395. *Condensation Products of Phenols and Ketones. Part XI.* A Rational Synthesis of Dianin's Compound.*

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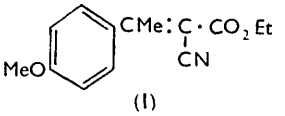
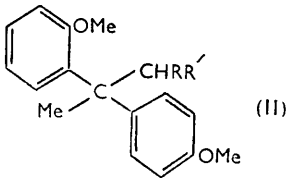
An unambiguous synthesis of Dianin's compound, 4-*p*-hydroxyphenyl-2 : 2 : 4-trimethylchroman, is described.

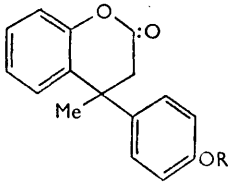
In the preceding paper, Dianin's compound obtained by condensation of phenol with mesityl oxide was shown to be 4-*p*-hydroxyphenyl-2 : 2 : 4-trimethylchroman. This structure was in part confirmed by a not entirely unambiguous synthesis from 4-methylcoumarin. The synthesis described below establishes conclusively the proposed structure.



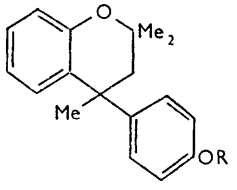
(I)



(II)



(III)



(IV)

Ethyl α-cyano-β-*p*-methoxyphenylcrotonate (I) was obtained in two forms (probably *cis*- and *trans*-isomers) by a modification of the method of Cope *et al.*[1] In a similar reaction, Elderfield and King [2] obtained two isomers of ethyl α-cyano-β-*o*-methoxyphenylcinnamate. Conjugate addition of *o*-methoxyphenylmagnesium bromide to the ester gave a poor yield of ethyl α-cyano-β-*o*-methoxyphenyl-β-*p*-methoxyphenyl-*n*-butyrate (II; R = CO_2Et, R′ = CN). The low yield is attributable partly to steric hindrance and partly to the deactivating influence of the *para*-methoxy-group on the double bond of the substituted crotonic ester. Attempts to hydrolyse, decarboxylate, demethylate, and cyclise the cyano-butyrate to give the dihydrocoumarin (III; R = H) in one operation by boiling with hydrobromic acid were unsuccessful. Instead, it proved necessary to hydrolyse the cyano-ester to the cyano-acid (II; R = CO_2H, R′ = CN), then to decarboxylate the acid giving the cyanide (II; R = H, R′ = CN), and finally to demethylate and cyclise the product to 3 : 4-dihydro-4-*p*-hydroxyphenyl-4-methylcoumarin (III; R = H) by heating it with pyridine hydrochloride. That no rearrangement occurred during this reaction was shown by vigorous treatment of the dihydrocoumarin with dimethyl sulphate and sodium hydroxide, which gave β-*o*-methoxyphenyl-β-*p*-methoxyphenylbutyric acid (II; R = H, R′ = CO_2H); this was also obtainable, albeit in low yield, by alkaline hydrolysis of the cyanide (II; R = H, R′ = CN). When methylation was carried out with methyl iodide and anhydrous potassium carbonate in acetone, the methyl ether (III; R = Me) was obtained. Treatment of the latter with an excess of methylmagnesium iodide gave 4-*p*-methoxyphenyl-2 : 2 : 4-trimethylchroman (IV; R = Me) which was identical with the methyl ether of Dianin's compound. The synthesis was completed by demethylating this methyl ether, giving Dianin's compound itself.

In connection with an alternative synthesis, attempts were made to add phenol to *p*-methoxy-β-methylcinnamic acid, a variety of condensing agents being used. With concentrated sulphuric acid, fluorosulphonic acid, or with aluminium chloride in nitrobenzene

* Part X, preceding paper.

[1] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.
[2] Elderfield and King, *ibid.*, 1954, **76**, 5439.

(see Experimental), the sole isolable product was 4-methylcoumarin which might have been formed by loss of anisole from the desired intermediate, 3 : 4-dihydro-4-*p*-methoxyphenyl-4-methylcoumarin (III; R = H) (cf. the loss of phenol from Dianin's compound by pyrolysis; preceding paper). The preparation of phenyl *p*-methoxy-β-methylcinnamate is described in the Experimental section, but we were unable to effect ring closure to the dihydrocoumarin (III; R = H or Me) under the conditions used by Colonge and Chambard [3] for the ring closure of similar phenyl esters of αβ-unsaturated acids.

