345. *Studies in the Pyrone Series. Part II. Chromones and Coumarins derived from 2-Hydroxy-4-methoxy-aceto- and -propio-phenones.*

By I. M. HEILBRON, D. H. HEY, and B. LYTHGOE.

PREVIOUS work has shown (Heilbron, Heslop, and Howard, J., 1933, 1263; Heilbron, Hey, and Lowe, this vol., p. 1311) that the Kostanecki reaction is not reliable as a general method of chromone synthesis, since its course is dependent not only on the sodium salt and anhydride of the acid used but also on the *o*-hydroxy-ketone. For example, 2-hydroxy-4-methoxyacetophenone with sodium acetate and acetic anhydride gives 7-methoxy-2-methylchromone (Nagai, *Ber.*, 1892, **25**, 1284; Kostanecki and Rózycki, *Ber.*, 1901, **34**, 102), whereas with sodium propionate and propionic anhydride the product is 7-methoxy-3 : 4-dimethylcoumarin (Heilbron, Heslop, and Howard, *loc. cit.*). On the other hand, respropiophenone gives a chromone with sodium acetate and acetic anhydride (Canter, Curd, and Robertson, J., 1931, 1263) and its 4-methoxy-derivative reacts similarly with sodium propionate and propionic anhydride (Heilbron, Heslop, and Irving, J., 1933, 433). Wittig and his co-workers (*Ber.*, 1924, **57**, 88; *Annalen*, 1925, **446**, 155; *Ber.*, 1926, **59**, 116) also have carried out a number of reactions of this type and have shown that in some cases both chromones and coumarins are formed simultaneously, but they were concerned generally with the use of sodium acetate and acetic anhydride on derivatives of acetophenone only.

We have now studied the action of the anhydrides and sodium salts of propionic and butyric acids on 2-hydroxy-4-methoxyacetophenone and on 2-hydroxy-4-methoxypropiophenone, the products of each reaction being exhaustively examined for both chromones and coumarins. In all four cases more than one product is formed, but *while with the former ketone the main product is the coumarin, with the latter it is the chromone.* In these cases, therefore, varying the sodium salt and anhydride is of subsidiary importance to the effect of changing from the methyl ketone to the ethyl ketone. The method employed for the separation of the chromone or coumarin from the other products of the reaction is based on the use of sodium ethoxide, as employed by Wittig and his co-workers (*loc. cit.*).

The action of sodium propionate and propionic anhydride on 2-hydroxy-4-methoxyacetophenone gave mainly 7-methoxy-3 : 4-dimethylcoumarin (compare Heilbron, Heslop, and Howard, *loc. cit.*), but we have also isolated a small quantity of the corresponding 7-hydroxycoumarin. None of the anticipated chromone was found, but a small amount of an apparently isomeric compound was obtained and will be further investigated. With sodium butyrate and butyric anhydride the same ketone gave 7-methoxy-4-methyl-3-ethylcoumarin together with 7-methoxy-2-propylchromone as by-product. The former was identical with the compound prepared from resorcinol and ethyl α-ethylacetoacetate by the method of Canter, Curd, and Robertson (*loc. cit.*, p. 1264), and the latter was identical with the chromone described by Heilbron, Hey, and Lowe (*loc. cit.*).

2-Hydroxy-4-methoxypropiophenone, sodium propionate, and propionic anhydride gave mainly 7-methoxy-3-methyl-2-ethylchromone, identical with the product previously obtained by Heilbron, Hey, and Lowe (*loc. cit.*) ; in addition a small quantity of 7-*methoxy*-3-*methyl*-4-*ethylcoumarin* was isolated and found to be identical with the compound obtained from resorcinol and α-methylpropioacetic ester with subsequent methylation (unpublished work). With sodium butyrate and butyric anhydride, 7-methoxy-3-methyl-2-propylchromone was obtained (compare Heilbron, Hey, and Lowe, *loc. cit.*) together with a small quantity of the corresponding 7-*hydroxychromone* and a still smaller quantity of what is provisionally regarded as the hitherto unknown 7-*methoxy*-3 : 4-*diethylcoumarin*.

