47. *Hydroxy-carbonyl Compounds. Part X. Coumarins and Chromones from* m-4-*Xylenol.*

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In the present work it has been found that the condensation of *m*-4-xylenol with ethyl acetoacetate and its α-methyl and α-ethyl substitution products gives (a) coumarins by the method of Pechmann and (b) chromones by that of Simonis, with ethyl α-benzylacetoacetate and with ethyl benzoylacetate the Simonis reaction failed to yield condensation products, and the use of methyl- or ethyl-alcoholic hydrogen chloride in place of sulphuric acid in the Pechmann method gave disappointing yields of the coumarins (compare Crabtree, Robinson, and Turner, J., 1918, **113**, 879; Appel, J., 1935, 1031).

The methods employed to establish the coumarin and the chromone structure place the constitution of the products in question beyond doubt and in this connexion we have studied the application of the Kostanecki reaction to 2-hydroxy-3 : 5-dimethylacetophenone, using the anhydrides and sodium salts of acetic, propionic, and benzoic acids. With acetic anhydride and sodium acetate the three possible products are formed—2 : 6 : 8-*trimethylchromone* and its 3-acetyl derivative (isolated as the *oxime*) together with 4 : 6 : 8-trimethylcoumarin. Propionylation of this ketone affords a mixture in which only 3 : 4 : 6 : 8-tetramethylcoumarin (converted into 2-*methoxy*-α : β : 3 : 5-*tetramethylcinnamic acid*) and 3-propionyl-6 : 8-dimethyl-2-ethylchromone (isolated as the *oxime*) can be detected, although the presence of 6 : 8-*dimethyl*-2-*ethylchromone* is not excluded. Benzoylation, on the other hand, gives only 3-*benzoyl*-6 : 8-*dimethylflavone*.

The results obtained with the Kostanecki reaction fall into line with those described by Wittig (*Ber.*, 1924, **57**, 88; *Annalen*, 1925, **446**, 155) and by Heilbron and his co-workers (J., 1933, 1263; 1934, 1311, 1581) in their more extensive investigations in this field. These authors have clearly shown that the course of the Kostanecki reaction is uncertain and therefore by itself cannot be relied upon to establish chromone structure. Nevertheless in certain cases arising in the course of the present series of investigations this reaction has a limited use and affords clear evidence on this point, *e.g.*, the compound obtained by the condensation of *m*-4-xylenol with ethyl α-methylacetoacetate by the method of Simonis is identical with the only product formed by the vigorous acetylation of 2-*hydroxy*-3 : 5-*dimethylpropiophenone* and therefore can only be 2 : 3 : 6 : 8-*tetramethylchromone*, confirmed by conversion into 2-(3′ : 4′-*methylenedioxystyryl*)-3 : 6 : 8-*trimethylchromone*. This would be equally true if, in addition to the chromone, the Kostanecki reaction had simultaneously given rise to isomeric 6 : 8-dimethyl-4-ethylcoumarin.

Experimental.

2-*Methoxy*-β : 3 : 5-*trimethylcinnamic Acid*.—Condensation of *m*-4-xylenol (10 g.) with ethyl acetoacetate (13 c.c.) by 86% sulphuric acid (80 c.c.) during 3 days gave 4 : 6 : 8-trimethylcoumarin, which formed needles (15 g.), m. p. 114—114·5°, from light petroleum (b. p. 40—60°) or aqueous alcohol (Clayton, J., 1908, **93**, 2019, gives m. p. 116—117°). Prepared from the coumarin (5·8 g.) by the standard procedure of Canter and Robertson (J., 1931, 1875), the *cinnamic acid* separated from light petroleum (b. p. 60—80°) in colourless rhombic plates (4·5 g.), m. p. 139° (Found : C, 71·0; H, 7·6. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%). Oxidation of this acid according to Canter and Robertson's directions (*loc. cit.*) yielded 2-methoxy-3 : 5-dimethylacetophenone, characterised by the *semicarbazone*, m. p. 193°, identical with an authentic specimen (Found : C, 61·5; H, 7·3; N, 17·4. $C_{12}H_{17}O_2N_3$ requires C, 61·2; H, 7·3; N, 17·8%).

