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SYNTHETICAL EXPERIMENTS IN THE CHROMONE GROUP—XXXV*

SYNTHESIS OF DIHYDROJACAREUBIN AND A NEW GENERAL METHOD FOR THE SYNTHESIS OF 2,2-DIMETHYLCHROMANONES†

H. B. BHAT and K. VENKATARAMAN
National Chemical Laboratory, Poona

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Abstract—A new method for the synthesis of 2,2-dimethylchromanones is described in which β-hydroxyisovaleric acid is condensed with a phenol in presence of boron fluoride-etherate. Chromanones are reduced to chromans in good yield by diborane. Condensation of pyrogallol-α-carboxylic acid with 5,7-dihydroxy-2,2-dimethylchroman in presence of phosphorus oxychloride and zinc chloride gave a xanthone identical with dihydrojacareubin. 6,7-Dihydroxy-2,2-dimethylchromanone on methylation followed by diborane reduction gave dihydroageratochromene.

IN CONNEXION with work on the constitution of morellin and the synthesis of certain products obtained by the alkali fusion of octahydromorellin, it became necessary to synthesize several 2,2-dimethylchromanone derivatives. 2,2-Dimethylchromanones are also of interest as intermediates for the synthesis of 2,2-dimethylchromenes, of which there are many representatives among plant products.

The first synthesis of 5,7-dihydroxy-2,2-dimethylchromanone (I) was carried out by Robertson *et al.*[1] by the Friedel-Crafts reaction between phloroglucinol and ββ-dimethylacrylyl chloride; the yield of the crude product was 54%. A similar yield was obtained by Robertson[2] in a subsequent synthesis, in which ββ-dimethylacrylyl chloride was replaced by β-bromoisovaleryl chloride and phloroglucinol by resorcinol. More recently Miyano and Matsui[3] reviewed the available methods and found that the most convenient procedure was to condense phloroglucinol with ββ-dimethylacrylic acid in presence of antimony trichloride at 140–145°; the yield was 30%. It has now been found that the condensation of phloroglucinol with β-hydroxyisovaleric acid in presence of boron fluoride-etherate under mild conditions results in a 65% yield of the chromanone (I). The product obtained on heating the reaction mixture with water was a boron complex, which was broken by dissolving it in 10% aqueous sodium hydroxide. The IR spectrum (KBr disc) of I showed prominent bands at 3115 (OH), 1637 (chelated carbonyl), 1595 and 1575 (benzenoid in conjugation with a C=O group), 1376 and 1364 (*gem*-dimethyl), 1295 and 1083 cm^{-1} (ether). The product recovered from the mother liquors after the isolation of

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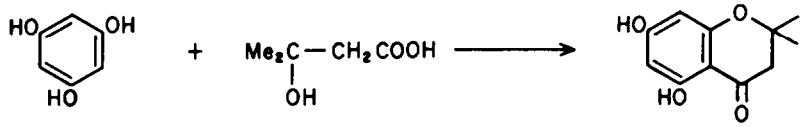
† Part XXXIV *J. Sci. Ind. Res.* **21B**, 477 (1962).

[1] W. Bridge, R. G. Heyes and A. Robertson, *J. Chem. Soc.* 284 (1937).

[2] W. Bridge, A. J. Crocker, T. Cubin and A. Robertson, *J. Chem. Soc.* 1532 (1937).

