[Contribution from the Department of Chemistry, University of Bristol]

STUDIES IN THE CHROMAN SERIES. II

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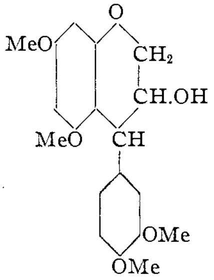
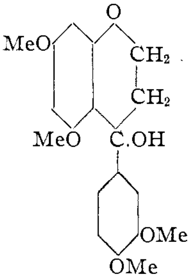
In a series of publications[1] several reactions were described which have led to the synthesis of acacatechin tetramethyl ether (**I**) and to the conversion of the latter into iso-acacatechin tetramethyl ether (**II**).

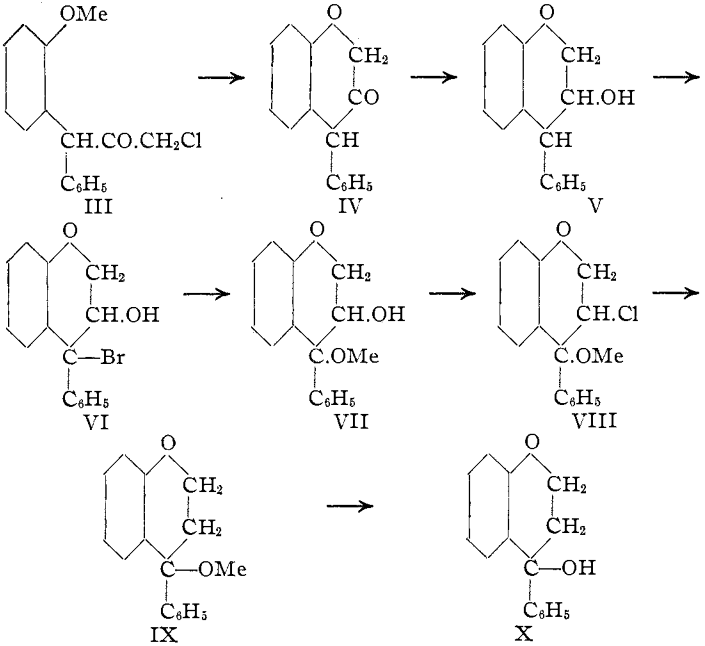


I



II

To confirm these reactions we have prepared by the same methods 2-hydroxy-3-phenylchroman (V) and converted it into 3-hydroxy-3-phenylchroman (X) as shown in the following scheme of reactions fully described in the experimental part.



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[1] Nierenstein, *J. Chem. Soc.*, **117**, 971, 1157 (1920); **119**, 164 (1921); **121**, 604 (1922); *Ber.*, **56**, 1877 (1923).

Experimental Part

2-Methoxy-diphenylmethyl-chloromethyl Ketone (III)

This ketone was prepared by the action of diazomethane on *2-methoxy-diphenylacetyl chloride*[2] which involved the preparation of the following substances.

1. **2-Methoxydiphenyl Carbinol.**—The bulk of this substance was prepared according to the method of Stoermer and Friderici.[3] About 20 g. was, however, also prepared by reducing 2-methoxy-benzophenone[4] with zinc dust in alkaline solution. Both preparations melted correctly at 141°.

2. **2-Methoxy-diphenylmethyl Chloride.**—The chloride is obtained by the interaction on a boiling water-bath of 20 g. of the carbinol dissolved in dry chloroform and 15 g. of thionyl chloride. The solid left on evaporation of the chloroform under diminished pressure crystallizes from ligroin in small, star-shaped needles; m. p., 73°. The average yield from five preparations is 94%.

Anal. Subs., 0.1185: AgCl, 0.0741 g. Calc. for $C_{14}H_{14}OCl$: Cl, 15.2. Found: 15.5.

