266. *Rottlerin. Part III.*

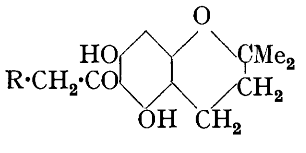
By Thomas Backhouse and Alexander Robertson.

The condensation of 5 : 7-dihydroxy-2 : 2-dimethylchroman with acetonitrile and with β-phenylpropionitrile by the method of Hoesch gave rise to pairs of isomeric ketones, (I, R = H) and (II, R = H) and (I, R = CH_2Ph) and (II, R = CH_2Ph) respectively, the orientations of which have been established. Interaction of the chroman with acetyl chloride in the presence of aluminium chloride gave only the ketone (I, R = H).

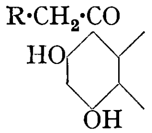
Tetrahydrorottlerone is not identical with either (I, R = CH_2Ph) or (II, R = CH_2Ph).

On the basis of the available analytical evidence it was suggested in Part II (J., **1938**, 309; compare Brockmann and Maier, *Annalen*, 1938, **535**, 149) that tetrahydrorottlerone had either formula (I, R = CH_2Ph) or (II, R = CH_2Ph), of which the former was preferred, and it seemed highly desirable that decisive synthetical evidence on this question should be obtained.

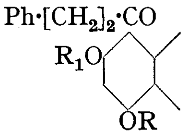
Attempts to effect a synthesis of the dimethyl ether of (I, R = CH_2Ph) by the action of β-phenylethylmagnesium bromide on 6-*cyano*-5 : 7-*dimethoxy*-2 : 2-*dimethylchroman* gave unsatisfactory results, but in the course of a study on the synthesis of ketonic derivatives of 5 : 7-dihydroxy-2 : 2-dimethylchroman it has been found that the condensation of the latter with acetonitrile according to the method of Hoesch gave rise to (II, R = H) along with smaller amounts of (I, R = H); the ketone (I, R = H) appears to be the only product formed by the condensation of the chroman with acetyl chloride by the Friedel–Crafts method. When acetonitrile was replaced by β-phenylpropionitrile in the Hoesch reaction, 5 : 7-*dihydroxy*-6-β-*phenylpropionyl*- (I, R = CH_2Ph) and 5 : 7-*dihydroxy*-8-β-*phenylpropionyl*-2 : 2-*dimethylchroman* (II, R = CH_2Ph) were obtained. These compounds in some respects resembled tetrahydrorottlerone, but direct comparison showed that neither was identical with the natural derivative, a result which was confirmed by comparison of the respective dimethyl ethers. Consequently the structures suggested for rottlerone and its tetrahydro-derivative (Part II, *loc. cit.*) can no longer be maintained.



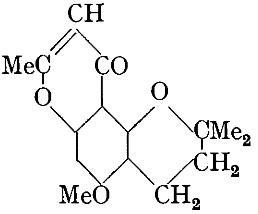
(I.)



(II.)



(III.)



(IV.)

The orientation of the ketone (II, R = CH_2Ph) depends on the following results: Unlike the isomeride (I, R = CH_2Ph), the compound (II, R = CH_2Ph) is readily soluble in 1% aqueous sodium hydroxide, indicating that it contains a hydroxyl group in the *p*-position to the carbonyl group. On alkylation (II, R = CH_2Ph) readily forms a *monomethyl* (III, R = Me; R_1 = H) and a *monobenzyl* ether (III, R = CH_2Ph; R_1 = H), which are insoluble in 1% aqueous sodium hydroxide and give strong ferric reactions in alcohol, thus indicating that in these derivatives there is a free hydroxyl in the *o*-position to the carbonyl group. Methylation of (III; R = Me, R_1 = H) and (III; R = CH_2Ph, R_1 = H) gave rise to the ethers (III; R = Me, R_1 = Me) and (III; R = CH_2Ph, R_1 = Me) respectively and on debenzylation by the catalytic method the last substance (III; R = CH_2Ph, R_1 = Me) yielded the *ether* (III; R = H, R_1 = Me), which in agreement with the orientation assigned to it is readily soluble in dilute aqueous sodium hydroxide and has a negative ferric reaction. On the other hand the ketone (I, R = CH_2Ph) does not appear to be very reactive towards methylating agents, but by the methyl sulphate–potassium carbonate method the dimethyl ether was obtained as an oil, conveniently characterised by the formation of the *oxime*. In this connexion it may be noted that, whilst two isomeric monomethyl ethers of the ketone (I, R = CH_2Ph) are possible neither derivative would be expected to be easily soluble in dilute aqueous alkalis and both would give strong ferric reactions.