Experimental

Ethyl α-Cyano-β-p-methoxyphenylcrotonate (I).—*p*-Methoxyacetophenone (37·5 g.), redistilled ethyl cyanoacetate (42·5 g.), ammonium acetate (7·7 g.), glacial acetic acid (12 g.), and dry benzene (100 ml.) were heated under reflux at 140—150°; the water formed was separated in a modified Dean–Stark separator. After 24 hr., the mixture was cooled, washed with 10% aqueous sodium chloride (3 × 50 ml.), and dried ($MgSO_4$). Distillation then gave ethyl cyanoacetate (22 g.), b. p. 50—70°/0·5 mm., *p*-methoxyacetophenone (10·9 g.), b. p. 90—120°/0·5 mm., and an oil (36·5 g.), b. p. 140—164°/0·5 mm., which was redistilled giving *ethyl α-cyano-β-p-methoxyphenylcrotonate* as a pale yellow, viscous oil (33·7 g., 55%; allowing for recovered ketone the yield is 80%), b. p. 158—162°/0·5 mm. (Found: C, 68·9; H, 6·2; N, 5·6. $C_{14}H_{15}O_3N$ requires C, 68·8; H, 6·1; N, 5·7%). The ester partly crystallised after 2 months and the solid after recrystallisation from aqueous ethanol formed pale yellow needles, m. p. 66—67°, while the rest remained as an oil.

Ethyl α-Cyano-β-o-methoxyphenyl-β-p-methoxyphenylbutyrate (II; R = CO_2Et, R′ = CN).—The above ester (I) (20 g.) in dry ether (100 ml.) was added (30 min.) to a stirred solution of *o*-methoxyphenylmagnesium bromide, prepared from *o*-bromoanisole (18·7 g.) and magnesium (2·43 g.) in ether (100 ml.). After being stirred for a further 30 min., the viscous mixture was heated under reflux for another hour. The mixture was cooled and ice-cold 5% sulphuric acid (100 ml.) added. The product was collected in ether and distilled, giving anisole, b. p. 40—70°/1 mm., unchanged ester (I) (8·75 g.), b. p. 160—180°/1 mm., and a third fraction, b. p. 190—220°/1 mm., which after two recrystallisations from ethanol (charcoal) gave *ethyl α-cyano-β-o-methoxyphenyl-β-p-methoxyphenylbutyrate* as needles (4·2 g., 15%; allowing for recovered ester the yield was 26%), m. p. 99—100° (Found: C, 71·7; H, 6·4; N, 3·9. $C_{21}H_{23}O_4N$ requires C, 71·4; H, 6·5; N, 4·0%).

α-Cyano-β-o-methoxyphenyl-β-p-methoxyphenylbutyric Acid (II; R = CO_2H, R′ = CN).—The above butyrate (5 g.) was boiled with 10% aqueous sodium hydroxide (50 ml.) for 2 hr. The solution was diluted with water (50 ml.), and unchanged ester extracted into ether (2 × 30 ml.); concentrated hydrochloric acid was then added and the solution cooled to 0°. The solid was collected and recrystallised twice from 50% ethanol, giving the required *α-cyano-β-o-methoxyphenyl-β-p-methoxyphenylbutyric acid* as needles (4·1 g., 88%), m. p. 186—189° (placed into a bath at 180° and heated at the rate of 5°/min.) (Found: C, 70·6; H, 5·5; N, 4·6; OMe, 19·4. $C_{19}H_{19}O_4N$ requires C, 70·2; H, 5·8; N, 4·3; OMe, 19·1%).

β-o-*Methoxyphenyl-β-p-methoxyphenylbutyronitrile* (II; R = H, R′ = CN).—The above acid (4·1 g.) was heated at 200° until evolution of carbon dioxide ceased. The residual oil was crystallised twice from ethanol (charcoal) yielding the *nitrile* as rectangular prisms (3·5 g., 80%), m. p. 98—99° (Found: C, 76·7; H, 6·7; N, 4·9. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%).

β-o-*Methoxyphenyl-β-p-methoxyphenylbutyric Acid* (II; R = H, R′ = CO_2H).—The nitrile (II, R = H, R′ = CN) (0·25 g.), potassium hydroxide (7·5 g.), ethanol (10 ml.), and water (15 ml.) were boiled under reflux until ammonia evolution almost ceased (48 hr.). The mixture was poured into water (50 ml.), the ethanol removed by distillation, and the solid which then separated was collected in ether. Recrystallisation of the solid from benzene–light petroleum (b. p. 60—80°) gave rectangular plates (0·15 g.), m. p. 173—174°. This compound was not further investigated, but was presumed to be β-*o*-methoxyphenyl-β-*p*-methoxyphenylbutyramide. After extraction with ether, the above alkaline solution was acidified with concentrated hydrochloric acid and cooled to 0°, and the solid collected in ether (3 × 20 ml.). The sticky solid obtained was recrystallised from light petroleum (b. p. 60—80°) giving β-o-*methoxyphenyl-β-p-methoxyphenylbutyric acid* as prisms (0·051 g., 19%), m. p. 122—123° (Found: C, 71·8; H, 6·6; OMe, 19·9. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7; OMe, 20·7%).

[3] Colonge and Chambard, *Bull. Soc. chim. France*, 1953, **20**, 573.

3 : 4-*Dihydro*-4-p-*hydroxyphenyl*-4-*methylcoumarin* (III; R = H).—The nitrile (II; R = H, R′ = CN) (1 g.) and anhydrous pyridine hydrochloride (*ca.* 5 g.) were boiled under reflux in an oil-bath for 15 min. After water (50 ml.) had been added and the mixture cooled to 0°, the buff-coloured solid was collected, and crystallised twice from benzene (charcoal) giving the 3 : 4-*dihydro*-4-p-*hydroxyphenyl*-4-*methylcoumarin* as prisms (0·74 g., 82%), m. p. 169—170° (Found : C, 75·9; H, 5·6. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%).