3. **2-Methoxy-diphenylacetic Acid.**—A solution of 12 g. of the chloride in dry ether (Grignard) is heated on a water-bath with 2 g. of "activated" magnesium,[5] dry carbon dioxide being passed through the solution for three and a half hours. The solution turns red and becomes filled with a flocculent, yellow product, which reaches its maximum in about three hours. The ether is evaporated, and the residue first covered with ice water and then decomposed with 40 cc. of carefully cooled concd. hydrochloric acid. The yellow, brittle solid is warmed with 75 cc. of a solution consisting of 50 cc. of concd. ammonia and 50 cc. of water, when the greater part dissolves. The filtrate is acidified with dil. sulfuric acid and the precipitate crystallized from water with the aid of animal charcoal. Long, silky needles are obtained; m. p., 176–177°, carbon dioxide being evolved. The average yield from five preparations is 87%.

Anal. Subs., 0.0906: CO_2, 0.2464; H_2O, 0.0458. Calc. for $C_{15}H_{14}O_3$: C, 74.4; H, 5.8. Found: C, 74.2; H, 5.7.

4. **2-Methoxy-diphenylacetyl Chloride.**—A solution of 50 g. of 2-methoxy-diphenylacetic acid in dry chloroform is heated for 40 minutes on a boiling water-bath with 50 g. of phosphorus pentachloride and the liquid decanted while still warm. The unchanged phosphorus pentachloride is extracted several times with hot chloroform and the combined chloroform solutions are diluted with ligroin. The viscous oil thus formed is washed several times with ligroin and is then allowed to stand in a vacuum over paraffin wax and solid sodium hydroxide, when it solidifies. It crystallizes from ligroin in long needles; m. p., 67°; yield, 93%.

Anal. Subs., 0.2733: AgCl, 0.1355. Calc. for $C_{15}H_{13}O_2Cl$: Cl, 13.6. Found: 13.9.

5. **2-Methoxy-diphenylmethyl-chloromethyl Ketone (III).**—A solution of 10 g. of the acyl chloride in dry ether (Grignard) is treated with an excess of diazomethane,

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[2] Clibbens and Nierenstein, *J. Chem. Soc.*, **107**, 1391 (1915).

[3] Stoermer and Friderici, *Ber.*, **41**, 332 (1908).

[4] 2-Methoxy-benzophenone is described as an oil [Cohen, *Monatsh.*, **17**, 107 (1896)] and as a solid which melts at 39° [Ref. 3, p. 333]. We have obtained it as a solid; m. p., 41°.

[5] Baeyer, *Ber.*, **38**, 2759 (1905).

prepared according to the method of Staudinger and Kupfer.[6] The solid left on evaporation of the ether crystallizes from ligroin in large plates, m. p., 107°, and has the characteristic odor of the chloromethyl ketones. The average yield from four preparations is 87%.

Anal. Subs., 0.1781: AgCl, 0.0984. Subs., 0.1605: CO_2, 0.4095; H_2O, 0.0731. Calc. for $C_{16}H_{15}O_2Cl$: C, 69.9; H, 5.5; Cl, 13.0. Found: C, 69.6; H, 5.1; Cl, 13.5.

3-Phenylchroman-2-one (IV)

To a solution of 10 g. of 2-methoxy-diphenylmethyl-chloromethyl ketone (III) in 75 cc. of dry benzene, 1 g. of freshly prepared aluminum chloride is added, and the solution heated on a boiling water-bath for 16 hours. The solid left on evaporation of the benzene is extracted several times with warm ligroin, the extracts are filtered, united and evaporated in a vacuum at room temperature to about one-third of the original volume. On standing in ice, large cubes are formed; m. p., 76°. The filtrate from these gives on standing in ice a second crop of somewhat smaller crystals which melt at the same temperature. The average yield of four preparations is 92%. The product is very soluble in the usual organic solvents, but it may be also crystallized from carbon disulfide, from which it separates in small plates; m. p., 76°. The addition of ferric chloride to a suspension of 3-phenylchroman-2-one in concd. sulfuric acid produces a reddish-violet coloration, which is identical with that given by 3-phenylchroman.[7]

Anal. Subs., 0.1532: CO_2, 0.4508; H_2O, 0.0732. Calc. for $C_{15}H_{12}O_2$: C, 80.3; H, 5.3. Found: C, 80.4; H, 5.3.

