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# Constituents of Pine Heartwood

## XXIX.* A Synthesis of Strobochrysin Dimethyl Ether (5,7-Dimethoxy-6-methylflavone)

GÖSTA LINDSTEDT and ALFONS MISIORNY

*Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden*

In Part XXIV of this series [1], the isolation from the heartwood of *Pinus strobus* L. of a new flavone, named strobochrysin, was recorded. It was found to be a C-methylchrysin with the methyl group in either the 6- or the 8-position. The dimethyl ether, m.p. 170—171° **, was also prepared, and as this compound was not identical with 5,7-dimethoxy-8-methylflavone (m.p. 230—231°), we concluded that the C-methyl group in strobochrysin occupies the 6-position. Lack of material prevented us from proving this structure in a more direct way.

An unambigous synthesis of 5,7-dimethoxy-6-methylflavone has now been carried out by a method analogous to that used for the synthesis of the 8-methyl isomer [1]. The main difficulty lies in the relative inaccessibility of the key intermediate, 2,6-dimethoxy-4-hydroxytoluene (I). Of the three published methods of synthesising this substance, that of Gruber [2] appears to be the simplest, consisting as it does of a Gattermann aldehyde synthesis on phloroglucinol dimethyl ether and reduction of the *p*-hydroxyaldehyde (formed as a by-product) by the Clemmensen method. In our hands, however, the Gattermann synthesis (using zinc cyanide and hydrogen chloride) yielded the *o*-hydroxyaldehyde exclusively. Of the other two methods available, we preferred that described by Asahina and co-workers [3,4] to the older synthesis due to Robertson and co-workers [5]. We have modified one of the steps of the synthesis slightly.

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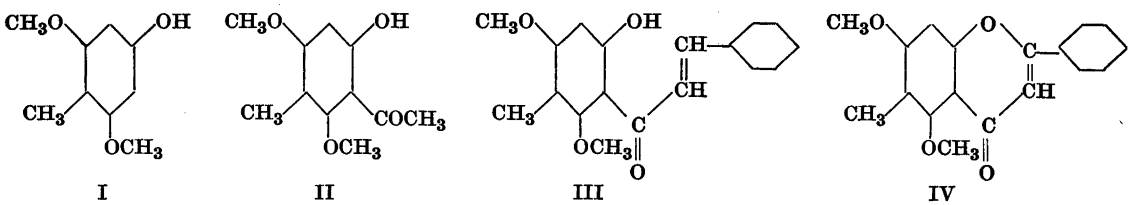
** All melting points uncorrected.



I II III IV

Robertson and co-workers [6] prepared 2-hydroxy-5-methyl-4,6-dimethoxyacetophenone (II) from the phenol (I) by Fries rearrangement of the acetate, and obtained the ketone as an oil. We, however, succeeded in getting the substance crystalline, m.p. 38—39°, after purification by vacuum distillation. Condensation of this ketone with benzaldehyde gave 2′-hydroxy-5′-methyl-4′,6′-dimethoxychalkone (III), m.p. 94—95°, oxidised in good yield to the desired 5,7-dimethoxy-6-methylflavone (IV) by selenium dioxide. This flavone, m.p. 170—171°, was found to be identical with strobochrysin dimethyl ether, which we had previously prepared in an impure state [1], and thus, strobochrysin is 6-methylchrysin.

The chalkone (III) was rearranged to the corresponding 5,7-dimethoxy-6-methylflavanone, m.p. 130—131°, either by boiling with hydrochloric acid in alcohol or by allowing it to stand in dilute sodium hydroxide at room temperature (method of Löwenbein [7]). The flavanone was obtained in good yield, in contrast to the 8-methyl isomer, which is very difficult to prepare from the corresponding chalkone [1]. The difficulty of rearranging the latter chalkone is probably due to steric hindrance.

The following table lists the melting points and the reduction colours of the fully methylated 6- and 8-methylflavones and -flavanones we have prepared.

| Substance | M.p. | Mg-HCl colour |
|---|---|---|
| 5,7-dimethoxy-**6**-methylflavone | 170—171° | Lemon yellow |
| —»— flavanone | 130—131° | Pale yellow |
| 5,7-dimethoxy-**8**-methylflavone [1] | 230—231° | Pink |
| —»— flavanone [1] | 141—142° | Pale pink |
| 3,5,7-trimethoxy-**8**-methylflavone [8] | 154—155° | Pink |

It is noteworthy that the 8-methyl derivatives have higher melting points and give deeper colours on reduction than the corresponding 6-methyl derivatives.

The information now available sheds some light on the structure of strobobanksin, a C-methylflavanone isolated from the heartwood of *P. strobus* [1]. Strobobanksin is a

3,5,7-trihydroxyflavanone with a C-methyl group either in the 6- or in the 8-position. When its partial methylation product was dehydrogenated to a flavonol with palladium-cinnamic acid, a yellow substance was obtained, which on exhaustive methylation yielded a product which was not purified owing to lack of material. However, it gave a strong yellow colour with magnesium-hydrochloric acid and, therefore, it can not be 3,5,7-trimethoxy-8-methylflavone, but is probably the 6-methyl isomer. Consequently, strobobanksin should belong to the 6-methyl series.

