ACTA CHEMICA SCANDINAVICA 22 (1968) 995–1003

The Action of Phenylmagnesium Bromide on Ethyl 4-Methoxy-3-coumarincarboxylate

GUST.-AD. HOLMBERG and FOLKE MALMSTRÖM

Institutet för organisk kemi, Åbo Akademi, Åbo, Finland

The product first formed in the reaction between phenylmagnesium bromide and ethyl 4-methoxy-3-coumarincarboxylate is ethyl 4-phenyl-3-coumarincarboxylate. It is probably formed by 1,4-addition of the Grignard reagent followed by 1,4-elimination of methoxymagnesium bromide. The primary reaction product readily adds phenylmagnesium bromide with the formation of compounds of which ethyl 2-ethoxy-2,4-diphenyl-2*H*-1-benzopyran-3-carboxylate, 3-benzoyl-4-phenylcoumarin, 2-ethoxy-3-benzoyl-2,4-diphenyl-2*H*-1-benzopyran, and 3-benzoyl-2,2,4-triphenyl-2*H*-1-benzopyran were isolated. The two 2-ethoxy-2*H*-1-benzopyran derivatives are considered to have been formed during the isolation from the original reaction products, *i.e.* from the corresponding 2-hydroxy derivatives or the corresponding open chain ketones. On the basis of previous experience, the latter alternatives seem more probable.

In the reaction between phenylmagnesium bromide and ethyl 3-coumarincarboxylate, ethyl 4-phenyl-3,4-dihydro-3-coumarincarboxylate and a still unknown compound that on hydrolysis gives 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone are formed.[1,2] On the other hand it has been repeatedly established that an alkoxy group at the position 4 of the conjugated double bond system C=C—C=O is replaced by an alkyl or an aryl group in reactions with Grignard reagents.[3–5] On basis of these facts, it seemed logical to study the products of the reaction of ethyl 4-methoxy-3-coumarincarboxylate (I) with phenylmagnesium bromide.

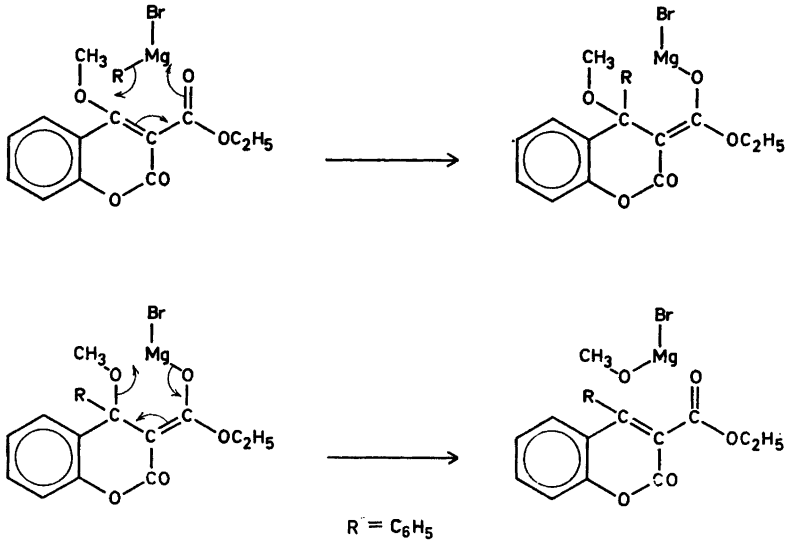
Five experiments were performed with different molar ratios of the ester and the Grignard reagent, different initial reaction temperatures, and different reaction times at room temperature. On gas chromatographic analysis of the reaction products using silicon gum SE-30 as the stationary phase, seven peaks were obtained (for details, see Table 1). The compounds giving rise to these peaks were benzophenone (peak 1), unchanged ethyl 4-methoxy-3-coumarincarboxylate (peak 2), ethyl 4-phenyl-3-coumarincarboxylate (II; peak 3), ethyl 2-ethoxy-2,4-diphenyl-2*H*-1-benzopyran-3-carboxylate (III; peak 4), 3-benzoyl-4-phenylcoumarin (IV; peak 5), 2-ethoxy-3-benzoyl-2,4-

Table 1. Experimental data concerning Grignard reactions.