EXPERIMENTAL.

Action of Sodium Propionate and Propionic Anhydride on 2-*Hydroxy*-4-*methoxyacetophenone*.—2-Hydroxy-4-methoxyacetophenone (10 g.), sodium propionate (15 g.) and propionic anhydride (20 g.) were heated together under reflux at 190° for 16 hours. The product was poured into water, distilled with steam to remove unchanged reactants, and extracted with ether. Distillation of the ethereal extract at 3 mm. yielded a yellow oil, which was dissolved in ether and washed with aqueous sodium hydroxide to remove any compounds demethylated during the reaction. Acidification of the aqueous layer precipitated a small amount of a white solid, which on crystallisation from light petroleum yielded 7-hydroxy-3 : 4-dimethylcoumarin, m. p. and mixed m. p. 256° (Found : C, 70·0; H, 5·6. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%). Evaporation of the ethereal solution left a yellow oil, which was allowed to stand over-night with sodium ethoxide in alcohol (4·5 g. of sodium in 50 c.c. of ethyl alcohol). Dilution with water precipitated a dark oil, which on crystallisation from light petroleum gave (*a*) 7-methoxy-3 : 4-dimethylcoumarin (0·1 g.), m. p. and mixed m. p. 140—141°, and (*b*) pale yellow, cubic crystals (0·3 g.), m. p. 81—82° (Found : C, 70·6; H, 5·95. Calc. for $C_{12}H_{12}O_3$: C, 70·6; H, 5·9%). The latter compound strongly depressed the m. p. of 7-methoxy-2-ethylchromone. The dilute aqueous alkaline layer was acidified with acetic acid, extracted with ether, and the ethereal extract washed with aqueous alkali to remove any diketone which might be formed through rupture of any chromone present. Evaporation of the ether left a crystalline residue, which on recrystallisation from aqueous alcohol gave 7-methoxy-3 : 4-dimethylcoumarin (3·3 g.), m. p. 141—142°, as the main product of the reaction. The alkaline washings were acidified and extracted with ether, evaporation of which gave a small tarry residue only.

The following reactions were carried out and the products treated as described above, except where otherwise stated.

Action of Sodium Butyrate and Butyric Anhydride on 2-*Hydroxy*-4-*methoxyacetophenone*.—2-Hydroxy-4-methoxyacetophenone (8 g.), sodium butyrate (12 g.), and butyric anhydride (20 g.) yielded a pale yellow oil (7 g., distilled at 5 mm.). After treatment with sodium ethoxide, dilution and filtration, the filtrate was acidified and extracted with ether. The ethereal extract, washed with aqueous sodium hydroxide, yielded on evaporation 7-methoxy-4-methyl-3-ethylcoumarin (2 g.), m. p. 94° (Found : C, 71·9; H, 6·8. Calc. for $C_{13}H_{14}O_3$: C, 71·5; H, 6·4%). There was no depression of m. p. on admixture with the compound prepared as described by Canter, Curd, and Robertson (*loc. cit.*, p. 1264). Samples of the coumarin, prepared by both methods, were hydrolysed by the method of Canter and Robertson (J., 1931, 1875) to give 2 : 4-*dimethoxy*-β-*methyl*-α-*ethylcinnamic acid* in rectangular plates (from benzene), m. p. 127·5° (Found : C, 67·4; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

Acidification of the alkaline washings and extraction with ether yielded presumably 5-

methoxy-2-butyroacetylphenol as an oil which, without further treatment, was boiled with acetic acid containing a few drops of hydrochloric acid and poured into water. Recrystallisation of the precipitated tar from light petroleum gave 7-methoxy-2-propylchromone in colourless needles (1·1 g.), m. p. 83° (Found : C, 71·3; H, 6·55. Calc. for $C_{13}H_{14}O_3$: C, 71·5; H, 6·4%). No depression in m. p. was produced on admixture with the chromone prepared by Heilbron, Hey, and Lowe (*loc. cit.*).

