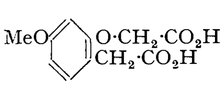
325. *Experiments on the Synthesis of Rotenone and its Derivatives. Part XV.*

By James H. Richards, Alexander Robertson, and Joseph Ward.

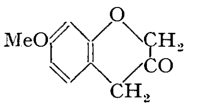
The synthesis of 7- and 8-methoxychroman-3-one by the cyclisation of acids of the type (I) is described.

Condensation of β-chloropropionyl chloride and resorcinol by means of aluminium chloride gave ω-chlororespropiophenone and a compound believed to be ω-hydroxyrespropiophenone, but, when crotonyl chloride was used, 7-hydroxy-2-methylchroman-4-one (VI) was obtained together with a hydroxy-ketone (VII) which on cyclisation gave (VI).

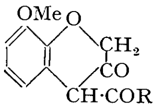
The method developed for the synthesis of chromeno(3′ : 4′ : 2 : 3)chromones of the dehydrorotenone type (Part III, *J.*, 1933, 489), involving the application of the Hoesch reaction in the preparation of intermediate keto-acids of the derrisic acid type, is limited with regard to the phenols which can be employed, *e.g.*, methyl 3-methoxy-2-cyanomethylphenoxyacetate fails to condense with tubanol or dihydrotubanol, whilst with 5 : 7-dihydroxy-2 : 2-dimethylchroman the acyl group enters the 8-position of the chroman residue and not the required 6-position (unpublished results from this laboratory). Accordingly, in the course of a search for suitable alternate routes to the required chromenochromones we prepared examples of the hitherto unknown chroman-3-ones with a view to condensing them with suitably protected ethyl *o*-hydroxybenzoates in order to obtain compounds of the type (III) which would be expected to undergo cyclisation to chromano(3′ : 4′ : 2 : 3)chromones.



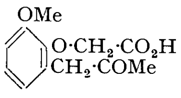
(I.)



(II.)



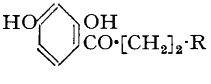
(III.)



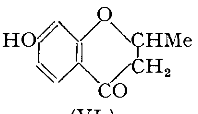
(IV.)

Cyclisation of 5-methoxy-2-carboxymethylphenoxyacetic acid (I) with boiling acetic anhydride containing sodium acetate gave the O-*acetyl* derivative of the enolic form of (II) which on deacetylation furnished the *chroman*-3-*one* (II). When subjected to similar treatment, 2-methoxy-6-carboxymethylphenoxyacetic acid yielded a mixed product which was resolved into 8-*methoxychroman*-3-*one* and a C-*acetyl* derivative considered to be (III; R = Me) since it gave a strong ferric reaction and on hydrolysis a *keto-acid* believed to have formula (IV). Attempts to condense 7- or 8-methoxychroman-3-one with ethyl benzoate or ethyl *o*-benzyloxybenzoate under a variety of conditions were unsuccessful; only small amounts of indefinite products were obtained.

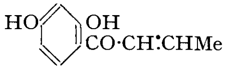
In connection with the synthesis of hydroxy-2 : 2-dimethylchroman-4-ones (Parts XII and XIII, *J.*, 1937, 279, 1530) by the Friedel–Crafts route, the condensation of β-chloropropionyl and of crotonyl chloride with resorcinol under the same conditions has been examined. ω-*Chlororespropiophenone* (V; R = Cl) and a substance which appears to be ω-*hydroxyrespropiophenone* (V; R = OH) were isolated from the resinous product formed in the condensation with β-chloropropionyl chloride, but formation of 7-hydroxychromanone or the isomeric coumaranone did not appear to take place.



(V.)



(VI.)



(VII.)

On the other hand crotonyl chloride gave 7-*hydroxy*-2-*methylchroman*-4-*one* (VI) together with a ketone which in all probability has formula (VII) since on cyclisation it is quantitatively converted into the isomeric chroman-4-one. That the latter is the chroman-4-one and not the isomeric 6-hydroxy-2-ethylcoumaranone is proved by the fact that the *methyl ether* readily condenses with *o*-vanillin giving 7′ : 8-dimethoxy-2′-methylchromeno(4′ : 3′ : 2 : 3)benzopyrylium chloride which was characterised by the formation of the *perchlorate* and the *ferrichloride*.

