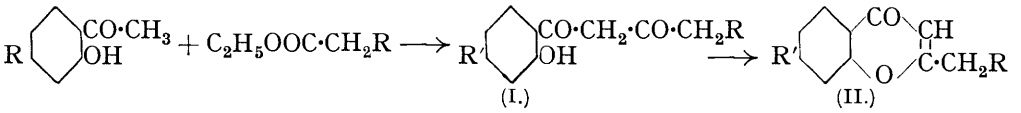
284. *Studies in the Pyrone Series. Part I. Alkyl Benzo-γ-pyrones and α-Naphtha-γ-pyrones.*

By I. M. Heilbron, D. H. Hey, and A. Lowe.

In a previous communication (Heilbron, Heslop, and Howard, J., 1933, 1263) it was pointed out that, whereas the action of acetic anhydride and fused sodium acetate on 2-hydroxy-4-methoxyacetophenone gave rise to 7-methoxy-2-methylchromone (Nagai, *Ber.*, 1892, **25**, 1284; Kostanecki and Różycki, *Ber.*, 1901, **34**, 102), the use of propionic anhydride and fused sodium propionate resulted in the formation of 7-methoxy-3 : 4-dimethylcoumarin. It was therefore evident that the Kostanecki reaction could not be relied upon as a general method of chromone synthesis. This conclusion is further confirmed by the fact that Wittig, Baugert, and Richter (*Annalen*, 1925, **446**, 178) were able to isolate both 2-methylchromone and 4-methylcoumarin from the product of the action of acetic anhydride and fused sodium acetate on *o*-hydroxyacetophenone. The applicability of this compound to the Kostanecki reaction has also been the subject of comment by Venkataraman and his co-workers (J., 1931, 1165; 1933, 1073). It has further been observed (Bargellini, *Atti R. Accad. Lincei*, 1925, **2**, 178, 261; Baker and Eastwood, J., 1929, 2900) that the use of phenylacetic anhydride and sodium phenylacetate in the Kostanecki reaction leads to coumarin, and not chromone, formation. This has been attributed to the reactivity of the methylene group in phenylacetic acid (Baker and Eastwood, *loc. cit.*; Chadha, Mahal, and Venkataraman, J., 1933, 1460), but the present investigation clearly shows that other considerations may also be involved.

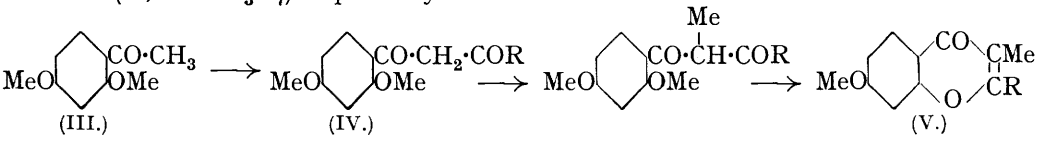
As a preliminary to the investigation of the effect of the anhydrides and sodium salts of various acids on *o*-hydroxy-ketones, it became necessary to prepare certain 2-alkylchromones by methods devoid of all ambiguity. Recourse was therefore made to the condensation of ethyl esters of the aliphatic series with the appropriate aromatic *o*-hydroxy-ketone in the presence of metallic sodium, with subsequent ring closure of the resulting diketone. This reaction has been previously employed by Kostanecki and others (*Ber.*, 1900, **33**, 330, 471; 1901, **34**, 2942, etc.), and more recently by Wittig and his co-workers (*Ber.*, 1924, **57**, 88; *Annalen*, 1925, **446**, 155) and by Baker (J., 1933, 1388), and by its means it is possible to isolate the diketone (I) as an intermediate product, which on ring closure can give only the required chromone (II).



