CCCXXX.—*Hydroxy-carbonyl Compounds. Part V. The Preparation of Coumarins and* 1 : 4-*Pyrones from Phenol,* p-*Cresol, Quinol, and* α-*Naphthol.*

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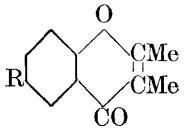
In developing their procedure for the preparation of 1 : 4-benzopyrones by condensation of phenols with esters of acylacetic acids, Simonis and his collaborators (*Ber.*, 1913, **46**, 2014; 1914, **47**, 697, 2229) depended mainly on the results of hydrolytic decomposition experiments to establish the nature of their products. They do not appear to have made direct comparisons of their 1 : 4-pyrones either with authentic specimens or with the isomeric coumarins. Continuing the studies on this reaction described in Parts III and IV of the present series of papers (this vol., pp. 1255, 1877), we have repeated the experiments of Simonis and his co-workers on the condensation of ethyl α-methylacetoacetate with phenol, *p*-cresol, and quinol and have confirmed the conclusions of these authors.

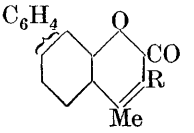
* The analysis figures also agree with $NO_2 \cdot C_6H_4 \cdot CO \cdot CHO, 0 \cdot 5Me \cdot CO_2Et$.

On ring closure with acetic anhydride and sodium acetate the ketones (II, R = H), (II, R = Me), and (II, R = OH) gave rise to the 1 : 4-benzopyrones (I, R = H), (I, R = Me), and (I, R = OH) respectively. The same 1 : 4-pyrones resulted from the condensation of ethyl α-methylacetoacetate with the appropriate phenols in the presence of phosphoric oxide.



(I.)

(II.)



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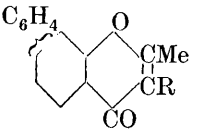

(IV.)

The products in each case can be identical only if both reactions give rise to 1 : 4-benzopyrones. Further, these results support the conclusions of Canter, Curd, and Robertson (this vol., p. 1245) that, in general, ω-substituted *o*-hydroxyacetophenones * ($R{\cdot}CO{\cdot}CH_2X$; X = OMe, Me, etc.) on vigorous acetylation behave in the normal manner, yielding 1 : 4-pyrones.

Attempts to condense quinol and ethyl acetoacetate were entirely unsuccessful.

Compared with that of the simpler monohydric phenols, the behaviour of α-naphthol is interesting, for on condensation with ethyl acetoacetate and with ethyl α-methylacetoacetate by means of phosphoric oxide it affords the naphthacoumarins (III, R = H) and (III, R = Me) respectively. In each case the nature of the product was conclusively established by comparison with an authentic specimen of the coumarin and with the isomeric 1 : 4-α-naphthapyrone (type IV).

A discussion on the possible reasons for the difference in the behaviour of phenols on submission to the Simonis reaction is reserved until more complete data have been collected. At this stage, however, it may be noted that the condensation of esters of acylacetic acids with phenols in the presence of sulphuric acid (Pechmann reaction) invariably gives rise to coumarins. On the other hand, when phosphoric oxide replaces sulphuric acid as the condensing agent, the course of the reaction depends entirely on the nature of the phenol and appears to be independent of the nature of the ester involved. The simpler monohydric phenols which have

* Bhullar and Venkataraman (this vol., p. 1165) erroneously state that Allan and Robinson (J., 1924, **125**, 2192) found that ω-methoxyresacetophenone on vigorous benzoylation gave rise to a product which they considered to be 7-hydroxy-3-benzoylflavone. Allan and Robinson obtained the latter compound from resacetophenone and also showed that the ring closure of ω-methoxyresacetophenone in this manner was not accompanied by nuclear acylation.

been tested (Simonis and co-workers, *loc. cit.*), together with quinol and guaiacol (Heilbron, Barnes, and Morton, J., 1923, **123**, 2559), give rise to 1 : 4-benzopyrones, whereas resorcinol, phloroglucinol, pyrogallol, and α-naphthol yield coumarins.

