223. *Hydroxy-carbonyl Compounds. Part VII. Coumarins and* 1 : 4-*Benzopyrones derived from* m-*Cresol.*

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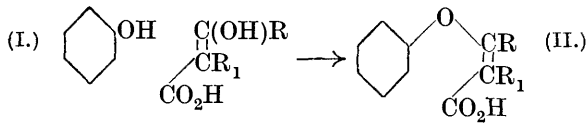
THE experiments described in this paper prove that (a) the Pechmann reaction with *m*-cresol invariably gives only 7-methylcoumarins, and (b) with ethyl α-methyl- and α-ethyl-acetoacetate the Simonis reaction applied to *m*-cresol yields pairs of isomeric 1 : 4-pyrones, whereas with ethyl acetoacetate and ethyl benzoylacetate 4 : 7-dimethylcoumarin and 5-methylflavone respectively are obtained.

The production of pairs of isomeric 1 : 4-pyrones from *m*-cresol in our opinion affords reasonable evidence that in general the first stage in the reaction is the formation of the phenoxy-acid (or its ester) (type II) by the interaction of the enolic form of the ester (I) and the phenol with the removal of the elements of water. The phenoxy-compound then undergoes ring closure, forming a 1 : 4-

pyrone, and in the case of simple *m*-substituted compounds this can take place in two ways.



In support of this mechanism it may be noted that the second stage in the reaction is practically identical with the synthesis of 1 : 4-pyrones from phenoxyfumaric acids (type II; R = CO_2H; R_1 = H) and from β-phenoxycinnamic acids (II; R = Ph; R_1 = H) (Ruhemann and co-workers, J., 1900, **77**, 984, 1119, 1179; 1901, **79**, 470, 918, 1185; *Ber.*, 1913, **46**, 2188). Further, from β-*m*-tolyloxycinnamic acid, Ruhemann (*loc. cit.*) obtained a mixture of 5- and 7-methylflavones which he was unable to separate.

In the synthesis of coumarins by Pechmann's method and in certain instances by the Simonis reaction (Parts III to VI; J., 1931, 1255, 1877, 2426; this vol., p. 1180) the production of a cinnamic acid is probably an intermediate step. On attempting to demonstrate this experimentally it was found that *m*-tolyl methyl ether gave rise directly to 4 : 7-dimethylcoumarin. Similarly, 7-methoxy-4-methylcoumarin and 7-methoxy-3 : 4-dimethylcoumarin were obtained from *O*-dimethylresorcinol. That the initial step in such condensations is the formation of a cinnamic acid is not entirely excluded by these experiments, since it was subsequently observed that *2-methoxy-β : 4-dimethylcinnamic acid* was transformed into 4 : 7-dimethylcoumarin by 86% sulphuric acid.

Experimental.

4 : 7-*Dimethylcoumarin.*—(A) Phosphoric oxide (20 g.) was added to a mixture of ethyl acetoacetate (13 g.) and *m*-cresol (15 g.), the resulting hot paste stirred for 15 minutes, more oxide (20 g.) added, and the whole heated on the steam-bath for ½ hour. An aqueous solution of the reaction mixture was basified with sodium hydroxide; the product, after being drained on porous plate, crystallised from dilute alcohol in colourless thick needles (2 g.), m. p. 132° alone or mixed with authentic 4 : 7-dimethylcoumarin (Fries and Klostermann, *Ber.*, 1906, **39**, 871) (Found : C, 75·8; H, 5·7. Calc. for $C_{11}H_{10}O_2$: C, 75·9; H, 5·8%) and about 80° mixed with 2 : 7-dimethyl-1 : 4-benzopyrone (Wittig, *Annalen*, 1926, **446**, 155).

(B) 86% Sulphuric acid (50 c.c.) was gradually added to a well-cooled mixture of *m*-tolyl methyl ether (5 g.) and ethyl acetoacetate (5 g.), the light brown solution kept at room temperature for 3 days and poured on ice (300 g.), and the mixture basified with aqueous sodium hydroxide. The yellow gummy material which had first

separated was then replaced by a colourless precipitate of 4 : 7-dimethylcoumarin, m. p. and mixed m. p. 132° after crystallisation from dilute alcohol.

