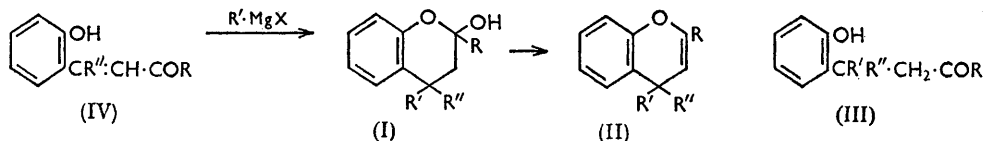


578. *The Preparation of Some Chroman Derivatives.*

By R. H. HALL and B. K. HOWE.

2-Methyl-4-phenylchroman-2-ol and 2-methyl-4-phenylchrom-2-en have been prepared from salicylideneacetone and phenylmagnesium bromide. The chromanol has been degraded to 4-*o*-methoxyphenyl-4-phenylbutan-2-one, the structure of which was proved by synthesis from ethyl  $\alpha$ -cyanocinnamate. Methylmagnesium bromide and salicylideneacetophenone gave 3'-*o*-hydroxyphenylbutyrophenone, which on dehydration afforded 4-methyl-2-phenylchrom-2-en.

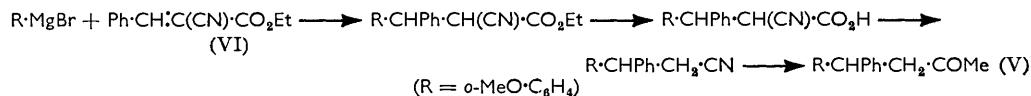
2-METHYL-4 (I; R = Me, R' = Ph, R'' = H) and 4-METHYL-2-PHENYL-CHROMAN-2-OL (I; R = Ph, R' = Me, R'' = H) and the related chromens were required during a recent investigation.<sup>1</sup> This paper describes the preparation of the two chromens and of one (I; R = Me, R' = Ph, R'' = H) of the chromanols; the other chromanol could not be obtained, the keto-phenol (III; R = Ph, R' = Me, R'' = H) being the stable form.



Chroman-2-ols have been obtained, *inter alia*, by treatment of coumarins with Grignard reagents,<sup>2-4</sup> by 1,4-addition of Grignard reagents to aryl *o*-hydroxystyryl ketones<sup>2</sup> [although it has been claimed<sup>5</sup> that this gives the isomeric keto-phenols (III)], by decarbonylation of chroman-2-carboxylic acids,<sup>6</sup> and by alkaline hydrolysis of 3-acetyl-3,4-dihydrocoumarins.<sup>7</sup> The last route furnished the chromanols admixed with the isomeric keto-phenols (III) from which they could be separated by virtue of their insolubility in alkali. Both species gave the same 2,4-dinitrophenylhydrazone.

In the present investigation addition of phenylmagnesium bromide to salicylideneacetone (IV; R = Me, R'' = H) gave a mixture of 2-methyl-4-phenylchroman-2-ol and its dehydration product, 2-methyl-4-phenylchrom-2-en, which were separated by distillation. The infrared absorption spectrum of the former resembled that of 2,4,4-trimethylchroman-2-ol (I; R = R' = R'' = Me);<sup>6,8</sup> in particular the absence of any appreciable bands between 1600 and 1800  $\text{cm}^{-1}$  indicated that no carbonyl group was present and excluded the structure (III; R = Me, R' = Ph, R'' = H). In agreement with the spectral data the compound did not give a semicarbazone. It did, however, dissolve very slowly on being shaken with aqueous alkali, from which solution it was reprecipitated unchanged (infrared) by acidification. As the infrared data indicate that not more than a trace of the keto-phenol form can be present isomerisation must occur as this dissolution in alkali takes place.

On methylating cleavage under drastic conditions (cf. refs. 6 and 8), the chromanol furnished 4-*o*-methoxyphenyl-4-phenylbutan-2-one (V) which was characterised as the 2,4-dinitrophenylhydrazone. The structure of this ketone was established by its synthesis from ethyl  $\alpha$ -cyanocinnamate (see diagram).