Experimental.

o-*Methoxypropiophenone.*—(A) *o*-Methoxybenzoyl chloride (Fischer and Slimmer, *Ber.*, 1903, **36**, 2585) (59 g.) was gradually added to a suspension of ethyl sodio-α-methylacetoacetate [from sodium (7 g.) and ethyl α-methylacetoacetate (50 g.)] in dry ether (400 c.c.). A mild reaction ensued and after 16 hours the mixture was heated on the water-bath for 4 hours. Sufficient water was added to dissolve the sodium chloride, and the ethereal layer was separated and dried over sodium sulphate. Removal of the solvent left the product as a viscous brown oil (83 g.). This oil (23 g.) was hydrolysed by boiling with a solution of potassium hydroxide (20 g.) in 50% alcohol (200 c.c.) for 3 hours. After the greater part of the alcohol had been removed by distillation, the residue was diluted with water (400 c.c.) and the solution was neutralised with hydrochloric acid. *o*-Methoxypropiophenone was isolated by means of ether and had b. p. 125—127°/14 mm.; yield, 6·5 g. (Found : OMe, 18·4. Calc. for $C_{10}H_{12}O_2$: OMe, 18·9%) (compare Fischer and Slimmer, *loc. cit.*). The *semicarbazone* separated from dilute methyl alcohol in thick rectangular plates, m. p. 154° (Found : N, 19·1. $C_{11}H_{15}O_2N_3$ requires N, 19·0%).

(B) To a solution of ethylmagnesium iodide [from magnesium turnings (4 g.) and ethyl iodide (26 g.) in ether (300 c.c.) cooled below 0°], *o*-methoxybenzonitrile (Ahrens, *Ber.*, 1887, **20**, 2955) (25 g.) in ether (30 c.c.) was added, and after 16 hours, the addition compound was worked up as usual. The resulting oil was distilled in a vacuum and gave almost pure *o*-methoxypropiophenone (15 g.), b. p. 130—131°/12 mm. The semicarbazone had m. p. and mixed m. p. 154°.

o-*Hydroxypropiophenone.*—The foregoing ketone (7·5 g.) was demethylated by refluxing in benzene (40 c.c.), with anhydrous aluminium chloride (7·5 g.). A brownish-yellow layer gradually formed below the benzene, and after one hour the mixture was cooled, and the product decomposed with ice. The crude ketone was isolated by means of ether, and extracted from the ethereal solution with 10% aqueous potassium hydroxide. *o*-Hydroxypropiophenone was then obtained by acidification, ether extraction and vacuum distillation as a colourless oil (4 g.), b. p. 116°/12 mm., which gave a violet coloration with aqueous ferric chloride (compare Fischer and Slimmer, *loc. cit.*). The *semicarbazone* crystallised from

methyl alcohol in rectangular prisms, m. p. 213° (Found : N, 19·7. $C_{10}H_{13}O_2N_3$ requires N, 20·2%).

2 : 3-*Dimethyl*-1 : 4-*benzopyrone* (I; R = H).—A mixture of *o*-hydroxypropiophenone (3 g.), sodium acetate (5 g.), and acetic anhydride (30 g.) was heated at 170—180° (oil-bath) for 10 hours, and the warm solution was poured into dilute hydrochloric acid (200 c.c.). Next day the mixture was neutralised with sodium hydroxide, and the oily product (1·6 g.) gradually solidified. Crystallised from dilute alcohol (charcoal), the 1 : 4-pyrone formed rhombic plates, m. p. 96—97° (Found : C, 75·8; H, 6·1. Calc. for $C_{11}H_{10}O_2$: C, 75·9; H, 5·8%). A specimen of the pyrone, prepared according to the directions of Petschek and Simonis (*loc. cit.*), was found to be identical (m. p. and mixed m. p. 96—97°).

Mixed with 3 : 4-dimethylcoumarin (Peters and Simonis, *Ber.*, 1908, **41**, 837), the pyrone (obtained by either method) showed a depression in m. p. of about 33°.

2 : 3 : 6-*Trimethyl*-1 : 4-*benzopyrone* (I; R = Me).—2-Hydroxy-5-methylpropiophenone was conveniently prepared by the following modification of Auwers's method (*Ber.*, 1914, **47**, 3318) : Propionyl chloride (25 g.) was gradually added to a mixture of *p*-tolyl methyl ether (30 g.) and anhydrous aluminium chloride (60 g.) in carbon disulphide (150 c.c.). After having been kept at room temperature for 2 hours, the mixture was heated on the steam-bath for 2 minutes and then cooled. The solvent was decanted, and the residual double compound was washed with carbon disulphide and then decomposed with ice and water. The resulting oil was isolated by means of chloroform and distilled under diminished pressure, b. p. 125—130°/12 mm.; yield, 23·4 g. The hydroxy-ketone thus obtained was contaminated with traces of the methyl ether and was purified by solution in 5% sodium hydroxide and removal of the insoluble oil with ether. Recovered from the alkaline solution, 2-hydroxy-5-methylpropiophenone was obtained as a colourless oil (15 g.), b. p. 128—129°/14 mm.

