A Synthesis of 2-Hydroxy-3-methyl-4,6-ω,-trimethoxyaceto-phenone and Some Related Compounds

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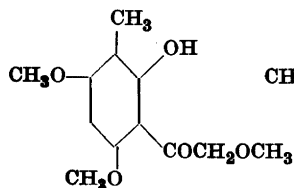*Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden*

In connection with certain studies in the field of C-methylflavones, the previously not synthesised 2-hydroxy-3-methyl-4,6,-ω-trimethoxyacetophenone (I) was required as a starting product. This ketone has now been synthesised by two independent methods which are exactly analogous to those adopted for the synthesis of 2-hydroxy-3-methyl-4,6-dimethoxyacetophenone by Curd and Robertson [1]. The first and most convenient method involves methylation of ω-methoxyphloroacetophenone with methyl iodide and potassium carbonate in acetone, and the second consists of the condensation of 2-hydroxy-4,6-dimethoxytoluene (II) with methoxyacetonitrile by the Hoesch method. Both procedures yielded a colourless compound $C_{12}H_{16}O_5$, m. p. 148—149° *. The second method, starting from the phenol (II), can lead to two possible isomers, an o- and a p-hydroxyketone. On the other hand, the methylation of ω-methoxyphloroacetophenone must be expected to yield an o-hydroxyketone, since

* All melting points uncorrected.

the hydroxyl groups in o-positions are less reactive because of hydrogen bonding to the carbonyl oxygen. Thus, (I) represents the only possible structure for the ketone synthesised.
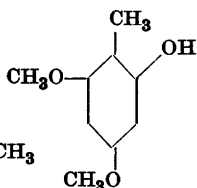
On condensation with benzaldehyde, the ketone yielded 2'-hydroxy-3'-methyl-4',6', α-trimethoxychalkone (III), m. p. 117—119°. Selenium dioxide oxidation of this chalkone gave a colourless crystalline compound in 4 % yield. This had m. p. 154—155° and gave a pink colour on reduction with magnesium-hydrochloric acid. Since chalkones are generally oxidised to flavones by selenium dioxide [2], this product must be 3,5,7-trimethoxy-8-methyl-flavone (IV). To test the validity of this reaction for other α-methoxychalkones, we oxidised 2'-hydroxy-4',6', α-trimethoxy-chalkone and isolated the expected galangin trimethyl ether, although in very low yield.

The ketone (I) is probably identical with "methoxymethylfisetol dimethyl ether", m.p. 148—149°, which was isolated after alkaline degradation of the product obtained by methylating quercetin with methyl iodide and alkali [3]. Assuming this to be so, the methylation product of quercetin should be 8-methylquercetin pentamethyl ether.
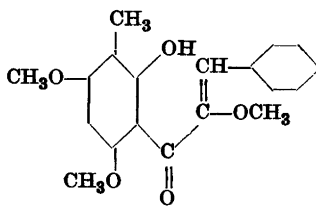
EXPERIMENTAL: Synthesis of the ketone (I), Method A: Dry ω-methoxyphloroacetophenone (10 g) was refluxed with methyl iodide (30 ml) and freshly ignited potassium carbonate (30 g) in acetone (100 ml) for three hours. The precipitate was filtered off and washed with hot acetone, and the yellow filtrate evaporated to dryness. The crystalline
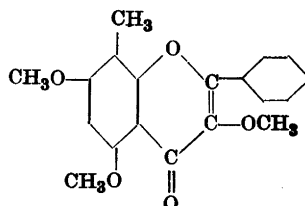

I   II   III   IV

residue was dissolved in ether, and the solution washed with sodium carbonate solution, dried over anhydrous sodium sulphate and filtered through aluminium oxide. The filtrate was concentrated, yielding a crystalline residue, which was recrystallised from ethanol, giving colourless needles, m.p. 143—144° (2.2 g). Further recrystallisation raised the m.p. to 148—149°. With ferric chloride in alcoholic solution, the substance gives a brownish-violet colour.

$C_{13}H_{16}O_5$ (240.3)
  Calc. C 59.9 H 6.70 OCH_3 38.7
  Found » 59.6 » 6.74   »   38.6

Method B: 2-Hydroxy-4,6-dimethoxytolu-ene [4] (II) was condensed with methoxy-acetonitrile by the Hoesch method, and the reaction product worked up as described by Curd and Robertson [1]. After recrystallisation from ethanol, the substance melted at 146—148° alone or in admixture with a sample prepared by method A.

Synthesis of 2'-hydroxy-3'-methyl-4',6',α-trimethoxychalkone (III): A suspension of 2-hydroxy-3-methyl-4,6,ω-trimethoxyaceto-phenone (0.5 g) in ethanol (8 ml) was added to a mixture of benzaldehyde (0.5 ml) and potassium hydroxide (2 g) in water (2 ml). The resulting red solution was left overnight in a stoppered flask and then acidified, giving a yellow crystalline precipitate. This material, after three recrystallisations from ethanol, formed pale yellow leaflets, m.p. 117—119° (0.6 g). Ferric chloride in alcoholic solution gives a strong brownish-violet colour.

$C_{19}H_{20}O_5$ (328.4)
  Calc. C 69.5 H 6.14 OCH_3 28.3
  Found » 70.0 » 6.19   »   28.2

Synthesis of 3,5,7-trimethoxy-8-methylflavone (IV): The chalkone (1.0 g) was refluxed with selenium dioxide (1.2 g) in *iso*-amyl alcohol (10 ml) for 40 hours. The solvent was then removed by steam distillation and the residue was dissolved in chloroform. This solution was washed with 2 N sodium hydroxide and with water, dried and filtered through aluminium oxide to remove coloured impurities. The filtrate, on concentration, slowly deposited yellow crystals, which were recrystallised twice from methanol, yielding colourless needles (0.04 g), m.p. 154—155°. Colour reactions: ferric chloride, none; magnesium-hydrochloric acid, pink.

$C_{19}H_{18}O_5$ (326.3)
  Calc. C 69.9 H 5.56 OCH_3 28.5
  Found » 69.1 » 5.05   »   28.1

Oxidation of 2'-hydroxy-4',6', α-trimethoxy-chalkone by the same method gave a 5 % yield of galangin trimethyl ether, m.p. and mixed m.p. 196—198°.

1. Curd, F. H., and Robertson, A. *J. Chem. Soc.* **1933** 437.
2. Mahal, H. S., Rai, H. S., and Venkatara-man, K. *J. Chem. Soc.* **1935** 866.
3. Perkin, A. G. *J. Chem. Soc.* **103** (1913) 1632.
4. Weidel, H. *Monatsh.* **19** (1898) 232.

Intermolecular Free Lengths in Liquids in Relation to Compressibility, Surface Tension and Viscosity

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The intermolecular free length between molecules in the liquid state is an essential and characteristic feature. This is evident from the simplicity and generality of application obtained when empirical relations are sought between the inter-molecular free length and the properties in liquids which are dependent on inter-molecular processes. Those properties include compressibility, surface tension and viscosity. If these properties are designated j the following simple relation prevails:

$$j = k \cdot L^p$$

where k and p assume for each property and each temperature certain constant values irrespective of composition, structure, size and shape of the molecules in the liquid or liquid mixture. The free inter-molecular length is defined as

$$L = \frac{2(V_T - V_0)}{Y} \qquad (2)$$