The dihydrocoumarin was soluble in cold 10% sodium hydroxide, but insoluble in cold saturated sodium carbonate solution. A solution in boiling aqueous sodium carbonate gave a deep blue colour with 2 : 6-dichloroquinone chloroimide.

Treatment with acetic anhydride and sodium acetate gave the *acetate* as cubes (79%), m. p. 115—116°, from aqueous ethanol (Found : C, 72·7; H, 5·1. $C_{18}H_{16}O_4$ requires C, 73·0; H, 5·4%). Vigorous methylation of the dihydro-coumarin in 10% sodium hydroxide gave β-*o*-methoxyphenyl-β-*p*-methoxyphenylbutyric acid (72%), m. p. 122—123° alone or mixed with the acid obtained as above by alkaline hydrolysis of the nitrile (II; R = H, R′ = CN).

3 : 4-*Dihydro*-4-p-*methoxyphenyl*-4-*methylcoumarin* (III; R = Me).—3 : 4-Dihydro-4-*p*-hydroxyphenyl-4-methylcoumarin (3 g.), methyl iodide (10 ml.), and fused potassium carbonate (10 g.) in acetone (100 ml.) were boiled under reflux for 6 hr. After being cooled and filtered, the acetone solution yielded a pale yellow oil which was distilled giving the methyl ether (2·8 g., 89%), b. p. 183—185°/0·2 mm.

4-p-*Methoxyphenyl*-2 : 2 : 4-*trimethylchroman* (IV; R = Me).—The above methyl ether (5 g.) in ether (50 ml.) was added slowly to methylmagnesium iodide, prepared from methyl iodide (27·5 ml.) and magnesium (5 g.) in ether (100 ml.). After being boiled for 8 hr. the solution was cooled and acidified with ice-cold 10% sulphuric acid (100 ml.). The oily product, collected in ether, was distilled giving a very viscous oil (3·9 g., 75%), b. p. 151—153°/0·5 mm., which slowly crystallised. Recrystallisation from light petroleum (b. p. 40—60°) gave 4-*p*-methoxyphenyl-2 : 2 : 4-trimethylchroman as prisms, m. p. 50° alone or mixed with the methyl ether of Dianin's compound (Found : C, 80·5; H, 7·8. Calc. for $C_{19}H_{22}O_2$: C, 80·8; H, 7·8%).

4-p-*Hydroxyphenyl*-2 : 2 : 4-*trimethylchroman* (*Dianin's Compound*) (IV; R = H).—4-*p*-Methoxyphenyl-2 : 2 : 4-trimethylchroman (1 g.) and anhydrous pyridine hydrochloride (5 g.) were boiled under reflux in an oil-bath for 15 min. The resulting solution was poured into water (100 ml.), and the solid collected at 0° and recrystallised from ethanol (charcoal) giving the ethanol adduct of 4-*p*-hydroxyphenyl-2 : 2 : 4-trimethylchroman (0·71 g., 74%), m. p. 162—163°, as hexagonal needles, which were identical with the ethanol adduct of Dianin's compound. The benzoate, leaflets from ethanol, m. p. 160°, did not depress the m. p. of the benzoate prepared from Dianin's compound.

Reaction of Phenol with p-*Methoxy*-β-*methylcinnamic Acid. Formation of* 4-*Methylcoumarin.*—Aluminium chloride (2 g.) in nitrobenzene (10 ml.) was added to phenol (0·6 g.) and *p*-methoxy-β-methylcinnamic acid (1 g.) in nitrobenzene (10 ml.), and the mixture was heated on a steam-bath for 2 hr. Next day the solution was poured into dilute hydrochloric acid (50 ml.) and steam-distilled. The residue was extracted with ether (3 × 30 ml.) which, after being washed with N-sodium hydroxide and dried, yielded a red oil (0·26 g.) which rapidly solidified. Three recrystallisations from light petroleum (b. p. 60—80°) (charcoal) gave 4-methylcoumarin (0·19 g.), m. p. 81—82° alone or mixed with authentic material (Found : C, 75·3; H, 5·1. Calc. for $C_{10}H_8O_2$: C, 75·0; H, 5·0%).

Phenyl p-*Methoxy*-β-*methylcinnamate.*—*p*-Methoxy-β-methylcinnamic acid (5 g.) and purified thionyl chloride (5 ml.) in chloroform (50 ml.) were boiled under reflux for 3 hr. After removal of solvent and excess of thionyl chloride, the residue was taken up in benzene (50 ml.) and phenol (2·5 g.) and magnesium turnings (0·3 g.) were added. After boiling for 2 hr., the product was isolated and crystallised twice from light petroleum (b. p. 60—80°) (charcoal) giving *phenyl* p-*methoxy*-β-*methylcinnamate* (5·1 g.) as rectangular prisms, m. p. 72—73° (Found : C, 75·8; H, 6·1. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). The ester gave a positive hydroxylamine test and decolorised a solution of potassium permanganate in acetone.

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