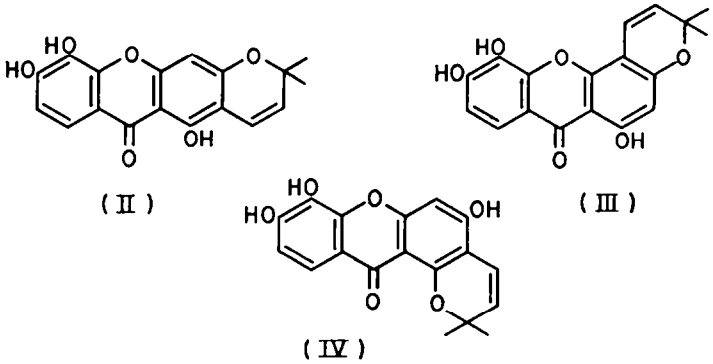
[3] M. Miyano and M. Matsui, *Bull. Chem. Soc. Japan* **31**, 397 (1958).

the pure chromanone (I) exhibited a similar IR spectrum and the hydroxamic acid test for lactones was negative, indicating the complete absence of the isomeric dihydrocoumarin. Steric control of the reaction appears to be involved in the exclusive formation of the chromanones when phenols are condensed with β-hydroxyisovaleric acid. Condensation of β-hydroxyisovaleric acid with resorcinol or hydroxyhydroquinone (used as the triacetate) readily gives the corresponding 2,2-dimethylchromanone. One advantage of the method is that β-hydroxyisovaleric acid is readily obtained by the sodium hypochlorite or hypobromite oxidation of the commercially available diacetone alcohol.[4]



(I)

From the heartwood of the tropical American tree, *Calophyllum brasiliense* Camb., King *et al.*[5] isolated a deep yellow crystalline pigment to which the structure II was assigned. The degradative experiments did not distinguish between II and the isomeric structures III and IV; but the chelate character of the hydroxyl group in jacareubin dimethyl ether excluded IV, and III was eliminated by the fact that the ether gives a positive Gibbs reaction.[6]

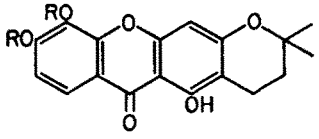


(II) (III) (IV)

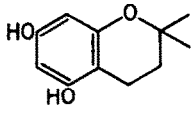
We have confirmed structure II by the synthesis of dihydrojacareubin (V; R = H). The chromanone (I) was reduced to the chroman (VI) in 65% yield by using diborane;[7] the Clemmensen method used earlier[1] gave a similar yield. Condensation of pyrogallol-α-carboxylic acid with the chroman VI using the Shah reagent (phosphorus oxychloride-zinc chloride[8]) yielded the xanthone (V; R = H), which was identical with the dihydro-derivative of natural jacareubin kindly supplied by Professor

[4] D. D. Coffman, R. Cramer and W. E. Mochel, *J. Amer. Chem. Soc.* **80**, 2882 (1958).
[5] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 3932 (1953).
[6] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.* 563 (1957).
[7] D. S. Bapat, B. C. Subba Rao, M. K. Unni and K. Venkataraman, *Tetrahedron Letters* No. 5, 15 (1960).
[8] P. K. Grover, R. C. Shah and G. D. Shah, *Chem. & Ind.* 62 (1955).

F. E. King. The formation of the dihydro-derivatives of the isomers III and IV is possible, but neither of them was isolated. Although the present synthesis does not distinguish between structures II, III and IV, the ferric colour of our product and the positive Gibbs test given by the dimethyl ether (V; R = Me) support the linear character of the ring system as in V and therefore the structure II for jacareubin proposed by King *et al.* The dimethyl ether (V; R = Me) was prepared by methylation of synthetic dihydrojacareubin.

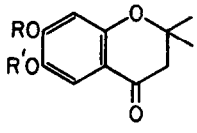


(V)

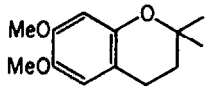


(VI)

When 1,2,4-triacetoxybenzene was condensed with β-hydroxyisovaleric acid in presence of boron fluoride-etherate, the boron complex obtained by treatment with water led to 6,7-dihydroxy-2,2-dimethylchromanone (VII; R, R′ = H) or the 7-monoacetyl derivative (VII; R = Ac, R′ = H) depending on the conditions of alkaline hydrolysis. The presence of the O-acetyl group in the 7-position was shown by methylation with diazomethane and hydrolysis, which gave 7-hydroxy-6-methoxy-2,2-dimethylchromanone (VII; R = H, R′ = Me), soluble in aqueous sodium carbonate. 6,7-Dimethoxy-2,2-dimethylchromanone (VII; R, R′ = Me) was prepared from the dihydroxy compound by the usual dimethyl sulphate-potassium carbonate method.