<sup>1</sup> Howe, B.P. 796,794 (Distillers Co., Ltd.).

<sup>2</sup> Löwenbein, *Ber.*, 1924, **57**, 1517.

<sup>3</sup> Löwenbein and Rosenbaum, *Annalen*, 1926, **448**, 223.

<sup>4</sup> Heilbron and Hill, *J.*, 1927, 2005.

<sup>5</sup> Geissman, *J. Amer. Chem. Soc.*, 1940, **62**, 1363.

<sup>6</sup> Baker, Curtis, and McOmie, *J.*, 1952, 1774.

<sup>7</sup> Dean, Robertson, and Whalley, *J.*, 1950, 895.

<sup>8</sup> Webster and Young, *J.*, 1956, 4785.

The infrared absorption spectrum of the 2-methyl-4-phenylchrom-2-en was consistent with this formulation [in carbon tetrachloride; band in the region 1225—1250  $\text{cm}^{-1}$  (C—O—C of alkyl aryl ether) and a sharp band at 1702  $\text{cm}^{-1}$  (C=C of chrom-2-en; cf. 2,4,4-trimethylchrom-2-en<sup>8</sup> which has a band at 1704  $\text{cm}^{-1}$ )]. With bromine in carbon tetrachloride at 0° in the dark a solid dibromochroman was obtained. At room temperature hydrogen bromide was disengaged and a monobromochromen obtained (cf. refs. 6 and 8).

Brief attempts were made to convert the ketone (V) into 2-methyl-4-phenylchroman-2-ol and/or 2-methyl-4-phenylchrom-2-en by dealkylation with hydrogen bromide<sup>9</sup> or with boron trichloride;<sup>10</sup> in the former case, a low yield of an impure product containing the chromen (detected spectroscopically) was eventually obtained, but the latter reagent was ineffective. The matter was not pursued further.

Addition of methylmagnesium bromide to salicylideneacetophenone (IV; R = Ph, R'' = H) failed to give any 4-methyl-2-phenylchroman-2-ol. Instead, the product was the open-chain tautomer, 3'-*o*-hydroxyphenylbutyrophenone (III; R = Ph, R' = Me, R'' = H), as shown by its ready solubility in alkali, formation of a semicarbazone, and infrared absorption spectrum. The spectrum contained a strong band (1665  $\text{cm}^{-1}$  in crystalline state; 1680  $\text{cm}^{-1}$  in chloroform) indicative of a carbonyl or ethylenic group; the absence of strong bands in the 1060—1150  $\text{cm}^{-1}$  region excluded an alkyl aryl ether grouping. Treatment of the keto-phenol with oxalic acid caused elimination of water and production of a compound which from its method of formation, spectral properties, and behaviour towards bromine was the chromen (II; R = Ph, R' = Me, R'' = H). Its infrared absorption spectrum (carbon tetrachloride) contained bands at 1225  $\text{cm}^{-1}$  (C—O—C of alkyl aryl ether) and 1671  $\text{cm}^{-1}$ ; the latter was assigned to the C=C of the chrom-2-en, the displacement from the more usual position around 1700  $\text{cm}^{-1}$  being attributed to conjugation of the C=C group with the 2-phenyl group [cf. 2,4-diphenylchrom-2-en (below)]. With bromine in carbon tetrachloride at room temperature immediate decolorisation occurred and hydrogen bromide was evolved; a solid derivative could not, however, be isolated.