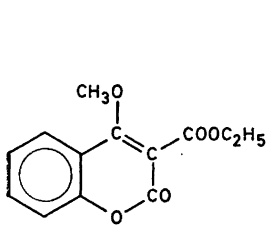
Experiment	Molar ratio of ester to Grignard reagent	Cooling bath temperature	Reaction time at room temperature	Peaks in gas chromatogram (Almost negligible peaks within parentheses.)
1	1:2.5	0°	15 min	(1) 2 (3) 4 5 6 (7)
2	1:3.5	−15°	—	(1) (2) 3 4 5 (6) (7)
3	1:3.5	0°	1 h	(1) (2) (3) 4 5 6 (7)
4	1:3.5	0°	24 h	(1) — (3) 4 5 6 7
5	1:5.0	0°	48 h	(1) — — 4 5 6 7

diphenyl-2*H*-1-benzopyran (V; peak 6), and 3-benzoyl-2,2,4-triphenyl-2*H*-1-benzopyran (VI; peak 7). The two 2-ethoxy-2*H*-1-benzopyran derivatives are apparently not immediate reaction products, but were formed from ethanol and the corresponding open chain ketones (VII) or their cyclic semiketals (VIII) during the isolation of the reaction products. Similar rapid cyclic ketal formation has previously been reported, *e.g.* from 3-(*o*-hydroxyphenyl)-3-phenylpropiophenone.[2] On the basis of experience from this compound, the former alternatives even seem more probable.

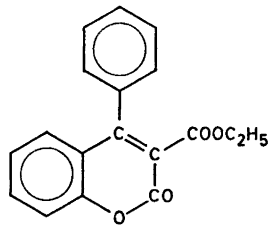
The small amounts of benzophenone are apparently produced by the action of carbon dioxide of the air on the large excess of the Grignard reagent. The fact that this ketone has not previously been detected as a reaction product of carbon dioxide and phenylmagnesium bromide [6] probably depends on the greater resolving power of the gas chromatographic method.



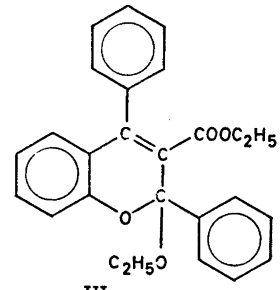
Reaction sequence A



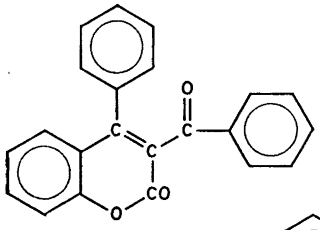
I



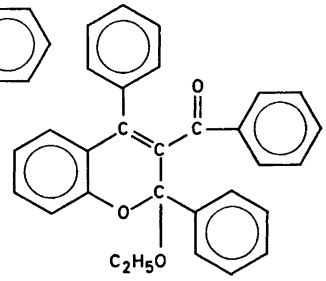
II



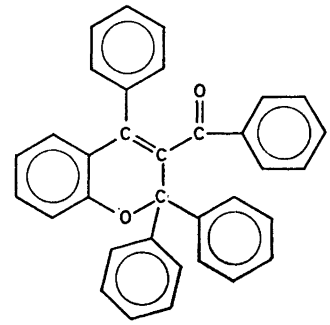
III



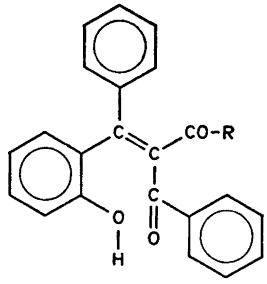
IV



V

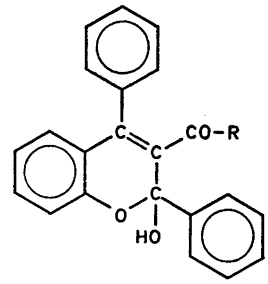


VI



VII

R= OC_2H_5 or C_6H_5



VIII

A study of the results indicates that ethyl 4-phenyl-3-coumarincarboxylate is the primary reaction product. It can be detected in greater quantities only in an experiment at the lowest initial temperature without prolonging the reaction time at room temperature and completely disappears when the reaction time at room temperature is extented to 48 h.

