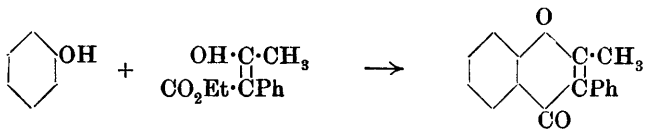
CXVI.—*Syntheses of Benzo-γ-pyrones and Flavones. Part III.*

By Serge Jacobson and Brojendranath Ghosh.

In Parts I and II of this series (this vol., pp. 424, 959), it has been shown that when the α-hydrogen atom in ethyl aceto- or benzoyl-acetate is substituted by a complex group, such as benzyl, the ordinary course of condensation with phenols is changed, the products being substituted benzo-γ-pyrones or flavones, instead of the corresponding coumarins. In this paper, the study of the reaction has been extended to substances which contain the phenyl group as substituent, such as ethyl phenyl-aceto- or -formyl-acetate. As anticipated, the result was the production of substituted benzo-γ-pyrones, the reaction being expressed as follows:



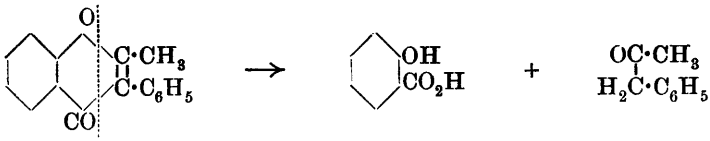
It is interesting to note that the formula suggested for scutellarein by Molisch and Goldschmidt (*Monatsh.*, 1901, **22**, 679) represents this substance as belonging to this class of compounds, and it is hoped that the experiments now described may lead to a method of synthesising this substance.

The condensing agents employed in the present investigation were concentrated sulphuric acid and anhydrous zinc chloride. With ethyl α-phenylacetoacetate, the condensations of resorcinol, pyrogallol, and α-naphthol proceeded smoothly in the presence of concentrated sulphuric acid, but with phloroglucinol, the use of anhydrous zinc chloride was found to be necessary.

The condensation of ethyl α-phenylformylacetate with phenols did not take place with concentrated sulphuric acid, but with anhydrous zinc chloride, the reaction proceeded in the normal manner. This apparent inactivity of the ester with concentrated sulphuric acid might be explained by the existence of the ester in the ketonic form (Wislicenus, *Ber.*, 1887, **20**, 2933) in sulphuric acid, whereas it is probable that the ester reacts most readily with the phenols when in the enolic form. On being heated with zinc chloride, the ketonic form melts, and, according to Wislicenus (*loc. cit.*), passes into the enolic form, which is then capable of interaction. In concentrated sulphuric acid, however, the mixture

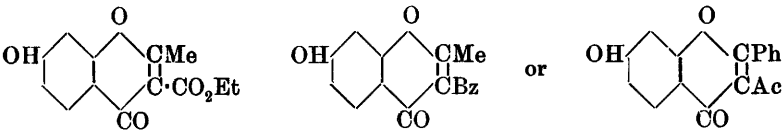
cannot be heated, because of the tendency of the phenols to become sulphonated.

In order to prove the constitution of the compounds, they were decomposed with concentrated alkali, whereby a hydroxy-acid and a neutral ketone, benzyl methyl ketone, were obtained. The decomposition may be represented as follows:



The constitution of the condensation product of resorcinol and ethyl α-phenylformylacetate was not determined, as it decomposed into substances which could not be separated from one another.

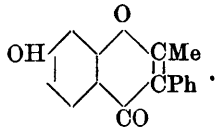
The condensation of ethyl acetylmalonate and benzoylacetoacetate with resorcinol were attempted, using concentrated sulphuric acid as condensing agent, with the object of synthesising compounds of the formulæ:



Unfortunately, however, the condensations proceeded in another way, yielding, in the case of ethyl acetylmalonate, β-methylumbelliferon, and in that of ethyl benzoylacetoacetate, β-phenylumbelliferon. In the case of ethyl benzoylacetoacetate and resorcinol, anhydrous zinc chloride was also used as condensing agent, but the result was the same as with sulphuric acid. These results support the view expressed in Part I (*loc. cit.*), that the direction of the condensation depends on the reactivity of the α-hydrogen atom in ethyl acetoacetate. When it is very reactive, the condensation yields the coumarin, but when the reactivity is diminished, it takes the alternative course, yielding benzo-γ-pyrones. In the present instance, the hydrogen atom being situated between three carbonyl groups, becomes very reactive, and coumarins are formed instead of benzo-γ-pyrones. The condensation of ethyl α-phenylacetoacetate with *m*-cresol was attempted, but no definite product could be isolated.