## EXPERIMENTAL

*2,6-Dimethoxy-4-hydroxytoluene (I).* The methylation of 3,5-dihydroxy-4-methylbenzoic acid [3] proved to be the most difficult step in the synthesis. Methylation with dimethyl sulphate and alkali, as described by the Japanese workers [3], led to mixtures, which were difficult to separate. Better results were obtained using the following method:

3,5-dihydroxy-4-methylbenzoic acid (26.5 g) in acetone (1 l) was refluxed for three hours with dimethyl sulphate (62 ml) and freshly ignited potassium carbonate (180 g). The precipitate was filtered off and washed with hot acetone, and the filtrate was concentrated to a syrup, which soon deposited crystals. Recrystallisation of the solid material from methanol gave colourless crystals of 3,5-dimethoxy-4-methylbenzoic acid methyl ester, m.p. 104—105°. The syrupy fraction, on distillation at low pressure, yielded four fractions, the highest-boiling of which (b.p. 148—150°/4 mm) consisted of an additional amount of the substance desired. The total yield of the pure ester was 13.0 g.

The preparation of the phenol (I) from this ester by Curtius rearrangement and diazotisation of the amine formed was carried out as described by Asahina and Yanagita [4], and with about the same yields as found by those authors.

*2-Hydroxy-5-methyl-4,6-dimethoxyacetophenone (II).* — The phenol (I) was acetylated (97 % yield), and the acetate was rearranged with aluminium chloride in nitrobenzene as described by Robertson and co-workers [6]. The product, after distillation at 1 mm pressure (b.p. 131—135°), was a yellow oil which solidified after being set aside in the refrigerator. M.p. 35—36°; 2.3 g from 3.0 g of the acetate.

The solid product was dissolved in light petroleum and the solution was cooled to 0°. A small amount (0.2 g) of the phenol (I) which separated was removed and the solution was evaporated and the residue again distilled at 1 mm pressure. B.p. 128—131°, m.p. 38—39°. The melting point remained unchanged after a third distillation. The substance gives a violet colour with ferric chloride.

$C_{11}H_{14}O_4$ (210.2) Calc. $OCH_3$ 29.5 Found $OCH_3$ 29.5

*2'-Hydroxy-5'-methyl-4',6'-dimethoxychalkone* (III). — The ketone (II) (1.5 g) was dissolved in ethanol (15 ml), and benzaldehyde (1.1 ml) and potassium hydroxide (6 g) in water (6 ml) were added. The red homogeneous solution was left overnight at room temperature; then acidified and extracted with ether. The ether solution was dried over anhydrous sodium sulphate and filtered through aluminium oxide, which adsorbed part of the red colour. The filtrate was concentrated to a reddish syrup, which crystallised on standing. The crude product (2.0 g) was recrystallised once from methanol and thrice from ethanol, and then formed yellow needles, m.p. 94—95°. The chalkone gives a brownish colour with alcoholic ferric chloride.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $C_{18}H_{18}O_4$ (298.3) | Calc. | C | 72.5 | H | 6.08 | $OCH_3$ | 20.8 |
| | Found | » | 72.6 | » | 6.05 | » | 20.0 |

*5,7-Dimethoxy-6-methylflavone (IV).* — The chalkone (III) (0.5 g) was refluxed with selenium dioxide (0.7 g) in *iso*-amyl alcohol (8 ml) for 42 hours. The precipitated selenium was filtered off, and the alcohol was removed by steam distillation. The residue was dissolved in chloroform, and the solution washed with dilute sodium hydroxide, dried over anhydrous sodium sulphate, filtered through aluminium oxide and evaporated. The brownish crystalline residue was washed with a little ether and recrystallised twice from ethanol, yielding colourless needles (0.4 g), m.p. 170—171°, undepressed in admixture with the crude strobochrysin dimethyl ether (m.p. 170—171°) previously prepared [1]. The compound gives a lemon yellow colour with magnesium-hydrochloric acid.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{18}H_{16}O_4$ (296.3) | Calc. | C 73.0 | H 5.44 | $OCH_3$ 20.9 |
| | Found | » 72.8 | » 5.40 | » 20.0 |

*5,7-dimethoxy-6-methylflavanone.* — The chalkone (III) (0.2 g) was dissolved in ethanol (5 ml) and refluxed with 2 *N* hydrochloric acid (4 ml) for 30 hours. After evaporation of the ethanol, the solution was extracted with ether. The ether solution was dried over anhydrous sodium sulphate, filtered through aluminium oxide and concentrated to a reddish brown oil, which soon crystallised. The coloured impurities were removed by washing with a little ether, and the residue, after two recrystallisations from methanol, yielded colourless crystals, m.p. 130—131° (0.15 g). The substance gives a faint yellow colour on reduction with magnesium-hydrochloric acid.

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{18}H_{18}O_4$ (298.3) | Calc. | C 72.5 | H 6.08 | $OCH_3$ 20.8 |
| | Found | » 71.7 | » 6.09 | » 20.7 |

The rearrangement could also be carried out by dilute sodium hydroxide at room temperature. The chalkone (0.1 g) in ethanol (1 ml) was heated with 1.5% sodium hydroxide (1.5 ml) until the solution was homogeneous, then set aside for two days, during which time a yellow precipitate formed. The solid was collected, decolourised by washing with ethanol and ether, and then recrystallised from methanol. The m.p. either alone or in admixture with the flavanone prepared by the first method was 130—131°.

## SUMMARY

5,7-Dimethoxy-6-methylflavone and -flavanone have been synthesised by unambigous methods. The flavone has been shown to be identical with the dimethyl ether of strobochrysin, which thus must be 5,7-dihydroxy-6-methylflavone.

The evidence now available indicates that strobobanksin belongs to the 6-methyl series (3,5,7-trihydroxy-6-methylflavanone).

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