When condensed with phenylhydrazine in acetic acid solution in the presence of sodium acetate the *phenylhydrazone* is obtained. It crystallizes from alcohol in faintly yellow needles; m. p., 127–128°.

Anal. Subs., 0.1952: 14.3 cc. of *N* (12°, 753 mm.; over 33% KOH). Calc. for $C_{21}H_{18}ON_2$: N, 8.9. Found: 8.7.

2-Hydroxy-3-phenylchroman (V)

A solution of 10 g. of 3-phenylchroman-2-one (IV) in 100 cc. of acetic anhydride is heated on a boiling water-bath for eight hours with zinc dust that has been dried at 100° for a short time. The filtered solution is diluted with water, and the solid formed collected after 24 hours. The crude product is dissolved in alcohol and heated for several hours with dil. sulfuric acid. It is then again precipitated with water. The solid thus obtained is treated in the cold with dil. sodium hydroxide when nearly all the solid dissolves. The filtered alkaline solution is acidified with dil. sulfuric acid and the oil formed extracted with ether. The ether leaves, after drying over anhydrous sodium sulfate, a semi-solid mass, which solidifies on standing over paraffin wax in a vacuum. 2-Hydroxy-3-phenylchroman crystallizes from a mixture of benzene and ligroin (1:3) in small needles; m. p., 87°. The average yield of three preparations is 72%. The addition of ferric chloride to a suspension of the substance in concd. sulfuric acid produces a reddish-violet coloration, in which the red shade predominates. 2-Hydroxy-3-phenylchroman differs in this respect from 3-phenylchroman and 3-phenylchroman-2-one, which do not show a predominance of red.

Anal. Subs., 0.1476: CO_2, 0.4306; H_2O, 0.0863. Calc. for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.6; H, 6.5.

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[6] Staudinger and Kupfer, *Ber.*, **45**, 501 (1912).

[7] Greenwood and Nierenstein, *J. Chem. Soc.*, **117**, 1597 (1920).

The ACETYL DERIVATIVE crystallizes from alcohol and acetone in small needles; m. p., 117°.

Anal. Subs., 0.1639: CO_2, 0.4548; H_2O, 0.0867. Calc. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: C, 75.7; H, 5.9.

2-Hydroxy-3-bromo-3-phenylchroman (VI)

To a solution of 22 g. of 2-hydroxy-3-phenylchroman (V) in 75 cc. of dry chloroform is added 15.5 g. of bromine dissolved in the same solvent. The solid formed on standing in diffused sunlight crystallizes from benzene in long, colorless needles; m. p., 157–158°.

Anal. Subs., 0.2035: AgBr, 0.1254. Calc. for $C_{15}H_{13}O_2Br$: Br, 26.2. Found: 26.3.

2-Hydroxy-3-methoxy-3-phenylchroman (VII)

A solution of 20 g. of the bromo derivative (VI) in 150 cc. of methyl alcohol that had been refluxed over calcium oxide is boiled for 70 hours. The solid formed on precipitation with water crystallizes from dil. alcohol in prismatic needles; m. p., 127°; the calculated yield is obtained. The product is soluble in the usual organic solvents, and may be crystallized from alcohol and benzene (1:2), when it also melts at 127°. The addition of ferric chloride to a suspension in concd. sulfuric acid produces the same coloration as given by 2-hydroxy-3-phenylchroman.

Anal. Subs., 0.2171: CO_2, 0.5942; H_2O, 0.1221. Calc. for $C_{16}H_{16}O_3$: C, 75.0; H, 6.2. Found: C, 74.7; H, 6.3.

The ACETYL DERIVATIVE crystallizes from alcohol and melts at 167–168°.

Anal. Subs., 0.1449: CO_2, 0.3828; H_2O, 0.0843. Calc. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.0. Found: C, 72.1; H, 6.5.