The above results recalled the disagreement in the literature, noted earlier, concerning the structure of 2,4-diphenylchroman-2-ol (I; R = R' = Ph, R'' = H). Prepared originally by Löwenbein<sup>2</sup> and formulated by him as the chromanol, this compound was stated by Geissman<sup>5</sup> to be the keto-phenol (III; R = R' = Ph, R'' = H). Re-examination has confirmed the correctness of Geissman's views: the compound dissolved, albeit slowly, in aqueous sodium hydroxide, formed a semicarbazone, and contained a carbonyl group conjugated with an aromatic ring [infrared absorption band (in chloroform) at 1683  $\text{cm}^{-1}$ ]. Dehydration in boiling acetic acid (cf. ref. 2) furnished 2,4-diphenylchrom-2-en whose infrared absorption spectrum (in chloroform) contained bands at 1225  $\text{cm}^{-1}$  (C—O—C of alkyl aryl ether) and 1672  $\text{cm}^{-1}$  (C=C of chrom-2-en).

Generalisation from the limited number of examples available is probably of doubtful value, but nevertheless it appears that, when the group R is phenyl, compounds which theoretically can have either structure (I) or (III) exist solely as (III). Presumably the gain in delocalisation energy resulting from conjugation of the carbonyl group with the aromatic ring stabilises the keto-phenol form. When R is not phenyl (aryl) other factors such as the presence of a substituent on the carbon atom  $\beta$  to the potential carbonyl group appear to be important, since although the chromanol form (I) is the preferred one when R = Me, R' = Ph, and R'' = H (see above), and when R = R' = R'' = Me,<sup>6,8</sup> both forms exist when R = Me and R' = R'' = H.<sup>7</sup> In the latter case, however, no spectral data are recorded, and it is conceivable that a rapid isomerisation from the chromanol to the keto-phenol form occurs under the influence of the alkali which is used to separate the isomers.

<sup>9</sup> Cf. Elderfield and King, *J. Amer. Chem. Soc.*, 1954, **76**, 5439.

<sup>10</sup> Cf. Gerrard and Lappert, *J.*, 1952, 1486.

## EXPERIMENTAL

*Reaction of Salicylideneacetone with Phenylmagnesium Bromide.*—Salicylideneacetone (13.5 g.) was added to phenylmagnesium bromide prepared from magnesium (7.3 g.), a trace of iodine, and redistilled bromobenzene (44.1 g.) in ether. The red solution was refluxed for 3 hr., cooled, and poured on ice-ammonium chloride. The ether layer was decanted and the residue shaken twice more with ether. The combined ether extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated, and part (16.4 g.) of the semi-solid residue (18.0 g.) was distilled through a short Vigreux column. A small fore-run (1.1 g.) of diphenyl was followed by (i) 2-methyl-4-phenylchrom-2-en (8.5 g., 50%), b. p. 115—117°/0.3—0.4 mm.,  $n_D^{20}$  1.6032 (Found: C, 86.55; H, 6.35.  $\text{C}_{16}\text{H}_{14}\text{O}$  requires C, 86.45; H, 6.35%), and (ii) 2-methyl-4-phenylchroman-2-ol (3.2 g., 18%), b. p. 138—160°/0.3 mm., m. p. 116° [from light petroleum (b. p. 100—120°)] (Found: C, 80.2; H, 6.75.  $\text{C}_{16}\text{H}_{16}\text{O}_2$  requires C, 79.95; H, 6.7%).

Repetition of the condensation in the absence of iodine resulted in a higher yield (25%) of chromanol. Little chromen was obtained. Both preparations afforded considerable quantities of very high-boiling residues.

*Reactions of 2-Methyl-4-phenylchrom-2-en.*—(a) Bromine (0.80 g.) in carbon tetrachloride (5 ml.) was added to the chromen (1.11 g.) in carbon tetrachloride (10 ml.) at 0° in the dark during 30 min. After a further 15 min. the solution was concentrated to about one-half of its bulk and then kept overnight at room temperature. Treatment with charcoal and evaporation *in vacuo* afforded a gum which was dissolved in light petroleum (b. p. 40—60°). Crystals (0.95 g.) slowly separated from this solution at 3°. Recrystallisation from the same solvent afforded 2,3-dibromo-2-methyl-4-phenylchroman, m. p. 110° (Found: C, 50.1, 50.25; H, 3.6, 3.6; Br, 42.1.  $\text{C}_{16}\text{H}_{14}\text{OBr}_2$  requires C, 50.3; H, 3.7; Br, 41.85%). The infrared absorption spectrum contained no bands near 1680—1700  $\text{cm}^{-1}$ , indicating absence of C=C groups.

