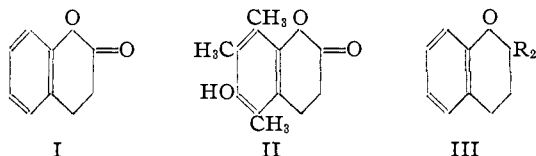


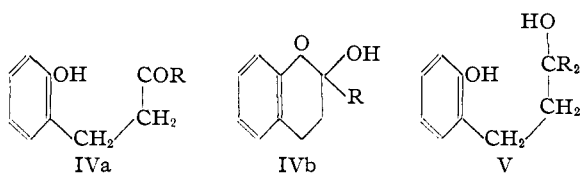
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XXII. The Reaction between Grignard Reagents and Coumarins and Hydrocoumarins<sup>1</sup>BY LEE IRVIN SMITH AND P. M. RUOFF<sup>2</sup>

In paper XII of this series<sup>3</sup> a preliminary report has been given of the results obtained when certain Grignard reagents reacted with the dihydrocoumarins I and II. The products of these reac-



tions were 2,2-dialkylchromans, III, and it was assumed that in all cases the intermediates were the ketones IVa (or IVb) and related carbinols V.

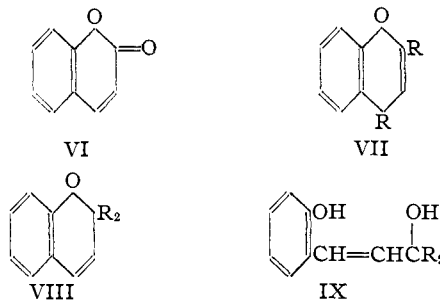


In one case, that in which R was ethyl, the carbinol V was isolated as a solid which melted at 71–72°; but in the other case studied (R = *n*-propyl) the carbinol appeared as an oil which was not characterized except by conversion to the chroman III (R = *n*-propyl).<sup>4</sup>

The reaction between hydrocoumarin (I) and Grignard reagents has now been extended and the series at present includes the products obtained from ethyl-, *n*-propyl- and *n*-butyl- Grignard reagents. In addition Claisen<sup>5</sup> prepared the carbinol V, R = CH<sub>3</sub>, from methylmagnesium iodide and ethyl β-phenyl-propionate; he cyclized the carbinol to the chroman (III, R = CH<sub>3</sub>) which he synthesized independently by condensation of phenol with isoprene.<sup>6</sup> Thus the series now includes all four of the chromans III (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, *n*-C<sub>3</sub>H<sub>7</sub> and *n*-C<sub>4</sub>H<sub>9</sub>) as well as three of the

carbinols V (R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, *n*-C<sub>4</sub>H<sub>9</sub>). In view of this work, and the results reported in the previous paper,<sup>1</sup> it appears definitely established that the products obtained by action of Grignard reagents upon dihydrocoumarins consist of the carbinols V and the 2,2-dialkylchromans III derived from them. No ketones such as IVa or IVb have been isolated from these products although one such ketone recently has been synthesized in another way by John and Schmeil.<sup>7</sup> It is interesting that this ketone, 2,5-dihydroxy-3,4,6-trimethylbenzylacetone, shows properties which indicate that its structure may be analogous to IVb rather than to IVa.

On the other hand, the action of Grignard reagents upon coumarins VI is much more complicated because of the presence of the conjugated double bond, and a variety of products, including



pyrylium salts,<sup>8</sup> Δ<sup>2</sup>- and Δ<sup>3</sup>-chromenes (VII and VIII),<sup>4,9</sup> chromanols<sup>10</sup> as well as the unsaturated carbinols IX<sup>9a,9b</sup> have been reported. The evidence concerning the carbonols IX is conflicting, however, and from the work of Löwenbein<sup>9b</sup> it appears that Houben<sup>9a</sup> was in error in assigning structure IX to the product he obtained from coumarin and phenylmagnesium bromide. Nevertheless, formation of all the products so far reported can be accounted for on the basis of 1,2- or 1,4-addition of the reagent, or a combination of

(1) Vitamin E. XXI, THIS JOURNAL, 61, 142 (1939).

