

## 155. *Hydroxy-carbonyl Compounds. Part VI. The Application of the Simonis Reaction to p-Cresol.*

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THE observation of Simonis (*Ber.*, 1913, **46**, 2014; 1914, **47**, 692), that the condensation of *p*-cresol and ethyl  $\alpha$ -methylacetoacetate with the aid of phosphoric oxide gave 2 : 3 : 6-trimethyl-1 : 4-benzopyrone, was confirmed in Part V (*J.*, 1931, 2426), and we accepted the statement that, although all three cresols yielded 1 : 4-pyrones under such conditions, only the *o*-isomeride condensed with the unsubstituted ester. The formation of 4 : 7-dimethylcoumarin from *m*-cresol by this method (Robertson, *Nature*, 1931, **128**, 908), however, led us to make a more extensive study of the Simonis reaction with *p*-cresol, which has now been found to condense with ethyl acetoacetate to give 4 : 6-dimethylcoumarin. The interaction of *p*-cresol and ethyl  $\alpha$ -chloroacetoacetate in the presence of phosphoric oxide gave rise, not to a 1 : 4-pyrone (compare Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 619), but to 3-chloro-4 : 6-dimethylcoumarin in small yield. On the other hand, ethyl  $\alpha$ -ethylacetoacetate and *p*-cresol gave an oily product which was shown to consist mainly of 2 : 6-dimethyl-3-ethyl-1 : 4-benzopyrone, since it readily reacted with piperonal in the presence of sodium ethoxide, yielding a *styrilbenzopyrone* (compare Heilbron, Barnes, and Morton, *J.*, 1923, **123**, 2559; Chakravarti, *J. Indian Chem. Soc.*, 1931, **8**, 129). The formation of a 1 : 4-pyrone in this instance was confirmed by the fact that the product of the ring closure of 2-hydroxy-5-methyl-*n*-butyrophenone with sodium acetate and acetic anhydride afforded the same styrilbenzopyrone.

Ethyl benzoylacetate and *p*-cresol gave 6-methylflavone, together with a crystalline by-product which was not 4-*phenyl*-6-*methyl*-coumarin.

The formation of analogous by-products in other instances is not improbable. To avoid confusion, and to establish the formation of 1 : 4-pyrones by the procedure of Simonis, it is essential that the compounds should be compared with authentic specimens of the 1 : 4-pyrones, as well as with the isomeric coumarins. Simonis and his collaborators relied mainly on the results of alkaline hydrolytic experiments to prove the 1 : 4-pyrone structure of their compounds, but Baker (*J.*, 1925, **127**, 2349) has shown that such results are not always decisive. It appears to us that, apart from the standard synthetical processes, the only trustworthy method of determining the presence of a coumarin structure is the conversion of the compound into the corresponding *o*-methoxycinnamic acid (compare

Canter and Robertson, J., 1931, 1875). On the other hand, the detection of a 1 : 4-benzopyrone structure by opening of the pyrone ring and formation of the *o*-hydroxy-diketone is of limited application (compare Wittig, *Annalen*, 1926, **446**, 155).

From the then available evidence we concluded in Part V (*loc. cit.*) that the course taken by the Simonis reaction depended entirely on the nature of the phenol and was independent of the nature of the ester. In view of the behaviour of *m*- and *p*-cresol, that conclusion can no longer be maintained.

#### EXPERIMENTAL.

**4 : 6-Dimethylcoumarin.**—The condensation of *p*-cresol (6 g.) and ethyl acetoacetate (6 g.) was effected by means of excess of phosphoric oxide and completed by  $\frac{1}{2}$  hour's heating on the steam-bath. The cooled reaction mixture was decomposed with water, and the oily product triturated with dilute aqueous sodium hydroxide and then with water. Crystallisation of the resulting semi-solid from alcohol gave a small amount of 4 : 6-dimethylcoumarin in colourless, elongated, hexagonal prisms, m. p. 152° (Found : C, 75.9; H, 5.6. Calc. for  $C_{11}H_{10}O_2$  : C, 75.8; H, 5.8%), identical with a specimen prepared by the method of Pechmann and Cohen (*Ber.*, 1884, **17**, 2187; compare Dey, J., 1915, **117**, 1646. These authors give m. p. 148°), and depressing the m. p. of 2 : 6-dimethyl-1 : 4-benzopyrone (Wittig, *Ber.*, 1924, **57**, 88) from 100° to 85—87°. The colourless solution of the substance in concentrated sulphuric acid exhibits a violet fluorescence.