The formation of ethyl 4-phenyl-3-coumarincarboxylate is formally equivalent to the substitution of a phenyl group for the methoxy group in the initial compound. Heilbron and Hill [7] have shown that 4-methoxy-2,2-diphenyl-2*H*-1-benzopyran is formed in the reaction between phenylmagnesium bromide and 4-methoxycoumarin. In this case in which the methoxy group and the carbonyl group of the lactone are in *trans* positions relative to the double bond, the methoxy group is not replaced. But if an alkoxy group and a carbonyl group are in *cis* positions as in diethyl ethoxymethylenemalonate,[4] 3-methoxy-2-benzoylindene,[5] and the present compound, the alkoxy group is replaced by an alkyl or an aryl group with Grignard reagents. Against this background, cyclic 1,4-addition of the Grignard reagent to the conjugated double bond system C=C—C=O followed by cyclic 1,4-elimination of alkoxymagnesium halide best explains the substitution reaction. The present case is illustrated by the reaction sequence A.

The ester (II) that is formed in these primary reactions reacts further with phenylmagnesium bromide by 1,2-addition to the carbonyl group of either the ester or the lactone group. In the former case 3-benzoyl-4-phenylcoumarin (IV) and in the latter case the compound from which ethyl 2-ethoxy-2,4-diphenyl-2*H*-1-benzopyran-3-carboxylate (III) originates are formed.

The next reaction step involves the formation of the compound that was isolated as 2-ethoxy-3-benzoyl-2,4-diphenyl-2*H*-1-benzopyran (V). The present investigation does not give an answer to the question whether this tertiary product is formed from both secondary products or form only one of them.

The last reaction product is 3-benzoyl-2,2,4-triphenyl-2*H*-1-benzopyran (VI). The most dominant feature of this reaction is its slowness. Although present among the reaction products from all experiments, VI appears in greater quantities only after the reaction time is extended to 24 h.

Ethyl 4-methoxy-3-coumarincarboxylate was obtained by the action of diazomethane on ethyl 4-hydroxy-3-coumarincarboxylate, which had been prepared by ring closure from diethyl *o*-acetoxybenzoylmalonate. This latter compound, which has not been isolated previously, was obtained from *o*-acetoxybenzoyl chloride and diethyl ethoxymagnesiummalonate.

Ethyl 4-phenyl-3-coumarincarboxylate was prepared for identification purposes from ethyl 3-coumarincarboxylate by the method which Widegren [8] used to synthesise diethyl diphenylmethylenemalonate from diethyl benzylidenemalonate. Ethyl 3-bromo-4-phenyl-3,4-dihydro-3-coumarincarboxylate was isolated as an intermediate.

EXPERIMENTAL

o-Acetoxybenzoyl chloride was prepared from acetylsalicylic acid (200 g) and thionyl chloride (160 ml) in benzene (360 ml). After the mixture had been refluxed for 6 h, the solvent and the excess thionyl chloride were distilled off. When the residue was distilled under reduced pressure, *o*-acetoxybenzoyl chloride, b.p. 140—141°/15 mm, passed over. The yield was 60.5 % (133.2 g).

Diethyl o-acetoxybenzoylmalonate. An alcohol-free benzene solution of diethyl ethoxymagnesiummalonate was prepared according to Holmberg [9] from magnesium (8.30 g), diethyl malonate (55.4 g), absolute ethanol (27 ml), dry ether (125 ml), and benzene (450 ml in all). The solution was cooled to about 30° and *o*-acetoxybenzoyl chloride (68.68 g) dissolved in benzene (100 ml) was then gradually added with stirring. After it had been

kept for half an hour in a boiling water bath and 3 h at room temperature, the reaction mixture was poured into an ice-cold solution of hydrochloric acid (45 ml) and water (200 ml). The benzene phase was twice washed with water and then dried with anhydrous sodium sulphate. The solvent was distilled off, finally under reduced pressure, and ethyl alcohol (75 ml) was added to the residue. After the solution had been kept for one night in a refrigerator, crystals of crude diethyl *o*-acetoxybenzoylmalonate were filtered off. Repeated recrystallization from mixtures of absolute ethanol and ligroin gave the pure compound, m.p. 50—51°. (Found: C 59.68; H 5.75. Calc. for $C_{16}H_{18}O_7$: C 59.62; H 5.63). The yield of pure diethyl *o*-acetoxybenzoylmalonate was 76.4 % (85.2 g).