In this way the hitherto unknown 2-*ethylchromone* (II; R = CH_3, R′ = H), 7-*methoxy*-2-*ethylchromone* (II; R = CH_3, R′ = OCH_3), 2-*ethyl*-α-*naphtha*-γ-*pyrone*, and 7-*methoxy*-2-*propylchromone* (II; R = C_2H_5, R′ = OCH_3) have been prepared from ethyl propionate or butyrate and the appropriate *o*-hydroxyaryl methyl ketone. The 2-ethyl-α-naphtha-γ-pyrone thus prepared (m. p. 111°) differs from the compound, m. p. 199—200°, prepared by Heilbron, Heslop, and Irving (J., 1933, 433) from 2-aceto-1-naphthol, propionic anhydride, and sodium propionate. The latter must thus be the isomeric 3 : 4-dimethyl-α-naphtha-α-pyrone, previously described by Chakravarti (*J. Indian. Chem. Soc.*, 1931, **8**, 407), who gives m. p. 197—199°. Arising from this, the so-called 4-phenyl-2-ethyl-α-naphthapyrylium perchlorate and 4-phenyl-3′-methyl-αβ-dinaphtha*spiro*pyran of Heilbron, Heslop, and Irving (*loc. cit.*) are in reality 2-phenyl-3 : 4-dimethyl-α-naphthapyrylium perchlorate and 2-phenyl-3-methyl-αβ-dinaphtha*isospiro*pyran respectively (see also Heilbron, Heslop, and Howard, *loc. cit.*).

Attempts to prepare the corresponding 3-methyl derivatives of the above chromones by employing an *o*-hydroxypropiophenone met with little success, although small yields of the required products could be obtained if sodamide was used in place of sodium during the condensation with fatty ester. The difficulty was effectively overcome, however, by methylating the intermediate diketone, obtained by condensation of the corresponding

o-methoxyacetophenone with the fatty ester, prior to ring closure. For instance, 2 : 4-dimethoxyacetophenone (III) and ethyl propionate gave *ω-propiono-2 : 4-dimethoxyacetophenone* (IV; R = C_2H_5), which on methylation and ring closure yielded 7-methoxy-3-methyl-2-ethylchromone (V; R = C_2H_5), while with ethyl butyrate the products were ω-butyro-2 : 4-dimethoxyacetophenone (IV; R = C_3H_7) and *7-methoxy-3-methyl-2-propylchromone* (V; R = C_3H_7) respectively.



Similarly *1-methoxy-2-naphthyl methyl ketone* on condensation with ethyl propionate yielded 2-propionoacetyl-1-naphthyl methyl ether, which on methylation and ring closure gave 3-methyl-2-ethyl-α-naphtha-γ-pyrone. This procedure serves as a convenient method for the preparation of 3-methylchromones; the diketone obtained on condensation with the fatty ester need not be isolated, since, being obtained in the form of its sodium salt, it is ready for direct methylation. The final ring closure, which now involves the separation of methyl alcohol, is effected by means of hydrogen bromide in glacial acetic acid. In the examples quoted above, specimens of the intermediate diketones were isolated in each case, either in the free state or as *pyrazole-carbonamides* by condensation with semicarbazide.

The 7-methoxy-3-methyl-2-ethylchromone and 3-methyl-2-ethyl-α-naphtha-γ-pyrone thus obtained were identical with the corresponding compounds prepared by Heilbron, Heslop, and Irving (*loc. cit.*) from 2-hydroxy-4-methoxypropiophenone and 2-propiono-1-naphthol respectively by fusion with propionic anhydride and sodium propionate. The surprising result is thus revealed that, whereas an *o*-hydroxyaryl methyl ketone leads to coumarin production in the Kostanecki reaction with propionic anhydride and sodium propionate, the corresponding ethyl ketone under similar treatment gives a chromone. The course followed by the Kostanecki reaction is thus not only dependent on the acid anhydride and salt used, but is also influenced by the nature of the ketone.

Methylenedioxystyryl derivatives were prepared from each of the 2-ethylchromones by the method of Heilbron, Barnes, and Morton (J., 1923, **123**, 2565). The applicability of this reaction in establishing the γ-pyrone structure is thus extended to 2-ethyl-γ-pyrones, but the condensation is somewhat slower than with the corresponding 2-methyl-γ-pyrones.

Experimental.