2-*Methoxy*-β : 4-*dimethylcinnamic Acid*.—The foregoing coumarin (6 g.) was converted into the disodium derivative of the hydroxycinnamic acid by boiling with 20% aqueous sodium hydroxide (20 c.c.) and methyl alcohol (20 c.c.) for 20 minutes; dilution of a sample with water then did not precipitate unchanged material. The acid was methylated in the usual manner with methyl sulphate (50 c.c.) and 20% aqueous sodium hydroxide (100 c.c.), and after acidification with hydrochloric acid the ester, mixed with a small amount of the free acid, was isolated by means of ether and hydrolysed by boiling with 80% alcohol (100 c.c.) containing sodium hydroxide (8 g.) for 2 hours. A filtered solution of the crude acid in aqueous sodium carbonate was acidified with concentrated hydrochloric acid. 2-*Methoxy*-β : 4-*dimethylcinnamic acid* crystallised from benzene–ligroin in short colourless prisms (5·8 g.), m. p. 140—141° with slight sintering at 130° (Found: C, 69·9; H, 6·7. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%), and from warm benzene or aqueous acetone in elongated prisms; it rapidly decolorised bromine water and aqueous potassium permanganate.

A solution of 2-methoxy-β : 4-dimethylcinnamic acid (2·4 g.) in 86% sulphuric acid (25 c.c.) was kept at room temperature for 40 hours and poured into ice-water (250 g.). The solid, after being washed with 5% aqueous sodium hydroxide, and with water to remove a trace of a yellow impurity, crystallised from aqueous alcohol in thick needles (2 g.), m. p. 132° alone or mixed with authentic 4 : 7-dimethylcoumarin.

The acid (2 g.), dissolved in acetone (40 c.c.), was gradually treated with a warm solution of potassium permanganate (3 g.) in water (150 c.c. at 35—40°). The cooled reaction mixture was cleared with sulphur dioxide and saturated with ammonium sulphate; three extractions with ether then removed an oil consisting mainly of 2-methoxy-4-methylacetophenone; the *semicarbazone*, which separated from alcohol in colourless thick prisms, m. p. 200—201°, was identical with an authentic specimen (Found: C, 59·7; H, 6·8. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8%).

2-Methoxy-4-methylacetophenone was conveniently prepared by methylating the hydroxy-ketone (Rosenmund and Schnurr, *Annalen*, 1927, **460**, 88) with methyl sulphate and potassium hydroxide (compare Eijkmann, *Chem. Weekblad*, 1904, **1**, 453).

2 : 3 : 7-*Trimethyl*-1 : 4-*benzopyrone*.—A mixture of 2-hydroxy-4-methylpropiophenone (4 g.) (Auwers, *Annalen*, 1924, **439**, 132), sodium acetate (4 g.), and acetic anhydride (40 c.c.) was kept at

210° for 20 hours, and poured into water (200 c.c.). Next day the solution was extracted with ether, and the extract washed with aqueous sodium bicarbonate, dried, and evaporated. Distillation of the residual oil in a vacuum gave a solid fraction, b. p. 190—210°/15 mm., consisting chiefly of the 1 : 4-*pyrone*, which crystallised from light petroleum in colourless, long, flat prisms (1 g.), m. p. 86° (Found : C, 76·5; H, 6·3. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4).

The compound on condensation with piperonal by means of 2% alcoholic sodium ethoxide according to the directions of Heilbron and his co-workers (J., 1923, **123**, 2559) gave 2-(3′ : 4′-*methylenedioxystyryl*)-3 : 7-*dimethyl*-1 : 4-*benzopyrone*, which separated from warm alcohol in clusters of bright yellow needles, m. p. 191° (Found : C, 75·0; H, 5·1. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

2-*Methoxy*-6-*methylpropiophenone*.—A solution of 3-methoxy-*o*-toluonitrile (4 g.) (Gibson, J., 1923, **123**, 1269) in ether (30 c.c.) was gradually added to a well-cooled solution of ethylmagnesium iodide (from 0·8 g. of magnesium and 2·8 c.c. of ethyl iodide in 10 c.c. of ether), and the mixture refluxed for 6 hours. Next day the ether was decanted, the residual double compound decomposed with cold water and then with sulphuric acid; the product, isolated by means of ether and distilled under diminished pressure, gave the *ketone* as a colourless oil (3·3 g.), b. p. 137°/16 mm., which at 0° formed a mass of needles, m. p. about 8° (Found : C, 73·9; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). The *semicarbazone* crystallised from benzene–ligroin in thick iridescent needles, m. p. 145° (Found : C, 61·3; H, 7·2. $C_{12}H_{17}O_2N_3$ requires C, 61·3; H, 7·3%).