Action of Sodium Propionate and Propionic Anhydride on 2-*Hydroxy*-4-*methoxypropiophenone.*—After the steam distillation of the product from 2-hydroxy-4-methoxypropiophenone (10 g.), sodium propionate (15 g.), and propionic anhydride (25 g.), a solid residue remained (12 g.), which was crystallised repeatedly from methyl alcohol, 7-methoxy-3-methyl-2-ethylchromone (7·5 g.) being obtained in colourless needles, m. p. 86·5° (Found : C, 71·2; H, 6·4. Calc. for $C_{13}H_{14}O_3$: C, 71·5; H, 6·4%). No depression in m. p. was observed on admixture with the chromone prepared by Heilbron, Hey, and Lowe (*loc. cit.*). When it was subjected to hydrolytic fission by the method described by Canter and Robertson (*loc. cit.*), 2-hydroxy-4-methoxybenzoic acid was obtained in colourless needles (from dilute acetic acid), m. p. and mixed m. p. 156° (Found : C, 57·3; H, 4·7. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%). The isolation of a substituted benzoic acid in place of a substituted cinnamic acid confirms the γ-pyrone structure.

The residue from the mother-liquors was treated, as before, with sodium ethoxide in alcohol and on dilution a further quantity of 7-methoxy-3-methyl-2-ethylchromone (1 g.) was precipitated. Acidification of the filtrate, followed by ether extraction, gave on evaporation of the solvent 7-*methoxy*-3-*methyl*-4-*ethylcoumarin* (0·4 g.) in plates (from light petroleum), m. p. 89° (Found : C, 71·1; H, 6·4. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%).

Action of Sodium Butyrate and Butyric Anhydride on 2-*Hydroxy*-4-*methoxypropiophenone.*—The product from 2-hydroxy-4-methoxypropiophenone (10 g.), sodium butyrate (15 g.), and butyric anhydride (20 g.) was extracted with ether and washed with aqueous sodium hydroxide. Acidification of the alkaline washings yielded 7-*hydroxy*-3-*methyl*-2-*propylchromone* (1·6 g.) in long needles (from light petroleum), m. p. 212° (Found : C, 71·7; H, 6·3. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%). Its methyl ether, prepared by refluxing with methyl iodide and potassium carbonate in acetone for 20 hours, melted at 77° and gave no depression on admixture with the compound previously prepared by Heilbron, Hey, and Lowe (*loc. cit.*).

The residue from the ethereal extract gave a yellow oil on distillation at 3 mm., which was treated as before with alcoholic sodium ethoxide. On dilution the chromone was precipitated, which on crystallisation from alcohol gave 7-methoxy-3-methyl-2-propylchromone (6·8 g.) in needles, m. p. and mixed m. p. 78° (Found : C, 72·6; H, 6·8. Calc. for $C_{14}H_{16}O_3$: C, 72·4; H, 6·9%). Hydrolytic fission gave 2-hydroxy-4-methoxybenzoic acid, m. p. and mixed m. p. 156°. The alkaline filtrate was acidified and extracted with ether, and the extract washed with aqueous sodium hydroxide. Evaporation of the ether gave a very small quantity of an oil which slowly solidified, and after crystallisation from dilute alcohol melted at 63° (Found : C, 72·1; H, 6·6. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). It is tentatively regarded as 7-*methoxy*-3 : 4-*diethylcoumarin.* Acidification of the alkaline washings deposited a further quantity of 7-hydroxy-3-methyl-2-propylchromone (1·6 g.), m. p. and mixed m. p. 212°, its presence at this stage being undoubtedly due to demethylation in the sodium ethoxide treatment.

Our thanks are due to Dr. R. N. Heslop for his helpful co-operation.

THE UNIVERSITY, MANCHESTER. [*Received, August 4th,* 1934.]