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(3) Smith, Ungnade and Prichard, *J. Org. Chem.*, 4, 358 (1939).(4) In writing the previous report (Ref. 2) a paper by Bridge, Crocker, Cubin and Robertson, *J. Chem. Soc.*, 1530 (1937), was overlooked. We desire to acknowledge here the priority of Robertson and his associates; they, apparently, are the first to carry out the reaction between a dihydrocoumarin and a Grignard reagent, leading to a 2,2-dialkylchroman.(5) *Ber.*, 54, 200 (1921).(6) See also Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, 4, 311 (1939).(7) *Ber.*, 72, 1653 (1939); see also John, Gunther and Schmeil, *ibid.*, 71, 2617 (1938).(8) Decker and Fellenberg, (a) *ibid.*, 40, 3816 (1907); (b) *Ann.*, 356, 300 (1907); (c) Willstätter and Schmidt, *ibid.*, 57, 1945 (1924); (d) Heilbron, Hill and Wells, *J. Chem. Soc.*, 1701 (1931).(9) (a) Houben, *Ber.*, 37, 489 (1904); (b) Löwenbein, *ibid.*, 57, 1517 (1924); (c) Bergel, Jacob, Todd and Work, *J. Chem. Soc.*, 1375 (1938).(10) (a) Löwenbein and Rosenbaum, *Ann.*, 448, 223 (1926); (b) Heilbron and Hill, *J. Chem. Soc.*, 2005 (1927).

1,4- and 1,2-addition, with cyclization possible at almost any point in the sequence of reactions.

It has now been found that the carbinols IX ( $R = CH_3$  and  $C_2H_5$ ) are readily obtained by addition of coumarin to aliphatic Grignard reagents under carefully controlled conditions. These unsaturated carbinols IX are readily reduced to the saturated carbinols V, identical with the products obtained from Grignard reagents and dihydrocoumarin. Thus the same product, V, results regardless of whether addition of the Grignard reagent precedes or follows reduction and this could be true only when the action of the reagent is confined to the carbonyl group. From these facts, it follows that these carbinols must be derived from coumarin and dihydrocoumarin by 1,2-addition of the reagent to the carbonyl group, and that the conjugated system in coumarin is not involved in the reaction when the procedure described below is used.

The unsaturated carbinols IX were cyclized by acids to chromenes, which, from the structure of the carbinols, must have the double bond in the 3,4-position (VIII). Elimination of water from the carbinols occurred quite readily; even distillation of the crude carbinol gave a product which separated into two layers, one of them aqueous. Cyclization, however, was not the only reaction which occurred when the carbinols were dehydrated for by-products, consisting of viscous, brown oils were always formed in considerable amounts. These by-products were probably formed by dehydration of the carbinols to dienes and polymerization of the latter. Steam distillation of the carbinols from a slightly acid suspension yielded colorless oils in the distillate, but this process was too slow to serve as a practical method for obtaining the chromenes. Cyclization of the carbinols IX by acids was always accompanied by the appearance of highly colored solutions; similar colors were developed when the magnesium complexes from the Grignard reaction were hydrolyzed. These colors indicated the presence of benzopyrylium salts, but no attempt was made to isolate them.<sup>10a</sup>

(10a) Since this manuscript was submitted for publication, a paper by Shriner and Sharp, *J. Org. Chem.*, **4**, 575 (1939), appeared on the same subject. While Shriner and Sharp did not isolate the intermediate ketones, our results in general agree with theirs, and their reaction mechanism, which we regard as essentially correct, readily can be modified to provide for the formation of the ketones. Thus their compound XII could coordinate at the heterocyclic oxygen atom with a second molecule of the Grignard reagent and the resulting complex could rearrange to give either the chromene or the magnesium derivative of the ketone.

### Experimental Part<sup>11</sup>

**Diethyl-*o*-hydroxystyrylcarbinol IX ( $R = C_2H_5$ ).**—Coumarin (25 g., 0.17 mole) in ether (500 cc.) was added slowly (two hours) at room temperature to a Grignard solution prepared from ethyl bromide (40 g., 0.37 mole) and magnesium (8 g., 0.33 mole) in ether (250 cc.). Each drop of the coumarin solution produced in the reaction mixture a yellow precipitate which quickly dissolved; after about half of the coumarin was added, this transitory precipitate was white. The mixture was refluxed for an hour and the clear brownish-green and slightly fluorescent solution was allowed to stand overnight. It was then decomposed by slowly stirring it into sulfuric acid (10%, 200 cc.) and ice. After standing for an hour, the ether layer was removed and the aqueous layer was extracted (with ether) until it was colorless. The combined ether solutions were washed with water and dried over anhydrous sodium carbonate. Removal of the solvent left a yellow oil (32 g.) which partially solidified. The oily solid was spread on a porous plate and after the oil was absorbed, the solid was removed and crystallized twice from a mixture of equal parts of petroleum ether b. p. 30–60° and b. p. 60–68° using Norite the second time. Approximately 20 g. of white needles, melting at 67–68°, was obtained. The carbinol gave a deep red color with concd. sulfuric acid and an olive-green color with ferric chloride. It rapidly decolorized a dilute solution of bromine in carbon tetrachloride, and gave no reaction with phenylhydrazine. It was soluble in 10% sodium hydroxide.