7 : 8-*Dihydroxy*-2 : 2-*dimethylchroman*-4-*one* was prepared by the general method but could not be reduced to the corresponding chroman by Clemmensen's procedure.

EXPERIMENTAL.

7-*Methoxychroman*-3-*one* (II).—A mixture of 5-methoxy-2-carboxymethylphenoxyacetic acid (Robertson *et al.*, *J.*, 1936, 422) (5 g.), sodium acetate (7 g.), and acetic anhydride (20 ml.) was gently refluxed for 20 minutes, cooled, and treated with water. 2 Days later the solid (4·3 g.) was collected, washed, dried, and crystallised from light petroleum (b. p. 60—80°), yielding 7-*methoxy*-3-*acetoxy*-Δ^3-*chromen* in colourless rectangular prisms (3 g.), m. p. 97°, soluble in alcohol, benzene, or ethyl acetate, and having a negative ferric reaction (Found : C, 65·7; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). 8% Aqueous sodium hydroxide (100 ml.) was added to a solution of this compound (2 g.) in alcohol (150 ml.) kept at 15°, and 10 minutes later the red solution was acidified with hydrochloric acid and extracted with ether (10 × 100 ml.). After having been washed with aqueous sodium hydrogen carbonate (2 × 200 ml.) and water (2 × 200 ml.) and then dried, the combined extracts were evaporated, leaving a red-brown oil which slowly solidified and was triturated with a little ether. Crystallisation of the resulting solid from benzene gave the *chroman*-3-*one* (II) in diamond-shaped plates (1·1 g.), m. p. 163°, insoluble in cold aqueous sodium hydroxide and having a negative ferric reaction (Found : C, 67·7; H, 5·7. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The 2 : 4-*dinitrophenylhydrazone* formed orange prisms, m. p. 186°, from alcohol (Found : N, 15·2. $C_{16}H_{14}O_4N_4$ requires N, 15·6%).

8-*Methoxychroman*-3-*one*.—Cyclisation of 2-methoxy-6-carboxymethylphenoxyacetic acid (20 g.) by the procedure employed in the case of 5-methoxy-2-carboxymethylphenoxyacetic acid gave a viscous oil (11 g.), b. p. 128°/0·8 mm., which was dissolved in 2·5% methyl-alcoholic sodium hydroxide (80 ml.) kept at 0°. 5 Minutes later the mixture was acidified with 10% acetic acid and extracted with ether, and the dried ethereal extracts evaporated, leaving the product as a pale yellow oil which partly solidified and was repeatedly extracted with light petroleum (b. p. 60—80°). Evaporation of the combined extracts left crystalline material (8·4 g.) with a purple ferric reaction which appeared to be a mixture and was repeatedly triturated with saturated aqueous sodium hydrogen carbonate until a sample did not give a ferric reaction. Crystallised from light petroleum (b. p. 60—80°), the residual solid (5·6 g.) gave the *chroman*-3-*one* in colourless needles, soluble in alcohol, benzene, or ethyl acetate (Found : C, 67·6; H, 5·6. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). The 2 : 4-*dinitrophenylhydrazone* formed orange prisms, m. p. 192°, from much alcohol (Found : C, 53·5; H, 4·0; N, 15·3. $C_{16}H_{14}O_6N_4$ requires C, 53·6; H, 4·0; N, 15·6%).

Acidification of the combined aqueous sodium hydrogen carbonate washings with 10% acetic acid gave 8-*methoxy*-4-*acetylchroman*-3-*one* (III; R = Me) (2·7 g.) which separated from light petroleum (b. p. 60—80°) in hexagonal plates, m. p. 108°, exhibiting a purple ferric reaction in alcohol and giving a crystalline precipitate with alcoholic 2 : 4-dinitrophenylhydrazine hydrochloride (Found : C, 65·5; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). A solution of this chromanone derivative (1 g.) in 6% aqueous sodium hydroxide (25 ml.) was heated on the steam-bath for 45 minutes, cooled, acidified with hydrochloric acid, and extracted with ether (5 × 120 ml.). Evaporation of the combined, dried extracts left 2-*methoxy*-6-*acetoxylphenoxyacetic acid* (IV) which formed rectangular prisms, m. p. 92°, from light petroleum, having a negative ferric reaction and forming a crystalline precipitate with 2 : 4-dinitrophenylhydrazine solution [Found : C, 60·7; H, 6·0; OMe, 12·8. $C_{11}H_{11}O_4(OMe)$ requires C, 60·7; H, 5·9; OMe, 13·0%].

