CCLXIV.—*Studies in the Coumarin Series. Part I. The Action of the Grignard Reagent upon Substituted Coumarins.*

By Isidor Morris Heilbron and Douglas William Hill.

Decker and Fellenberg (*Annalen*, 1907, **356**, 281) have shown that the interaction of coumarins and the Grignard reagent leads, under carefully specified conditions, to the production of mono-alkyl- or -aryl-pyrylium salts, and more recently Willstätter and his

* Whilst this paper was in the press, our attention was drawn to a paper by Pohl (*Nach. Ges. Wiss. Gottingen*, Mathematisch-Physikalische Klasse, 1927) in which the absorption curves of ergosterol and vitamin *D* are described. The photoelectric and photographic methods are in substantial agreement.

co-workers (*Ber.*, 1924, **57**, 1938, 1945) have used this reaction for the synthesis of anthocyanidins from 3-methoxycoumarins. On the other hand, Houben (*Ber.*, 1904, **37**, 498) has described the formation of dialkyl and diaryl derivatives of coumarin itself. Whereas magnesium alkyl halides led to the formation of 2 : 2-dialkyl-Δ^3-chromens, magnesium phenyl bromide gave rise to the carbinol (I), the formation of which he attributed to a steric hindrance preventing the loss of water necessary for the production of the 2 : 2-diphenylchromen.

The work described in the present paper was initially undertaken with the intention of synthesising flavylium chlorides containing methoxyl or hydroxyl in the 4-position; the latter would probably readily lose hydrogen chloride and pass into flavones. As, however, only diaryl products were obtained, a detailed investigation of coumarins substituted in the 3- and 4-positions was initiated which has led to the isolation of three distinct types of product. Two of these, differently constituted diarylchromens, are now described; the third, a series of benzopyrylium salts, will form the subject of a subsequent communication. While this work was in progress, a most noteworthy contribution to the subject was published by Löwenbein (*Ber.*, 1924, **57**, 1517), who showed that the supposed diphenyl-*o*-hydroxystyrylcarbinol (I) of Houben is in reality 2 : 4-diphenylchroman-2-ol (II), which readily loses water on heating with glacial acetic acid, yielding 2 : 4-diphenyl-Δ^2-chromen (III).

(I.) $C_6H_4<^{CH:CH\cdot CPh_2\cdot OH}_{OH}$ $\qquad$ $C_6H_4<^{CHPh\cdot CH_2}_{O\text{——}CPh\cdot OH}$ (II.)

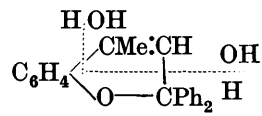
In addition to the chromanol, he obtained a second compound which proved to be 2 : 2-diphenyl-Δ^3-chromen (IV).

(III.) $C_6H_4<^{CHPh\cdot CH}_{O\text{——}CPh}$ $\qquad$ $C_6H_4<^{CH:CH}_{O\text{—}CPh_2}$ (IV.)

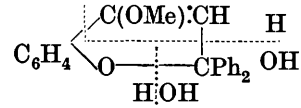
Löwenbein also examined the 5 : 7-, 4 : 6-, and 4 : 7-dimethylcoumarins, all of which, according to him, yielded the corresponding chromanols analogous to (II).

In the course of our own experiments, the action of magnesium phenyl bromide upon both 3-methyl- and 3-phenyl-coumarin was studied. In each case the corresponding chromanol was isolated, from which the elements of water were readily eliminated on heating with glacial acetic acid, 2 : 4-diphenyl-3-methyl-Δ^2-chromen and 2 : 3 : 4-triphenyl-Δ^2-chromen, respectively, being formed. Since these compounds were prepared, a full description of the latter has been published by Löwenbein and Rosenbaum (*Annalen*, 1926, **448**, 223), who have prepared it both from 3-phenylcoumarin and

by the interaction of magnesium phenyl bromide upon 2 : 3-diphenylbenzopyrylium perchlorate.*

(V.)  (VI.) $CH_3 \cdot CH(OH) \cdot CHO + CHPh_2 \cdot OPh$

On the other hand, 4-methyl- and 4-methoxy-coumarins yield 2 : 2-*diphenyl*-4-*methyl*-Δ^3-*chromen* (V) and 4-*methoxy*-2 : 2-*diphenyl*-Δ^3-*chromen* (VII), respectively.