*Anal.* Calcd. for  $C_{13}H_{18}O_2$ : C, 75.69; H, 8.78. Found: C, 75.64; H, 8.89.

**1-[*o*-Hydroxyphenyl]-3-ethyl-3-pentanol V ( $R = C_2H_5$ ).**—The above carbinol 2.0 g. in ethanol (50 cc.) was subjected at room temperature to the action of hydrogen under slight pressure in the presence of a platinum oxide catalyst (0.01 g.). Practically the theoretical volume of hydrogen was absorbed in two hours. After removal of the catalyst, the solvent was evaporated and the residue was crystallized from petroleum ether. The product (1.5 g.) was white and melted at 74–75° alone or when mixed with a specimen prepared from dihydrocoumarin and ethylmagnesium bromide.<sup>3</sup> When mixed with the unsaturated carbinol (m. p. 67–68°) the substance melted at 50–54°.

**2,2-Diethyl- $\Delta^3$ -chromene, VIII ( $R = C_2H_5$ ).**—The unsaturated carbinol (4 g.) was refluxed in acetic acid (20 cc.) for an hour and the mixture was allowed to stand overnight. The solution was diluted with water and extracted with ether. The ether solution was extracted with sodium hydroxide (10%), then washed with water and dried over calcium chloride. Removal of the solvent left a clear amber oil (3.5 g.). Distilled from a small Claisen flask, this gave 2.5 g. of a clear colorless liquid boiling at 129–132° under 19 mm.; the residue (1 g.) in the flask was dark viscous non-volatile oil. Redistillation of the crude chromene gave a turbid distillate (2.0 g.) and to complete the cyclization this distillate was again refluxed in acetic acid and the product was isolated and purified as described above. Somewhat less than 1 g. of a colorless liquid, b. p. 125–126° under 14 mm., was obtained. The remainder

(11) Microanalyses by J. W. Opie and E. E. Renfrew.

of the product was a dark viscous oil. The chromene gave a bright red color with concd. sulfuric acid.

*Anal.* Calcd. for  $C_{13}H_{16}O$ : C, 82.98; H, 8.51. Found: C, 83.07; H, 8.65.

**Dimethyl-*o*-hydroxystyrylcarbinol, IX (R = CH<sub>3</sub>).**—Coumarin was added to methylmagnesium iodide in the same molar quantities and by the same procedure as that described for preparation of the diethylcarbinol above. About a third of the reaction product was collected on a porous plate as a yellowish solid (10 g.). After crystallization from petroleum ether (as above) and decolorization with Norite, the substance was obtained as a white solid which melted at 53–55°. It gave the same color reaction with sulfuric acid and ferric chloride as those given by the ethyl compound; likewise it was soluble in 10% sodium hydroxide. Due to an accident, the analytical sample was destroyed.

**2,2-Dimethyl- $\Delta^3$ -chromene, VIII (R = CH<sub>3</sub>).**—The porous plate used for absorbing the oil accompanying the above dimethylcarbinol was extracted with ether. The ether was removed and the residue was distilled under 19 mm. pressure. The chromene (2 g.) boiling at 102–103° resulted as a clear, colorless liquid.<sup>12</sup>

Cyclization of the solid carbinol (from above) as described for the ethyl compound gave only about 1 g. of the chromene. Consequently, the Grignard reaction was repeated, and the crude product (solid and oil) was distilled under 15 mm. At 90° an oil and water appeared in the distillate; as soon as water ceased to appear, the temperature gradually rose to 142°. Only a small amount of residue remained in the flask. The distillate solidified partially, showing unchanged carbinol. The entire distillate was dissolved in acetic acid (50 cc.), a drop of sulfuric acid was added and the mixture was refluxed for half an hour. The product was isolated and purified as described for the ethyl compound above. There resulted 6 g. of the pure chromene boiling at 96–97° under 15 mm. About half the material remained in the flask as a dark viscous oil. The methyl chromene, like the ethyl compound, gave a red color with sulfuric acid.

*Anal.* Calcd. for  $C_{11}H_{12}O$ : C, 82.50; H, 7.50. Found: C, 82.19; H, 7.86.