(VII)



(VIII)

Alertsen[9] isolated 6,7-dimethoxy-2,2-dimethylchromene from the essential oil of *Ageratum mexicanum;* hydrogenation in presence of Raney nickel gave the chroman VIII,[10] which has now been synthesized by the diborane reduction (in 86% yield) of 6,7-dimethoxy-2,2-dimethylchromanone (VII; R, R′ = Me); Clemmensen reduction gave a 60% yield. The properties (m.p. and UV spectrum) of VIII correspond with those of dihydroageratochromene, but direct comparison could not be made because of the nonavailability of the natural product. The IR spectrum (CCl_4) shows bands at 1616 and 1513 (benzenoid), 1377 and 1362 (*gem*-dimethyl), 1271, 1241 and 1125 cm^{-1} (ether); Alertsen[9] has mentioned that the IR spectrum of dihydroageratochromene shows many similarities to that of 5,7-dimethoxy-2,2-dimethylchroman, but he did not record the spectra of the two compounds. Ageratochromene was synthesized earlier by Huls[10] from 1,2,4-trimethoxybenzene and ββ-dimethylacrylyl chloride; the chromanone obtained by the Friedel-Crafts reaction was reduced by lithium

[9] A. R. Alertsen, *Acta Chem. Scand.* **9**, 1725 (1955).
[10] R. Huls, *Bull. Soc. Chim. Blg.* **67**, 22 (1958).

aluminium hydride to the chromanol, which was dehydrated with alumina. Huls also reduced his synthetic ageratochromene to 6,7-dimethoxy-2,2-dimethylchroman (VIII).

EXPERIMENTAL

5,7-Dihydroxy-2,2-dimethylchromanone (I)

A mixture of phloroglucinol (2·0 g), β-hydroxyisovaleric acid (1·87 g; 1 mole) and boron fluoride-etherate (10 ml) was heated on a steam-bath for 2 min and the deep wine-red solution left at room temp overnight. The reaction mixture was then poured into water and boiled for 10 min. The yellow crystalline product proved to be a boron complex, which was decomposed by dissolving it in 10% aqueous sodium hydroxide. Acidification of the red solution gave a precipitate, which was collected and warmed with aqueous sodium carbonate. The solution was filtered to remove a small amount of insoluble material and acidified. The precipitate readily crystallized from aqueous ethanol in colourless needles (2·0 g; 65%), m.p. 198° (lit.[1] m.p. 198°). (Found: C, 63·5; H, 5·8. Calc. for $C_{11}H_{12}O_4$: C, 63·5; H, 5·6%). The substance gives a deep purple ferric colour and an orange colour with magnesium and hydrochloric acid; the latter colour reaction of chromanones does not appear to have been recorded earlier, although red to violet colourations are characteristic of flavanones. The mother liquor gave a negative hydroxamic acid test indicating the absence of a dihydrocoumarin derivative. The traces of carbonate-insoluble product also gave a purple ferric colour and negative hydroxamic acid test. The chromanone I on coupling with diazotized aniline yielded 6,8-bisbenzeneazo-5,7-dihydroxy-2,2-dimethylchromanone which was crystallized from ethanol in orange-red needles, m.p. 237°. (Found: C, 66.5; H, 5·1; N, 13·9. $C_{23}H_{20}N_4O_4$ requires: C, 66·3; H, 4·8; N, 13.5%).