**2-Methoxy- $\beta$  : 5-dimethylcinnamic Acid.**—A solution of the foregoing coumarin (4 g.) in methyl alcohol (30 c.c.) and 20% aqueous sodium hydroxide (20 c.c.) was refluxed on the water-bath until fission of the pyrone ring was complete (indicated by a cooled sample not giving a precipitate on dilution with water). The warm solution was agitated with methyl sulphate (80 g.) and 20% aqueous sodium hydroxide (150 c.c.), the mixture acidified (Congo-red), and the ester of the cinnamic acid, mixed with traces of the free acid and unchanged coumarin, isolated by means of ether and hydrolysed by boiling with 6% alcoholic potassium hydroxide (70 c.c.) for 2 hours. The cooled solution was diluted with water (300 c.c.) and acidified with concentrated hydrochloric acid. Next day the solid was collected and dissolved in 5% aqueous sodium carbonate, and the filtered solution was acidified with hydrochloric acid, giving 2-methoxy- $\beta$  : 5-dimethylcinnamic acid (3.4 g.), which crystallised from benzene-ligroin in colourless rhombic prisms, m. p. 120° (Found : C, 70.0; H, 6.7.  $C_{12}H_{14}O_3$  requires C, 69.9; H, 6.8%). The compound is easily soluble in benzene, acetone, or

alcohol and rapidly decolorises bromine water and aqueous potassium permanganate.

The cinnamic acid (2 g.) was oxidised in acetone (30 c.c. at 45°) with 2% aqueous potassium permanganate (150 c.c.), the cooled mixture cleared with sulphur dioxide, and 2-methoxy-5-methylacetophenone isolated by means of ether. The *semicarbazone* of this product crystallised from alcohol in silky prismatic needles, m. p. 201—202°, and was identical with the derivative obtained from an authentic specimen of the ketone (Found : C, 59.7; H, 6.8.  $C_{11}H_{15}O_2N_3$  requires C, 59.7; H, 6.8%).

4 : 6-*Dimethyl-3-ethylcoumarin*.—The interaction of ethyl  $\alpha$ -ethylacetoacetate (15 g.) and *p*-cresol (15 g.) in the presence of 84% sulphuric acid (100 c.c.) during 2 days gave the *coumarin*, which crystallised from alcohol in needles (2 g.), m. p. 106° (Found : C, 77.2; H, 6.9.  $C_{13}H_{14}O_2$  requires C, 77.2; H, 6.9%). The solution in concentrated sulphuric acid has a faint violet fluorescence.

2-*Methoxy- $\beta$  : 5-dimethyl- $\alpha$ -ethylcinnamic Acid*.—The above coumarin (3.8 g.) was converted, by the procedure already described, into the *methoxycinnamic acid* (3 g.), which crystallised from warm ligroin in clusters of colourless needles, m. p. 113° (Found : C, 71.7; H, 7.6.  $C_{14}H_{18}O_3$  requires C, 71.8; H, 7.7%), readily soluble in alcohol, acetone, or benzene. Oxidation of this acid in aqueous acetone with potassium permanganate gave 2-methoxy-5-methylacetophenone; *semicarbazone*, m. p. and mixed m. p. 201—202°.

2-(3' : 4'-*Methylenedioxystyryl*)-6-methyl-3-ethyl-1 : 4-*benzopyrone*.—(A) Phosphoric oxide (20 g.) was added with stirring to a mixture of *p*-cresol (15 g.) and ethyl  $\alpha$ -ethylacetoacetate (15 g.) during  $\frac{1}{2}$  hour, the mixture kept at 80° for 1 hour, and more oxide (20 g.) added in portions. Next day the product was isolated in the usual manner and distilled in a vacuum. The main fraction (3 g.) was a pale yellow oil, b. p. 140—158°/6 mm. A mixture of this oil and piperonal (3 g.) was dissolved in a 3% alcoholic solution of sodium ethoxide (30 c.c.); the *styryl* derivative, which gradually separated, was collected after 2 days and crystallised from alcohol, forming clusters of bright yellow, prismatic needles, m. p. 154° (Found : C, 75.2; H, 5.4.  $C_{21}H_{18}O_4$  requires C, 75.5; H, 5.4%).