**2,2-Di-*n*-butyl- $\Delta^3$ -chromene, VIII (R = *n*-C<sub>4</sub>H<sub>9</sub>).**—Coumarin (22 g., 0.15 mole) in ether (450 cc.) was added to *n*-butylmagnesium bromide (7.3 g., 0.30 mole of magnesium, 45.2 g., 0.33 mole of butyl bromide) in ether (225 cc.). No attempt was made to isolate the small amount of solid (carbinol) which appeared in the product; instead, the crude product was distilled directly. The distillate (23 g., b. p. 161–163° under 15 mm.) contained some water, indicating dehydration of the carbinol. The ethereal solution of the distillate was extracted several times with sodium hydroxide (10%), then washed with water and dried over calcium chloride. The solvent was removed and the residue was distilled under 15 mm. The chromene (17–18 g.), a clear oil with a faint yellow cast, boiled at 164–165° and had  $n_D^{20}$  1.5220. It gave a red color with sulfuric acid.

*Anal.* Calcd. for  $C_{17}H_{24}O$ : C, 83.53; H, 9.91. Found: C, 83.10; H, 9.76.

(12) See Ref. (9a); Houben gives the b. p. as 92–93° under 11 mm.

**1-[*o*-Hydroxyphenyl]-3-*n*-butyl-3-heptanol V (R = *n*-C<sub>4</sub>H<sub>9</sub>).**—Dihydrocoumarin (14.8 g., 0.1 mole) in ether (125 cc.) was slowly (1.5 hours) added to *n*-butylmagnesium bromide (butyl bromide, 28 g., 0.2 mole; magnesium, 4.8 g., 0.2 mole) in ether (200 cc.). The reaction mixture was allowed to stand at room temperature overnight and was then decomposed by pouring it into ice (300 g.) and sulfuric acid (20 cc.). The ether layer was removed, washed with dilute carbonate solution, then with water and was dried over anhydrous sodium carbonate. Removal of the solvent left an oil (25 g.) which soon solidified. After two crystallizations from petroleum ether (b. p. 30–68°) the substance was white and melted at 67–68.5°. It gave a strongly positive phenol test (Folin).

*Anal.* Calcd. for  $C_{17}H_{28}O_2$ : C, 77.27; H, 10.60. Found: C, 76.5; H, 10.0.

**2,2-Di-*n*-butylchroman, III (R = *n*-C<sub>4</sub>H<sub>9</sub>).**—The above carbinol (16.1 g.) was dissolved in acetic acid (100 cc.). Sulfuric acid (15 cc., 50%) was added. The solution turned red and an oil separated at the top. More acetic acid (50 cc.) was added to dissolve the oil, and the mixture was refluxed for an hour. The solution was diluted with water, and extracted with ether several times. The combined ether solutions were washed with dilute carbonate, then with water, and dried over anhydrous potassium carbonate. The solvent was removed and the residue (9 g.) was distilled. The distillate (5 g., b. p. 172–173° under 16 mm.) was slightly yellow and had a faint odor of butyl acetate. Considerable brown viscous oil remained in the flask. Much better results were obtained by refluxing the crude carbinol from a duplicate preparation with 25% sulfuric acid. Steam distillation of the mixture gave a colorless oil in the distillate but the process was very slow. The oil in the flask was taken up in ether, washed free of acid and dried. After the solvent was removed, the chroman was distilled from a Claisen flask. The distillate (12 g.) was a faintly yellow liquid which boiled at 165–168° under 8 mm., and it had  $n_D^{20}$  1.5097.

*Anal.* Calcd. for  $C_{17}H_{26}O$ : C, 82.92; H, 10.57. Found: C, 82.70, 82.33; H, 10.10, 10.72.

### Summary

1. *o*-Hydroxystyryldialkylcarbinols have been obtained by reaction between coumarin and Grignard reagents.

2. The structures of these carbinols have been proved by reducing the diethyl compound to the saturated carbinol and preparing the same substance from dihydrocoumarin and ethylmagnesium bromide.

3. The unsaturated carbinols have been cyclized to 2,2-dialkyl- $\Delta^3$ -chromenes, VIII but the chromenes are accompanied by large amounts of dark viscous oils, probably polymeric substances.

4. Previous work on the preparation of 2,2-dialkylchromans by action of Grignard reagents on dihydrocoumarins has been extended. At present the series of chromans III is complete

from  $R = \text{CH}_3$  to  $R = n\text{-C}_4\text{H}_9$ ; the series of saturated carbonols V includes those in which  $R = \text{CH}_3$ ,  $\text{C}_2\text{H}_5$  and  $n\text{-C}_4\text{H}_9$ ; the series of unsaturated carbinols IX includes those in which  $R = \text{CH}_3$

and  $\text{C}_2\text{H}_5$ ; the series of chromenes VIII includes those in which  $R = \text{CH}_3$ ,  $\text{C}_2\text{H}_5$  and  $n\text{-C}_4\text{H}_9$ .