(VII.)  $\longrightarrow Ph_2CO$

According to Löwenbein (*loc. cit.*), certain Δ^3-chromens are converted into coumarone derivatives of the same empirical formula on boiling with glacial acetic acid. Neither of the above compounds (V and VII) was altered under such conditions. That, however, they are in reality Δ^3-chromens has been definitely established by a study of their products of hydrolysis. 2 : 2-Diphenyl-4-methyl-Δ^3-chromen was refluxed for 24 hours with 50% potassium hydroxide solution; ring scission then occurred with production of *benzhydryl phenyl ether* (VI). With 4-methoxy-2 : 2-diphenyl-Δ^3-chromen, refluxing for 5 hours with 33% potassium hydroxide solution was sufficient to cause complete scission. The product isolated in this case was benzophenone, cleavage occurring in the same manner as found by Baker (J., 1925, **127**, 2349). These results, although not wholly in agreement with Löwenbein's findings in the case of the 4 : 6- and 4 : 7-dimethylcoumarins, harmonise well with the work of Kohler (*Amer. Chem. J.*, 1907, **38**, 511), who has shown that addition of the Grignard reagent to $\alpha\beta$-unsaturated ketones takes place both in the 1 : 2 and in the 1 : 4 positions, the relative amounts of each compound formed being dependent on the nature of the unsaturated compound; *e.g.*, the unsaturated ketone $C_6H_5 \cdot CH{:}CH \cdot CO \cdot C_6H_5$ gives mainly 1 : 4 addition (94—96%), whereas $(C_6H_5)_2C{:}CH \cdot CO \cdot C_6H_5$ yields 100% of unsaturated alcohol owing to complete 1 : 2 addition.

Our experiments with coumarins have led us to the definite conclusion that the primary reactions with the Grignard reagent follow a common course, the ultimate formation of a Δ^2- or Δ^3-chromen being influenced solely by the position of the substituent

* Dr. Löwenbein informs me (private communication) that he has also prepared 2 : 4-diphenyl-3-methyl-Δ^2-chromen (m. p. 94°) by the decomposition of 2-phenyl-3-methylbenzopyrylium perchlorate with magnesium phenyl bromide—I. M. H.

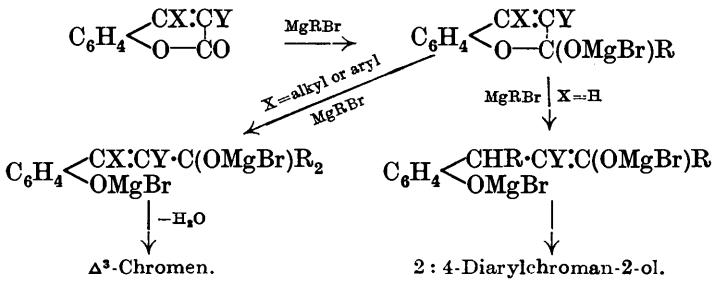
in the pyran ring. Two explanations may be presented to meet the above postulation. In the first place, the primary reaction involving one molecule of the Grignard reagent may result in the production of an αβ-unsaturated ketone (VIII) and the subsequent

(VIII.) $C_6H_4<^{CX:CH\cdot COR}_{OMgBr}$ $C_6H_4<^{CHR\cdot CH:CR\cdot OH}_{OH}$ (IX.)

reactions would then directly follow the Kohler rule. Where X = hydrogen, 1 : 4 addition would chiefly occur with production of the enol (IX), from which the chromanol (X) would result, as pointed out by Löwenbein (*Ber.*, 1924, **57**, 1517), through intra-

(X.) $C_6H_4<^{CHR\cdot CH_2}_{O\text{——}CR\cdot OH}$ $C_6H_4<^{CX:CH\cdot CR_2\cdot OH}_{OH}$ (XI.)