EXPERIMENTAL.

7-Hydroxy-3-phenyl-2-methylbenzo-γ-pyrone,



Three grams of resorcinol were mixed with 5 grams of ethyl α-phenylacetoacetate (Beckh, *Ber.*, 1898, **31**, 3161), and to this about 10 c.c. of concentrated sulphuric acid were slowly added, the flask being constantly cooled to prevent any rise in temperature. The mixture was kept overnight, and then poured on ice. The solid matter was collected, washed, and then crystallised from dilute alcohol:

0·1312 gave 0·3666 CO_2 and 0·0575 H_2O. C = 76·21; H = 4·87.
$C_{16}H_{12}O_3$ requires C = 76·19; H = 4·76 per cent.

7-Hydroxy-3-phenyl-2-methylbenzo-γ-pyrone crystallises in colourless needles, melting at 226°. It dissolves in aqueous sodium hydroxide with a yellow colour and a slight violet fluorescence. With concentrated sulphuric acid it yields a colourless solution, which exhibits an intensely bluish-violet fluorescence. In alcoholic solution it gives a violet coloration with ferric chloride.

The *acetyl* dervative was prepared by boiling the substance with acetic anhydride and fused sodium acetate. It crystallised from dilute alcohol in colourless needles, melting at 185°. In concentrated sulphuric acid it develops a bluish-violet fluorescence:

0·1075 gave 0·2904 CO_2 and 0·0484 H_2O. C = 73·67; H = 5·00.
$C_{18}H_{14}O_4$ requires C = 73·47; H = 4·76 per cent.

The *benzoyl* derivative, prepared by dissolving the substance in dry pyridine, and adding excess of benzoyl chloride to the solution, crystallises from dilute acetic acid in colourless needles, melting at 187—188°:

0·1396 gave 0·3972 CO_2 and 0·0572 H_2O. C = 77·59; H = 4·41.
$C_{23}H_{16}O_4$ requires C = 77·52; H = 4·49 per cent.

The *ethyl ether*, prepared by warming the substance with excess of dilute sodium hydroxide and ethyl sulphate, crystallises from alcohol in short, colourless prisms, melting at 89—90°:

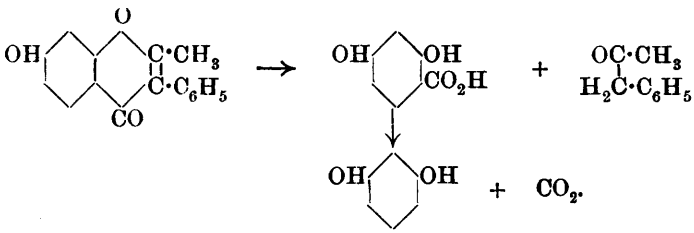
0·1329 gave 0·3625 CO_2 and 0·0691 H_2O. C = 74·39; H = 5·77.
$C_{18}H_{16}O_3,\frac{1}{2}H_2O$ requires C = 74·74; H = 5·88 per cent.

The *methyl ether* was prepared in the same way as the ethyl ether. It crystallises from dilute alcohol in colourless needles, melting at 87°.

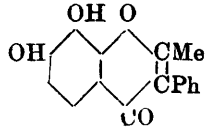
Decomposition with Potassium Hydroxide.

In order to prove the constitution of the substance, it was decomposed with 33 per cent. alkali. Three grams of 7-hydroxy-3-phenyl-2-methylbenzo-γ-pyrone were boiled with a solution of 15 grams of potassium hydroxide in 30 c.c. of water for about five hours, and the product was distilled in a current of steam. The oil which passed over was extracted with ether, and the ethereal solution evaporated. An oil was left, which on shaking with a solution of semicarbazide hydrochloride and excess of sodium acetate gave a solid semicarbazone, which separated from benzene in colourless needles, melting at 187° (the melting point of the semicarbazone of benzyl methyl ketone is 188°, Wolff, *Annalen*, 1902, **325**, 147). (Found, N = 22·10. Calc., N = 21·99 per cent.)

