XLIII.—*The* 4- *and* 4′-*Methoxybenzoylbenzoins.*

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ALKALINE reagents and notably sodium ethoxide convert benzoylmandelonitrile (Francis and Davis, J., 1909, **95**, 1404) into benzoylbenzoin (Robinson and Robinson, P., 1913, **29**, 266; J., 1914, **105**, 1456). By adding benzaldehyde to the reaction mixture, Greene and Robinson (J., 1922, **121**, 2182) increased the yield of this product and found similarly that benzoylpiperoin was advantageously prepared from a mixture of benzoyl-3 : 4-methylenedioxymandelonitrile and piperonal. These observations were in harmony with Lapworth's view of the course of the benzoin reaction (J., 1903, **83**, 1004) and further evidence of a condensation of the aldol type was obtained when the interaction of benzoylmandelonitrile and anisaldehyde resulted in the isolation of a methoxybenzoylbenzoin melting at 119·5—120·5°. The structure of this product is discussed below.

It was also shown that 3 : 4-methylenedioxybenzoylbenzoin, $CH_2O_2{:}C_6H_3{\cdot}CO{\cdot}CH(OBz)Ph$ (I), is the main product of condensation between benzoyl-3 : 4-methylenedioxymandelonitrile and benzaldehyde, whereas 3′ : 4′-methylenedioxybenzoylbenzoin,

$$PhCO{\cdot}CH(OBz){\cdot}C_6H_3{:}O_2CH_2$$

(II), is obtained from benzoylmandelonitrile and piperonal. A migration of the benzoyl group was therefore definitely established.

By reducing the time of reaction, these products may be obtained almost pure, and the same is true of the piperonyl-furyl isomerides,

to which, by analogy, structures (III) and (IV) are assigned. The similarity existing between benzaldehyde and furfuraldehyde extends in this case to the yields of " mixed " benzoin. Thus substances (I) and (III) are obtained in small yield only (5 to 10%), whereas piperonal reacts with the benzoylcyanohydrins of these two aldehydes to give substances (II) and (IV) in much larger amount (25 to 30%).

$$CH_2O_2{:}C_6H_3{\cdot}CH(OBz){\cdot}CN + CHO{\cdot}C_4H_3O \longrightarrow CH_2O_2{:}C_6H_3{\cdot}CO{\cdot}CH(OBz){\cdot}C_4H_3O \quad \text{(III.)}$$

$$\text{(VII.)}\quad C_4H_3O{\cdot}CH(OBz){\cdot}CN + CH_2O_2{:}C_6H_3{\cdot}CHO \longrightarrow C_4H_3O{\cdot}CO{\cdot}CH(OBz){\cdot}C_6H_3{:}O_2CH_2 \quad \text{(IV.)}$$

In the same way, anisaldehyde and benzoylmandelonitrile react to give 4′-methoxybenzoylbenzoin (V; m. p. 127—128°), whilst benzoyl-*p*-methoxymandelonitrile and benzaldehyde yield the isomeric 4-methoxybenzoylbenzoin (VI; m. p. 119·5—120·5°). Here, however, the allocation of formulæ is not so simple, for the lower-melting isomeride is also obtainable from the other reaction mixture (Greene and Robinson,* *loc. cit.*, p. 2189). In fact, either of the isomerides may be obtained from benzoylmandelonitrile and anisaldehyde. The reaction system is very sensitive to changes in the experimental conditions, which have therefore been studied in detail.

On standing in contact with cold sodium ethoxide solution, both isomerides are hydrolysed to *p*-methoxybenzoin (Ekecrantz and Ahlqvist, *Arkiv Kem. Min. Geol.*, 1908, **3**, No. 13, 26). It is desirable, therefore, to interrupt the reactions some 15 minutes after addition of the condensing agent, and when this is done the yields are roughly as follows :

	Benzoylmandelonitrile and anisaldehyde.	Benzoyl-*p*-methoxymandelonitrile and benzaldehyde.
½ Mol. of NaOEt. Rapid interruption.	Higher-melting isomeride, 30%.	No crystalline product.
1 Mol. of NaOEt. Rapid interruption.	Lower-melting isomeride, 8%.	Lower-melting isomeride, 15%.
½ Mol. of NaOEt. Gradual addition.	Both isomerides.	Benzoylbenzoin.

