

The Action of Phenylmagnesium Bromide on Ethyl Chromone-2-carboxylate and its 3-Methyl Derivative

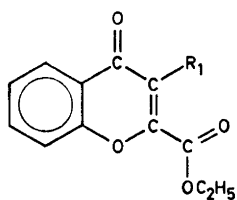
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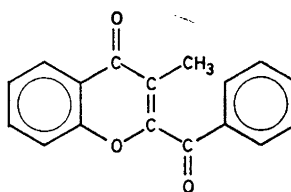
When phenylmagnesium bromide reacts with ethyl chromone-2-carboxylate, 2-(diphenylhydroxymethyl)-chromone is formed by 1,2-addition of the Grignard reagent to the carbethoxy group. The 3-methyl derivative of the ester reacts similarly. The mass spectrometric fragmentation of the reaction products is discussed.

In the reactions of phenylmagnesium bromide with ethyl 3-coumarincarboxylate and its 4-methoxy derivative a strong tendency of the Grignard reagent to react with the conjugated double bond system $C=C-C=O$ by 1,4-addition has been observed.^{1,2} In these coumarin compounds the carbon to carbon double bond is conjugated not only with the carbonyl group in the carbethoxy group but also with the carbonyl group in the lactone ring, *i.e.* the carbonyl groups operate in the same direction. In ethyl chromone-2-carboxylate (I a), an isomer of ethyl 3-coumarincarboxylate, there are also one carbon to carbon double bond and two carbonyl groups which are conjugated, but the carbonyl groups operate in opposite directions. An investigation of the way in which this affects the reaction seemed interesting. A 1,4-addition can scarcely occur, but the molecule contains two carbonyl groups for 1,2-addition of the Grignard reagent.

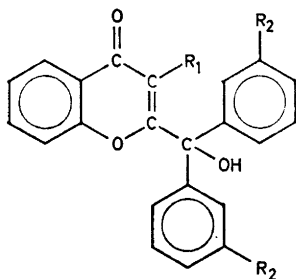
As ethyl chromone-2-carboxylate (I a) and ethyl 3-methylchromone-2-carboxylate (I b) are easily prepared, they were used as initial materials. When phenylmagnesium bromide was allowed to react with the former ester, a substance $C_{22}H_{16}O_3$ was obtained. Under the same conditions the latter ester gave a methyl derivative of the above substance and in addition small amounts of 2-benzoyl-3-methyl-4*H*-1-benzopyranone-4 (II). It is remarkable that the former ester gave, besides the isolated product, intensely coloured reaction products. Unfortunately, these compounds could not be isolated, probably because the amounts of coloured matter were small. Ethyl 3-methylchromone-2-carboxylate did not give similar coloured products.



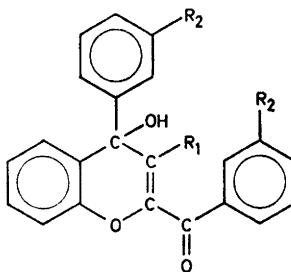
I



II



III



IV

- a: $R_1 = R_2 = H$
 b: $R_1 = CH_3, R_2 = H$
 c: $R_1 = H, R_2 = CH_3$

The composition of the main products showed that two moles of the Grignard reagent had reacted and that the ethoxy groups in the esters had been eliminated. IR spectra of the compounds showed that the main products contained hydroxy groups and carbonyl groups in conjugation with a double bond and/or phenyl groups. Mass spectra definitely excluded 1,4-addition and consequently only two possible constitutions (III a and IV a or III b and IV b) remained.