The alkaline solution left in the flask after distillation with steam was acidified, and the precipitate was collected. From the acid filtrate, on extraction with ether and subsequent evaporation, a solid was obtained, which was identified as resorcinol. The precipitate just mentioned was dissolved in aqueous sodium hydroxide, and a current of carbon dioxide was passed through the solution in order to liberate some of the original material which had escaped interaction. This was removed, and the solution was acidified and extracted with ether. The ethereal solution, on evaporation, gave a residue of a solid containing an oily impurity, which was treated with aqueous ammonia, and the insoluble oil dissolved in ether. The ammoniacal solution, on acidification, gave a solid, crystallising from hot water in colourless needles, which, after drying at 120°, melted at 204—205°, but when quickly heated melted at 211° (the melting point of anhydrous β-resorcylic acid is 204—206°; when quickly heated, it melts at 213°, Kostanecki and Bistrzycki, *Ber.*, 1885, **18**, 1985):



7 : 8-*Dihydroxy*-3-*phenyl*-2-*methylbenzo*-γ-*pyrone*,



This substance was prepared in the manner described in the foregoing paragraph from 4 grams of pyrogallol, 6 grams of ethyl α-phenylacetoacetate, and 15 c.c. of concentrated sulphuric acid. It crystallises from acetic acid in pale yellow prisms, melting at 268°. With concentrated sulphuric acid, it exhibits a green fluorescence:

0·1248 gave 0·3268 CO_2 and 0·0528 H_2O. C = 71·41; H = 4·70.
$C_{16}H_{12}O_4$ requires C = 71·64; H = 4·44 per cent.

The *acetyl* derivative, prepared in the usual way, crystallises from acetic acid in colourless needles, melting at 211°:

0·1234 gave 0·3094 CO_2 and 0·0528 H_2O. C = 68·38; H = 4·75.
$C_{20}H_{16}O_6$ requires C = 68·18; H = 4·55 per cent.

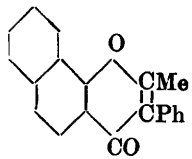
The *benzoyl* derivative, prepared by the Schotten-Baumann method, crystallises from acetic acid in glistening, yellow prisms, melting at 204°:

0·1400 gave 0·3802 CO_2 and 0·0535 H_2O. C = 74·06; H = 4·25.
$C_{30}H_{20}O_6,\frac{1}{2}H_2O$ requires C = 74·22; H = 4·33 per cent.

The *ethyl ether* was prepared by warming the substance with excess of dilute sodium hydroxide and ethyl sulphate. It crystallises from alcohol in colourless needles, melting at 132°:

0·1110 gave 0·2742 CO_2 and 0·0579 H_2O. C = 67·37; H = 5·79.
$C_{20}H_{20}O_6$ requires C = 67·41; H = 5·71 per cent.

3-*Phenyl*-2-*methyl*-1 : 4-α-*naphthapyrone*,

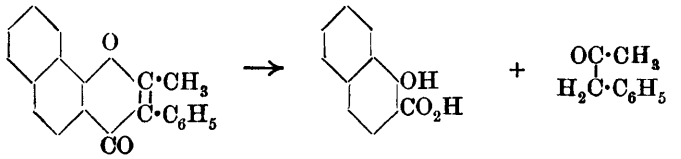


This was prepared from 3 grams of α-naphthol, 5 grams of ethyl α-phenylacetoacetate, and 10 c.c. of concentrated sulphuric acid. On pouring the acid solution on ice, a viscid oil separated, which solidified on keeping. The product crystallises from alcohol in lemon-yellow needles, melting at 209°. In concentrated sulphuric acid it develops a dark green fluorescence:

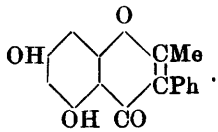
0·1215 gave 0·3725 CO_2 and 0·0548 H_2O. C = 83·62; H = 5·01.
$C_{20}H_{14}O_2$ requires C = 83·92; H = 4·89 per cent.

Decomposition with Potassium Hydroxide.