molecular rearrangement from the keto-form. On the other hand, where X is other than hydrogen, 1 : 2 addition will take place, giving the styrylcarbinol (XI), which will immediately pass into the Δ^3-chromen by loss of a molecule of water. Löwenbein considers, however, that Δ^3-chromen formation occurs directly without opening of the lactone ring, since phenyl *o*-hydroxystyryl ketone yields only 2 : 4-diphenylchroman-2-ol when treated with magnesium phenyl bromide, whereas, as previously mentioned, coumarin gives both the chromanol and the Δ^3-chromen. It will be conceded, however, that the reactions involved with the two compounds are not identical and that the presence of the free *o*-hydroxyl group in the ketone may well favourably influence the 1 : 4 addition. An alternative mechanism differing only in degree from the above, and equally explicable on the Kohler rule, may also be reached by assuming that the first reaction with the Grignard reagent comprises direct addition without ring opening. The course of the subsequent reactions under these conditions is expressed by the following formulæ :

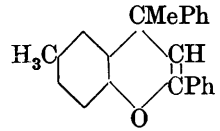


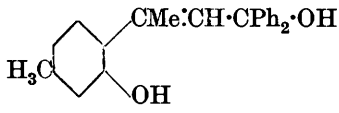
Either explanation provides a perfectly general interpretation of the Δ^2- or Δ^3-diarylchromen formation and meets the problem presented by the 3-substituted coumarins which fail to yield

Δ^3-diarylchromens, a result incompatible with the idea that interaction can occur directly without scission of the lactone ring. The fact that whereas coumarin itself gives both the 1 : 4- and 1 : 2-addition products, whilst the 3-substituted coumarins give only 1 : 4-addition, is also in agreement with Kohler's findings in the case of the unsaturated ketones $C_6H_5 \cdot CH{:}CMe \cdot CO \cdot C_6H_5$ and $C_6H_5 \cdot CH{:}CPh \cdot CO \cdot C_6H_5$.

The complete harmony between our experimental results and these theoretical deductions induced us to re-examine the products obtained from both 4 : 6- and 4 : 7-dimethylcoumarin, which, according to Löwenbein, yielded 2 : 4-diphenylchroman-2-ol derivatives. Working in exact accordance with this author's conditions, we failed to obtain from 4 : 6-dimethylcoumarin any trace of the so-called chromanol, m. p. 110°, but isolated in good yield a substance, m. p. 127°, which corresponded to the compound obtained by Löwenbein by treatment of the chromanol with glacial acetic acid and to which he assigned the structure of 2 : 4-diphenyl-4 : 6-dimethyl-Δ^2-chromen (XII). The main yield from 4 : 7-dimethylcoumarin was a compound, m. p. 86°, apparently identical with the supposed 2 : 4-diphenyl-4 : 7-dimethyl-Δ^2-chromen (m. p. 87°). In addition, a very small yield of a substance, m. p. 146°, was obtained of empirical formula $C_{23}H_{22}O_2$, corresponding to the supposed 2 : 4-diphenyl-4 : 7-dimethylchroman-2-ol of m. p. 144°.

(XII.)





(XIII.)

The fact that chromens were obtained directly from the products of the reaction is in itself some indication that these do not belong to the Δ^2-series, and this we have proved by an examination of their scission products. Benzhydryl *p*-tolyl ether was obtained in good yield from the 4 : 6-dimethyl compound. In the case of 2 : 2-diphenyl-4 : 7-dimethyl-Δ^3-chromen, in addition to benzhydryl *m*-tolyl ether, lactaldehyde, m. p. 105°, was isolated, thus definitely establishing the constitution of these compounds as diaryl-Δ^3-chromens.

The substance, m. p. 146°, is probably the intermediate *diphenyl-2-hydroxy-*β : *4-dimethylstyrylcarbinol* (XIII), but the quantity at our disposal did not allow of detailed examination.

We acknowledge our indebtedness to Dr. A. Löwenbein, with whom we have been in communication concerning the mechanism of the changes involved in these reactions, and who has freely given us the advantage of his views.

EXPERIMENTAL.

4-Hydroxy-2 : 2-diphenyl-Δ^3-chromen.—Magnesium phenyl bromide (prepared from bromobenzene, 14·5 g., magnesium turnings, 2·5 g., and ether, 100 c.c.) was added to 4-hydroxycoumarin (5 g.), suspended in benzene (250 c.c.). A solid was rapidly precipitated which did not redissolve after 5 hours' heating under reflux. The reaction mixture was decomposed by ice-cold, dilute hydrochloric acid, unchanged bromobenzene and diphenyl were removed by steam distillation, and the residual solid was separated from unacted-upon 4-hydroxycoumarin by boiling with water, in which the latter was readily soluble. After drying, the *chromen* was crystallised from benzene and then twice from absolute alcohol, from which it separated in colourless needles, m. p. 230—231°. It is strongly acidic and dissolves readily in sodium hydroxide and sodium carbonate solutions; it gives no coloration with ferric chloride (Found: C, 83·9; H, 5·1. $C_{21}H_{16}O_2$ requires C, 84·0; H, 5·3%).