In the cases mentioned above, the diminution of the quantity of sodium ethoxide to a half-molecular proportion leads to the spontaneous separation of substances I, II, III, and IV. It seems reasonable, therefore, to regard the isomeride melting at 127—128° as the normal product of condensation between benzoylmandelonitrile and anisaldehyde, and this substance is therefore 4′-methoxybenzoylbenzoin. The isomeride of m. p. 119·5—120·5° is accord-

* Compare this communication for the scheme of numbering.

ingly 4-methoxybenzoylbenzoin and its occurrence as a product of condensation of benzoylmandelonitrile and anisaldehyde appears to be due to a double decomposition which results in the formation of benzaldehyde and benzoyl-*p*-methoxymandelonitrile. The following results demonstrate that such a reaction can occur. Attempted condensations of benzoylmandelonitrile and furfuraldehyde on the one hand and of benzoylfurfuraldehydecyanohydrin (VII) and benzaldehyde on the other have uniformly furnished mixtures of benzoylbenzoin (m. p. 125°) and benzoylfuroin (m. p. 92—93°) in slightly varying proportions.

It is clear that the formation of benzoylfuroin from benzoylmandelonitrile and furfuraldehyde involves preliminary transference of the benzoyl cyanide addenda from benzaldehyde to furfuraldehyde. The benzoylfurfuraldehydecyanohydrin so formed then reacts with unchanged furfuraldehyde in the normal manner, and benzoylfurion is, in fact, readily accessible through this derivative. In the second series of experiments, we have the inverse change. Some benzoylmandelonitrile is formed at the expense of the benzoylfurfuraldehydecyanohydrin, and it then reacts with unchanged benzaldehyde, yielding benzoylbenzoin. All these reaction mixtures originally contained excess of free aldehyde, and accordingly, where the gradual addition of sodium ethoxide during a period of three or four hours has favoured equilibrium, the products of this type of change are present in relatively greater amount.

Under similar conditions, benzoylbenzoin was actually the only crystalline product obtained from benzoyl-*p*-methoxymandelonitrile and benzaldehyde (table above). Here again we must infer degradation of the original nitrile and formation of benzoylmandelonitrile, which subsequently undergoes its normal condensation with unchanged benzaldehyde. With benzoylmandelonitrile and anisaldehyde, the concomitant processes are represented by the scheme below, in which it has not been considered necessary to illustrate the contemporaneous formation of benzoylbenzoin and benzoylanisoin.

$$MeO\cdot C_6H_4\cdot CHO + Ph\cdot CH(OBz)\cdot CN \longrightarrow \underset{(V.)}{MeO\cdot C_6H_4\cdot CH(OBz)\cdot COPh}$$

$$MeO\cdot C_6H_4\cdot CH(OBz)\cdot CN + Ph\cdot CHO \longrightarrow \underset{(VI.)}{MeO\cdot C_6H_4\cdot CO\cdot CH(OBz)Ph}$$

In the studies now recorded, the formation of isomeric derivatives of mixed benzoins was observed in three out of four cases. It is apparently favoured by disparity of the constituent aldehydes.

EXPERIMENTAL.

Benzoylfurfuraldehydecyanohydrin.—Always a good and, on one occasion, a practically theoretical yield of this substance was

obtained by application of the general method of Francis and Davis (*loc. cit.*). Furfuraldehyde (24 g.), benzoyl chloride (35 g.), and a solution of potassium cyanide (17 g.) in water (200 c.c.) were shaken together for 1 hour with cooling. The product separated from 90% alcohol in colourless, hexagonal plates (Found : C, 68·9; H, 4·3. $C_{13}H_9O_3N$ requires C, 68·7; H, 4·0%). This material, m. p. 48°, was used for the preparation of the derivatives described below. Distillation under reduced pressure and recrystallisation from alcohol raise the melting point to 49°.

Benzoylfuroin, $C_4H_3O{\cdot}CO{\cdot}CH(OBz){\cdot}C_4H_3O$.—A cold solution of sodium ethoxide (0·6 g. of sodium) in ethyl alcohol (30 c.c.) was rapidly added to one of benzoylfurfuraldehydecyanohydrin (11 g.) and furfuraldehyde (12 g.) in ethyl alcohol (25 c.c.). The reaction mixture was shaken for 4 minutes in running water, which checked a slight rise of temperature, and then cooled in ice-water. The product that separated was collected after 15 minutes and extracted with boiling ethyl alcohol (20 c.c.). The filtered solution yielded 6·15 g., m. p. 92—93° (Found for twice recrystallised material : C, 68·7; H, 4·1. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·0%); a further 1·2 g., m. p. 91—93°, could be isolated. The substance separates from alcohol in colourless octahedra, the predominant prismatic modification being derived by prolongation along one axis. With cold concentrated sulphuric acid, an intense green colour is developed and this gradually changes to brown on warming. By the action of alcoholic sodium ethoxide, a small amount of furil, m. p. 164°, was produced, which was identified by the melting point of its mixture with an authentic sample (E. Fischer, *Annalen*, 1882, **211**, 221).

