HETEROCYCLIC COMPOUNDS

Part XX. The Kostanecki Acylation of Quinacetophenone, Quinbenzophenone and γ-Orcacetophenone, and Synthesis of 6-Hydroxy and 5-Hydroxy Chromones and Coumarins

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Received October 14, 1946

DURING the last twenty years, a considerable amount of work has been published on the limited applicability of the Kostanecki Reaction by various workers,[1] and the conclusion has been drawn that this reaction may give either chromones, or the coumarins or the mixture of both and depends not only on the nature of the acid anhydrides and the salts used but also on the nature of the O-hydroxyarylmethyl ketone.

We thought it worth while to subject quinacetophenone and quinbenzophenone to this reaction in order to see how far it can be used as a method for the synthesis of 6-hydroxy-chromones and coumarins, the number of which is very scanty. Thus some 6-hydroxy-flavones have been described by Chadha and Venkataraman,[2] while Borche[3] has described the synthesis of three 6-hydroxy coumarins.

Quinacetophenone gave only 6-acetoxy-3-acetyl-2-methyl chromone on heating with acetic anhydride and sodium acetate, while propionic anhydride and sodium propionate gave a mixture of 6-hydroxy-3-propionyl-2-ethylchromone and 6-hydroxy-3:4-dimethyl coumarin approximately in 3:2 proportion. Similarly butyric anhydride and sodium butyrate gave 6-hydroxy-3-butyryl-2-methyl-chromone and 6-hydroxy-4-methyl-3-ethyl coumarin in almost the same proportion. Quinbenzophenone reacted with acetic anhydride and sodium acetate giving 6-acetony-4-phenyl coumarin (excellent yield) and this constitutes a convenient method of preparing 6-hydroxy-4-phenyl coumarins, as the Pechmann condensation between hydroquinone and ethyl benzoylacetate does not take place.

In light of the recent interesting observations of Sethna and Shah (*loc. cit.*) that β-orcacetophenone gave exclusively the coumarins on heating with fatty acid anhydrides and their salts, and of Desai and (Miss) Vakil that γ-orcacetophenone gave only the chromone with acetic anhydride and sodium acetate, it was interesting to see its behaviour on heating with other

acid anhydrides in presence of their sodium salts. γ-Orcacetophenone, on heating with propionic anhydride and sodium propionate, gave a mixture of 2-ethyl-3-propionyl-5-hydroxy-7-methyl chromone and 3:4:7-trimethyl-5-hydroxy-coumarin, approximately in proportions of 2:1, while the mixture of 2-propyl-3-butyryl-5-hydroxy-7-methyl chromone and 3-ethyl-4:7-dimethyl-5-hydroxy-coumarin in almost the same proportion was obtained on heating γ-orcacetophenone with butyric anhydride and sodium butyrate. Finally benzoic anhydride and sodium benzoate gave 2-phenyl-3-benzoyl-5-hydroxy-7-methyl-chromone.

These results support the observations of Heilbron and co-workers (*loc. cit.*) and emphasise the limited character of the Kostanecki Reaction for the chromone formation.

Experimental

Quinacetophenone was prepared by the Fries migration of hydroquinone diacetate. The following method gave the best yield of this ketone as it is dependent upon temperature and the amount of aluminium chloride used.

An intimate mixture of hydroquinone diacetate (14 g.) and aluminium chloride (28 g.) was heated in an oil-bath at 195–200° for one hour and a half hour, cooled, and decomposed with ice-cold water. The solid crystallised from dilute alcohol in needles, m.p. 202° (yield = 10 g.).

6-Acetoxy-3-acetyl-2-methyl chromone.—A mixture of quinacetophenone (5 g.), sodium acetate (10 g.) and acetic anhydride (35 c.c.) was heated at 200–210° for twelve hours and poured into water. The solid crystallised from dilute alcohol in colourless needles, m.p. 125° (yield = 3 gm.). (Found: C, 64·4; H, 4·8. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6 per cent.)

6-Hydroxy-3-acetyl-2-methyl-chromone was obtained by pouring the solution of the *acetoxy chromone* in 85 per cent. sulphuric acid on ice after three hours and crystallised from alcohol in thick needles, m.p. 221°. Its solution in alkali as well as concentrated sulphuric acid was yellow and non-fluorescent. (Found: C, 65·9; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6 per cent.)

The above conversion of *acetoxy-chromone* into *hydroxy-chromone* can also be effected by heating (1 g.) with aluminium chloride (3 g.) at 180° for two hours.