The mass spectrum (Fig. 1) of the compound prepared from ethyl chromone-2-carboxylate showed, besides phenyl and benzoyl ions, abundant ions at m/e 328, 312, 251, 223, 183, and 121. The first-mentioned is obviously the molecular ion. The ions at m/e 251 and 223 correspond to molecular ions from which a phenyl and a benzoyl group, respectively, have been split away. These facts point to the structure IV a. Even the ion at m/e 121 can be fitted into the fragmentation of this molecule although m/e 120 is a more expected value for a chromone derivative.³ The ion m/e 183 apparently contains two phenyl groups and one carbon, one oxygen, and one hydrogen atom. Such a fragment corresponding to a diphenylhydroxymethyl group is the natural ion to be split off from a compound with the structure III a. On the other hand, it is possible that a fragment ion with m/e 183 could be formed from parts of the

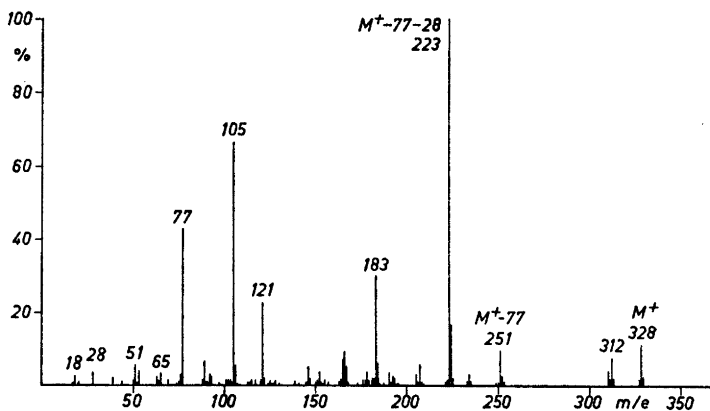


Fig. 1. Mass spectrum of 2-(diphenylhydroxymethyl)-chromone.

chromone group and the phenyl group in position 4 of the compound IV a. The mass spectrum (Fig. 2) of the product prepared from ethyl 3-methylchromone-2-carboxylate showed the same abundant ions up to about 190 and ions with masses higher by 14 a.u., *i.e.* with a methyl group substituted for a hydrogen atom.

In order to establish the constitution, a dimethyl derivative was prepared from ethyl chromone-2-carboxylate and *m*-tolylmagnesium bromide. The mass spectrum (Fig. 3) of this substance showed abundant ions at *m/e* 356, 265, 237, 211, 121, 119 and 91. If these masses are compared with the masses in the spectrum of the compound prepared from ethyl chromone-2-carboxylate and phenylmagnesium bromide, it is observed that the molecular ion and the

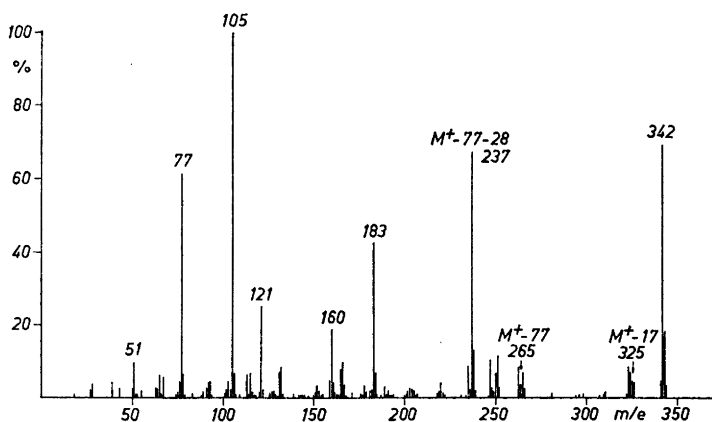


Fig. 2. Mass spectrum of 2-(diphenylhydroxymethyl)-3-methylchromone.