2-Propionoacetylphenol.—A solution of *o*-hydroxyacetophenone (20 g.; Freudenberg and Orthner, *Ber.*, 1922, **55**, 1749) in redistilled ethyl propionate (50 c.c.) was added to powdered sodium (8 g.), the whole being cooled in ice. After the initial vigorous action had subsided, the reaction was completed by ½ hour's heating under reflux on the water-bath. The product was added to crushed ice (100 g.), and the yellow sodium salt collected, washed with ice-water and with ether, and then decomposed by treatment with glacial acetic acid (25 c.c.). Addition of water caused the separation of *2-propionoacetylphenol* (15 g.) as an oil, which rapidly solidified. Recrystallisation from light petroleum gave colourless plates, m. p. 60° (Found : C, 68·8; H, 6·4. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·3%).

2-Ethylchromone.—The foregoing compound (10 g.) was boiled for 10 minutes with glacial acetic acid (40 c.c.) containing a few drops of concentrated hydrochloric acid. The solution was poured into water, and the yellow oil which separated was extracted with ether, washed successively with dilute alkali and water, and dried. On evaporation of the solvent, *2-ethylchromone* (8·5 g.) was obtained as a yellow oil which slowly solidified. It separated from ether–light petroleum in colourless needles, m. p. 18° (Found : C, 76·1; H, 6·0. $C_{11}H_{10}O_2$ requires C, 75·8; H, 5·8%). After hydrolysis by 1 hour's boiling with 2*N*-sodium hydroxide, salicylic acid (m. p. and mixed m. p. 155°) was obtained on acidification.

3′ : 4′-Methylenedioxy-2-α-methylstyrylchromone.—(*a*) A solution of 2-ethylchromone (2 g.) and piperonal (1·8 g.) in alcohol was treated with a solution of sodium ethoxide (from 0·3 g. Na), and the whole kept at room temperature for 4 days. The crude condensation product was

separated from the dark red solution and crystallised from alcohol, giving pale yellow needles, m. p. 147° (Found : C, 74·8; H, 4·6. $C_{19}H_{14}O_4$ requires C, 74·6; H, 4·6%). A further crop of the styryl *compound* was obtained on dilution of the mother-liquor with water.

(*b*) A solution of 2-ethylchromone (2 g.) and piperonal (1·8 g.) in dry chloroform was saturated with dry hydrogen chloride at 0°. After standing at room temperature for several days, the chloroform was evaporated and the styryl compound recovered from the dark red residue by addition of dilute alcoholic ammonia. Recrystallisation from absolute alcohol gave yellow needles, m. p. 146—147°.

Unless other details are given, the following compounds were prepared by the general methods described above, method (*a*) being used for the styryl derivatives.

5-*Methoxy*-2-*propionoacetylphenol*.—Prepared from 2-hydroxy-4-methoxyacetophenone (23 g.), dry ethyl propionate (50 c.c.), and powdered sodium (8 g.), pure 5-*methoxy*-2-*propionoacetylphenol* (16 g.) separates from light petroleum in needles, m. p. 101° (Found : C, 64·8; H, 6·4. $C_{12}H_{14}O_4$ requires C, 64·8; H, 6·3%).

7-*Methoxy*-2-*ethylchromone* (8·5 g.), prepared from the foregoing compound (10 g.), crystallises from light petroleum in needles, m. p. 81° (Found : C, 70·6; H, 6·2. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%). The 3′ : 4′-*methylenedioxystyryl* derivative forms pale yellow needles (from alcohol), m. p. 130° (Found : C, 71·6; H, 4·6. $C_{20}H_{16}O_5$ requires C, 71·4; H, 4·8%).

2-*Propionoacetyl*-1-*naphthol*.—2-Aceto-1-naphthol (32 g.), ethyl propionate (60 c.c.), and powdered sodium (8 g.) gave 2-*propionoacetyl*-1-*naphthol* (20 g.), which crystallises from light petroleum in brown needles, m. p. 75—76° (Found : C, 74·9; H, 5·7. $C_{15}H_{14}O_3$ requires C, 74·5; H, 5·8%). This preparation, up to the decomposition of the sodium salt with acetic acid, must be carried out in an atmosphere of nitrogen.