MINNEAPOLIS, MINNESOTA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

## The Ultraviolet Absorption Spectra of Some Derivatives of 1,2-Benzanthracene

BY R. NORMAN JONES<sup>1</sup>

The ultraviolet absorption spectrum of 1,2-benzanthracene has been measured by Capper and Marsh,<sup>2</sup> by Clar<sup>3</sup> and by Mayneord and Roe.<sup>4</sup> Because of the carcinogenic activity of some of its simple alkyl and ace-derivatives, a large number of such compounds have been synthesized and their chemical and biological behavior investigated in several laboratories.<sup>5,6,7</sup> Since eleven such derivatives complementary to those previously studied were available in this Laboratory it seemed desirable to make a careful study of their absorption spectra.

### Experimental Procedure

In this study a Bausch and Lomb Medium Quartz Spectrograph was used in conjunction with a Hilger Spekker Photometer and a hydrogen discharge tube designed by Dr. Hugh H. Darby.<sup>8</sup> Some difficulty was initially found in lining up the spectrograph with a photometer of different manufacture. This was overcome by mounting the photometer on a Hilger "Short Bar," the base support of which was replaced by a specially designed casting underslung from the projecting front platform of the spectrograph and accurately machined to fit the Short Bar. By means of set screws and lock nuts in the casting a lateral variation of about  $10^\circ$  on either side of the optical axis was possible to assist the correct alignment of the photometer and spectrograph. To obtain a sharp image it was found necessary to remove the quartz window from in front of the slit and bring the photometer to within 1 mm. of the slit cover.

The use of a hydrogen discharge tube as a source of continuous ultraviolet light is exceedingly convenient and much to be preferred to the tungsten steel spark. The Darby tube has the advantage over other designs of operating at 15 kilovolts, making it possible to interchange with the tungsten steel spark without alteration of the electrical

supply circuit. It also requires no water cooling system. The Spekker photometer needs a point source of light and as the discharge in the hydrogen tube occurs along a 10 cm. capillary tube, the correct alignment of the tube with the photometer is difficult and it is necessary to mount the tube in a precision micrometer stand. Incorrect alignment is indicated by a difference in the intensities of the two spectra with no cells in the light path and the photometer drum set at zero. Once correctly aligned the tube has needed no further attention over a period of six months.

Eastman Process plates were used and developed for four minutes at  $20\text{--}22^\circ$  in Eastman high contrast developer (Formula D. 19). They were analyzed by visual spotting of the match points directly on the plate against a suitable uniformly illuminated background and the reading was facilitated by projection onto a ground glass screen.<sup>9</sup> The wave length scale was photographed onto the top and bottom of each plate and was calibrated against the spectrum of a copper spark.

All measurements were made in quartz cells of 1-cm. length with fused ends (Hilger Type H. 292). Absolute alcohol was used as solvent and solutions were prepared by progressive dilution of an initial sample weighed out on a microbalance. Measurements were made with a slit width of 0.12 mm. at  $20\text{--}25^\circ$ . The results are calculated in terms of  $\log_{10} E_{\text{molar}}$  where  $E_{\text{molar}} = \log_{10} I_0/I \cdot 1/cl$ .

$c$  = concentration of solute in moles per liter

$l$  = cell length in cm.

$\log_{10} I_0/I$  = extinction coefficient read directly from the photometer drum

By suitable adjustment of the concentration it was possible to take the whole spectrum on four or five plates with thirty-one exposures on each, at the same time making certain that regions where fine structure was present were photographed under conditions of maximum sensitivity ( $\log I_0/I > 1$ ).

### Results

**1,2-Benzanthracene.**—Measurements on 1,2-benzanthracene itself were first made in order to compare the results obtained using this equipment with those of prior investigators. The first measurements of the absorption spectrum of 1,2-benzanthracene were made by Capper and Marsh,<sup>2</sup> whose curve agrees qualitatively in shape with that of the more recent investigators. The intensity

(1) Commonwealth Fund Fellow.

(2) Capper and Marsh, *J. Chem. Soc.*, 724 (1926).

(3) Clar, *Ber.*, 65, 503 (1932).

(4) Mayneord and Roe, *Proc. Roy. Soc. (London)*, **A152**, 299 (1935); **A158**, 634 (1937).

(5) Fieser, *Am. J. Cancer*, **34**, 37 (1933).

(6) Shear, *ibid.*, **33**, 499 (1933).

(7) Cook, *Ergebnisse der Vitamin- und Hormonforschung*, **2**, 213 (1939).

(8) Private communication.

(9) Rosebury, *Science*, **83**, 86 (1936).