6,7-Dihydroxy-2,2-dimethylchromanone (VII; R, R′ = H)

1,2,4-Triacetoxybenzene (10 g), β-hydroxyisovaleric acid (4·8 g) and boron fluoride-etherate (20 ml) were heated on a steam bath for 2 min. The clear orange-red solution was diluted with water after 16 hr, when a deep yellow crystalline complex separated. Decomposition with 5% aqueous sodium hydroxide at room temp (about 30°), acidification, purification through ether, and crystallization from dil alcohol gave colourless needles (2·5 g), m.p. 208°. (Found: C, 63·8; H, 6·2. $C_{11}H_{12}O_4$ requires: C, 63·5; H, 5·8%). The 2,4-dinitrophenylhydrazone crystallized from methanol in dark red needles, m.p. 296° (dec). (Found: C, 53·1; H, 4·2; N, 13·9. $C_{17}H_{16}O_7N_4$ requires: C, 52·6; H, 4·1; N, 14·4%).

If the red solution of the complex in aqueous sodium hydroxide was cooled in ice and neutralized to pH 4·5 with hydrochloric acid, a lemon-yellow precipitate separated, which readily crystallized from benzene in needles (4·0 g), m.p. 158°, and proved to be 7-acetoxy-6-hydroxy-2,2-dimethylchromanone. (Found: C, 62·5; H, 6·1. $C_{13}H_{14}O_5$ requires: C, 62·4; H, 5·6%). Hydrolysis with hot hydrochloric acid in acetic acid yielded 6,7-dihydroxy-2,2-dimethylchromanone, m.p. 208°.

7-Acetoxy-6-methoxy-2,2-dimethylchromanone (VII; R = Ac, R′ = H)

The monoacetate (1·0 g) in ether (30 ml) and methanol (30 ml) was treated with excess diazomethane in ether at 10° for 24 hr, and then with a few drops of acetic acid. Removal of solvent gave a pale yellow crystalline residue, which crystallized from dil methanol in pale yellow needles, m.p. 134°. (Found: C, 63.2; H, 5·8. $C_{14}H_{16}O_5$ requires: C, 63·6; H, 6·1%).

7-Hydroxy-6-methoxy-2,2-dimethylchromanone (VII; R = H, R′ = Me)

The above compound (0·4 g) was warmed on a steam-bath with 5% aqueous sodium hydroxide (15 ml) and the resulting red solution was acidified with 50% sulphuric acid. The mixture was extracted with ether and washed with water. The residue obtained after removal of the solvent was distilled at 150°/4·33 × 10^{-3} mm. The distillate crystallized from hexane in colourless needles, m.p. 81°. (Found: C, 65·0; H, 6·4; OCH_3, 14·0. $C_{12}H_{14}O_4$ requires: C, 64·9; H, 6·7; OCH_3, 14·0%). The compound readily dissolves in aqueous sodium carbonate indicating a free 7-hydroxyl group.

6,7-Dimethoxy-2,2-dimethylchromanone (VII; R, R′ = Me)

The dihydroxychromanone (0·5 g) was refluxed with acetone (30 ml), anhydrous potassium carbonate (3.0 g) and dimethyl sulphate (0·6 ml) for 17 hr. Crystallization from dil methanol gave colourless needles (0·35 g), m.p. 106° (lit.[10] m.p. 106°). (Found: OCH_3, 26·7. $C_{13}H_{16}O_4$ requires: OCH_3, 26·3%).

Colour reactions of chromanones

Although there are well-known colour reactions for flavones,[11] colour reactions with same reagents for chromanones do not appear to have been recorded and some are listed in Table 1.