6-Hydroxy-γ-methylchromone.—The above chromone (1 g.) was heated with 5 per cent. sodium carbonate solution (20 c.c.) on a sand-bath for two hours. The filtered solution on acidification with concentrated hydrochloric

acid gave a solid which crystallised from dilute alcohol in colourless, lustrous needles, m.p. 245°. Its solution in alkali as well as concentrated sulphuric acid was yellow and non-fluorescent. (Found: C, 67·9; H, 4·6. $C_{10}H_8O_3$ requires C, 68·2; H, 4·5 per cent.) Similar hydrolysis of the above chromone with sodium hydroxide solution gave 2:5-dihydroxy-benzoic and m.p. 196° (undepressed by admixtures with an authentic specimen).

6-Hydroxy-3-propionyl-2-ethyl-chromone and 6-hydroxy 3: 4-dimethyl-coumarin.—

The mixture of quinacetophenone (5 g.), sodium propionate (10 g.) and propionic anhydride (35 c.c.) was heated at 200–10° for 12 hours. The pasty mass obtained by pouring into water was kept in contact with 85 per cent. sulphuric acid, overnight, as it showed no tendency to crystallise from any solvent, and poured into water. The solid thus obtained was treated with benzene. The benzene-soluble product crystallised from dilute alcohol in needles, m.p. 151°, and was identified as *6-hydroxy-3-propionyl-2-ethyl-chromone* as it gave 2:5-dihydroxy benzoic acid on alkaline hydrolysis (yield = 1·5 g.) (Found: C, 68·1; H, 5·8. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7 per cent.)

The *benzene-insoluble* product crystallised from alcohol in pale-yellow needles, m.p. 241°, and was identified as 3:4-dimethyl-6-hydroxy-coumain with an authentic specimen (yield = 1·0 g.). The coumarin underwent nitration readily by the addition of finely powdered sodium nitrate (0·8 g.) to its solution in concentrated sulphuric acid (1·0 g. in 20 c.c.). After keeping the mixture overnight the yellow product obtained by pouring the mixture over ice-cold water crystallised from alcohol in yellow flakes, m.p. 213°, and was probably the 5-nitro-derivative. (Found: N, 5·9. $C_{11}H_9O_5N$ requires N, 6·0 per cent.)

6-Hydroxy-3-butyryl-2-propyl-chromone and 6-hydroxy-4-methyl-3-ethyl-coumarin.—The mixture of quinacetophenone (5 g.), sodium butyrate (12·5 g.) and butyric anhydride (40 c.c.) was heated at 220–30° for 18 hours. As the pasty mass did not solidify, it was kept in contact with 85 per cent. sulphuric acid overnight and poured into water. The solid was treated with benzene, and the *benzene*-soluble product crystallised from dilute alcohol in pale-yellow needles, m.p. 151° (depressed to 120–25° by 3-propionyl-2-ethyl-6-hydroxy chromone which has curiously the same m.p.) (yield = 1·5 g.). It gave 2:5-dihydroxybenzoic acid on alkaline hydrolysis. (Found: C, 69·8; H, 96·7. $C_{16}H_{18}O_4$ requires C, 70·0; H, 6·6 per cent.)

The *benzene-insoluble* product crystallised from dilute alcohol in pale yellow needles, m.p. 211°, and was identified as 6-hydroxy-4-methyl-3-ethyl coumarin, by comparing with a specimen prepared by condensing ethyl ethylaceto-acetate with hydroquinone in presence of aluminium chloride (yield = 1·0 g.). (Found: C, 70·3; H, 6·1. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9 per cent.)

Quinbenzophenone was obtained by the Fries migration of hydroquinone dibenzoate and melted at 125°.

6-*Acetoxy*-4-*phenyl-coumarin* was obtained by heating the mixture of quinbenzophenone (5 g.), sodium acetate (10 g.) and acetic anhydride (35 c.c.) at 210-20° for twelve hours, and crystallised from dilute acetic acid in colourless, lustrous needles, m.p. 162° (yield = 4 gm.). (Found: C, 72·9; H, 4·5. $C_{17}H_{24}O_4$ requires C, 72·9; H, 4·3 per cent.)

6-*Hydroxy*-4-*phenyl coumarin* was obtained by deacetylating the above coumarin with 85 per cent. sulphuric acid or aluminium chloride, and crystallised from alcohol in pale-yellow needles, m.p. 242–43°. (Found: C, 75·4; H, 4·3. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2 per cent.)

The *dibromo derivative* crystallised from alcohol in pale-yellow needles, m.p. 217°. (Found: Br, 40·1. $C_{15}H_8O_3Br_2$ requires Br, 40·4 per cent.

B. Kostanecki Reaction with γ-Orcacetophenone.

The most convenient method of preparing γ-orcacetophenone is the deacetylation of 2:4-diacetyl-orcinol, which can be prepared by the Fries migration of orcinol diacetate. The method which is general, is described as follows:—

A mixture of orcinol diacetate (16 g.) and aluminium chloride is heated at 145–55° for 1·5 hours, and decomposed with ice-cold water. The crude solid (7 g.) which is a mixture of 2:4-diacetylorcinol, β-orcacetophenone and γ-orcacetophenone was dissolved in 85 per cent. sulphuric acid (75 c.c.) the mixture was poured over ice after four hours. The resulting solid (5 g.) was almost pure γ-orcacetophenone, and crystallised from dilute alcohol in needles, m.p. 146°.