2-Methoxy-3 : 5-dimethylacetophenone (oil, b. p. 134—135°/21 mm.) was obtained by the methylation of 2-hydroxy-3 : 5-dimethylacetophenone (Auwers and Mauss, *Annalen*, 1928, **464**, 311) with methyl iodide and potassium carbonate in boiling acetone during 16 hours; the semicarbazone formed plates, m. p. 193°, from benzene–ligroin (Found : C, 61·4; H, 7·2; N, 17·7%).

2-*Methoxy*-α : β : 3 : 5-*tetramethylcinnamic Acid*.—3 : 4 : 6 : 8-Tetramethylcoumarin, m. p. 108° (Clayton, *loc. cit.*, gives m. p. 110—111°), yielded the *acid*, which formed colourless rectangular prisms from light petroleum (b. p. 60—80°), m. p. 139·5—140° (Found : C, 72·1; H, 7·8.

$C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). On oxidation, the acid gave 2-methoxy-3 : 5-dimethylacetophenone (semicarbazone, m. p. and mixed m. p. 193°).

4 : 6 : 8-*Trimethyl*-3-*ethylcoumarin* crystallised from 60% alcohol in clusters of needles, m. p. 112·5—113° (Found : C, 77·7; H, 7·3. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). It is considerably more stable to boiling 14% aqueous methyl-alcoholic potassium hydroxide than either 4 : 6 : 8-trimethyl- or 3 : 4 : 6 : 8-tetramethyl-coumarin; conversion into the *o*-hydroxycinnamic acid was not complete after 12½ hours. Under similar conditions the latter coumarins are completely converted into the corresponding cinnamic acids after 3 hours.

Prepared by the standard method, **2-*methoxy*-β : 3 : 5-*trimethyl*-α-*ethylcinnamic acid*** crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 112° (Found : C, 72·6; H, 7·9. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%). On oxidation it gave 2-methoxy-3 : 5-dimethylacetophenone (semicarbazone, m. p. and mixed m. p. 193°).

4-*Phenyl*-6 : 8-*dimethylcoumarin* was obtained from *m*-4-xylenol (4 g.) and ethyl benzoylacetate (4 g.) with 86% sulphuric acid (32 c.c.), forming colourless needles (4 g.) from 80% alcohol, m. p. 111° (Found : C, 81·8; H, 5·7. $C_{17}H_{14}O_2$ requires C, 81·6; H, 5·6%).

Replacement of ethyl benzoylacetate with ethyl α-benzylacetoacetate gave rise to **3-*benzyl*-4 : 6 : 8-*trimethylcoumarin***, which formed colourless needles (4·5 g.) from aqueous alcohol, m. p. 112—113° (Found : C, 82·1; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

2 : 6 : 8-*Trimethylchromone*.—(A) 2-Hydroxy-3 : 5-dimethylacetophenone (6 g.) was heated with ethyl acetate (15 c.c.) and sodium (3 g. in small pieces) on the steam-bath for 4 hours; further quantities of ester (50 c.c.) and sodium (2·3 g.) were added after 1½ hours. Acidification of a solution of the cold homogeneous reaction mixture in water with acetic acid precipitated **2-*hydroxy*-ω-*acetyl*-3 : 5-*dimethylacetophenone***, which crystallised from dilute alcohol in colourless needles (4·5 g.), m. p. 85°, giving a red ferric chloride reaction (Found : C, 69·6; H, 6·5. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). Cyclisation of this compound in warm acetic acid containing a little hydrochloric acid produced a quantitative yield of the ***chromone***, forming colourless prisms from ether, m. p. 125° (Found : C, 77·0; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·7; H, 6·4%).

(B) An intimate mixture of *m*-4-xylenol (5 g.), ethyl acetoacetate (5 g.), and phosphoric oxide (7·5 g.) was heated on the steam-bath for 2 hours; after 1 hour, more oxide (7·5 g.) was added. The product was isolated from a cold alkaline digest of the reaction mixture with much ether, distilled in a high vacuum, and crystallised from ether (yield, 1—1·5 g.), m. p. and mixed m. p. 125° (Found : C, 76·9; H, 6·5%). Condensation of this compound (0·5 g.) and piperonal (0·38 g.) with boiling alcoholic sodium ethoxide (0·06 g. of metal in 15 c.c.) for 1½ hours gave **2-(3′ : 4′-*methylenedioxystyryl*)-6 : 8-*dimethylchromone***, which separated from warm alcohol in pale yellow prisms, m. p. 195° (Found : C, 75·1; H, 5·1. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