4-Methoxy-2 : 2-diphenyl-Δ^3-chromen (VII).—This was prepared in an analogous manner by the action of magnesium phenyl bromide (from 14 g. of bromobenzene) upon a solution of 4-methoxycoumarin (5 g.) in dry benzene (200 c.c.). The residue left after steam distillation was filtered off, dried, and twice recrystallised from absolute alcohol, the *chromen* being obtained in colourless plates, m. p. 135° (yield, 7 g.) (Found: C, 84·1; H, 5·5. $C_{22}H_{18}O_2$ requires C, 84·1; H, 5·7%). It is readily soluble in the usual organic solvents.

Hydrolysis.—The chromen (2 g.) was heated under reflux with 33% potassium hydroxide solution (25 c.c.) for 5 hours. After dilution with water, the whole was extracted with ether, and the oil isolated from the extract was treated with hydroxylamine. The solid thus obtained, after crystallisation from alcohol, melted at 139° and was shown to be identical with benzophenoneoxime by a mixed melting point with an authentic specimen.

4-Methoxy-2 : 2-dianisyl-Δ^3-chromen, prepared from magnesium *p*-anisyl bromide by the method previously described, crystallised from benzene in colourless needles, m. p. 155° (Found: C, 76·8; H, 6·0. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%).

2 : 2-Diphenyl-4-methyl-Δ^3-chromen (V).—This was prepared by treating a solution of 4-methylcoumarin (10 g.) in benzene (150 c.c.) with magnesium phenyl bromide (bromobenzene, 30 g.) in dry ether (100 c.c.). After boiling under reflux for 4 hours on the water-bath, the whole was steam-distilled and the residue extracted with ether. After removal of the solvent from the dried extract, crystals contaminated with some oily material were obtained. The oil was removed by treatment with a small quantity of alcohol, and the yellow solid recrystallised from benzene and again from glacial

acetic acid; the *chromen* then separated in colourless prisms, m. p. 89° (Found: C, 88·7; H, 6·4. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%).

Hydrolysis. Isolation of benzhydryl phenyl ether (VI). The above chromen (0·5 g.) was gently boiled under reflux with 50% potassium hydroxide solution (15 c.c.) for 24 hours. After cooling, the reaction mixture was extracted with ether. The oil left after removal of the solvent from the washed and dried extract solidified on standing and then crystallised from a very small volume of light petroleum in colourless needles, m. p. 56°. The compound was insoluble in aqueous sodium hydroxide and gave no colour reaction with ferric chloride (Found: C, 88·0; H, 6·4. $C_{19}H_{16}O$ requires C, 87·8; H, 6·2%).

2 : 2-*Diphenyl*-4 : 6-*dimethyl*-Δ^3-*chromen*.—The Grignard reaction in this case was carried out in a similar manner to that described by Löwenbein (*loc. cit.*) by the slow addition of magnesium phenyl bromide (from bromobenzene, 14 g.) to a hot solution of 4 : 6-dimethylcoumarin (5 g.) in benzene (120 c.c.). The reaction mixture was then heated on the water-bath for ½ hour, decomposed by means of cold ammonium chloride solution, and steam-distilled to remove bromobenzene and diphenyl. The residue, which became solid after 24 hours, was then separated and rubbed with a small quantity of ether, which induced it to crystallise. The product was recrystallised from alcohol, separating in colourless rhombs, m. p. 126°. The ether used to crystallise the residue from the steam distillation deposited more of the same compound (Found: C, 88·3; H, 6·5. $C_{23}H_{20}O$ requires C, 88·4; H, 6·4%).