2-Chloro-3-methoxy-3-phenylchroman (VIII)

A solution of 16 g. of 2-hydroxy-3-methoxy-3-phenylchroman (VII) in 50 cc. of dry benzene mixed with 50 g. of thionyl chloride is heated on a water-bath for three hours. The unchanged thionyl chloride and also the benzene are distilled in a vacuum and the semi-solid left kept in a vacuum over paraffin wax and solid sodium hydroxide, when it solidifies. The substance crystallizes from ligroin in prismatic needles; m. p., 84°; yield, 82%.

Anal. Subs., 0.2372: AgCl, 0.1215. Calc. for $C_{16}H_{15}O_2Cl$: Cl, 12.9. Found: 12.7.

3-Methoxy-3-phenylchroman (IX)

A solution of 8 g. of the chloro derivative (VIII) in 500 cc. of dry ether (Grignard) and 2 g. of "activated" magnesium are heated on a water-bath.[8] The solution becomes deep red in about 40 minutes, after which the heating is continued for another two hours. The solid left on distillation of the ether is treated with ice and hydrochloric acid. It is then dissolved in alcohol, the solution filtered and the substance precipitated with water. The solid thus obtained is dried over phosphorus pentoxide in a vacuum and crystallized from chloroform, from which it separates in long needles; m. p., 41°; yield, 52%. This is due to the formation of a by-product (so far not examined) which is insoluble in hot chloroform.

Anal. Subs., 0.1738: CO_2, 0.5088; H_2O, 0.1087. Calc. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.9; H, 7.0.

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[8] Compare Grignard and Tissier, *Compt. rend.*, **132**, 835 (1901).

3-Hydroxy-3-phenylchroman (X)

A solution of 5 g. of 3-methoxy-3-phenylchroman (IX) in 25 cc. of dry benzene is shaken for five hours with 2.5 g. of acetyl chloride in 10 cc. of benzene. The solid left on evaporation of the benzene is treated with dil. sodium hydroxide solution, the liquid filtered and then acidified. The precipitate thus obtained is dried in a vacuum over phosphorus pentoxide for some time and then crystallized from chloroform from which it separates in small needles; m. p., 101–102°; yield, 71%. The addition of ferric chloride to a suspension in concd. sulfuric acid produces a violet coloration. 3-Hydroxy-3-phenylchroman (X) differs thus from 2-hydroxy-3-phenylchroman (V) which gives a reddish-violet coloration, and exactly the same color differences are observed in the case of acacatechin-tetramethyl ether [2-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylchroman (I)] and isoacacatechin-tetramethyl ether [3-hydroxy-4,6,3′,4′-tetramethoxy-3-phenylchroman (II)].

Anal. Subs., 0.1500: CO_2, 0.4362; H_2O, 0.0862. Calc. for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.4; H, 6.4.

The ACETYL DERIVATIVE crystallizes from alcohol in small needles; m. p., 124–125°.

Anal. Subs., 0.1737: CO_2, 0.4853; H_2O, 0.0956. Calc. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: C, 76.2; H, 6.2.

In conclusion we wish to thank the Colston Research Society of the University of Bristol for a grant which has covered the expenses of this investigation.

Summary

2-Hydroxy-3-phenylchroman and 3-hydroxy-3-phenylchroman have been prepared by the same methods which had been used by Nierenstein for the syntheses of acacatechin-tetramethyl ether and isoacacatechin-tetramethyl ether.

BRISTOL, ENGLAND

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE REACTION BETWEEN METALLIC SODIUM AND AROMATIC ALDEHYDES, KETONES AND ESTERS. I. ALDEHYDES

BY F. F. BLICKE

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We became interested in this subject through the following incident. During the drying of solvent ether which had been used in the preparation of triphenylcarbinol a small quantity of a deep blue substance was formed. This material was observed after the impure ether had remained in contact with metallic sodium for several days at room temperature; the ether contained traces of methyl benzoate and bromobenzene. An investigation was then undertaken in order to determine what this blue precipitate was and how it was formed.

A preliminary experiment showed that sodium reacts readily with methyl benzoate, at room temperature, when the latter is dissolved in absolute