Three grams of the above compound were added to a solution of 15 grams of potassium hydroxide in 15 c.c. of water. The mixture was boiled for about six hours, and then treated with a current of steam. From the distillate, benzyl methyl ketone was isolated, which was recognised by its semicarbazone. The alkaline residue, after distillation in a current of steam, was diluted, and the insoluble matter removed by filtration. The subsequent treatment of the solution was the same as described in the previous case. The acid which separated was identified as 1-naphthol-2-carboxylic acid by its melting point, as well as by its characteristic reactions:



5 : 7-*Dihydroxy*-3-*phenyl*-2-*methylbenzo*-γ-*pyrone*,



A mixture of 4 grams of phloroglucinol and 5 grams of ethyl α-phenylacetoacetate was dissolved in a small quantity of glacial acetic acid, 20 grams of finely powdered anhydrous zinc chloride were added, and the whole was heated for about six hours at 105—110°. On pouring the mixture into water, a viscid oil separated, which solidified on stirring. This was collected, washed, and crystallised from dilute acetic acid:

0·1058 gave 0·2776 CO_2 and 0·0438 H_2O. C = 71·56; H = 4·60.

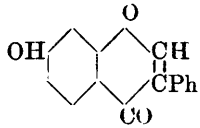
$C_{16}H_{12}O_4$ requires C = 71·64; H = 4·47 per cent.

5 : 7-*Dihydroxy*-3-*phenyl*-2-*methylbenzo*-γ-*pyrone* crystallises in lemon-yellow needles, melting at 178°. It dissolves in alkali hydroxide, giving a yellow colour, but no fluorescence. It is readily soluble in alcohol or acetic acid, sparingly so in hot water, and insoluble in benzene or light petroleum. In concentrated sulphuric acid it dissolves with a yellow colour, and exhibits a green fluorescence. It does not reduce ammoniacal silver nitrate solution, even on boiling.

The *acetyl* derivative crystallises from dilute alcohol in colourless needles, melting at 146°:

0·1164 gave 0·2758 CO_2 and 0·0490 H_2O. C = 64·62; H = 4·76.
$C_{20}H_{16}O_6$ requires C = 64·82; H = 4·86 per cent.

7-Hydroxy-3-phenylbenzo-γ-pyrone,



This substance was prepared from resorcinol and ethyl α-phenylformylacetate. A mixture of 4 grams of resorcinol and 5 grams of the ester was dissolved in a small amount of glacial acetic acid, and heated with about 15 grams of finely powdered anhydrous zinc chloride at 100—105° for five to six hours. The oil which at first separated on pouring the mixture in water partly solidified on being stirred. The product was freed from oily material by pressing it on porous earthenware, and was crystallised from dilute alcohol. The yield was poor:

0·1074 gave 0·2750 CO_2 and 0·0470 H_2O. C = 70·00; H = 4·86.
$C_{15}H_{10}O_2,H_2O$ requires C = 70·31; H = 4·68 per cent.

7-Hydroxy-3-phenylbenzo-γ-pyrone crystallises in pale yellow needles, melting at 131°. When dissolved in alcohol, it gives a green fluorescence, and the solution becomes violet on the addition of a drop of ferric chloride. It dissolves in sodium hydroxide with a red colour, and in concentrated sulphuric acid it develops a green fluorescence.

Condensation of Resorcinol with Ethyl Acetylmalonate and with Ethyl Benzoylacetoacetate.

A mixture of five grams of resorcinol and 10 grams of ethyl acetylmalonate or 11 grams of ethyl benzoylacetoacetate was cooled in ice, and 15 c.c. of concentrated sulphuric acid were slowly added. The mixture was kept overnight, and then poured on ice. The precipitate was collected, washed, and crystallised from alcohol. In the case of ethyl acetylmalonate, β-methylumbelliferon, and in the case of ethyl benzoylacetoacetate, β-phenylumbelliferon, was obtained. They were identified by their melting points and by the preparation of their acetyl derivatives.

In the case of ethyl benzoylacetoacetate, the condensation was also attempted with anhydrous zinc chloride, the product being the same as in the previous case.

Interaction of m-*Cresol and Ethyl* α-*Phenylacetoacetate.*

Three grams of *m*-cresol and 5 grams of the ester were mixed with 10 c.c. of concentrated sulphuric acid, and the mixture was kept overnight, when it was poured on ice, but nothing of the nature of a solid substance separated, even on long keeping. The result was the same when the reacting mixture was warmed on a water-bath.

Our thanks are due to Dr. Smiles and Dr. Tuck for their continued interest and encouragement during this investigation.

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