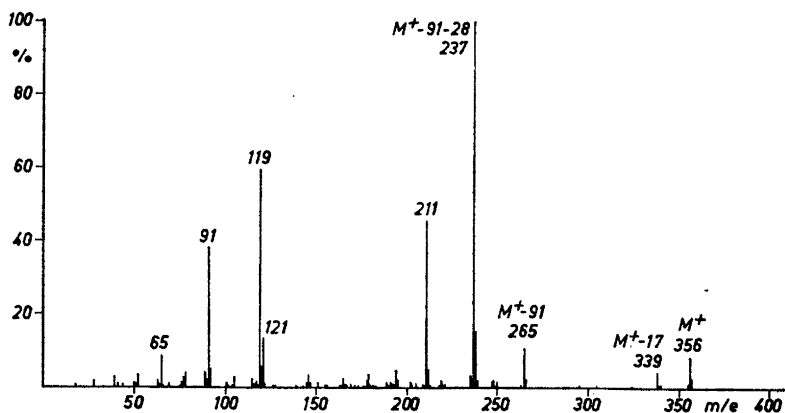
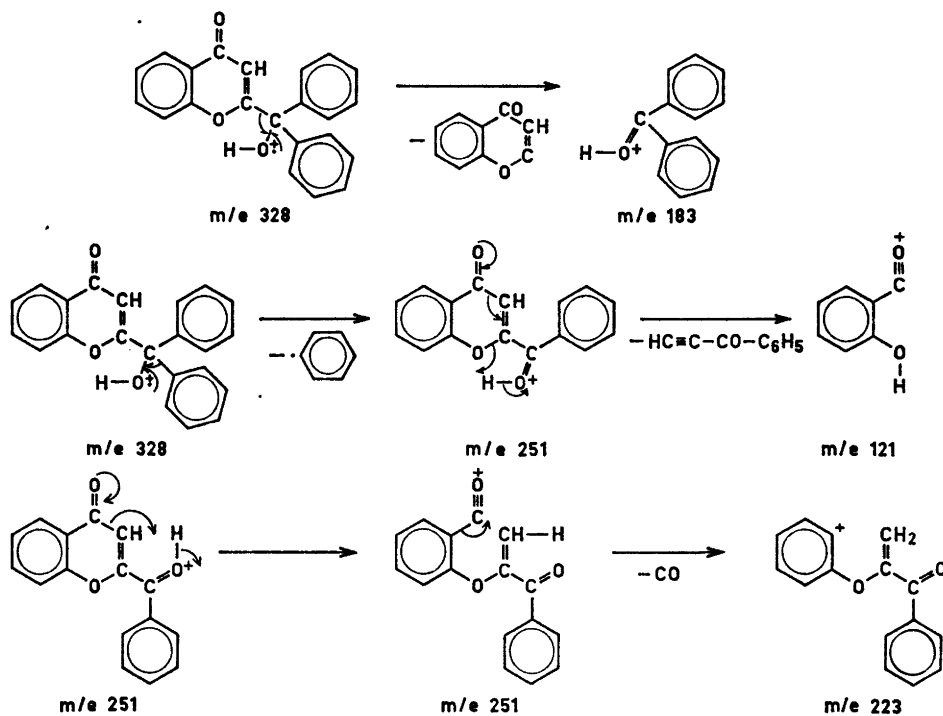


Fig. 3. Mass spectrum of 2-(di-*m*-tolylhydroxymethyl)-chromone.

ion at m/e 183 have masses 28 a.u. higher while the remaining ions, except for that at m/e 121, have masses greater by 14 a.u. These facts show that the two aromatic groups in the ion 183 and its dimethyl homolog are derived from



Possible reactions for the fragmentation of 2-(diphenylhydroxymethyl)-chromone.

the Grignard reagents. Consequently the three main products have the structures III a, III b, and III c.

The adjoining scheme for the fragmentation of 2-(diphenylhydroxymethyl)-chromone shows that common fragmentation reactions explain the presence of the most abundant ions.

It has thus been shown that the compounds isolated from the above described reactions have been formed by "normal" reactions between the ester groups and Grignard reagents. The carbonyl group in position 4 of the chromone ring in the studied esters does not seem to react to any greater extent with phenylmagnesium bromide.

EXPERIMENTAL

Ethyl chromone-2-carboxylate was prepared according to Vejdělek, Trčka, Chyba, and Chybová⁴ from *o*-hydroxyacetophenone and ethyl oxalate with sodium ethoxide as condensating agent.