Benzfuroin.—It seemed possible to clear up the question as to whether benzfuroin (E. Fischer, *loc. cit.*) is a single substance by benzoylating it and comparing the product with the isomeric benzoylbenzfuroins.

Benzfuroin was recovered unchanged after being shaken with aqueous potassium hydroxide and benzoyl chloride, even in presence of ether, or with pyridine and benzoyl chloride, and heating with the acid chloride alone resulted in profound decomposition. Difficulties of quite another kind were met in attempts, described in detail below, to prepare the isomeric derivatives; for the most part, mixtures of benzoylbenzoin and benzoylfuroin were obtained. Neither of the required isomerides being present in isolable amount, this method of attack was abandoned. There are, however, grounds for believing that benzfuroin is a mixture of two isomerides.

The melting points of four preparations of benzfuroin showed variations (recorded : 135—141°, 134—135°, 134—137°, 138—140°).

These may, of course, be due in part to the presence of benzoin or furoin. Benzfuroin was the sole product isolated in an attempt to prepare a benzoylbenzfuroin by the very slow addition, during 5 or 6 hours with water cooling, of sodium ethoxide (1·15 g. of sodium) in ethyl alcohol (40 c.c.) to a cold solution of benzoylmandelonitrile (11 g.) and furfuraldehyde (12 g.) in ethyl alcohol (40 c.c.). The product (1·9 g.) was isolated by means of ether and crystallised from boiling water, giving 0·5 g. of long, feathery crystals, m. p. 139—141°. The granular, amorphous residue was recrystallised from a little absolute alcohol and then from aqueous alcohol. This material (0·2 g.) melted at 141·5—143·5°, and at 138—140° when mixed with the other fraction or with benzfuroin (m. p. 137—139°) prepared by Fischer's method. The possibility that benzfuroin was here the product of hydrolysis again suggests its composite character. Finally, apart from decomposition, the material was practically unchanged by the action of boiling alcoholic sodium ethoxide, a reagent which doubtless induces enolisation. The recovered material softened at 136° and melted at 140—142°, alone or mixed with the original material.

Attempts to prepare Isomeric Benzoylbenzfuroins.—In each experiment the reaction mixture was treated with ether and water. The ethereal layer was washed successively with aqueous sodium bisulphite, sodium carbonate solution, and water, and dried with anhydrous sodium sulphate. The following table summarises the results of the experiments.

	Products from	
	Benzoylmandelonitrile and furfuraldehyde.	Benzoylfurfuraldehydecyanohydrin and benzaldehyde.
½ Mol. of NaOEt. Rapid interruption.	Benzoylbenzoin and benzoylfuroin.	Benzoylbenzoin and benzoylfuroin.
1 Mol. of NaOEt. Rapid interruption.	Ditto (together with benzfuroin).	Benzoylbenzoin and benzoylfuroin (A).
½ Mol. of NaOEt. Gradual addition.	Ditto (richer in benzoylfuroin).	Ditto (richer in benzoylbenzoin).

The following is a typical experiment resulting in the formation of the product (A). A solution of sodium ethoxide (1·15 g. of sodium) in ethyl alcohol (30 c.c.) was added in one portion to one of benzoylfurfuraldehydecyanohydrin (11·4 g.) and benzaldehyde (10 g.) in ethyl alcohol (30 c.c.). The mixture was shaken in running water for 15 minutes and then extracted as above. After removal of solvent and addition of a little methyl alcohol, crystals readily separated, which were filtered off after 3 hours (4·3 g.). Recrystallised from 90% alcohol (15 c.c.), they melted at 87—88° and showed under the microscope a variety of shapes strongly resembling those observed in the case of 4-methoxybenzoylbenzoin. This crop was

recrystallised from 90% alcohol (15 c.c.), giving two crops, and a third by addition of water : Crop I, 2·45 g., m. p. 86—87°; crop II, 0·75 g., m. p. 87°; crop III, 0·26 g., m. p. 85—87°. Crop I, recrystallised from absolute alcohol, gave two crops, of which the larger weighed 2·19 g. and melted at 86—87°. It still showed a variety of shapes under the microscope (Found : C, 74·0; H, 4·7. $C_{21}H_{16}O_3 + C_{17}H_{12}O_5$ requires C, 74·5; H, 4·6%). For comparative purposes, an equimolecular mixture of benzoylfuroin and benzoylbenzoin was prepared. After preliminary softening, this began to melt at 85·5° and still contained some solid at 90°, whilst when mixed with product (A) it melted at 84·5—88°. This leads us to conclude that both mixtures are in the neighbourhood of the eutectic. Product (A) is therefore a mixture containing benzoylfuroin, benzoylbenzoin, and probably some benzoylbenzfuroin, although this has on no occasion been isolated.