2-*Ethyl*-α-*naphtha*-γ-*pyrone*, obtained from 2-propionoacetyl-1-naphthol, separates from aqueous alcohol in pale yellow plates, m. p. 111° (Found : C, 80·3; H, 5·2. $C_{15}H_{12}O_2$ requires C, 80·4; H, 5·4%). The 3′ : 4′-*methylenedioxystyryl* derivative crystallises from absolute alcohol in brown needles, m. p. 209° (Found : C, 77·7; H, 4·3. $C_{23}H_{16}O_4$ requires C, 77·5; H, 4·5%).

5-*Methoxy*-2-*butyroacetylphenol*.—A solution of 2-hydroxy-4-methoxyacetophenone (20 g.) in redistilled ethyl butyrate (35 c.c.) was added to powdered sodium (5 g.), the whole being cooled in ice. The reaction was completed by heating under reflux at 120° for 45 minutes. The diketone, obtained on decomposition of the sodium salt in the usual manner, was extracted with ether, evaporation of which yielded 5-*methoxy*-2-*butyroacetylphenol* as a red oil (12 g.). It was characterised by its conversion (by treatment with alcoholic semicarbazide acetate) into 5(3 ?)-(2′-*hydroxy*-4′-*methoxyphenyl*)-3(5 ?)-*propylpyrazole*-1-*carbonamide*, which crystallised from absolute alcohol in fine yellow needles, m. p. 215° (Found : N, 15·5. $C_{14}H_{17}O_3N_3$ requires N, 15·3%).

7-*Methoxy*-2-*propylchromone*, obtained from 5-methoxy-2-butyroacetylphenol, separates from alcohol in plates, m. p. 83° (Found : C, 71·8; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

ω-*Propiono*-2 : 4-*dimethoxyacetophenone*.—A solution of 2 : 4-dimethoxyacetophenone (30 g., m. p. 39—40°; Perkin, Robinson, and Turner, J., 1908, **93**, 1108) in redistilled ethyl propionate (60 c.c.) was added to powdered sodium (4 g.). After the initial vigorous action, which was controlled by cooling in ice-water, had subsided, the action was completed by heating under reflux on the water-bath for ½ hour. The sodium salt of the diketone (25 g.) was precipitated with ether, filtered, and washed free from tarry by-products with ether. A portion of the sodium salt (2 g.) was converted into ω-*propiono*-2 : 4-*dimethoxyacetophenone* by treatment with acetic acid (5 c.c.) and pouring into water. The crude diketone was crystallised from alcohol, giving needles, m. p. 72° (Found : C, 66·4; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·7%).

α-*Propiono*-2 : 4-*dimethoxypropiophenone*.—(Method *a*.) The dry sodium salt of the foregoing compound (20 g.), dry acetone (250 c.c.), and methyl iodide (11 g.) were heated together for 4 hours under reflux. After removal of the acetone, the residue was treated with water, whereupon a yellow oil separated, which gradually solidified (16 g.). Pure α-*propiono*-2 : 4-*dimethoxypropiophenone* was isolated by repeated crystallisation from aqueous alcohol, separating in needles, m. p. 80° (Found : C, 67·1; H, 7·0. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

(Method *b*.) Condensation between 2-hydroxy-4-methoxypropiophenone and ethyl propionate could not be effected by means of sodium. Sodamide was therefore employed, and the difficulty of the small solubility of the sodium salt was overcome by using the dimethyl ether of respropiophenone. A solution of 2 : 4-dimethoxypropiophenone (10 g.) in dry ether (100 c.c.)

and dry ethyl propionate (5 g.) was shaken with powdered sodamide (2·5 g.) and the mixture kept for three days. The small quantity of solid which separated was collected, treated with acetic acid, and poured into water; the oil which separated slowly solidified. Recrystallisation from aqueous alcohol gave needles (1 g.), m. p. 79—80°, both alone and on admixture with the product obtained by method (*a*).