(B) A mixture of 2-hydroxy-5-methyl-*n*-butyrophenone (10 g.), sodium acetate (10 g.), and acetic anhydride (40 g.) was heated at 185—190° for 15 hours. After isolation the resulting oil was distilled in a vacuum and condensed with piperonal by means of alcoholic sodium ethoxide. The *styryl*-1 : 4-*benzopyrone* obtained crystallised from alcohol in bright yellow, prismatic needles, m. p. and mixed m. p. 154° (Found : C, 75.2; H, 5.5%).

4-*Phenyl-6-methylcoumarin*.—A mixture of *p*-cresol (6 g.) and

ethyl benzoylacetate (5 g.) in 84% sulphuric acid (25 c.c.) was kept at room temperature for 36 hours and poured into ice-water. Next day the *coumarin* was collected; it crystallised from alcohol in prisms (0.2 g.), m. p. 131° (Found: C, 81.2; H, 5.1.  $C_{16}H_{12}O_2$  requires C, 81.4; H, 5.1%). The solution in concentrated sulphuric acid has a violet fluorescence.

Attempts to obtain this coumarin by the ring closure of 2-hydroxy-5-methylbenzophenone with acetic anhydride and sodium acetate gave only the *acetate* of the ketone, which crystallised from 70% alcohol in colourless needles, m. p. 65° (Found: C, 75.6; H, 5.5.  $C_{16}H_{14}O_3$  requires C, 75.6; H, 5.5%).

6-*Methylflavone*.—(A) Vigorous benzoylation of 2-hydroxy-5-methylacetophenone (5 g.) with benzoic anhydride (18 g.) and sodium benzoate (9 g.) at 185–190° (oil-bath) for 15 hours gave a mixture of the flavone and its 3-benzoyl derivative (compare Wittig, *loc. cit.*). After the removal of the unchanged ketone the two products were separated by means of light petroleum. 3-*Benzoyl-6-methylflavone*, which was almost insoluble in hot light petroleum, crystallised from alcohol in clusters of tiny prisms, m. p. 184° (Found: C, 81.2; H, 4.6.  $C_{23}H_{16}O_3$  requires C, 81.2; H, 4.7%). 6-Methylflavone, recrystallised from benzene–ligroin and then from dilute alcohol, was obtained in colourless prismatic needles, m. p. 120° (Found: C, 81.4; H, 5.0. Calc. for  $C_{16}H_{12}O_2$ : C, 81.4; H, 5.1%). Ruhemann (*Ber.*, 1913, **46**, 2188) gives m. p. 122°.

(B) Sufficient phosphoric oxide was added in portions with stirring to a mixture of *p*-cresol (6 g.) and ethyl benzoylacetate to form a stiff paste. The mixture was heated on the steam-bath for 1 hour and decomposed with water. An ethereal solution of the resulting oil was washed several times with 10% aqueous sodium hydroxide and then with water and dried. Removal of the solvent left an amber-coloured resin, which was repeatedly extracted with boiling ligroin; on cooling, the combined extracts deposited masses of woolly needles, m. p. 86° after purification (Found: C, 75.3; H, 4.9%). On slow evaporation of the petroleum liquor a small amount of 6-methylflavone separated in clusters of prismatic needles, m. p. 118°, and m. p. 120° after purification.

3-*Chloro-4:6-dimethylcoumarin*.—The condensation of *p*-cresol (20 g.) and ethyl  $\alpha$ -chloroacetoacetate (10 g.) was effected with phosphoric oxide (40 g.). The warm mixture was stirred until it formed a stiff paste, and 3 hours later the resulting dark brown mass was dissolved in water (300 c.c.). By means of ether the product was isolated as an oil which solidified on trituration with ligroin. Recrystallised from acetic acid, the coumarin formed colourless

needles, m. p. 158°. Mixed with an authentic specimen, m. p. 159° (Dey, *loc. cit.*), it melted at 158—159° (Found : C, 63.3; H, 4.2. Calc. for  $C_{11}H_9O_2Cl$ : C, 63.3; H, 4.4%).

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