Vigorous acetylation of this ketone (2 g.) with acetic anhydride (20 c.c.) and sodium acetate (3 g.) was effected at 180—190° during 20 hours. On isolation, 2 : 3 : 6-trimethyl-1 : 4-benzopyrone was obtained as an oil which gradually crystallised. Recrystallised from dilute alcohol (charcoal), it formed colourless elongated prisms, m. p. 105—106° (Found : C, 76·9; H, 6·6. Calc. for $C_{12}H_{12}O_2$: C, 76·6; H, 6·4%). This pyrone was identical with a specimen prepared by the method of Petschek and Simonis (*loc. cit.*).

3 : 4 : 6-*Trimethylcoumarin*.—A mixture of *p*-cresol (4·5 g.) and ethyl α-methylacetoacetate (6 g.) was carefully added to cold 80% sulphuric acid (30 c.c.). Next day the reaction mixture was poured

into ice-water, and the product was crystallised from dilute alcohol (charcoal). The *coumarin* formed colourless, elongated, rectangular prisms, m. p. 165° (Found : C, 76·8; H, 6·5. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%). The compound is readily soluble in alcohol and acetic acid and the solutions are non-fluorescent. A mixture of this coumarin and 2 : 3 : 6-trimethyl-1 : 4-benzopyrone began to melt at about 90°.

6-*Hydroxy*-3 : 4-*dimethylcoumarin*.—The procedure described by Borsche (*Ber.*, 1907, **40**, 2731) for the preparation of this coumarin gave disappointing results. The following modification was more satisfactory : Concentrated sulphuric acid (20 c.c.) was gradually added to a solution of quinol (5 g.) and ethyl α-methylacetoacetate (5 g.) in alcohol (20 c.c.) cooled in ice-water, and the mixture was kept at room temperature for 7 days. The dark red liquid, which exhibited a striking green fluorescence, was poured on ice, and the solid (0·65 g.) collected. Crystallised from dilute alcohol, the coumarin melted at 236° (decomp., after sintering at 230°) (Borsche gives m. p. 235—236°). Acetylation of this compound (0·7 g.) with acetic anhydride (7 c.c.) and pyridine (6 c.c.) gave the *acetate*, which separated from alcohol in rectangular plates, m. p. 159—161° (Found : C, 67·7; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%).

6-*Hydroxy*-2 : 3-*dimethyl*-1 : 4-*benzopyrone*.—On applying the Nencki reaction to quinol as described by Goldzweig and Kaiser (*J. pr. Chem.*, 1891, **43**, 93), we obtained only traces of 2 : 5-dihydroxypropiophenone. The ketone, however, was conveniently obtained from quinol dipropionate by the method of Rosenmund and Lohfert (*Ber.*, 1928, **61**, 2606). This ester was prepared by the interaction of quinol (10 g.) and propionyl chloride (20 g.) in the presence of pyridine (40 c.c.) cooled in ice-water, and crystallised from alcohol in plates (14 g.), m. p. 112—113° (compare Hesse, *Annalen*, 1880, **200**, 246).

The reaction mixture resulting from the acetylation of 2 : 5-dihydroxypropiophenone (1 g.) by means of acetic anhydride (10 c.c.) and sodium acetate (1·5 g.) at 170—180° for 12 hours was poured into water. Next day the solid was collected, washed with water, and crystallised from dilute alcohol. The *acetate* of the pyrone formed colourless, elongated rectangular prisms (0·6 g.), m. p. 139° (Found : C, 67·5; H, 5·4. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). Deacetylation of this compound (0·6 g.) with cold 5% methyl-alcoholic potassium hydroxide (20 c.c.) during 3 hours afforded 6-hydroxy-2 : 3-dimethyl-1 : 4-benzopyrone, m. p. 247° after sintering at 241° (Found : C, 69·8; H, 5·5. Calc. for $C_{11}H_{10}O_3$: C, 69·5; H, 5·3%).