7-*Methoxy*-3-*methyl*-2-*ethylchromone*.—The preceding propiophenone (5 g.) was boiled for 15 minutes with glacial acetic acid (50 c.c.) and hydrobromic acid (4 c.c.; *d* 1·49). On pouring into dilute alkali, an oil separated which slowly solidified. Recrystallisation from aqueous alcohol gave the chromone as colourless needles, m. p. 87° (3 g.) (Found: C, 71·6; H, 6·6. Calc. for $C_{13}H_{14}O_3$: C, 71·5; H, 6·5%). No depression in m. p. was produced on admixture with the compound prepared by Heilbron, Heslop, and Irving as mentioned on p. 1312.

Acidification of the aqueous alkaline filtrate yielded 2-hydroxy-4-methoxypropiophenone, m. p. 58° (1·5 g.).

7-*Methoxy*-3′ : 4′-*methylenedioxy*-2-α-*methylstyryl*-3-*methylchromone* crystallised from absolute alcohol in yellow needles, m. p. 144—145° (Found: C, 72·3; H, 4·9. $C_{21}H_{18}O_5$ requires C, 72·0; H, 5·1%).

ω-*Butyro*-2 : 4-*dimethoxyacetophenone*.—A solution of 2 : 4-dimethoxyacetophenone (20 g.) in redistilled ethyl butyrate (30 c.c.) was added slowly to powdered sodium (3 g.). The initial reaction was controlled by cooling, after which the mixture was heated under reflux at 120° for 45 minutes. Ether was added to the orange-red product, and the precipitated sodium salt (10 g.) collected, washed with ether, and dried over phosphoric oxide. A portion of the sodium salt was treated with glacial acetic acid, diluted with water, and extracted with ether. Evaporation of the solvent left ω-butyro-2 : 4-dimethoxyacetophenone as a yellow oil, which would not solidify, but was characterised by formation of 5(3 ?)-(2′ : 4′-*dimethoxyphenyl*)-3(5 ?)-*propylpyrazole*-1-*carbonamide*, which separated from absolute alcohol in pale yellow needles, m. p. 189—190° (Found: N, 14·8. $C_{15}H_{19}O_3N_3$ requires N, 14·5%).

α-*Butyro*-2 : 4-*dimethoxypropiophenone*.—The dry sodium salt of ω-butyro-2 : 4-dimethoxyacetophenone (8 g.), dry acetone (75 c.c.), and methyl iodide (4 g.) were heated under reflux for 4 hours. After evaporation of the acetone, the residue was poured into water, extracted with ether, and dried. Removal of the ether left α-butyro-2 : 4-dimethoxypropiophenone as a pale yellow oil (4 g.). A portion of the diketone was treated with alcoholic semicarbazide acetate solution, and after 2 days at room temperature 5(3 ?)-(2′ : 4′-*dimethoxyphenyl*)-4-*methyl*-3(5 ?)-*propylpyrazole*-1-*carbonamide* separated, which crystallised from absolute alcohol in fine yellow-green needles, m. p. 226—227° (Found: N, 14·1. $C_{16}H_{21}O_3N_3$ requires N, 13·9%).

7-*Methoxy*-3-*methyl*-2-*propylchromone* was obtained on treatment of α-butyro-2 : 4-dimethoxypropiophenone (3 g.) with glacial acetic acid (15 c.c.) and hydrobromic acid (1 c.c.; *d* 1·49), as previously described. The *chromone* crystallises from aqueous alcohol in needles (1 g.), m. p. 79° (Found: C, 72·3; H, 6·8. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). Acidification of the alkaline filtrate gave 2-hydroxy-4-methoxypropiophenone (1 g.).

