[Contribution from the Department of Chemistry, University of California, Los Angeles]

The Reaction between Lactones and the Grignard Reagent. II. On the Intermediate Stages of the Reaction

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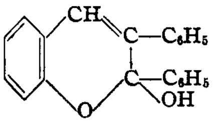
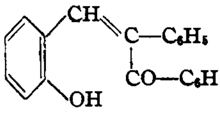
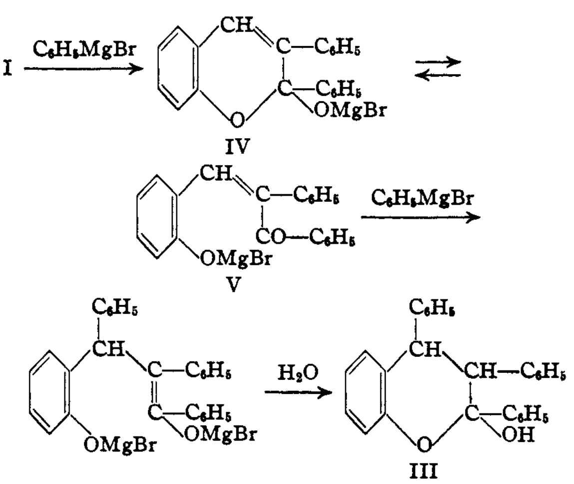
In a previous paper[1] were described the results of experiments designed to show that the halomagnesium derivative of 2,4-diphenylchromanol-2 could react as the halomagnesium derivative of the phenolic ketone to which it was related by ring-chain tautomerism. The purpose of that study was not achieved because of ambiguity in regard to the structure (ketophenol or chromanol) of the parent compound chosen, and, since the same uncertainty exists in regard to the structures of other 2-chromanols,[2] attention has been turned to a related substance, 2,3-diphenylchromenol-2 (I).[3] The formulation of this compound as (I) and not as the related ketone (II) is supported by a considerable amount of evidence. It is important for the subsequent discussion of the way (I) has been used in the present work briefly to review this evidence.


I


II

The compound is formed when the corresponding pyrilium salt, 3-phenylflavylium ferrichloride, is hydrolyzed by water.[3] The chromenol is colorless, while phenyl *o*-hydroxystyryl ketones in general are yellow in color; the methyl ethers of both the *cis* and *trans* forms of (II) have been prepared,[4] and both are described as yellow substances. The chromenol is insoluble in cold, aqueous sodium hydroxide solution under conditions identical with those under which the known *trans* form of (II) is readily converted into a salt.[4] Treatment of the chromenol with alcohols converts it into 2,3-diphenyl-2-alkoxychromenes.[4] Hopf and Le Fèvre[5] have expressed a preference for the chromenol structure (I) on the basis of dipole moment studies. Decker and Becker[4] have pointed out the analogy which exists between the chromenol (I) and salts of the *cis* form of (II), and coumarin and coumarinic acid; the latter exists only as its salt and reverts spontaneously to coumarin upon acidification.

Treatment of the chromenol (I) with phenylmagnesium bromide results in the formation in good yield of 2,3,4-triphenylchromanol-2 (III). Since the chromenol has the structure (I), the primary product of the reaction would be expected to be (IV). Since, so far as is known, 1,4- addition to a system such as is present in (IV) does not occur and since there is no experimental support for the possibility that the reagent might have added directly to the double bond in (IV), the production of the chromanol (III) must be the result of addition of phenylmagnesium bromide to the α,β-unsaturated ketone (V), and thus the interconversion (IV $\rightleftarrows$ V) must have occurred.



The chromenol (I) has the properties of a single substance and would not be expected to be actively tautomeric (I $\rightleftarrows$ II) in the necessarily dry, non-hydroxylic solution of a Grignard reagent. The change (I $\rightleftarrows$ II) bears a close resemblance to the related equilibria involved in the mutarotation of sugars[6] and, like these, would probably be acid-base catalyzed. Thus, while the change (I $\rightleftarrows$ II) is closely analogous to the change (IV $\rightleftarrows$ V), the difference is a fundamental one. It has been suggested previously[7] that an equilibrium such as that represented by (IV $\rightleftarrows$ V) may obtain generally in the case of halomagnesium derivatives of suitably constituted hydroxyketones.

There is at present no basis for a choice between a number of possible ways in which the shift of the halomagnesium group can occur. It is suggested, however, that a step involving the coördinating power of the magnesium atom is a necessary one in the process.

The present results coördinate the view, frequently expressed,[8] that the first step in the

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[1] Geissman, This Journal, 62, 1363 (1940).

[2] (a) Smith and Rupff, *ibid.*, 62, 145 (1940); (b) Smith and Carlin, *ibid.*, 64, 435 (1942).

[3] Decker and Fellenberg, *Ann.*, 364, 1 (1908).

[4] Decker and Becker, *Ber.*, 55, 375 (1922).

[5] Hopf and Le Fèvre, *J. Chem. Soc.*, 1582 (1938).

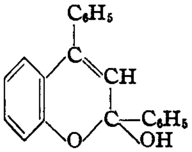
[6] Lowry and co-workers, *J. Chem. Soc.*, 127, 1385, 2883 (1925); *Proc. Roy. Soc.* (London), 119, 505 (1928).