All mother liquors were combined and the solvents were distilled off. The residue was dissolved in a small quantity of ethanol. In this way a small amount of less pure malonate was isolated.

Ethyl 4-hydroxy-3-coumarincarboxylate. Diethyl *o*-acetoxy benzoylmalonate (56.67 g) was dissolved in 2 N potassium hydroxide (176 ml). Immediately after the substance had dissolved, a thick precipitate formed. The mixture was cooled and the separated substance was filtered and dissolved in water. When this solution was acidified, crude ethyl 4-hydroxy-3-coumarincarboxylate (33.15 g) separated. Addition of hydrochloric acid to the first alkaline filtrate gave another sample (6.50 g) of the same substance. After recrystallization from ethanol, the substance melted at 100—101°. The total yield of ethyl 4-hydroxy-3-coumarincarboxylate was 79.2 % (33.10 g).

Ethyl 4-methoxy-3-coumarincarboxylate. Ethyl 4-hydroxy-3-coumarincarboxylate (7.60 g) dissolved in ether (100 ml) was methylated with a small excess of diazomethane. This excess was destroyed by adding a small quantity of acetic acid and acidic matter was extracted with 5 % sodium carbonate solution. After the ether phase had been dried with sodium sulphate and the solvent had been distilled off, the residue was crystallized from ethanol. The yield of pure ethyl 4-methoxy-3-coumarincarboxylate, m.p. 91—92°, was 87 % (7.00 g).

Although the melting point given in the literature (95°)[10] was not reached, the product was uniform when examined by IR spectroscopy.

The reaction between phenylmagnesium bromide and ethyl 4-methoxy-3-coumarincarboxylate. Five experiments were performed with different ratios of the reactants and different reaction times and addition temperatures (for details, see Table 1). As an illustration, the first experiment is described.

A solution of ethyl 4-methoxy-3-coumarincarboxylate (12.4 g) in dry ether (400 ml) was gradually added to the Grignard reagent prepared from bromobenzene (19.63 g), magnesium (3.00 g), and dry ether (50 ml). During this operation the reaction flask was cooled in ice-water. After the addition was completed, the reaction mixture was stirred for 15 min at room temperature. The reaction products were then decomposed by pouring the solution into a mixture of hydrochloric acid (30 ml), water (200 ml), and ice (about 200 g). The ether phase was separated and dried with sodium sulphate. After evaporation of the solvent, a light brown oil remained.

A small amount of this oil was dissolved in ethanol and examined by gas chromatography. Seven different peaks resulted and their distributions on chromatograms of the five reaction mixtures are recorded in Table 1. The chromatograms could not be used for quantitative evaluation because the peaks partly overlapped.

Separation of the reaction products. The substances which gave the *peaks 1 and 2* were identified as benzophenone and ethyl 4-methoxy-3-coumarincarboxylate, respectively.

The substance giving *peak 3* could not be isolated from any of the oils. It was, however, identified as ethyl 4-phenyl-3-coumarincarboxylate (II) on the basis of its retention times in gas chromatography on different stationary phases. The synthesis of the ester is described below.

After addition of ethanol to the oil (5 g) from experiment 2, crystals consisting of the substance giving the peaks 5 and 6 were isolated. The solvent was evaporated from the filtrate and the residue was dissolved in a small volume of benzene. By column adsorption chromatography on aluminium oxide using benzene as solvent, fractions containing almost pure substance giving *peak 4* were obtained. The solvent was evaporated from these fractions and after repeated recrystallization of the residues from ethanol, crystals melting at 107—108° were obtained. A mass spectrum and an IR spectrum showed that the substance was ethyl 2-ethoxy-2,4-diphenyl-2*H*-1-benzopyran-3-car-

boxylate (III). (Found: C 77.75; H 6.06; mol. wt. 400. Calc. for $C_{26}H_{24}O_4$: C 77.98; H 6.04; mol. wt. 400).

When ethanol was added to the oils from experiments 3 and 4, crystals separated. They consisted of a mixture of the substances giving *peaks 5 and 6*. Because the substance yielding peak 5 was more soluble in ethanol, the substances could be isolated by fractional recrystallization from this solvent.

