

686. *The Synthesis of 8-isoAmyl-5-hydroxy-7-methoxy-2 : 2-dimethylchroman, a Degradation Product of Osajin and Pomiferin.*

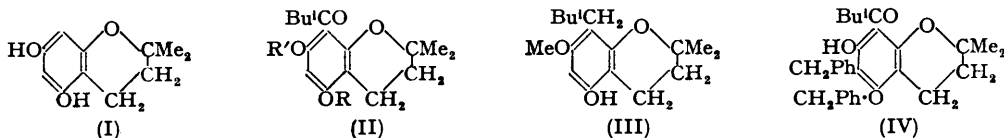
By E. K. PIERPOINT, ALEXANDER ROBERTSON, and W. B. WHALLEY.

Prepared from *isobutyl* cyanide and 5 : 7-dihydroxy-2 : 2-dimethylchroman (I), the 8-*isovaleroyl* compound (II; R = R' = H) was converted by successive monobenylation and methylation into the 5-benzyloxy- (II; R = CH₂Ph, R' = H) and the 5-benzyloxy-7-methoxy- (II; R = CH₂Ph, R' = Me) chroman, respectively. Reduction of the latter, followed by debenylation furnished 8-*isoamyl*-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III), identical with a degradation product of osajin and pomiferin.

By the hydrolytic fission of tetrahydro-osajin dimethyl ether and of tetrahydropomiferin trimethyl ether, Wolf from *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 406) obtained small amounts of a compound which they characterised as the 3 : 5-dinitrobenzoate, and considered to be 8-*isoamyl*-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III).

In an investigation on chromans (unpublished work) we had occasion to prepare 5 : 7-dihydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (II; R = R' = H) and from this compound have now synthesised the degradation product (III).

The application of the Hoesch ketone synthesis to 5 : 7-dihydroxy-2 : 2-dimethylchroman (I) with *isobutyl cyanide* gave predominantly the 8-*isovaleroyl*chroman (II; R = R' = H), together with a small quantity of the isomeride, 5 : 7-dihydroxy-2 : 2-dimethyl-6-*isovaleroyl*-



chroman (cf. the use of methyl cyanide in this reaction by Backhouse and Robertson, *J.*, 1939, 1257). Benzylation of (II; R = R' = H) gave rise to a monobenzyl ether, having a positive ferric reaction, together with small amounts of a compound which is regarded as the *C*-benzylated derivative (IV). Methylation of the monobenzyl ether followed by debenylation of the product furnished a monomethyl ether readily soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction. Consequently, by analogy with 5 : 7-dihydroxy-8- β -phenylpropionylchroman (Backhouse and Robertson, *loc. cit.*), it is clear that the parent ketochroman has the structure (II; R = R' = H) now assigned and hence its *O*-monomethyl derivative is 5-hydroxy-7-methoxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (II; R = H; R' = Me). The isomeride formed in small quantity with (II; R = R' = H) is, therefore, 5 : 7-dihydroxy-2 : 2-dimethyl-6-*isovaleroyl*chroman.

Attempts to reduce the methyl ether (II; R = H, R' = Me) by Clemmensen's method were unsuccessful and only amorphous products were obtained. By the same method, however, 5-benzyloxy-7-methoxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (II; R = CH₂Ph, R' = Me) gave 8-*isoamyl*-5-benzyloxy-7-methoxy-2 : 2-dimethylchroman and on debenylation this compound furnished 8-*isoamyl*-5-hydroxy-7-methoxy-2 : 2-dimethylchroman (III), which was characterised by the formation of the 3 : 5-dinitrobenzoate, identical in every way (including the infra-red absorption spectra) with a natural specimen kindly provided by Professor M. L. Wolfrom.

EXPERIMENTAL.

5 : 7-Dihydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (II; R = R' = H).—A solution of *isobutyl cyanide* (1.5 g.) and 5 : 7-dihydroxy-2 : 2-dimethylchroman (Bridge, Heyes, and Robertson, *J.*, 1937, 279) (3 g.) in ether (60 ml.), containing powdered zinc chloride (2.5 g.), was saturated at 0° with hydrogen chloride, and 5 days later the crystalline ketimine complex was isolated. The combined product from five experiments was heated on the steam-bath for 5 hours with water (50 ml.) and after the aqueous layer had been decanted the brown semi-solid residue was washed with ether, giving a colourless solid, m. p. 286° (decomp.); a further small quantity of this product was deposited by the cooled aqueous extract. A solution of this compound (6 g.) in a mixture of water (100 ml.) and ethanol (40 ml.) was heated under reflux for 5½ hours, the cooled hydrolysate was repeatedly extracted with ether, the dried extracts were evaporated, and the residual gum was crystallised from light petroleum (b. p. 60–80°), giving 5 : 7-*dihydroxy*-2 : 2-*dimethyl*-8-*isovaleroyl*chroman (3 g.) in pale greenish-yellow plates, m. p. 138° (Found : C, 68.8; H, 8.2. C₁₈H₂₂O₄ requires C, 69.1; H, 7.9%). This compound, which gives an intense dark violet coloration with alcoholic ferric chloride, is readily soluble in methanol, ethanol, ethyl acetate, benzene, or 1% aqueous sodium hydroxide, and almost insoluble in cold petroleum or water. It does not form an oxime or 2 : 4-dinitrophenylhydrazone under the usual conditions.