[7] Geissman and Morris, This Journal, 63, 1111 (1941).

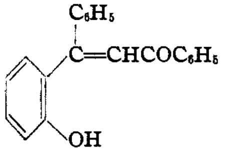
[8] (a) Price, *ibid.*, 61, 2761; (b) Shriner and Sharp, *J. Org. Chem.*, 4, 575 (1939); see also refs. 2, 7.

reaction of a lactone with a Grignard reagent is an addition to the carbonyl group, with the suggestions of Heilbron and Hill[9] that the reactions of substituted coumarins are best explained by the assumption that an α,β-unsaturated ketone is an intermediate in the reaction.

Previous to the present work the only 2-chromenols which had been obtained as crystalline substances have all been 2,3-disubstituted. Our efforts to prepare 2-phenylchromenol-2 were unsuccessful. However, we have prepared 2,4-diphenylchromenol-2 (VI) as a colorless, crystalline substance. This pseudo-base is very unstable and reverts readily to the yellow *trans*-chalcone, β-phenyl-*o*-hydroxystyryl phenyl ketone (VII). The reaction of the pseudo-base (IX) with phenylmagnesium bromide led to a mixture of the expected α-phenyl-*o*-hydroxystyryldiphenylcarbinol and the corresponding chromene.



VI



VII

Experimental

3-Phenylflavylium Ferrichloride.—This was most conveniently prepared by the method of Hopf and Le Fèvre.[5]

2,3-Diphenylchromanol-2 (I).—The procedure of Decker and Fellenberg[3] was less convenient than the following: a suspension of 3-phenylflavylium ferrichloride in ether was shaken with cold water until the solid had disappeared. The ether phase was well washed with fresh portions of water, dried over sodium sulfate and evaporated under reduced pressure. The residue was crystallized by the addition of ligroin (b. p. 90–110°). Recrystallization from ether-ligroin yielded a colorless product, m. p. 122–122.5°[10] (reported, 121–2°,[3] 124°.[5])

2,3,4-Triphenyl-2-chromanol (III).—To a solution of 0.12 mole of phenylmagnesium bromide in ether was added 7.5 g. (0.025 mole) of dry, finely powdered 2,3-diphenylchromanol-2 (I). The solution was refluxed for fifteen minutes and then decomposed with iced ammonium chloride solution. The ether solution was dried and evaporated, yielding 7.0 g. (72%) of the crude chromanol, m. p. 154–156°. Recrystallization from alcohol yielded a pure product, m. p. 158.5–159° (reported,[11] 159°).

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.72; H, 5.82. Found: C, 85.77; H, 5.95.

2,3,4-Triphenyl-2-chromene.—Dehydration of the chromanol (III) was readily effected by treating its solution in glacial acetic acid with a trace of phosphoric acid. The chromene formed colorless crystals, m. p. 129–129.5° (reported,[11] 131°).

Attempted Preparation of 2-Phenylchromenol-2.—Hydrolysis of flavylium perchlorate under a variety of conditions led only to green, amorphous materials. Our experience thus parallels that of Decker and Felser,[12] who reported similar results.

2,4-Diphenylchromenol-2 (VI).—4-Phenylflavylium ferrichloride was prepared by the oxidation of 2,4-diphenyl-2-chromene with ferric chloride.[11] An acetone solution of the flavylium salt was diluted with water to the point of incipient cloudiness and the solution was allowed to stand until a test portion diluted with much water gave a colorless oily precipitate. The solution was dried and evaporated under reduced pressure. The residue was taken up in dry ether and petroleum ether (b. p. 30–60°) added until the pseudo-base began to separate. The first precipitate was pale yellow. This was removed, and from the mother-liquor a white, crystalline material slowly separated. This material could be recrystallized only if care was taken to use dry solvents and to avoid heating the solutions. It melted at 68–71° when plunged into a preheated bath; when heated slowly it gradually turned yellow and melted at 136–8°. Material which had turned yellow on recrystallization also melted at 136–8°.

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 84.10; H, 5.33. Found (colorless material): C, 84.14; H, 5.42.

Treatment of the chromanol with phenylmagnesium bromide resulted in an 82% yield of what appeared to be a mixture of α-phenyl-*o*-hydroxystyryldiphenyl carbinol and 2,2,4-triphenyl-3-chromene. Recrystallization of the crude material from glacial acetic acid completed its dehydration to the chromene, m. p. 128.5–129° (reported,[13] 130°).

Summary

1. 2,3-Diphenylchromenol-2 reacts with phenylmagnesium bromide to give 2,3,4-triphenyl-2-chromanol. This observation clarifies the nature of the isomerization of the first product of the addition of a Grignard reagent to the carbonyl group of a lactone into the halomagnesium derivative of a hydroxyketone.

2. The colorless pseudo-base, 2,4-diphenylchromenol-2, has been prepared; it is the first 2-chromenol lacking a 3-substituent to be obtained as a crystalline substance.

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[9] Heilbron and Hill, *J. Chem. Soc.*, 2005 (1927).

[10] Melting points are uncorrected.

[11] Löwenbein, *Ber.*, **57**, 1517 (1924).

[12] Decker and Felser, *ibid.*, **41**, 2997 (1908).

[13] Heilbron, Hill and Walls, *J. Chem. Soc.*, 1701 (1931).