(b) On bromination at room temperature hydrogen bromide was evolved. Isolation of the product afforded a small yield of a solid, m. p. 145° (from ethanol). Analysis indicated that this was impure monobromochromen (Found: Br, 24.0. Calc. for  $\text{C}_{16}\text{H}_{13}\text{OBr}$ : Br, 26.55%).

*Reactions of 2-Methyl-4-phenylchroman-2-ol.*—(a) No semicarbazone could be prepared from the chromanol.

(b) When the chromanol (1 g.) was shaken with excess of *N*-sodium hydroxide for 72 hr., part (0.55 g.) of it remained undissolved. This was filtered off and the filtrate was acidified. Isolation of the product with ether afforded a crude solid, m. p. 109°, whose infrared absorption spectrum was virtually identical with that of the starting material.

(c) The chromanol (2 g.), sodium hydroxide (40 g.), and water (50 ml.) were refluxed for 15 min. and, as some oil remained undissolved, methanol (10 ml.) was added and refluxing continued for 30 min. The product was cooled and dimethyl sulphate (25 ml.) in methanol (25 ml.) added slowly (10 min.). The mixture was then refluxed for 15 min., cooled, and diluted with water (200 ml.). Isolation of the product with ether ( $2 \times 50$  ml.) afforded an oil (1.84 g.) which readily solidified. Recrystallisation from ethanol gave 4-*o*-methoxyphenyl-4-phenylbutan-2-one, m. p. 83°, identical (mixed m. p.) with that obtained below. The 2,4-dinitrophenylhydrazone separated from ethanol as yellowish-orange needles, m. p. and mixed m. p. with authentic material (see below) 166—167° (Found: C, 63.6; H, 5.15; N, 12.5. Calc. for  $\text{C}_{23}\text{H}_{22}\text{O}_5\text{N}_4$ : C, 63.6; H, 5.1; N, 12.9%).

*Ethyl  $\alpha$ -Cyano- $\beta$ -*o*-methoxyphenyl- $\beta$ -phenylpropionate.*—Ethyl  $\alpha$ -cyanocinnamate (129.3 g.; prepared in 85% yield from benzaldehyde and ethyl cyanoacetate by the procedure of Baker and Leeds<sup>11</sup>) was added at 5° to *o*-methoxyphenylmagnesium bromide prepared from magnesium (19.4 g.) and *o*-bromoanisole (149.6 g.) in ether containing a trace of iodine. An exothermic reaction ensued and the Grignard complex separated as a thick, viscous oil. The mixture was refluxed for 1 hr., cooled, and decomposed by addition of ice-cold 5% sulphuric acid (800 ml.). The thick oil gradually disappeared with evolution of heat. The ether layer was separated, washed successively with water, 5% aqueous sodium carbonate solution, and water, and dried ( $\text{CaCl}_2$ ). The ether was removed *in vacuo* and the residue distilled. The distillate (174.3 g.), b. p. 180°/0.4 mm., slowly crystallised. Repeated recrystallisations from 95% ethanol furnished ethyl  $\alpha$ -cyano- $\beta$ -*o*-methoxyphenyl- $\beta$ -phenylpropionate (88%), m. p. 91.5—92° (Found: C, 74.1; H, 6.25; N, 4.5.  $\text{C}_{19}\text{H}_{19}\text{O}_3\text{N}$  requires C, 73.75; H, 6.2; N, 4.55%).

<sup>11</sup> Baker and Leeds, *J.*, 1948, 974.