Propionylation of γ-orcacetophenone and formation of 5-hydroxy-7-methyl-3-propionyl-2-ethyl-chromone and 5-hydroxy-3:4:7-trimethyl coumarin.

The mixture of γ-orcacetophenone (5 g.), propionic anhydride (35 c.c.) and sodium propionate (10 g.) was heated at 200–10° for 18 hours, and the pasty mass obtained after pouring the mixture into water was dissolved in 85 per cent. sulphuric acid. The solid obtained by pouring the solution

over ice after 4 hours was treated with petrol (b.p. 60-80°), which dissolved a considerable portion of it, and on recrystallisation from the same solvent long, stout needles, m.p. 99-100° were obtained (1·5 g.). Its alcoholic solution gave deep violet coloration with ferric chloride, and as it gave *p*-orsellinic acid on alkaline hydrolysis it was identified as *5-hydroxy-7-methyl-3-propionylchromone*. Its yellow, alkaline solution was devoid of fluorescence. (Found: C, 69·0; H, 6·5. $C_{13}H_{16}O_4$ requires C, 69·2; H, 6·2 per cent.)

The petrol-insoluble product (0·75 g.) crystallised from alcohol in cubes, m.p. 250°, and was identified as 5-hydroxy-3:4:7-trimethyl-coumarin by comparison with an authentic specimen prepared by Chakravarti's method.[5] The *acetyl* derivative (m.p. 135°) of this coumarin underwent Fries migration giving 6-acetyl-5-hydroxy-3:4:7-trimethyl coumarin, which crystallised from alcohol in needles, m.p. 166°. Its alcoholic solution gave red coloration with ferric chloride. (Found: C, 68·1; H, 5·9. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7 per cent.)

Butyrylation of γ-Resacetophenone, and formation of 5-hydroxy-7-methyl-3-butyryl-3-propyl-chromone and 5-hydroxy-4:7-dimethyl-3-ethyl coumarin.

The mixture of γ-orcacetophenone (5 g.), sodium butyrate (12·5 g.) and butyric anhydride (40 c.c.) was heated at 210-20° for 18 hours, and poured into water. The viscous mass was dissolved in 85 per cent. sulphuric acid, and worked up after 4 hours. The petrol-soluble (60-80° b.p.) portion crystallised from light petrol (b.p. 40-60°) in thick needles, m.p. 95-96° (yield 0·8 g.). Its alcoholic solution gave deep violet coloration with ferric chloride and as its alkaline hydrolysis gave *p*-orsellinic acid, it was identified as 5-hydroxy-7-methyl-3-butyryl-2-propyl chromone. (Found: C, 70·5; H, 6·8. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9 per cent.)

The *petrol-insoluble* portion crystallised from alcohol in needles, m.p. 205-06° and was identified as 5-hydroxy-3-ethyl-4:7-dimethyl coumarin by comparison with an authentic specimen prepared by Chakravarti's method (*loc. cit.*) (yield 0·4 g.).

Benzoylation of γ-orcacetophenone and formation of 5-hydroxy-3-benzoyl-7-methyl-flavone.

A mixture of γ-orcacetophenone (2·5 g.), sodium benzoate (7·5 g.) and benzoic anhydride (25 g.) was heated at 200-10° for 20 hours. The resulting mass was alternately treated with petrol (b.p. 60-80), and water, the residue dissolved in concentrated sulphuric acid, and poured into water

after 4 hours. The solid, after the removal of benzoic acid with sodium bicarbonate solution crystallised from alcohol in colourless needles, m.p. 143° (yield = 0·75 g.). In alcoholic solution gave deep violet coloration with ferric chloride while its alkaline hydrolysis gave *p*-orsellinic acid. (Found: C, 77·3; H, 4·7. $C_{23}H_{16}O_4$ requires C, 77·5; H, 4·5 per cent.)

We take this opportunity of expressing our thanks to Rev. Father A. M. Coyne, S.J., for the kind interest in this work and provision of facilities.

SUMMARY

The propionylation as well as butyrylation of quinacetophenone gave a mixture of chromones and coumarins, while its acetylation gave only the chromone. Similarly the acetylation of quinbenzophenone gave the coumarin. Thus coumarins which cannot be obtained by the Pechmann method can be readily prepared by this method. Similarly propionylation and butyrylation of γ-orcacetophenone gave the mixture of chromones and coumarins, while the benzoylation gave the flavone.

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