at room temperature water was added. The oil which precipitated crystallised after some time and was recrystallised from methanol. M. p. 135–136°, undepressed when mixed with natural alpinone-3-acetate. (Found: C 65.33; H 5.11. $C_{18}H_{16}O_6$ requires C 65.85; H 4.91).

2',4',6'-Trimethoxy- β -methylchalcone (VII). Phloroglucinoltrimethylether¹¹ (18.1 g) and β -methylcinnamoylchloride¹² (19.5 g) were dissolved in nitrobenzene (100 ml). The mixture was cooled with ice and stirred, and powdered aluminium chloride (14.0 g) was added in small portions during two hours. Stirring was continued for three hours at room temperature. The precipitate was filtered off, washed with dry ether, and then added in small portions to ice-cold hydrochloric acid. The remaining solid was filtered off, dried, and recrystallised from methanol giving light yellow leaflets, m. p. 127–128°. Yield 16.5 g (50 %). (Found C 72.5; H 6.5. $C_{19}H_{20}O_4$ requires C 73.1; H 6.5).

2'-Hydroxy-4',6'-dimethoxy- β -methylchalcone (VIII). *2',4',6'-Trimethoxy- β -methylchalcone* (15.6 g) was dissolved in dry benzene (100 ml) and to this was added during half an hour a solution of aluminium bromide (14.5 g) in benzene (100 ml). The mixture was then refluxed on a water bath for two hours. The solvent was removed in vacuum and the residue was treated with ice-cold hydrochloric acid. The solid was filtered off and recrystallised from methanol. Yellow prisms, m. p. 75–77°. Yield 12.2 g (81 %). (Found: 72.1; H 6.1. $C_{18}H_{18}O_4$ requires C 72.5; H 6.1). Other demethylating agents gave much inferior yields.

The acetate was obtained by boiling the chalcone with acetic anhydride, either in pyridine solution or in the presence of anhydrous sodium acetate. Almost colourless leaflets, m. p. 87–88°. (Found: C 70.04; H 6.47 $C_{20}H_{20}O_5$ requires C 70.57; H 5.92 %).

5,7-Dimethoxy-2-methylflavanone (X). *2'-Hydroxy-4',6'-dimethoxy- β -methylchalcone* (6.0 g) was dissolved in hot ethanol (100 ml) and to this was added 2 N sodium hydroxide (50 ml). The mixture was then poured into 400 ml of cold water and allowed to stand for 24 hours. The precipitate was filtered off and recrystallised from ethanol. Colourless crystals, m. p. 135–136°. Yield 5.1 g (85 %). (Found: C 72.2; H 6.1. $C_{18}H_{18}O_4$ requires C 72.5; H 6.1).

3-Hydroxy-5,7-dimethoxy-2-methylflavanone (XI). *5,7-Dimethoxy-2-methylflavanone* (3.0 g) was dissolved in glacial acetic acid (50 ml) and lead tetra-acetate (4.7 g) was added. The mixture was kept at 85–90° for 3 hours and then poured into 200 ml of cold water. The precipitate was dissolved in ethanol (100 ml) and conc. hydrochloric acid was added. The mixture was then warmed for half an hour on a water bath in a stream of carbon dioxide, and poured into water (200 ml). This was allowed to stand for 24 hours, whereafter the precipitate was filtered off and recrystallised from methanol. Colourless needles, m. p. 166–167°. Yield 0.06 g. (Found: C 69.1; H 5.8. $C_{18}H_{18}O_5$ requires C 68.8; H 5.8).

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