4-*Methoxybenzoylbenzoin* (VI; m. p. 119·5—120·5°).—This substance, obtained with fortuitous ease from a reaction mixture of benzoylmandelonitrile and anisaldehyde, was described (Greene and Robinson, *loc. cit.*) as 4′-methoxybenzoylbenzoin. Reasons for adopting the alternative configuration have now been given.

4-Methoxybenzoylbenzoin is best prepared by condensing benzoyl-*p*-methoxymandelonitrile and benzaldehyde. The reaction requires rather more than 1 mol. of sodium ethoxide and should be rapidly interrupted. Thus 1·5 g. of nearly pure material were obtained when a solution of sodium ethoxide (0·6 g. of sodium) in alcohol (20 c.c.) was added in one portion to the nitrile (7·3 g.) and benzaldehyde (10 g.) in cold alcoholic solution (20 c.c.). The reaction lasted 10 minutes.

To observe the abnormal production of this isomeride from benzoylmandelonitrile and anisaldehyde, it is desirable to reduce the time of reaction and so check hydrolysis. A solution of sodium ethoxide (1·3 g. of sodium) in alcohol (25 c.c.) was added in one lot to a solution of benzoylmandelonitrile (12 g.) and anisaldehyde (11 g.) in alcohol (30 c.c.). Rise of temperature was checked by shaking the reaction mixture in running water, and after 7 minutes the material was extracted by addition of ether and water. After removal of the solvent, the residual liquor was treated with methyl alcohol and light petroleum. Cooling in ice and salt gave crystals which, once recrystallised from alcohol, weighed 0·9 g. and melted between 118° and 120°. These were identical with the original specimen (Greene and Robinson, *loc. cit.*) (Found : MeO, 7·9, 8·1. Calc. for $C_{22}H_{18}O_4$, MeO, 9·0%).

Abnormal Production of Benzoylbenzoin.—On three occasions when ½ mol. of sodium ethoxide was added drop by drop to alcoholic

solutions of benzoyl-*p*-methoxymandelonitrile and benzaldehyde, small quantities of benzoylbenzoin were obtained in a good state of purity. This unexpected result was ascertained in one case by combustion and the method of mixed melting point and in the others by the latter method only. The characteristic prismatic rods of benzoylbenzoin were also readily recognisable under the microscope. The yields of this product, starting in each case from 11·5 g. of benzoyl-*p*-methoxymandelonitrile and 11 g. of benzaldehyde, were 1·6 g. (m. p. 122—125°), 0·7 g. (m. p. 120—123°), and 0·6 g. (m. p. 119—122°), respectively. The condensation of benzoyl-*p*-methoxymandelonitrile with anisaldehyde does not afford a convenient means of preparing benzoylanisoin.

4′-*Methoxybenzoylbenzoin* (V; m. p. 127—128°).—A solution of sodium ethoxide (1·15 g. of sodium) in ethyl alcohol (30 c.c.) was added in one portion to benzoylmandelonitrile (23 g.) and anisaldehyde (22·5 g.) dissolved in ethyl alcohol (30 c.c.). The mixture was shaken in running water for 5 minutes and then worked up in the usual manner. The crystals (3·4 g.) which separated from the ether, recrystallised from 90% alcohol (75 c.c.), had m. p. 125—127°. The ethereal mother-liquor was treated as usual, and the crop recovered from the drying agent (magnesium sulphate) by addition of water, on recrystallisation, gave 4·9 g. of m. p. 124—127°; from the ethereal solution 2·4 g. of m. p. 121—124° were obtained. The pure product melted at 127—128° (Found : C, 76·1; H, 5·3; MeO, 8·5. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2; MeO, 9·0%). A mixture with the isomeride described above melted at 100—104°. 4′-Methoxybenzoylbenzoin crystallises from alcohol or ether in colourless, prismatic rods and dissolves in cold concentrated sulphuric acid to a brassy yellow solution which, on warming, remains yellow for a time and then suddenly passes through reddish-brown to dark greenish-brown.