Ethyl 3-methylchromone-2-carboxylate was obtained by allowing *o*-hydroxypropionophenone to react with ethoxalyl chloride in pyridine according to Clerc-Bory, Pachéco, and Mentzer.⁵

The reaction between ethyl chromone-2-carboxylate and phenylmagnesium bromide. Ethyl chromone-2-carboxylate (5.45 g; 0.025 mole) in dry ether (30 ml) was gradually added to a Grignard reagent prepared from bromobenzene (9.81 g; 0.0625 mole), magnesium (1.5 g; 0.0625 mole), and dry ether (30 ml). After the mixture had been kept at the boiling point of ether for 15 min, it was cooled and poured into a mixture of hydrochloric acid (15 ml), water (50 ml), and ice (100 g). The purple ether layer was separated and washed with water and a 5 % potassium hydrogen carbonate solution. After drying with sodium sulphate and evaporating the solvent, an oil (8.5 g) was recovered. It was dissolved in benzene and ligroin was added to the solution. After several hours in a refrigerator, crude crystals of 2-(diphenylhydroxymethyl)-chromone were isolated by filtration. The substance was purified by treating it with aluminium oxide and charcoal. The pure substance melted at 210–211°. (Found: C 80.33; H 5.01; mol. wt. 328. Calc. for C₂₂H₁₆O₃: C 80.47; H 4.91; mol. wt. 328.)

The reaction between ethyl chromone-2-carboxylate and m-tolylmagnesium bromide. When the equivalent amount of *m*-bromotoluene (10.67 g) was used instead of bromobenzene in the above reaction, 2-(di-*m*-tolylhydroxymethyl)-chromone, m.p. 205–206°, was obtained. (Found: C 81.05; H 5.77; mol. wt. 356. Calc. for C₂₄H₂₀O₃: C 80.88; H 5.66; mol. wt. 356.)

The reaction between ethyl 3-methylchromone-2-carboxylate and phenylmagnesium bromide. Ethyl 3-methylchromone-2-carboxylate (2.90 g; 0.0125 mole) in dry ether (15 ml) was gradually added to a Grignard reagent prepared from bromobenzene (4.90 g; 0.0312 mole), magnesium (0.75 g; 0.0312 mole), and dry ether (15 ml). After the mixture had been held at the boiling point of ether for 15 min, it was cooled and poured into a mixture of hydrochloric acid (10 ml), water (25 ml), and ice (about 50 g). The organic phase was separated and washed with potassium hydrogen carbonate solution. After drying with sodium sulphate and evaporating the solvent, an oil (4.0 g) was obtained. It was dissolved in methanol and after some time crystals of crude 2-benzoyl-3-methylchromone were isolated. The compound was purified by repeated recrystallization from methanol. The pure substance melted at 117–118°. (Found: C 77.10; H 4.58. Calc. for C₁₇H₁₂O₃: C 77.26; H 4.58.)

The experiment was repeated, but the reaction time was extended to 48 h at room temperature. By fractional recrystallization from ligroin, pure 2-(diphenylhydroxymethyl)-chromone, m.p. 200–201°, was isolated from the resulting oil. (Found: C 80.58; H 5.46; mol. wt. 342. Calc. for C₂₂H₁₆O₃: C 80.68; H 5.30; mol. wt. 342.)

It must be pointed out that 2-(diphenylhydroxymethyl)-chromone was the main product in the first experiment, although the separation was more easily performed after the longer reaction period.

The mass spectra were recorded at the Masspektrometrlaboratoriet, Karolinska Institutet, Stockholm, Sweden.

The analyses were carried out partly by Mr. P. Demoen, Janssen Pharmaceutica, Berse, Belgium, and partly by Dr. Alfred Bernhardt, Mülheim (Ruhr), Western Germany. *Statens Naturvetenskapliga Kommission* has supported the work.

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