The substance yielding *peak 5* melted at 169—170°. A mass spectrum and an IR spectrum showed that the substance was 3-benzoyl-4-phenylcoumarin (IV). (Found: C 80.86; H 4.26; mol. wt. 326. Calc. for $C_{22}H_{14}O_3$: C 80.97; H 4.32; mol. wt. 326). The IR spectrum resembles in many respects that of 3-benzoylcoumarin published by Bassignana and Cogrossi.[11] Absoption bands that in pair correspond are observed at the following wave numbers.

3-Benzoylcoumarin: 1726 1664 1607 1560 1442 1240 1160 cm^{-1}

Present derivative: 1715 1666 1608 1565 1452 1242 1157 cm^{-1}

The coumarin ring was opened as follows. 3-Benzoyl-4-phenylcoumarin (1.77 g) was dissolved in methanol and a solution of potassium hydroxide (6 g) in water (20 ml) was added. The mixture was shaken with dimethyl sulphate (10 ml) for 2 h. The substance that separated was extracted with ether. After the organic phase had been dried with sodium sulphate, the solvent was evaporated. The residue was dissolved in methanol and the whole procedure was repeated from beginning until only one peak was obtained when the products were examined by gas chromatography. After recrystallization from ethanol, methyl β-(*o*-methoxyphenyl)-α-benzoylcinnamate, m.p. 108—109°, was obtained. (Found: C 77.39; H 5.36. Calc. for $C_{24}H_{20}O_4$: C 77.40; H 5.41).

The substance causing *peak 6* melted at 153—154°. A mass spectrum and an IR spectrum showed that the substance was 2-ethoxy-3-benzoyl-2,4-diphenyl-2*H*-1-benzopyran (V). (Found: C 83.10; H 5.51; mol. wt. 432. Calc. for $C_{30}H_{24}O_3$: C 83.31; H 5.59; mol. wt. 432).

The substances in the oil from experiment 5 were separated by column chromatography on aluminium oxide with benzene as eluent. The fractions which contained principally only the substance causing *peak 7* were combined. The solvent was evaporated and the residue was crystallized from mixtures of chloroform and ligroin. After repeated recrystallization from similar mixtures and treatment with carbon black, the substance melted at 207—208°. A mass spectrum and an IR spectrum showed that the substance was 3-benzoyl-2,2,4-triphenyl-2*H*-1-benzopyran (VI). (Found: C 87.73; H 5.30; mol. wt. 464. Calc. for $C_{34}H_{24}O_2$: C 87.90; H 5.21; mol. wt. 464).

Structure determinations. The structures of ethyl 4-phenyl-3-coumarincarboxylate (II; peak 3) and 4-phenyl-3-benzoylcoumarin (IV; peak 5) were clarified above. A mass spectrum (Fig. 1) of the latter substance confirmed the result. Peaks of high abundances are present at *m/e* 77 and 105, *i.e.* for phenyl and benzoyl ions. The molecular ion (*m/e* 326) had a relative abundance of 100 %. The ions at *m/e* 249 and 221 correspond to molecular ions from which a phenyl or a benzoyl group, respectively, have been split away (M—77 and M—105). The only remaining ion of considerable abundance is that with *m/e* 297. The mass of this ion corresponds to M—29. However, the structure of the compound makes a loss of an ethyl group impossible and the fragment ion is probably formed by loss of a carbonyl group and a hydrogen atom. This is supported by the presence

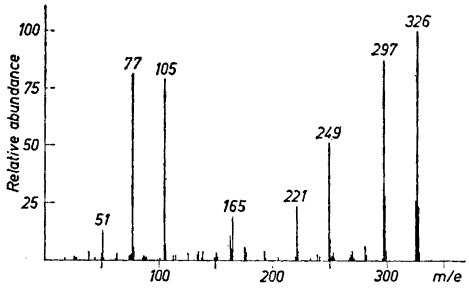


Fig. 1. Mass spectrum of 3-benzoyl-4-phenylcoumarin (IV).