A further illustration of the sensitive nature of the general reaction was provided by an experiment in which a cold solution of sodium ethoxide (0·6 g. of sodium) in alcohol (25 c.c.) was, during 3 or 4 hours, gradually added to a cold solution of benzoylmandelonitrile (12 g.) and anisaldehyde (11 g.) in ethyl alcohol (30 c.c.). Some crystals separated during the course of the reaction, which was controlled by water cooling. These were filtered off, washed with water and alcohol, and recrystallised from alcohol. The substance (0·1 g.) had m. p. 120—124°, which was raised to 120—126° by admixture with 4′-methoxybenzoylbenzoin and depressed by admixture with the other isomeride. The filtrate of the reaction mixture was extracted as usual and gave a syrup from which, by nucleation, 4-methoxybenzoylbenzoin (0·3 g.) was obtained.

Piperonoyl-α-furylcarbinyl Benzoate (III).—This substance was obtained from benzoylmethylenedioxymandelonitrile (28 g.) and furfuraldehyde (23 g.) in alcohol (30 c.c.) by addition in one lot of a solution of sodium ethoxide (1·15 g. of sodium) in ethyl alcohol (30 c.c.). The mixture was shaken in running water for 5 minutes and then extracted as in other cases. From the ethereal solution, a crop was obtained which, after one recrystallisation from 90% alcohol (45 c.c.), gave 3·3 g. of crystals, m. p. 130—132°. A smaller fraction (1·3 g.), m. p. 117—130°, was recovered from the drying agent. In two half-scale experiments the yields were 1·4 g. of m. p. 125—130° and 1·6 g. of m. p. 125—129°. In the former, the reaction was allowed to proceed for 20 minutes before extraction, and this delay seems to have decreased the yield. Increase of the proportion of sodium to 1·1 g. for 14·1 g. of nitrile in a reaction which lasted 15 minutes led to the isolation of an impure product (3·4 g.), m. p. 103—106°.

From the three earlier experiments were obtained 6·6 g. of material, m. p. 131·5—133·5°, and for analysis a portion of this was recrystallised from glacial acetic acid, toluene and rectified spirit. The pure product melted at 132·5—133·5° (Found : C, 68·5; H, 4·1. $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%). The substance crystallised from alcohol in colourless, prismatic rods and when mixed with its isomeride of m. p. 140—141°, melted at 110—115°.

α-Furoylpiperonylcarbinyl Benzoate (IV).—This substance was prepared readily and in good yield by the condensation of piperonal (12 g.) with benzoylfurfuraldehydecyanohydrin (11 g.) in ethyl alcohol (40 c.c.). Sodium ethoxide (0·6 g. of sodium) in ethyl alcohol (20 c.c.) was added in one portion and the mixture was shaken in running water. After 25 minutes, the solid was collected, and only a minute quantity was recovered from the mother-liquor. The substance was recrystallised from glacial acetic acid (25 c.c.) and from ethyl alcohol (80 c.c.), and the main crop (4·7 g.) had m. p. 136—138°. For analysis, this material was recrystallised from alcohol, glacial acetic acid, 90% alcohol, toluene, and 90% alcohol, giving 3·1 g. of the pure substance, m. p. 140—141° (Found : C, 68·8; H, 4·1. $C_{20}H_{14}O_6$ requires C, 68·6; H, 4·0%). The colourless, hexagonal plates dissolve in cold concentrated sulphuric acid to an intense crimson solution tinged with brown.

3 : 4- and 3′ : 4′-*Methylenedioxybenzoylbenzoins* (I and II).—By reducing the time of reaction hydrolysis has been lessened and more convenient methods of preparing these isomerides are now submitted.

A solution of sodium ethoxide (0·6 g. of sodium) in ethyl alcohol (20 c.c.) was added to benzoylmandelonitrile (12 g.) and piperonal (11 g.) in ethyl alcohol (40 c.c.). The mixture was shaken in

running water for 15 minutes and extracted with ether. The solid residue was crystallised from glacial acetic acid, giving 2·6 g. of material, m. p. 132·5—134·5°, and 1·1 g., m. p. 129—132°. The ethereal solution after the usual treatment gave 1·9 g. of crystals, m. p. 127—131°. A portion of this product, recrystallised once, was identical with authentic 3′ : 4′-methylenedioxybenzoylbenzoin, m. p. 134—135°.

From benzoylmethylenedioxymandelonitrile (14·1 g.) and benzaldehyde (11 g.) dissolved in alcohol (40 c.c.) there were obtained, by addition, in one portion, of a solution of sodium ethoxide (0·6 g. of sodium) in alcohol (20 c.c.), 1·1 g. of a product, m. p. 144—147°, and 146—148° when mixed with 3 : 4-methylenedioxybenzoylbenzoin (m. p. 147·5—148·5°). In this experiment, the reaction was allowed to continue for 35 minutes.

When the time of reaction and the quantities of nitrile and aldehyde (but not of sodium) were halved, the percentage yield was almost doubled.

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