By the procedure employed in the case of (II, R = CH_2Ph) the ketone (II, R = H) gave rise to 7-*hydroxy*-5-*methoxy*-8-*acetyl*-2 : 2-*dimethylchroman*, which closely resembled (III; R = Me, R_1 = H) in its behaviour towards 1% aqueous sodium hydroxide and alcoholic ferric chloride and on condensation with ethyl acetate by means of sodium yielded 7-hydroxy-5-methoxy-8-acetoacetyl-2 : 2-dimethylchroman, which on cyclisation in the usual manner gave rise to the chromano-γ-pyrone (IV). The orientation of the ketone (II, R = H) is also supported by the fact that on condensation with benzaldehyde in alkaline solution it furnished 5 : 7-*dihydroxy*-8-*cinnamoyl*-2 : 2-*dimethylchroman*, which on hydrogenation readily yielded the ketone (II, R = CH_2Ph).

EXPERIMENTAL.

Condensation of 5 : 7-*Dihydroxy*-2 : 2-*dimethylchroman with Acetonitrile*.—A solution of the chroman (Robertson and co-workers, J., 1937, 285) (2 g.) and acetonitrile (1 g.) in absolute ether (75 c.c.) containing powdered zinc chloride (2 g.) was saturated with hydrogen chloride and 6 days later more ether (20 c.c.) was added, the solvent decanted, and the solid (wash with ether) hydrolysed with water (100 c.c.) on the steam-bath for ½ hour and then under reflux for ½ hour, yielding a light brown oil which gradually solidified. The material, m. p. about 138°, obtained by crystallisation of this product from benzene appeared to be a mixture which could not be conveniently separated by crystallisation from solvents and was completely soluble in 1% aqueous sodium hydroxide. Samples of the two ketones were obtained in the first instance by manual separation of the large crystals formed by slow crystallisation of the material, m. p. 138°, from methyl alcohol, but the following method was ultimately found to be satisfactory. The crude reaction product from 2 g. of chroman was heated to boiling with benzene (15—20 c.c.) on the steam-bath, the extract immediately decanted, and the residue crystallised from benzene and then repeatedly from dilute methyl alcohol, yielding 5 : 7-*dihydroxy*-6-*acetyl*-2 : 2-*dimethylchroman* (I, R = H) in straw-coloured squat prisms (0·21 g.), m. p. 229°, soluble in ethyl acetate or alcohol and having a purple-violet ferric reaction in alcohol (Found in material dried in a high vacuum at 80° : C, 66·0; H, 7·0. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%). On being refluxed for 10 minutes, a solution of the ketone in alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride gave the 2 : 4-*dinitrophenylhydrazone*, which separated from dilute alcohol in dark red needles, m. p. 227·5° (Found : N, 13·7. $C_{19}H_{20}O_7N_4$ requires N, 13·5%).

Evaporation of the benzene liquors from the purification of the foregoing ketone left a residue which on recrystallisation from a little methyl alcohol and then from aqueous methyl alcohol gave 5 : 7-*dihydroxy*-8-*acetyl*-2 : 2-*dimethylchroman* (II, R = H) in clusters of pale yellow, elongated, rectangular prisms (1·3 g.), m. p. 150°, having a purple-violet ferric reaction in alcohol (Found in material dried in a high vacuum at 80° : C, 66·2; H, 6·9%). The 2 : 4-*dinitrophenylhydrazone* formed red prisms, m. p. 228·5°, from dilute alcohol (Found : N, 13·1%).