TABLE 1. COLOUR REACTIONS OF 2,2-DIMETHYLCHROMANONES

Substitution	Colour reaction			
	Aqueous sodium hydroxide	Conc sulphuric acid	Magnesium hydrochloric acid	Sodium amalgam; then acid
5,7-$(OH)_2$	pale yellow	deep yellow	deep orange	orange
6,7-$(OH)_2$	deep yellow	deep yellow	wine red	red violet
6-OCH_3-7-OH	yellow	deep yellow	reddish violet	orange
6,7-$(OCH_3)_2$	yellow	deep yellow	wine red	orange

Diborane reduction of 5,7-dihydroxy-2,2-dimethylchromanone (I) *to 5,7-dihydroxy-2,2-dimethylchroman* (VI)

Tetrahydrofuran (50 ml) cooled in ice was saturated with diborane prepared by the gradual addition of a 4% sodium borohydride solution in diglyme (20 ml) to boron fluoride-etherate (5 ml), and the chromanone (1·0 g) was added to the solution. The yellow colour which developed disappeared after 2 hr. After keeping the reaction mixture at room temp for 24 hr, excess diborane was decomposed by adding acetic acid (3 ml) and the solvent distilled. The residue was diluted with water (10 ml) and extracted with ether and washed with aqueous sodium bicarbonate. Removal of the ether gave a colourless crystalline mass which was recrystallized from benzene (0·6 g; 65%), m.p. 163° (lit.[1] m.p. 162–163°). (Found: C, 68·0; H, 7·7. $C_{11}H_{14}O_3$ requires: C, 68·1; H, 7·6%).

6,7-Dimethoxy-2,2-dimethylchroman (dihydroageratochromene; VIII)

(a) *Clemmensen reduction of 6,7-dimethoxy-2,2-dimethylchromanone.* Zinc amalgam (16 g) was mixed with a solution of the chromanone (0·4 g) in ethanol (4 ml) and acetic acid (2 ml). Conc hydrochloric acid (9·2 ml) and water (6·8 ml) were added and the mixture set aside for 2 days. After refluxing for 2 hr, hydrochloric acid (15%; 4 ml) was added, and heating continued for 6 hr. Ether extraction led to a gum which readily crystallized from aqueous methanol in colourless plates (0·22 g; 60%), m.p. 60°. (Found: C, 70·7; H, 8·5. Calc. for $C_{13}H_{18}O_3$: C, 70·3; H, 8·1%). The UV spectrum showed λ_{max} 293 (ε_{max} 5100); the absorption max. reported by Alertsen is λ_{max} 293 mμ (ε_{max} 6400) and by Huls λ_{max} 294 mμ (ε_{max} 4900).

(b) *Diborane reduction of 6,7-dimethoxy-2,2-dimethylchromanone.* The chromanone (1·0 g) was dissolved in diglyme (25 ml) and through the well-cooled solution diborane gas (from 20 ml of 4% sodium borohydride in diglyme) was passed. After leaving the reaction mixture overnight at room temp, acetic acid (5 ml) was added, and the solvent distilled *in vacuo*. The residue on treating with ice water gave a colourless crystalline product which was recrystallized from aqueous methanol (0·81 g; 86%); the m.p. and mixed m.p. with the Clemmensen reduction product was 60°.

Dihydrojacareubin (V; R = H)

5,7-Dihydroxy-2,2-dimethylchroman (VI; 1·0 g) and pyrogallol-α-carboxylic acid (1·4 g) were mixed with phosphorus oxychloride (20 ml) and freshly fused zinc chloride (5 g) in a current of carbon

[11] K. Venkataraman in *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman) p. 72. Pergamon Press, London (1962).