When the thorium salt of 2-methoxyphenoxyacetic acid (from 6 g. of acid) was gradually heated to 350° in a high vacuum a brown oil distilled at 290—320°. Evaporation of a light petroleum extract of this material left a product (0·9 g.) which partly solidified and gave the 2 : 4-dinitrophenylhydrazone (0·8 g.) of 8-methoxychroman-3-one, m. p. 192°, after purification (Found : C, 53·6; H, 4·0; N, 15·7%).

Condensation of β-Chloropropionyl Chloride with Resorcinol.—To a mixture of resorcinol (11 g.), β-chloropropionyl chloride (11·7 g.), and nitrobenzene (100 ml.), kept at room temperature, aluminium chloride (15 g.) was gradually introduced followed 5 days later by ice (100 g.) and concentrated hydrochloric acid (30 c.c.). An ethereal solution of the product and nitrobenzene was washed successively with aqueous sodium hydrogen carbonate, 4% hydrochloric acid, and water. After evaporation of the ether the nitrobenzene was removed with steam and the hot aqueous liquor decanted from viscous resin. On cooling, the liquor deposited ω-*chlororespropiophenone* (V; R = Cl), together with traces of (V; R = OH). The former ketone formed blunt prisms, m. p. 97°, from benzene–light petroleum (b. p. 60—80°), readily soluble in chloroform, alcohol, or benzene, and having an intense purple ferric reaction (Found : C, 53·8; H, 4·9; Cl, 15·1. $C_9H_9O_3Cl$ requires C, 53·8; H, 4·5; Cl, 17·7%). On being heated at 100° this substance decomposed with the evolution of hydrogen chloride.

When the condensation was effected at room temperature for 2 days and then at 130° for 2 hours, the resulting crystallisable material consisted mainly of ω-*hydroxyrespropiophenone* (V; R = OH) which formed long yellow needles, m. p. 91—92°, from dilute alcohol, having an intense purple ferric reaction and exhibiting ketonic properties (Found : C, 59·3; H, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%).

7-*Hydroxy*-2-*methylchroman*-4-*one* (VI).—Interaction of resorcinol (12 g.), crotonyl chloride (10·5 g.), and aluminium chloride (15 g.) in nitrobenzene (80 ml.) at room temperature for 4 days gave on isolation a mixture which was separated into two compounds by means of warm benzene. Crystallisation of the benzene-soluble material from alcohol gave 7-*hydroxy*-2-*methylchroman*-4-*one* in colourless plates, m. p. 177°, soluble in acetone, alcohol, or chloroform and having a negative ferric reaction (Found : C, 67·3; H, 5·7. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). This substance gave a 2 : 4-*dinitrophenylhydrazone*, forming dark red rhombic prisms, m. p. 259° (decomp.), from ethyl acetate (Found : N, 15·4 $C_{16}H_{14}O_6N_4$ requires N, 15·6%).

The compound insoluble in warm benzene was purified by sublimation in a high vacuum at 85° and obtained in yellow prisms, m. p. 117°, having an intense purple ferric reaction in alcohol and exhibiting ketonic properties (Found : C, 67·3; H, 5·6. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). On being heated to 200° this *ketone* was converted quantitatively into 7-hydroxy-2-methylchroman-4-one, m. p. 173°, identified by comparison with an authentic specimen. The same conversion was effected when the ketone (0·25 g.) was boiled with 2N-hydrochloric acid (25 ml.) containing alcohol (5 ml.) for 2 hours, and on isolation with ether the product (0·24 g.) had m. p. and mixed m. p. 177° after purification from alcohol.