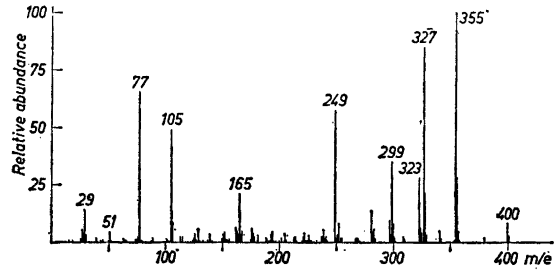


Fig. 2. Mass spectrum of ethyl 2-ethoxy-2,4-diphenyl-2*H*-1-benzopyran-3-carboxylate (III)

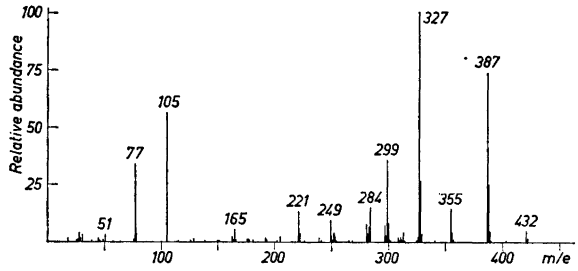


Fig. 3. Mass spectrum of 2-ethoxy-3-benzoyl-2,4-diphenyl-2*H*-1-benzopyran (V).

of a fragment ion at *m/e* 298 (M−28). Vul'fson, Zaretskii, and Zaikin [12] have observed a fragmentation of coumarin and its derivatives by loss of the carbonyl group of the lactone.

The mass spectrum (Fig. 4) of the substance causing peak 7 is quite clear. The molecular ion (*m/e* 464) is distinct, and by elimination of a phenyl or a benzoyl group, the

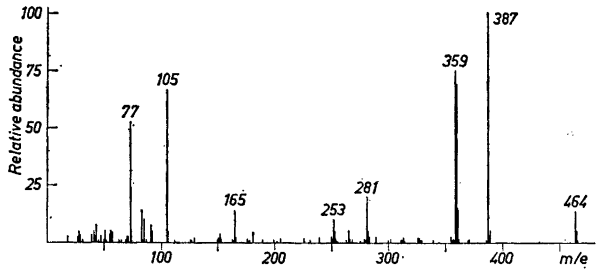


Fig. 4. Mass spectrum of 3-benzoyl-2,2,4-triphenyl-2*H*-1-benzopyran (VI).

ions at *m/e* 387 and 359 (M−77 and M−105) are formed. If the elements of benzene are split away from the latter ion, the result is the ion at *m/e* 281. High abundances are also present for phenyl and benzoyl ions. These facts points to the structure VI for the compound.

Table 2. Absorption bands in the carbonyl region in the IR spectra.

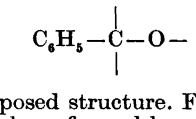
Peak No.	Substance	Wave numbers
2 [a]	(I)	1739, 1700
3	(II)	1742, 1712
4	(III)	1718,
5	(IV)	1715, 1666
6	(V)	1656
7	(VI)	1663

[a] This spectrum was recorded for the initial substance.

IR spectra are important for the determination of the structures of the two remaining substances. From Table 2 in which the absorptions in the carbonyl region of the prepared substances are collected it is seen that the substance causing peaks 5, 6, and 7 absorb at about 1660 cm^{-1}. Because the unsaturated phenone group ($C=C-CO-C_6H_5$) is present in the substances causing peaks 5 and 7 (IV and VI), it seems justified to associate this group with the absorption in question, *i.e.* to conclude that also the substance causing peak 6 contains an unsaturated phenone group. The mass spectrum of the substance (Fig. 3) shows a distinct molecular ion (*m/e* 432). The ions at *m/e* 387, 355, and 327 are formed from the molecular ion by elimination of an ethoxy, a phenyl, and a benzoyl group, respectively (M−45, M−77, and M−105). If ethylene is eliminated from the last mentioned ion, the ion at *m/e* 299 is formed. Even in this case the abundances of phenyl and benzoyl ions are high. Combination of these facts leads to the structure V.