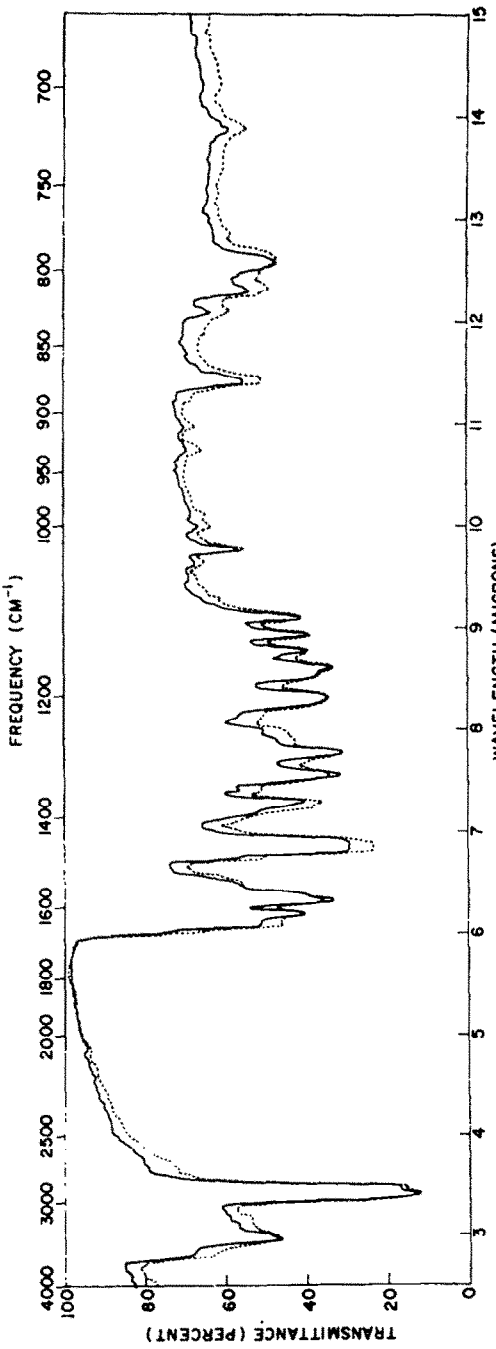


FIG. 1. IR spectrum of the dihydroderivative of natural jacareubin (———) and of synthetic dihydrojacareubin (- - - - - - -) in paraffin mull.

dioxide and stirred for 1 hr at room temp and at 75° for 2½ hr. The deep red mixture was poured into ice, and the precipitate collected, washed with aqueous sodium bicarbonate, and extracted with ethyl acetate. Removal of the solvent gave a pale yellow solid (0·5 g) which was sublimed initially at 170° at $7·7 \times 10^{-3}$ mm. The colourless sublimate (50 mg) containing pyrogallol and unreacted chroman was discarded. Subsequent sublimation at 300° and $7·7 \times 10^{-3}$ mm press, followed by crystallization of the sublimate from methanol, gave pale yellow needles (0·34 g), m.p. 245° (dec). The compound was dried at 170° for 24 hr at 0·05 mm and analysed. (Found: C, 65·7; H, 5·4. $C_{18}H_{16}O_6$ requires: C, 65·9; H, 4·9%). The mixed m.p. with dihydrojacareubin was undepressed. The substance gives a green ferric colour and an orange-red colour with magnesium and hydrochloric acid. The UV spectra of both natural and synthetic dihydrojacareubin showed maxima at 251, 284, 330 mμ (ε_{max} log 4·55, 4·05, 4·24). The IR spectra of the natural and synthetic samples were superposable. The UV spectra were determined in ethanol using Beckman DK-2 recording spectrophotometer, and the IR spectra in paraffin mull on a Perkin-Elmer 221 with NaCl optics.

Dihydrojacareubin dimethyl ether (V; R = Me)

Synthetic dihydrojacareubin (73·2 mg) in methanol (3 ml) was treated with excess of diazomethane in ether, and after 24 hr the mixture was decomposed with a few drops of acetic acid. Removal of the solvent gave a pale yellow residue, which crystallized from methanol in pale yellow needles (55 mg), m.p. 139°, which is the m.p. of the dimethyl ether of the natural product recorded by King.[5] The compound gives a deep green ferric colour.

Acknowledgement—We are indebted to Professor F. E. King, F.R.S., for a sample of dihydrojacareubin, to Mr. V. S. Pansare and Mr. V. N. Mulay for the microanalyses, and Mr. T. K. K. Srinivasan for the IR spectra recorded in the paper.