A specimen of this pyrone, prepared according to the directions of

Simonis and Lehmann (*Ber.*, 1914, **47**, 692), melted at 246° after sintering at 242° (these authors give m. p. 242°). Mixed with a specimen prepared from 2 : 5-dihydroxypropiophenone, it showed no depression in m. p. The acetyl derivative crystallised from dilute alcohol in elongated rectangular prisms, m. p. and mixed m. p. 139° (Found : C, 67·0; H, 5·4%).

A mixture of 6-hydroxy-2 : 3-dimethyl-1 : 4-benzopyrone and 6-hydroxy-3 : 4-dimethylcoumarin began to melt at 195°, and a mixture of the corresponding acetates melted at 110—128°.

4-*Methyl*-α-*naphthacoumarin* (III; R = H).—(A) Sufficient phosphoric oxide was gradually added to a mixture of α-naphthol (5 g.) and ethyl acetoacetate (5 g.) to form a thin paste, and the mixture was kept at 60—70° for a short time. Further quantities of α-naphthol (5 g.) and phosphoric oxide (excess) were added and the reaction was completed by heating on the steam-bath for 10 minutes. The product was isolated in the usual manner and washed with water, and the coloured impurities were removed by trituration with 5% aqueous sodium hydroxide. Crystallised from methyl alcohol (charcoal), the coumarin formed colourless needles (2·6 g.), m. p. 170° (Found : C, 79·6; H, 4·8. Calc. for $C_{14}H_{10}O_2$: C, 80·0; H, 4·8%). A solution of the compound in concentrated sulphuric acid exhibits a green fluorescence. Mixed with an authentic specimen of 2-methyl-1 : 4-α-naphthapyrone, m. p. 174—174·5° (Wittig, *Annalen*, 1925, **446**, 155), it showed a depression in m. p. of about 35°.

(B) The following modification of Bartsch's procedure (*Ber.*, 1903, **36**, 1966) gave an improved yield of the coumarin (compare Bacovescu, *Ber.*, 1910, **43**, 1280) : A mixture of α-naphthol (5 g.) and ethyl acetoacetate (5 g.) was dissolved in 84% sulphuric acid (50 c.c.). The solid which first separated dissolved during the course of 12 hours, and the coumarin was precipitated by pouring the reaction mixture on ice. It separated from warm methyl alcohol in needles (7·5 g.), m. p. 170° alone or mixed with a specimen prepared by method (A).

2 : 3-*Dimethyl*-1 : 4-α-*naphthapyrone* (IV; R = Me).—A mixture of 2-propionyl-α-naphthol (Hantzsch, *Ber.*, 1906, **39**, 3096) (3 g.), acetic anhydride (20 c.c.), and sodium acetate (5 g.) was heated for 16 hours at 180—190° and then poured into dilute hydrochloric acid. Next day the brown solid was crystallised from a small volume of alcohol (charcoal), and the product was well washed with ether to remove a small amount of the acetate of the unchanged ketone. Recrystallised from dilute alcohol, the 1 : 4-*pyrone* formed elongated prisms, m. p. 143—144° (Found : C, 80·3; H, 5·5. $C_{15}H_{12}O_2$ requires C, 80·4; H, 5·4%). The compound is readily soluble in

acetone, acetic acid, and hot ligroin. In concentrated sulphuric acid it exhibits a green fluorescence.

3 : 4-*Dimethyl-α-naphthacoumarin* (III; R = Me).—(A) The condensation of ethyl α-methylacetoacetate (5 g.) and α-naphthol (5 g.) by means of phosphoric oxide was effected by the procedure used in the case of ethyl acetoacetate. The *coumarin* crystallised from acetic acid in colourless, rod-like prisms (2·6 g.), m. p. 203—204° (Found : C, 80·2; H, 5·4. $C_{15}H_{12}O_2$ requires C, 80·4; H, 5·4%). The colourless solution of the compound in concentrated sulphuric acid has a green fluorescence.

(B) To a well-cooled mixture of α-naphthol (5 g.) and ethyl α-methylacetoacetate (5 g.), 84% sulphuric acid (50 c.c.) was added, and next day the mixture was poured into ice-water. The solid was collected, washed, and crystallised from acetic acid, forming colourless rod-like prisms, m. p. and mixed m. p. 203—204° (Found : C, 80·0; H, 5·5%). Mixed with 2 : 3-dimethyl-1 : 4-α-naphthapyrone, the coumarin (prepared by either method) showed a depression in m. p. of about 100°.

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