*α-Cyano-β-o-methoxyphenyl-β-phenylpropionic Acid.*—Ethyl *α*-cyano-β-*o*-methoxyphenyl-β-phenylpropionate (61.9 g.) was added to sodium hydroxide (21.7 g.) dissolved in water (630 ml.) at about 90°. The mixture was heated to boiling (5 min.) and refluxed for 5 min., by which time all the oil had reacted. The solution was cooled, diluted with water (600 ml.), extracted with ether (3 × 100 ml.) to remove neutral materials, then acidified with 10% hydrochloric acid and again extracted with ether (3 × 150 ml.). The combined ether solutions from this last extraction were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated *in vacuo*. The oil obtained slowly solidified. Recrystallisation from benzene afforded *α*-cyano-β-*o*-methoxyphenyl-β-phenylpropionic acid (56 g., 100%), m. p. 132° (Found: C, 72.8; H, 5.4; N, 5.1%; equiv., 282.0. C<sub>17</sub>H<sub>15</sub>O<sub>3</sub>N requires C, 72.6; H, 5.4; N, 5.0%; equiv., 281.3).

*β-o-Methoxyphenyl-β-phenylpropionitrile.*—*α*-Cyano-β-*o*-methoxyphenyl-β-phenylpropionic acid (51.3 g.) was heated at 190° for 30 min. to effect decarboxylation. Part (41.85 g.) of the product (44.0 g.) was carefully fractionated to give a colourless distillate (30.6 g., 74%), b. p. mainly 175°/0.7 mm., which readily solidified. A solution of the solid in chloroform was washed with sodium hydrogen carbonate solution, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated under reduced pressure. The product obtained was recrystallised from ethanol to give *β-o-methoxyphenyl-β-phenylpropionitrile*, m. p. 90.5–91° (Found: C, 80.75; H, 6.2; N, 5.8. C<sub>16</sub>H<sub>15</sub>ON requires C, 80.95; H, 6.35; N, 5.9%).

*4-o-Methoxyphenyl-4-phenylbutan-2-one.*—A suspension of *β-o-methoxyphenyl-β-phenylpropionitrile* (47.5 g.) in ether (200 ml.) was added to stirred methylmagnesium bromide prepared from methyl bromide and magnesium (14.6 g.) in ether (200 ml.). The exothermic reaction which ensued during the addition was controlled by external cooling and the final mixture was refluxed for 3 hr. Ice (240 g.) was added cautiously and the mixture was set aside overnight. The ether-soluble material was separated off and, after isolation, was boiled with 4% sulphuric acid (200 ml.) for 30 min. The material insoluble in ether was similarly treated with 4% sulphuric acid (265 ml.) and the products from the two hydrolyses were combined and isolated with ether. The dark brown solid (45.5 g., 89%), m. p. 75–80°, thus obtained was crystallised from ethanol (charcoal) to give *4-o-methoxyphenyl-4-phenylbutan-2-one*, m. p. 83.5–84° (Found: C, 80.2; H, 7.1. C<sub>17</sub>H<sub>16</sub>O<sub>2</sub> requires C, 80.3; H, 7.15%). The *2,4-dinitrophenylhydrazone* separated from ethanol as yellowish-orange needles, m. p. 167° (Found: C, 63.85; H, 5.0; N, 12.6. C<sub>23</sub>H<sub>22</sub>O<sub>5</sub>N<sub>4</sub> requires C, 63.6; H, 5.1; N, 12.9%).

*De-alkylation of 4-o-Methoxyphenyl-4-phenylbutan-2-one.*—A mixture of the ketone (10 g.) and a ~50% solution (350 ml.) of hydrobromic acid in acetic acid was refluxed for 15 hr. under nitrogen. Most (260 ml.) of the solvent was distilled off, the residue was diluted with water (300 ml.), and the mixture was extracted with ether (2 × 250 ml.). The combined ether extracts were washed successively with water, 2.5% aqueous sodium carbonate, and water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The red oily residue (8.9 g.) was chromatographed in benzene (15 ml.) over alumina (40 × 2 cm.). The column was washed with benzene. Evaporation of the first 500 ml. of effluent gave a red oil (6.2 g.) which was fractionated under reduced pressure. Only the first fraction (0.9 g.), b. p. 137–139°/0.35–0.4 mm., contained a detectable amount of 2-methyl-4-phenylchrom-2-en; the overall yield of the latter from the ketone was estimated by infrared spectrography to be about 3%. The higher-boiling fractions from the distillation contained some unchanged ketone and some unidentified material.