2-*Hydroxy*-3 : 5-*dimethylpropiophenone*.—The propionate of *m*-4-xylenol was prepared from the phenol with propionic anhydride and pyridine; b. p. 124—125°/20 mm. (compare Palfray and Duboi, *Compt. rend.*, 1927, **185**, 1479). When the vigorous reaction between this ester (10 g.) and aluminium chloride (15 g., added gradually) had subsided, the mixture was maintained at 130—140° for 5 hours; the ***ketone***, isolated in the usual manner, formed colourless plates (9 g.), m. p. 52—53°, from dilute alcohol and gave a deep blue ferric chloride reaction (Found : C, 74·0; H, 8·0. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%).

2 : 3 : 6 : 8-*Tetramethylchromone*.—Vigorous acetylation of the foregoing ketone (3 g.) with sodium acetate (5 g.) and acetic anhydride (30 c.c.) at 180° for 22 hours yielded the ***chromone*** (1·6 g.), which formed needles from ether, m. p. 136—137° (Found : C, 77·4; H, 6·7. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9%). The same compound (1·4 g.) was obtained by the condensation of ethyl α-methylacetoacetate (5 g.) with *m*-4-xylenol (5 g.) by means of phosphoric oxide (15 g.) at 100° during 3 hours; m. p. and mixed m. p. 136—137° (Found : C, 77·4; H, 6·8%). Prepared in the usual manner, **2-(3′ : 4′-*methylenedioxystyryl*)-3 : 6 : 8-*trimethylchromone*** separated from alcohol in yellow needles, m. p. 196° (Found : C, 75·2; H, 5·5. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%).

2-*Hydroxy*-3 : 5-*dimethyl*-n-*butyrophenone*.—Treatment of *m*-4-xylenol (15 g.) with *n*-butyryl chloride (15 c.c.) and pyridine (17 c.c.) on the steam-bath gave the ***butyrate***, a colourless oil (20 g.), b. p. 132—133°/17·5 mm. (Found : C, 74·8; H, 8·6. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·3%). The Fries reaction on this ester is best carried out at 110—115° (6·5 hours), and the ***ketone*** purified by distillation, b. p. 145—150°/30 mm., m. p. 30° (Found : C, 75·1; H, 8·4%); yield, 84% of the theoretical. It gives a deep blue ferric chloride reaction.

2 : 6 : 8-*Trimethyl*-3-*ethylchromone*, obtained by the application of the Simonis reaction to *m*-4-xylenol and the requisite ester (3 hours at 100°), separated from ether in colourless needles, m. p. 112·5° (Found : C, 78·0; H, 7·7. $C_{14}H_{16}O_2$ requires C, 77·8; H, 7·4%). Mixed with

4 : 6 : 8-trimethyl-3-ethylcoumarin, it melted at about 92°. The same chromone appeared to be the only product formed by acetylation of 2-hydroxy-3 : 5-dimethyl-*n*-butyrophenone at 180° for 18 hours; m. p. and mixed m. p. 112·5°. Prepared from this compound, 2-(3′ : 4′-*methylenedioxystyryl*)-6 : 8-*dimethyl*-3-*ethylchromone* crystallised from alcohol in pale yellow needles, m. p. 202—203° (Found : C, 75·7; H, 5·9. $C_{22}H_{20}O_4$ requires C, 75·8; H, 5·8%).

Acetylation of 2-*Hydroxy*-3 : 5-*dimethylacetophenone*.—The ketone (20 g.) was heated with acetic anhydride (50 c.c.) and sodium acetate (20 g.) at 170° for 6 hours and then at 200° for 14 hours, and the reaction product (18 g.) isolated in the usual manner. A solution of hydroxylamine hydrochloride (2·5 g.) and sodium acetate (2·5 g.) in water (25 c.c.) was added to a part of this material (5 g.) dissolved in acetic acid (25 c.c.) and the mixture was refluxed for 5 minutes, diluted with water, and neutralised with sodium carbonate. Next day the solid was collected, washed, and extracted with ten portions (10 c.c. each) of 5% aqueous sodium hydroxide, an insoluble residue being left. Acidification of the combined extracts with hydrochloric acid precipitated the *oxime* of 3-acetyl-2 : 6 : 8-trimethylchromone, which separated from methyl alcohol in rectangular plates (1·5 g.), m. p. 119° (Found : C, 68·6; H, 6·4; N, 5·7. $C_{14}H_{15}O_3N$ requires C, 68·6; H, 6·1; N, 5·7%).