In some experiments, for no apparent reason, the ketone was contaminated with a considerable amount of unchanged nitrile.

2 : 3 : 5-*Trimethyl*-1 : 4-*benzopyrone*.—A mixture of the foregoing ketone (16 g.), fused aluminium chloride (16 g.), and carbon disulphide (100 c.c.) was warmed under reflux for 6 hours. After the removal of the solvent in a vacuum the residue was decomposed with warm dilute hydrochloric acid (50 c.c.), and the product distilled with steam. 2-Hydroxy-6-methylpropiophenone was isolated from the distillate by means of ether, distilled under diminished pressure, and obtained as a colourless oil (2 g.) which partly solidified, b. p. 140°/5 mm.; the solid had m. p. 25—27° after being drained on porous plate (Simonis, *Ber.*, 1917, **50**, 782, records m. p. 28·5° for ketone obtained by hydrolytic decomposition of 2 : 3 : 5-trimethyl-1 : 4-benzopyrone). It readily dissolved in warm water or 10% aqueous sodium hydroxide and gave a weak brownish-violet ferric chloride reaction (stable). The non-volatile solid remaining after the steam distillation was found to be 4-hydroxy-2-methylpropiophenone (10 g.), m. p. 114° after crystallisation from

benzene (Auwers, *Annalen*, 1924, **439**, 158). Other experiments under different conditions failed to give an increased yield of the required 2-hydroxy-6-methylpropiophenone.

Crude 2-hydroxy-6-methylpropiophenone (1·5 g.) was acetylated with acetic anhydride (20 c.c.) and sodium acetate (2 g.) at 210—215°. Water (100 c.c.) was added to the reaction mixture, followed by a slight excess of 10% aqueous sodium hydroxide, and 2 : 3 : 5-trimethyl-1 : 4-benzopyrone gradually separated as a dark brown solid, which crystallised from light petroleum in almost colourless, prismatic needles, m. p. 96° (Found : C, 76·6; H, 6·3. Calc. for $C_{12}H_{12}O_2$: C, 76·6; H, 6·4%).

Condensation of m-*Cresol and Ethyl* α-*Methylacetoacetate with Phosphoric Oxide.*—The following modification of Simonis and Petschek's procedure was used (*Ber.*, 1913, **46**, 2014). When the vigorous reaction between *m*-cresol (15 g.), ethyl α-methylacetoacetate (10 g.), and phosphoric oxide (20 g.) had subsided, the mixture was heated on the steam-bath for 2 hours; after 45 minutes, further quantities of *m*-cresol (12 g.) and oxide (20 g.) were added. A solution of the reaction mixture in ice-water was basified with sodium hydroxide and thrice extracted with ether. The combined extracts were dried and evaporated and the residual oil was distilled in a vacuum. The semi-solid fraction, b. p. 175—200°/15 mm., consisted mainly of 2 : 3 : 5-trimethyl-1 : 4-benzopyrone, which crystallised from light petroleum in colourless thick needles (2 g.), m. p. 96° alone or mixed with an authentic specimen. On condensation with piperonal by means of alcoholic sodium ethoxide this compound gave 2-(3′ : 4′-*methylenedioxystyryl*)-3 : 5-*dimethyl*-1 : 4-*benzopyrone*, which crystallised from alcohol in masses of pale lemon-yellow needles, m. p. 166—167° (Found : C, 75·0; H, 5·1. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

The fraction, b. p. 200—220°/15 mm., did not crystallise on long cooling or on inoculation with 2 : 3 : 5-trimethyl- or 2 : 3 : 7-trimethyl-1 : 4-benzopyrone. Treated with piperonal and 2% alcoholic sodium ethoxide, the oil afforded an almost theoretical yield of a styryl derivative, m. p. about 180° after crystallisation from alcohol. Repeated crystallisation from the same solvent finally gave 2-(3′ : 4′-methylenedioxystyryl)-3 : 7-dimethyl-1 : 4-benzopyrone in clusters of bright yellow needles, m. p. 190° alone or mixed with an authentic specimen (Found : C, 75·0; H, 5·1%).