Methylation of 7-hydroxy-2-methylchroman-4-one by the methyl iodide–potassium carbonate method gave the *ether* which crystallised from dilute alcohol in diamond-shaped plates, m. p. 77°, soluble in the usual organic solvents and having a negative ferric reaction [Found: C, 68·8; H, 6·3; OMe, 15·8. $C_{10}H_9O_2(OMe)$ requires C, 68·7; H, 6·3; OMe, 16·1%]. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in red needles, m. p. 250° (decomp.) (Found: N, 15·1. $C_{17}H_{16}O_6N_4$ requires N, 15·2%). Crystallised from alcohol or light petroleum–dioxan, the *semicarbazone* formed rhombic prisms, m. p. 218—219° (Found: C, 57·9; H, 6·0; N, 17·0. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·0; N, 16·9%). The *thiosemicarbazone* was obtained in needles, m. p. 239° (decomp.), from alcohol (Found: C, 54·4; H, 5·8; N, 15·8. $C_{12}H_{15}O_2N_3S$ requires C, 54·3; H, 5·7; N, 15·9%), and the *oxime* in needles, m. p. 161°, from the same solvent (Found: N, 6·8. $C_{11}H_{13}O_3N$ requires N, 6·8%). Carefully purified specimens of the oxime, semicarbazone, and thiosemicarbazone gave a ferric reaction in alcohol.

A solution of 7-methoxy-2-methylchroman-4-one (0·1 g.) and *o*-vanillin (0·1 g.) in ethyl acetate (5 ml.) saturated with hydrogen chloride was kept for 3 days and the resulting chloride collected, washed with ether, and crystallised from 8% hydrochloric acid, forming red needles. The *perchlorate* separated from acetic acid in tiny orange needles, decomposing at above 280° (Found: C, 55·6; H, 4·4; Cl, 8·3. $C_{19}H_{17}O_8Cl$ requires C, 55·8; H, 4·2; Cl, 8·7%), and the *ferrichloride* formed small red-brown prisms, m. p. 199°, (decomp.), from acetic acid (Found: C, 45·5; H, 3·3. $C_{19}H_{17}O_4Cl_4Fe$ requires C, 45·0; H, 3·4%).

7 : 8-*Dihydroxy*-2 : 2-*dimethylchroman*-4-*one*.—After gradual addition of powdered aluminium chloride (17 g.) to a solution of ββ-dimethylacrylyl chloride (11·7 g.) and pyrogallol (15 g.) in nitrobenzene (100 ml.), the mixture was kept at room temperature for 5 days, then treated with ice (150 g.) and dilute hydrochloric acid (100 c.c.), and extracted several times with ether. The combined ethereal extracts were washed with water and evaporated, and, after the removal of the nitrobenzene by a current of steam, the hot liquor was decanted from a brown viscous resin. On cooling, the *chromanone* separated in rhombic prisms; a further quantity of product was obtained by boiling the resin with the residual liquor from the crystalline material (yield, 5 g.). Recrystallised from dilute alcohol or benzene–light petroleum (b. p. 60—80°), the compound formed yellow rhombic prisms, m. p. 142—143°, having a brownish-purple ferric reaction in alcohol (Found: C, 63·5; H, 5·8. $C_{11}H_{12}O_4$ requires C, 63·5; H, 5·8%). The 2 : 4-dinitrophenylhydrazone formed orange-red needles, m. p. 259° (decomp.), from alcohol. Methylation of the foregoing chromanone (0·5 g.) with methyl iodide (1 ml.) and potassium carbonate (1·5 g.) in boiling acetone for 6 hours with the addition of more iodide (1 ml.) and carbonate (1 g.) after 2 hours gave 7 : 8-*dimethoxy*-2 : 2-*dimethylchroman*-4-*one* which separated from dilute alcohol in colourless blunt prisms, m. p. 76° [Found: OMe, 26·2. $C_{11}H_{10}O_2(OMe)_2$ requires OMe, 26·3%].

UNIVERSITY OF LIVERPOOL.

[*Received, October 25th,* 1947.]