Hydrolysis. Isolation of benzhydryl p-*tolyl ether*. The chromen (2 g.) was gently boiled under reflux with potassium hydroxide solution (25 g. in 25 c.c. of water) for 24 hours. After cooling, the yellow, alkaline solution, together with some solid material, was extracted with ether, and the extract was well washed with water, dried, and evaporated. The residual solid crystallised from 90% alcohol (animal charcoal) in colourless rhombs, m. p. 96°, which were insoluble in sodium hydroxide solution (Found: C, 87·8; H, 5·9. $C_{20}H_{18}O$ requires C, 87·6; H, 5·8%).

Diphenyl-2-*hydroxy*-β : 4-*dimethylstyrylcarbinol* (XIII).—4 : 7-Dimethylcoumarin was treated with magnesium phenyl bromide as was the 4 : 6-isomeride. The resinous product from the steam distillation was dried between porous tiles and then vigorously scratched with ether, whereupon it crystallised. The crystalline mass so obtained was filtered off and twice recrystallised from 90% alcohol, from which the *carbinol* separated in colourless needles, m. p. 146° (yield, 10%) (Found: C, 83·4; H, 6·4. $C_{23}H_{22}O_2$ requires C, 83·6; H, 6·6%).

2 : 2-*Diphenyl*-4 : 7-*dimethyl*-Δ^3-*chromen*.—This compound was obtained in two ways : (*a*) The ethereal filtrate after removal of the preceding carbinol deposited, on slow evaporation, a large quantity of a solid, which crystallised from alcohol in colourless needles, m. p. 86° (yield, 75%). (*b*) Diphenyl-2-hydroxy-β : 4-dimethylstyrylcarbinol (1 g.) was heated under reflux for 1 hour with glacial acetic acid (20 c.c.). The gummy residue obtained on dilution with water was crystallised from alcohol, yielding glistening, colourless needles, m. p. 87°, identical with the product in (*a*) (Found : C, 88·3; H, 6·7. $C_{23}H_{20}O$ requires C, 88·4; H, 6·5%).

Isolation of Benzhydryl m-*Tolyl Ether*.—This hydrolysis was carried out in three ways : (*a*) As in previous cases, the chromen (2 g.) was heated for 24 hours with potassium hydroxide solution (25 g. in 25 c.c. of water). The crude product crystallised from alcohol in colourless needles, m. p. 125°. (*b*) The chromen (2 g.) was heated with potassium hydroxide (15 g. in 25 c.c. of water) at 180° in an autoclave for 4 hours. The product was washed with water (200 c.c.), and the solid crystallised twice from 75% alcohol in presence of animal charcoal. It was thus obtained in colourless needles identical with those in (*a*). (*c*) The chromen (1 g.) was fused with potassium hydroxide (10 g.) and, when cold, the mass was dissolved in water and extracted with ether. After purification, the substance described in (*a*) and (*b*) was obtained (Found : C, 87·4; H, 5·9. $C_{20}H_{18}O$ requires C, 87·6; H, 5·8%).

The alkaline solution from (*c*) was rendered acid, and the solution, which contained a small quantity of solid material, was extracted with ether. After removal of the solvent, the residue crystallised from a small volume of methyl alcohol in colourless needles, m. p. 103—105°. It readily reduced Fehling's solution and Tollens's reagent and was identical with lactaldehyde in all respects.

2 : 4-*Diphenyl*-3-*methylchroman*-2-*ol*.—3-Methylcoumarin (10 g.), dissolved in benzene, was heated for 4 hours on the water-bath with magnesium phenyl bromide (3 mols.). The reaction mixture was decomposed with dilute hydrochloric acid and steam-distilled. The non-volatile residue was collected and crystallised from alcohol and finally from benzene, from which the *chromanol* separated in colourless crystals, m. p. 149° (Found : C, 83·9; H, 6·1. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·3%).

2 : 4-*Diphenyl*-3-*methyl*-Δ^2-*chromen* was prepared by boiling the above chromanol (1·5 g.) with glacial acetic acid (10 c.c.) for 1 hour. The cold solution was diluted with water, and the precipitate crystallised from alcohol, the *chromen* separating in colourless needles, m. p. 91° (Found : C, 88·5; H, 6·2. $C_{22}H_{18}O$ requires C, 88·6; H, 6·1%).

In conclusion, we desire to express our thanks to the Council of the Department of Scientific and Industrial Research for a grant to one of us (D. W. H.) which has enabled this research to be carried out.

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