The ketone (I, R = H) was also formed when acetyl chloride (1·5 g.) was added dropwise to a solution of 5 : 7-dihydroxy-2 : 2-dimethylchroman (3·6 g.) and aluminium chloride (7 g.) in nitrobenzene (53 g.) maintained at room temperature, and the reaction mixture treated with ice 2 days later. After removal of the nitrobenzene with steam the compound was isolated from the residual liquor with ether and crystallised from benzene and then dilute alcohol (charcoal), forming pale yellow prisms, m. p. and mixed m. p. 229°.

7-*Hydroxy*-5-*methoxy*-8-*acetyl*-2 : 2-*dimethylchroman.*—A mixture of 5 : 7-dihydroxy-8-acetyl-2 : 2-dimethylchroman (1 g.), potassium carbonate (2·5 g.), methyl iodide (2·2 c.c.), and acetone (30 c.c.) was refluxed for 1 hour, filtered (wash potassium salts with acetone), and evaporated in a vacuum. On being triturated with water and then crystallised from dilute alcohol, the resulting *ether* formed pale yellow, elongated, rectangular prisms, m. p. 78°, which gave a brownish-purple ferric reaction in alcohol [Found : C, 67·2; H, 7·2; OMe, 12·5. $C_{13}H_{15}O_3(OMe)$ requires C, 67·2; H, 7·3; OMe, 12·4%].

A solution of this ether (2 g.) in ethyl acetate (25 c.c.), containing sodium (2 g., in thin slices), was heated on the steam-bath for 5½ hours; after 2½ hours more sodium (2 g.) was added. After the addition of a little methyl alcohol to destroy traces of sodium the cooled mixture was diluted with excess of water and acidified with acetic acid. The resulting diketone, which separated from a small volume of light petroleum in short prisms, m. p. about 100°, could not be economically purified and was cyclised by being boiled with a mixture of alcohol (10 c.c.) and concentrated hydrochloric acid (0·5 c.c.) for 5 minutes. The alcoholic solution was diluted with water and next day the crystalline product was collected and thoroughly extracted with 10% aqueous sodium hydroxide to remove traces of unchanged 7-hydroxy-5-methoxy-8-acetyl-2 : 2-dimethylchroman, washed, dried, and twice sublimed in a high vacuum at 135—140°, giving 5′-*methoxy*-2 : 2′ : 2′-*trimethylchromano*-8′ : 7′ : 5 : 6-γ-*pyrone* (IV) in colourless squat prisms which on recrystallisation from light petroleum (b. p. 60—80°) had m. p. 168° and had a negative ferric reaction [Found : C, 70·1; H, 6·6; OMe, 11·8. $C_{15}H_{15}O_3(OMe)$ requires C, 70·1; H, 6·6; OMe, 11·3%]. Interaction of the chromone (0·15 g.) with excess of piperonal in alcoholic sodium ethoxide (from 10 c.c. of alcohol and 0·2 g. of sodium) in the water-bath for 2 hours gave the styryl derivative, which separated from the reaction mixture on the addition of water and formed pale straw-coloured needles, m. p. 224° with slight sintering at 215°, from dilute alcohol and then alcohol.

5 : 7-*Dihydroxy*-8-*cinnamoyl*-2 : 2-*dimethylchroman.*—A solution of 5 : 7-dihydroxy-8-acetyl-2 : 2-dimethylchroman (1 g.) and benzaldehyde (1·5 g.) in alcohol (10 c.c.) was mixed with 50% aqueous potassium hydroxide, kept at 50° for 15 minutes and then at room temperature for 24 hours, diluted with water, and acidified with acetic acid. The resulting oil gradually solidified on being triturated with water and, on being crystallised from much light petroleum (b. p. 80—100°) and then from benzene, gave the *chalkone* in orange-red prisms, m. p. 176—177°, soluble in alcohol, chloroform, or acetone and having a dark brown ferric reaction in alcohol (Found : C, 74·0; H, 6·2. $C_{20}H_{20}O_4$ requires C, 74·0; H, 6·2%). Concentration of the filtrates left on purifying this compound gave a small amount of unchanged acetochroman in addition to a little impure chalkone.