1-*Methoxy*-2-*naphthyl Methyl Ketone*.—2-Aceto-1-naphthol (40 g.), dry acetone (300 c.c.), methyl iodide (50 c.c.), and anhydrous potassium carbonate (50 g.) were boiled under reflux with vigorous stirring for 24 hours. The residue obtained after removal of solvent was poured into ice-cold alkali, and the ketone separated as an oil which slowly solidified. Recrystallised from alcohol, it formed large prisms, m. p. 50° (cf. Fries, *Ber.*, 1921, **54**, 711) (Found: C, 78·1; H, 6·2. Calc. for $C_{13}H_{12}O_2$: C, 78·0; H, 6·0%). The *semicarbazone*, prepared in the usual manner, crystallised from alcohol in needles, m. p. 191° (Found: N, 16·5. $C_{14}H_{15}O_2N_3$ requires N, 16·3%).

2-*Propionoacetyl*-1-*naphthyl Methyl Ether*.—1-Methoxy-2-naphthyl methyl ketone (20 g.), dry ethyl propionate (30 c.c.), and powdered sodium (2·5 g.) gave, by the method described under ω-propiono-2 : 4-dimethoxyacetophenone, the sodium salt (15 g.), a portion of which was treated with acetic acid and diluted with water, the ether being obtained as a yellow oil. On treatment with alcoholic semicarbazide acetate at room temperature for two days, 5(3 ?)-(1′-*methoxy*-2′-*naphthyl*)-3(5 ?)-*ethylpyrazole*-1-*carbonamide* separated, and was purified by recrystallisation from absolute alcohol, separating in fine colourless needles, m. p. 174—175° (Found: N, 14·2. $C_{17}H_{17}O_2N_3$ requires N, 14·3%).

1-*Methoxy*-2-*naphthyl ethyl ketone* was prepared from 2-propiono-1-naphthol by an analogous method to that described above. Evaporation of the acetone left a yellow oil, which slowly solidified on pouring into water. The pure ketone crystallises from ligroin (b. p. 40—60°) in needles, m. p. 42—43° (Found: C, 78·8; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%). The *semicarbazone* forms needles (from alcohol), m. p. 192° (Found: N, 15·3. $C_{15}H_{17}O_2N_3$ requires

N, 15·5%). The *oxime*, prepared in the usual manner, separates from alcohol in colourless needles, m. p. 112—113° (Found : N, 6·3. $C_{14}H_{15}O_2N$ requires N, 6·1%).

2-(α-*Propionopropionyl*)-1-*naphthyl Methyl Ether*.—(Method *a*.) The dry sodium salt of 2-propionoacetyl-1-naphthyl methyl ether (10 g.), acetone (75 c.c.), and methyl iodide (5 g.), by the method described on p. 1314, gave 2-(α-propionopropionyl)-1-naphthyl methyl ether (8 g.) as a yellow oil, characterised as 5(3 ?)-(1′-*methoxy*-2′-*naphthyl*)-4-*methyl*-3(5 ?)-*ethylpyrazole*-1-*carbonamide*, which forms needles, m. p. 191° (from alcohol) (Found : N, 13·7. $C_{18}H_{19}O_2N_3$ requires N, 13·6%).

(Method *b*.) 1-Methoxy-2-naphthyl ethyl ketone (10 g.), dry ether (100 c.c.), and dry ethyl propionate (5 g.) were well shaken with powdered sodamide (4 g.), kept for 3—4 days, and then treated with ice-water. The aqueous solution was acidified with acetic acid, and the diketone separated as a red oil (2 g.). Treatment with alcoholic semicarbazide acetate solution gave the pyrazole-carbonamide, m. p. 191° both alone and on admixture with the compound prepared by method (*a*).

3-Methyl-2-ethyl-α-naphtha-γ-pyrone was prepared from 2-(α-propionopropionyl)-1-naphthyl methyl ether in the usual manner. It crystallises from aqueous alcohol in colourless needles (3·5 g.), m. p. 103° (Found : C, 80·6; H, 6·1. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%). No depression in m. p. is produced on admixture with the compound prepared by Heilbron, Heslop, and Irving (*loc. cit.*). Acidification of the alkaline filtrate gave 2-propiono-1-naphthol, m. p. 83—84° (1·2 g.). The 3′ : 4′-*methylenedioxy*-2-α-*methylstyryl* derivative separates from absolute alcohol in small yellow needles, m. p. 171—172° (Found : C, 77·9; H, 4·9. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%).

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