*Reaction of Salicylideneacetophenone with Methylmagnesium Bromide.*—Salicylideneacetophenone (44.8 g.) was added gradually to a stirred, refluxing ethereal solution of methylmagnesium bromide prepared from methyl bromide and magnesium (14.65 g.). The mixture was refluxed for 3 hr., cooled, and poured on ice and ammonium chloride. The aqueous phase was acidified with concentrated sulphuric acid (55 g.) to dissolve magnesium compounds and extracted with ether. The combined ether solutions were dried (Na<sub>2</sub>SO<sub>4</sub>-Na<sub>2</sub>CO<sub>3</sub>) and evaporated *in vacuo*. The residue was distilled. Most of the distillate had b. p. 173–173.5°/0.6 mm. and slowly crystallised. Recrystallisation from benzene–light petroleum (b. p. 100–120°) afforded 3'-*o*-hydroxyphenylbutyrophenone (37.2 g., 77.5%), m. p. 80–81° (Found: C, 80.25; H, 6.7. C<sub>16</sub>H<sub>16</sub>O<sub>2</sub> requires C, 79.95; H, 6.7%).

*4-Methyl-2-phenylchrom-2-en.*—3'-*o*-Hydroxyphenylbutyrophenone (10 g.), oxalic acid (0.2 g.), and benzene (50 ml.) were refluxed for 3 hr. under a Dean and Stark head to effect dehydration. The cooled benzene solution was washed with water (3 × 30 ml.), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was fractionated to give *4-methyl-2-phenylchrom-2-en* (7.6 g.,

82%), b. p. 109°/0.1 mm.,  $n_D^{20}$  1.6117 (Found: C, 86.75; H, 6.35.  $C_{16}H_{14}O$  requires C, 86.45; H, 6.35%).

*Reaction of Salicylideneacetophenone with Phenylmagnesium Bromide.*—Löwenbein's procedure <sup>2</sup> was employed. Recrystallisation of the crude product from benzene afforded 3'-*o*-hydroxyphenyl-3'-phenylpropiophenone, m. p. 165° (Found: C, 83.8; H, 6.0. Calc. for  $C_{21}H_{18}O_2$ : C, 83.4; H, 6.0%). Löwenbein <sup>2</sup> gives m. p. 165—166° for his product; Geissman <sup>1</sup> gives m. p. 167—167.5°. This ketone dissolved slowly on being shaken with an excess of aqueous *N*-sodium hydroxide.

The ketone gave a semicarbazone (with some difficulty), which on recrystallisation from dilute ethanol had m. p. 177° (Found: N, 11.85. Calc. for  $C_{22}H_{21}O_2N_3$ : N, 11.7%). Geissman <sup>1</sup> records m. p. 177—178°.

Dehydration of the ketone with boiling acetic acid (cf. ref. 2) afforded 2,4-diphenylchrom-2-en which separated from light petroleum (b. p. 60—80°) as white prisms, m. p. 109° (Found: C, 89.0; H, 5.55. Calc. for  $C_{21}H_{16}O$ : C, 88.7; H, 5.65%). Löwenbein <sup>2</sup> gives m. p. 110°.

The authors are indebted to Miss M. M. R. Gay-Knott and Miss P. E. Joyce for assistance with the experimental work and to Messrs. A. R. Philpotts, W. Maddams, and W. R. Ward for infrared data.

RESEARCH AND DEVELOPMENT DEPARTMENT,

THE DISTILLERS CO. LTD., GREAT BURGH, EPSOM, SURREY.

[Received, March 26th, 1959.]

---