Hydrogenation of the chalkone (0·5 g.), dissolved in alcohol (25 c.c.), with hydrogen (approx. 1 mol. absorbed) and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·1 g. of palladium chloride) was complete in ½ hour, and gave an almost quantitative yield of 5 : 7-*dihydroxy*-8-β-*phenylpropionyl*-2 : 2-*dimethylchroman* (II, R = CH_2Ph), which formed pale yellow plates, m. p. 172°, from aqueous alcohol, giving a purple-violet coloration with alcoholic ferric chloride (Found : C, 73·8; H, 7·0. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

Interaction of the ketone (I, R = H) with benzaldehyde in alkaline solution invariably gave rise to a pale yellow, amorphous product which was insoluble in dilute aqueous sodium hydroxide.

Condensation of β-Phenylpropionitrile and 5 : 7-Dihydroxy-2 : 2-dimethylchroman.—Interaction of the chroman (2 g.) and nitrile (Henley and Turner, J., 1931, 1183) (1·5 g.) in ether (100 c.c.) containing zinc chloride (3 g.) and excess of hydrogen chloride gave rise to a mixture of ketimine hydrochlorides, which was collected 6 days later, washed with ether, and hydrolysed with water (100 c.c.) on the water-bath for ½ hour and then under reflux for 4 hours. The product was thoroughly extracted with an excess of 1% aqueous sodium hydroxide, and the filtered extract acidified with dilute hydrochloric acid, giving 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman, which separated from dilute alcohol in pale yellow plates (1·8 g.), m. p. 172°, identical with a specimen prepared from the foregoing chalkone (Found : C, 73·5; H, 6·9%). This ketone did not form a 2 : 4-dinitrophenylhydrazone. Mixed with tetrahydrorottlerone, m. p. 173°, it melted at about 155°.

Crystallised from dilute alcohol, the well-washed, alkali-insoluble solid gave 5 : *7-dihydroxy-6-β-phenylpropionyl-2 : 2-dimethylchroman* in colourless needles (0·3 g.), m. p. 171°; this was soluble in benzene or methyl alcohol and gave a purple-violet ferric reaction in alcohol, but did not form a 2 : 4-dinitrophenylhydrazone under the usual conditions (Found: C, 73·6; H, 6·9%). Mixed with tetrahydrorottlerone, it melted at about 163°. Methylation of this ketone (0·5 g.) was effected with methyl sulphate (3 c.c.) and potassium carbonate (8 g.) in boiling acetone (38 c.c.) in the course of 9 hours; after 2 hours more sulphate (1·5 c.c.) and carbonate (2·5 g.) were added. The mixture was diluted with water (200 c.c.) and next day the product was isolated with ether as an oil, which would not crystallise or form a 2 : 4-dinitrophenylhydrazone. A solution of the substance (0·4 g.) and hydroxylamine (0·4 g.) in pyridine (4 c.c.) was heated on the steam-bath for 10 hours, cooled, and diluted with water. On being triturated with dilute acetic acid and then with water, the resulting *oxime* of the dimethyl ether gradually solidified and then separated from aqueous alcohol in colourless prisms, m. p. 129·5° [Found : C, 71·6; H, 7·3; N, 4·1; OMe, 16·6. $C_{20}H_{21}O_2N(OMe)_2$ requires C, 71·5; H, 7·4; N, 3·8; OMe, 16·8%].