Evaporation of the ethereal washings of the crude ketimine complex, and purification of the residue from light petroleum (80–100°), gave a small and variable yield of 5 : 7-*dihydroxy*-2 : 2-*dimethyl*-6-*isovaleroyl*chroman in almost colourless needles, m. p. 144–145° (Found : C, 68.9; H, 7.9%). An ethanolic solution of this ketone exhibited a purple coloration with ferric chloride, and a mixture with the isomeric ketone had m. p. 110°.

5-Benzyloxy-7-hydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman.—Prepared by the interaction of 5 : 7-dihydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (2 g.), benzyl bromide (1.3 g.), and anhydrous potassium carbonate (3 g.) in boiling acetone (100 ml.) during 2 hours and purified by fractional crystallisation from methanol, 5-benzyloxy-7-hydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (1.4 g.) was obtained in prisms or plates, m. p. 92–93°, insoluble in 1% aqueous sodium hydroxide and having a purple ferric reaction in alcohol (Found : C, 74.8; H, 7.6. C₂₃H₂₈O₄ requires C, 75.0; H, 7.6%). The impurity associated with this ether was much less soluble in methanol and appeared to be 6-benzyloxy-5-benzyloxy-7-hydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman which separated in long, thin, pale greenish prisms, m. p. 117° (Found : C, 77.9; H, 7.2. C₃₀H₃₄O₄ requires C, 78.6; H, 7.4%). This compound was readily soluble in cold light petroleum (b. p. 60–80°), and gave an olive green ferric reaction in alcohol.

5-Hydroxy-7-methoxy-2 : 2-dimethyl-8-*isovaleroyl*chroman.—Prepared by the interaction of 5-benzyloxy-7-hydroxy-2 : 2-dimethyl-8-*isovaleroyl*chroman (2 g.), excess of methyl iodide, and potassium carbonate (3 g.) in boiling acetone (100 ml.) during 60 hours, 5-benzyloxy-7-methoxy-2 : 2-dimethyl-8-*isovaleroyl*chroman separated from aqueous methanol in rectangular prisms (1.9 g.), m. p. 90–91°, soluble in the usual organic solvents except light petroleum, insoluble in 2*N*-sodium hydroxide, and having a negative ferric reaction in alcohol (Found : C, 75.1; H, 7.5. C₂₄H₂₈O₄ requires C, 75.4; H, 7.9%).

A solution of the foregoing keto-chroman (1 g.) in acetic acid (60 ml.), containing a palladium-charcoal catalyst (from 1 g. of charcoal and 20 ml. of 1% aqueous palladium chloride), was shaken with hydrogen until the absorption of gas had ceased (*ca.* 20 minutes). On isolation the resulting 5-hydroxy-7-methoxy-2:2-dimethyl-8-isovaleroylchroman (0.6 g.) formed small needles, m. p. 142–143°, from dilute methanol, readily soluble in 1% aqueous sodium hydroxide and having a negative ferric reaction in alcohol (Found: C, 69.9; H, 7.9. $C_{17}H_{24}O_4$ requires C, 69.9; H, 8.2%).

8-isoAmyl-5-hydroxy-7-methoxy-2:2-dimethylchroman.—A mixture of 5-benzyloxy-7-methoxy-2:2-dimethyl-8-isovaleroylchroman (0.5 g.), zinc amalgam (12 g.), hydrochloric acid (8 ml.), water (12 ml.), and toluene (20 ml.) was heated under reflux for 5 hours, the toluene layer was separated, and the aqueous liquors were extracted with ether. Evaporation of the combined toluene-ether solution gave 8-isoamyl-5-benzyloxy-7-methoxy-2:2-dimethylchroman (0.4 g.) which separated from methanol in hexagonal plates, m. p. 59–60° (Found: C, 77.9; H, 9.0. $C_{24}H_{32}O_3$ requires C, 78.3; H, 8.7%). This chroman (1.5 g.) was debenzylated with hydrogen and a palladium-charcoal catalyst (from 1 g. of charcoal and 20 ml. of 1% palladium chloride solution) in acetic acid. Evaporation of the filtered solution left a colourless gum which, on crystallisation from light petroleum (60–80°), gave 8-isoamyl-5-hydroxy-7-methoxy-2:2-dimethylchroman in plates (*ca.* 0.6 g.), m. p. 86°, having a negative ferric reaction in alcohol (Found: C, 73.5; H, 9.2. Calc. for $C_{17}H_{24}O_3$: C, 73.4; H, 9.4%). Prepared by the pyridine method, the 3:5-dinitrobenzoate separated from aqueous ethanol in golden leaflets, m. p. 131°, identical with the natural specimen (Found: C, 61.0; H, 5.9; N, 5.9. Calc. for $C_{24}H_{28}O_8N_2$: C, 61.1; H, 6.0; N, 6.0%).

UNIVERSITY OF LIVERPOOL.

[Received, August 8th, 1951.]