A dried ethereal solution of the residue left on removal of the oxime was saturated with hydrogen chloride and the resulting precipitate of the hydrochloride of 2 : 6 : 8-trimethylchromone was collected and decomposed with aqueous sodium carbonate. The chromone (1·8 g.), m. p. 125° after purification, was identical with an authentic specimen.

A solution of the crude reaction mixture (10 g.) in methyl alcohol (50 c.c.) and 25% aqueous sodium hydroxide (40 c.c.) was refluxed for 2 hours, cooled, diluted with water, filtered from insoluble material, and acidified with hydrochloric acid. Next day the solid was collected and digested with aqueous sodium bicarbonate, and the insoluble residue submitted to the process used for the conversion of 4 : 6 : 8-trimethylcoumarin into 2-methoxy-β : 3 : 5-trimethylcinnamic acid. The resulting product (0·4 g.) was identical with the latter cinnamic acid, m. p. and mixed m. p. 139—139·5° after crystallisation from light petroleum.

6 : 8-*Dimethyl*-2-*ethylchromone*.—A mixture of 2-hydroxy-3 : 5-dimethylacetophenone (6 g.), ethyl propionate (25 c.c.), and sodium (3 g., in small pieces) was refluxed for 3 hours (the solution became green and then brown), the cooled mixture acidified with acetic acid, and the unchanged ester and ketone removed in a current of steam. A solution of the residual solid (ferric chloride reaction negative) in warm light petroleum (b. p. 60—80°) deposited the *chromone* in elongated plates, m. p. 109—110° (Found : C, 77·1; H, 6·7. $C_{13}H_{14}O_2$ requires C, 77·3; H, 7·0%). Attempts to isolate the intermediate diketone were unsuccessful.

Propionylation of 2-*Hydroxy*-3 : 5-*dimethylacetophenone*.—A mixture of the ketone (20 g.), propionic anhydride (70 c.c.), and sodium propionate (40 g.) was heated at 160°, then to 210° in the course of 4 hours, and maintained at this temperature for 10½ hours. After isolation, the oily product (15 g.) was distilled in a high vacuum, b. p. 160—172°/1 mm., and then crystallised from light petroleum; m. p. 84—86° after softening at 78°. A solution of this material (0·5 g.) in methyl alcohol (4 c.c.) and 25% aqueous sodium hydroxide (4 c.c.) was refluxed for 3 hours, cooled, diluted with water, filtered, and acidified with hydrochloric acid, yielding a mixture, which, by means of aqueous sodium bicarbonate, was resolved into 3 : 4 : 6 : 8-tetramethylcoumarin, m. p. and mixed m. p. 108° after crystallisation from dilute alcohol, and an acid. The latter separated from benzene in colourless rods, m. p. 179°, giving a blue ferric chloride reaction and was identical with 2-hydroxy-3 : 5-dimethylbenzoic acid (Found : C, 65·2; H, 6·0. Calc. for $C_9H_{10}O_3$: C, 65·1; H, 5·9%).

Oximation of the crude reaction mixture, m. p. 84—86° (6 g.), with an aqueous solution of hydroxylamine (4 g. in 30 c.c.), first at 100° for 15 minutes and then at room temperature for 4 days, gave the *oxime* of 3-propionyl-6 : 8-dimethyl-2-ethylchromone, which was isolated by extraction of the crude product with 5% aqueous sodium hydroxide and acidification of the combined extracts. This derivative separated from methyl alcohol in diamond-shaped plates, m. p. 93° (Found : C, 70·1; H, 6·9; N, 5·3. $C_{16}H_{19}O_3N$ requires C, 70·3; H, 7·0; N, 5·1%).

3-*Benzoyl*-6 : 8-*dimethylflavone*.—Benzoylation of 2-hydroxy-3 : 5-dimethylacetophenone (5 g.) with benzoic anhydride (25 g.) and sodium benzoate (5 g.) at 180—190° for 16 hours and subsequent treatment of the reaction mixture with water and then sodium hydroxide gave rise to the *flavone*, which formed almost colourless, rectangular plates from alcohol, m. p. 191—192° (Found : C, 81·0; H, 5·2. $C_{24}H_{18}O_3$ requires C, 81·3; H, 5·1%).

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