7-Hydroxy-5-methoxy- (III; R = Me, R_1 = H) *and 5-Hydroxy-7-methoxy-8-β-phenylpropionyl-2 : 2-dimethylchroman* (III; R = H, R_1 = Me).—A mixture of the ketone (II, R = CH_2Ph) (1 g.), methyl iodide (0·4 c.c.), potassium carbonate (2 g.), and acetone (35 c.c.) was refluxed for 1 hour, the potassium salts (wash with acetone) removed by filtration, the filtrate evaporated in a vacuum, and the residue triturated with water. Crystallisation of the resulting solid (0·85 g.) from alcohol gave *7-hydroxy-5-methoxy-8-β-phenylpropionyl-2 : 2-dimethylchroman* in colourless plates, m. p. 104°, insoluble in 1% aqueous sodium hydroxide and having a brownish-violet ferric reaction in alcohol [Found: C, 74·1; H, 7·0; OMe, 10·4. $C_{20}H_{21}O_3(OMe)$ requires C, 74·1; H, 7·1; OMe, 9·1%]. Attempts to cyclise this compound with sodium acetate and acetic anhydride or to condense it with ethyl acetate by means of sodium were unsuccessful.

The corresponding *benzyl* ether (III; R = CH_2Ph, R_1 = H) was similarly prepared from the ketone (1 g.), benzyl bromide (0·6 c.c.), and potassium carbonate (1·5 g.) in the course of 1½ hours and formed colourless prisms (1·1 g.), m. p. 112—113°, from alcohol, insoluble in 1% aqueous sodium hydroxide and having a brownish-purple ferric reaction (Found: C, 77·8; H, 6·8. $C_{27}H_{28}O_4$ requires C, 77·8; H, 6·8%).

Methylation of 7-hydroxy-5-methoxy-8-β-phenylpropionyl-2 : 2-dimethylchroman (0·5 g.) with excess of methyl iodide and potassium carbonate in boiling acetone (30 c.c.) in the course of 20 hours gave 5 : *7-dimethoxy-8-β-phenylpropionyl-2 : 2-dimethylchroman*, which separated from light petroleum (b. p. 40—60°) in colourless prisms (0·4 g.), m. p. 74° [Found : C, 74·5; H, 7·4; OMe, 17·4. $C_{20}H_{20}O_2(OMe)_2$ requires C, 74·5; H, 7·4; OMe, 17·5%].

Methylation of the benzyl ether (1 g.) with excess of methyl iodide and potassium carbonate in boiling acetone (40 c.c.) was complete in about 20 hours and on isolation the *product* (III; R = CH_2Ph, R_1 = Me) separated from aqueous alcohol and then light petroleum (b. p. 40—60°) in colourless needles (0·6 g.), m. p. 67·5°, having a negative ferric reaction in alcohol [Found : C, 78·1; H, 7·0; OMe, 9·1. $C_{27}H_{27}O_3(OMe)$ requires C, 78·1; H, 7·0; OMe, 7·2%]. Debenzylation of this compound (1 g.), dissolved in acetic acid (50 c.c.), was effected with hydrogen (approx. 1 mol. absorbed) and a palladium–charcoal catalyst (from 1 g. of charcoal and 0·2 g. of palladium chloride) in the course of ½ hour and on isolation the resulting *5-hydroxy-7-methoxy-8-β-phenylpropionyl-2 : 2-dimethylchroman* formed colourless plates (0·7 g.), m. p. 158°, readily soluble in dilute aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 74·2: H, 7·1; OMe, 9·5%).

(With ALFRED B. PERCIVAL.) 6-*Cyano*-5 : 7-*dimethoxy*-2 : 2-*dimethylchroman*.—Oximation of 5 : 7-dimethoxy-6-formyl-2 : 2-dimethylchroman (Robertson and Subramaniam, J., 1937, 286) with hydroxylamine in aqueous alcoholic sodium carbonate gave an almost theoretical yield of the *oxime*, which formed small prisms, m. p. 184°, from light petroleum (b. p. 60—80°) (Found : N, 5·4. $C_{14}H_{19}O_4N$ requires N, 5·3%). Dehydration of this compound (1 g.) with acetic anhydride (10 c.c.) during 1½ hours on the steam-bath and subsequent decomposition of the excess of anhydride with water yielded the *nitrile*, which separated from alcohol in colourless plates (0·65 g.), m. p. 126—127°, moderately soluble in benzene or ethyl acetate and sparingly soluble in light petroleum (Found : N, 5·8. $C_{14}H_{17}O_3N$ requires N, 5·7%).

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