The IR spectrum of the substance giving peak 4 shows only one absorption band in the carbonyl region. Its wave number, 1718 cm^{-1}, eliminates the presence of an unsaturated phenone group. In the mass spectrum (Fig. 2) of the substance, a distinct molecular ion (*m/e* 400) is observed. The ions at *m/e* 355, 327, and 323 are obtained from the molecular ion by elimination of an ethoxy, a carbethoxy, and a phenyl group, respectively (M−45, M−73, and M−77). Even in this case the ion at *m/e* 299 is found. It has obviously been formed in the same way as in the mass spectrum of the next preceding substance, *i.e.* elimination of ethylene from the ion at *m/e* 327. All these facts leads to the structure III.

Phenyl and benzoyl ions are observed even in this lastmentioned mass spectrum. The presence of the latter seems to contradict the structure just established. However, it must be pointed out that the benzoyl ion is formed very easily and that its presence in a mass spectrum can be due to the structural element



which is really present in the proposed structure. Further, it was not possible to detect an ion (M−105) that should have been formed by splitting off a benzoyl group. Finally, the abundance of the benzoyl ion is in this case lower than that of the phenyl group. In the other cases in which benzoyl substituents are present the abundances are the inverse. This fact might show that the benzoyl ion formed from the last substance and the benzoyl ions from the other substances have different origins.

The synthesis of ethyl 4-phenyl-3-coumarincarboxylate. Ethyl 3-coumarincarboxylate (28.4 g) dissolved in benzene (300 ml) was gradually added with cooling to a Grignard reagent prepared from bromobenzene (34.0 g), magnesium (5.00 g), and dry ether (85 ml). After the addition, the mixture was warmed for 15 min on a water bath. The resulting solution was cooled on ice. Bromine (34.6 g) dissolved in benzene was gradually added. The reaction mixture was then poured into ice-water. The benzene phase was shaken with sodium sulphite solution to reduce the excess bromine. The organic phase was separated and dried with calcium chloride. The solvent was evaporated and the residue

was crystallized from ethanol. After recrystallization, the yield of ethyl 3-bromo-4-phenyl-3,4-dihydro-3-coumarincarboxylate, m.p. 112—113°, was 46 % (22.23 g). (Found: Br 21.08. Calc. for $C_{18}H_{15}O_4Br$: Br 21.30).

This substance (15.46 g) was dissolved in pyridine (50 ml) and the solution was boiled for 6 h. When the solution had cooled, crystals of pyridinium bromide separated and were filtered off. The solvent was evaporated from the filtrate and the residue treated with dilute sulphuric acid and ether. After the ether phase had been dried with sodium sulphate and the solvent evaporated, the residue was crystallized from ethanol. The yield of ethyl 4-phenyl-3-coumarincarboxylate, m.p. 111—112°, was 86 % (10.40 g). (Found: C 73.44; H 4.75. Calc. for $C_{18}H_{14}O_4$: C 73.46; H 4.80).

The mass spectra were most kindly recorded at Masspektrometrilaboratoriet, Karolinska Institutet, Stockholm, Sweden.

The analyses were carried out by Mr. P. Demoen, Janssen Pharmaceutica, Berse, Belgium.

REFERENCES

1. Holmberg, G. A. *Acta Chem. Scand.* **15** (1961) 1255.
2. Holmberg, G. A. *Acta Chem. Scand.* **17** (1963) 967.
3. Reynolds, G. P. *Am. Chem. J.* **44** (1910) 305.
4. du Vigneaud, V., Stacy, G. W. and Todd, D. *J. Biol. Chem.* **176** (1948) 907.
5. Auld, D. and Heller, H. G. *J. Chem. Soc.* **C 1967** 680.
6. Holmberg, G. A. *Acta Chem. Scand.* **6** (1952) 1137.
7. Heilbron, I. M. and Hill, D. W. *J. Chem. Soc.* **1927** 2005.
8. Widegren, S. *Arkiv Kemi, Mineral. Geol.* **B 23** (1946), No. 4.
9. Holmberg, G. A. *Acta Acad. Aboensis, Math. Phys.* **16** (1949), No. 6.
10. Arndt, F., Loewe, L., Ün, R. and Ayça, E. *Chem. Ber.* **84** (1951) 319.
11. Bassignana, P. and Cogrossi, C. *Tetrahedron* **20** (1964) 2859.
12. Vul'fson, N. S., Zaretskii, V. I. and Zaikin, V. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1963** 2215; as abstracted in *Chem. Abstr.* **60** (1964) 10040.

Received October 11, 1967.