2-*Methoxy*-α : β : 4-*trimethylcinnamic Acid.*—3 : 4 : 7-Trimethylcoumarin (6 g.) (Fries and Klostermann, *Ber.*, 1906, **39**, 871) was converted, by the procedure already described, into the *methoxycinnamic acid*, which crystallised from warm benzene in colourless squat prisms, m. p. 159° with slight sintering at 150° (Found : C

71·0; H, 7·1. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). It is readily soluble in alcohol or acetone and rapidly decolorises bromine water. Oxidation of this acid in aqueous acetone by means of potassium permanganate gave 2-methoxy-4-methylacetophenone; semicarbazone, m. p. and mixed m. p. 200—201°.

2-(3′ : 4′-*Methylenedioxystyryl*)-7-*methyl*-3-*ethyl*-1 : 4-*benzopyrone*.—A mixture of 2-hydroxy-4-methyl-*n*-butyrophenone (5 g.) (Pyman and co-workers, J., 1930, 288), sodium acetate (5 g.), and acetic anhydride (50 c.c.) was heated at 220° for 24 hours. After the decomposition of the anhydride with water the product was isolated by means of ether and distilled under diminished pressure. A solution of the main fraction, b. p. 140—190°/15 mm., in 5% alcoholic sodium hydroxide (20 c.c.) was kept for 24 hours, diluted with water, and extracted with ether. On evaporation the dried extract left a pale yellow oil (2 g.), b. p. 180—190°/15 mm. This material consisted mainly of 2 : 7-dimethyl-3-ethyl-1 : 4-benzopyrone, since on condensation with piperonal in alcoholic sodium ethoxide it gave an almost theoretical yield of the *styryl*-1 : 4-*benzopyrone*, which separated from warm alcohol in stellate aggregates of slender yellow needles, m. p. 160° (Found: C, 75·3; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

Condensation of m-*Cresol and Ethyl* α-*Ethylacetoacetate with Phosphoric Oxide*.—The vigorous interaction between *m*-cresol (20 g.), ethyl α-ethylacetoacetate (5 g.), and phosphoric oxide (20 g.) (agitate) was controlled by occasional cooling in tap-water and further quantities of *m*-cresol (10 g.) and oxide (20 g.) were added. The mixture was heated at 140° (oil-bath) for ¼ hour and then on the steam-bath for 1 hour. An aqueous solution of the dark coloured product was basified with sodium hydroxide and extracted with ether. After the evaporation of the solvent the extract was distilled under reduced pressure and the main fraction, b. p. 170—190°/20 mm., was mixed with an equal volume of light petroleum. 2 : 5-*Dimethyl*-3-*ethyl*-1 : 4-*benzopyrone*, which gradually crystallised, was separated and after the removal of the light petroleum the mother-liquor was distilled in a vacuum; when the distillate was mixed with light petroleum, a further quantity of the solid was obtained. Recrystallised from light petroleum, the pyrone formed thick pointed prisms (1 g.), m. p. 86° (Found: C, 77·1; H, 7·0. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%). On condensation with piperonal, it gave 2-(3′ : 4′-*methylenedioxystyryl*)-5-*methyl*-3-*ethyl*-1 : 4-*benzopyrone*, which separated from warm alcohol in rosettes of canary-yellow needles, m. p. 180° (Found: C, 75·3; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

The mother-liquor left after the removal of the second portion of

the foregoing pyrone was distilled under diminished pressure; the colourless oil (1 g.) obtained, b. p. 180—190°/20 mm., appeared to consist mainly of 2 : 7-dimethyl-3-ethyl-1 : 4-benzopyrone, since on treatment with piperonal and alcoholic sodium ethoxide it formed a styryl derivative, m. p. 150° after one crystallisation from alcohol. Repeated crystallisation from the same solvent finally gave 2-(3′ : 4′-methylenedioxystyryl)-7-methyl-3-ethyl-1 : 4-benzopyrone in clusters of slender, canary-yellow needles, m. p. and mixed m. p. 159—160° (Found : C, 75·3; H, 5·5%).

2-*Methoxy*-β : 4-*dimethyl*-α-*ethylcinnamic acid* (2·3 g.), which was prepared from 4 : 7-dimethyl-3-ethylcoumarin (5 g.) (Fries and Klostermann, *Annalen*, 1908, **362**, 1), separated from warm benzene–ligroin in squat prisms, m. p. 123° (Found : C, 71·8; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). It was readily soluble in alcohol, benzene, or acetone, instantaneously decolorised bromine water, and on oxidation in aqueous acetone with potassium permanganate gave 2-methoxy-4-methylacetophenone (semicarbazone, m. p. and mixed m. p. 200—201°).

7-*Methylflavone*.—2-Hydroxy-4-methylacetophenone (3 g.) was heated with benzoic anhydride (18 g.) and sodium benzoate (4 g.) at 180—200° for 12 hours. The product was dissolved in warm alcohol (80 c.c.), a solution of potassium hydroxide (10 g.) in water (10 c.c.) added, and the liquid refluxed for 15 minutes and then diluted with water (200 c.c.). An ethereal solution of the oil thus precipitated was separated and dried and on the removal of the greater part of the solvent the residue slowly deposited crystals of the *flavone*. These were drained on porous plate and crystallised from a small volume of alcohol, giving yellow, elongated, hexagonal prisms (0·8 g.), m. p. 120° (Found : C, 81·4; H, 5·0. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1%).

5-*Methylflavone*.—When the vigorous reaction between *m*-cresol (30 g.), ethyl benzoylacetate (10 g.), and phosphoric oxide (20 g.) had subsided, the mixture was heated at 140° (oil-bath) for 20 minutes and then on the steam-bath for 1 hour. An aqueous solution of the product was basified with sodium hydroxide and twice extracted with ether, the combined extracts were dried and evaporated, and the residual oil was distilled under diminished pressure. The first fraction (4 g.), b. p. 180—200°/5 mm., which solidified on cooling, was drained and crystallised from aqueous alcohol, giving *5-methylflavone* in colourless hexagonal plates (1 g.), m. p. 129—130° (Found : C, 81·3; H, 5·2%), readily soluble in alcohol or benzene; mixed with 7-methylflavone, it had m. p. about 100°. The second fraction (3 g.), b. p. 200—230°/5 mm., did not crystallise alone or on inoculation with either of the isomeric flavones.

4-Phenyl-7-methylcoumarin.—A solution of *m*-cresol (2 g.) and ethyl benzoylacetate (1·5 g.) in concentrated sulphuric acid (5 c.c.) was kept at room temperature for 24 hours, poured into ice-water, and basified with sodium hydroxide. Next day the *coumarin* was collected and crystallised from 80% alcohol, forming long colourless needles (0·7 g.), m. p. 96° (Found: C, 81·3; H, 5·0. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1%).

The *phenylhydrazone* of 2-hydroxy-4-methylbenzophenone (Rosenmund and Schnurr, *loc. cit.*) separated from alcohol in pale yellow, hexagonal plates, m. p. 137—138° (Found: C, 79·3; H, 6·0. $C_{20}H_{18}ON_2$ requires C, 79·5; H, 6·0%). Attempts to convert the ketone into 4-phenyl-7-methylcoumarin by ring closure with acetic anhydride and sodium acetate were unsuccessful: *e.g.*, an experiment carried out at 230—240° for 20 hours gave only the *acetate* of the ketone, which crystallised from alcohol in rhombic plates, m. p. 97°, and was identical with a specimen prepared with acetic anhydride and pyridine at room temperature (Found: C, 75·7; H, 5·4. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·5%). A mixture of the acetate and 4-phenyl-7-methylcoumarin melted at 75—78°.

Condensation of O-Dimethylresorcinol with Ethyl Acetoacetate and with Ethyl α-Methylacetoacetate.—A mixture of *O*-dimethylresorcinol (2·5 c.c.) and ethyl acetoacetate (4 c.c.) was dissolved in 80% (or 87%) sulphuric acid (25 c.c.) cooled to below 20°, and the light brown solution was kept at room temperature for ½ hour and poured on ice. Next day the solid was drained to remove unchanged dimethylresorcinol, washed with dilute sodium hydroxide solution and then with water, and crystallised from dilute alcohol. 7-Methoxy-4-methylcoumarin thus obtained, m. p. 159°, was identified by comparison with an authentic specimen (Part III; J., 1931, 1263).

To 85% sulphuric acid (50 c.c.) cooled in ice-water, a mixture of *O*-dimethylresorcinol (9 c.c.) and ethyl α-methylacetoacetate (14 c.c.) was gradually added. 14 Hours later the reddish-coloured solution was poured into ice-water and the solid was collected, agitated with dilute sodium hydroxide solution to remove a small amount of alkali-soluble material, washed with water, and crystallised from 80% alcohol. 7-Methoxy-3 : 4-dimethylcoumarin formed elongated prisms, m. p. and mixed m. p. 142—143° (Part III; *loc. cit.*). The use of 80% sulphuric acid gave a similar result.

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