CCCLXXXIII.—*Substitution Products of 4-Hydroxybenzophenone and of its Methyl Ether.*

By WILLIAM BLAKEY, WALTER IDRIS JONES, and HAROLD ARCHIBALD SCARBOROUGH.

THE orientation of substituents in the benzophenone series has been investigated in but few cases, *e.g.*, the introduction of bromine (Kottenhahn, *Annalen*, 1891, **264**, 170; Kunkel, *Ber.*, 1904, **37**, 3485), the direct nitration of benzophenone and of the isomeric mononitrobenzophenones (Staedel, *Annalen*, 1878, **194**, 347; 1883, **218**, 344; 1895, **283**, 164), and the introduction of a nitro-group into certain 4-halogenobenzophenones (Montagne, *Ber.*, 1916, **49**, 2262), and it was found that the first substituent entered the unsubstituted nucleus, usually with the production of the three possible isomerides.

The nitration of 4-methylbenzophenone gave derivatives the structure of which seems to be uncertain (Zincke, *Ber.*, 1872, **5**, 685; 1874, **7**, 983; Limpricht, *Annalen*, 1895, **286**, 324).

These results and those observed in the diphenyl series show marked similarities, and it therefore seemed of interest to consider the substitution products of 4-hydroxybenzophenone and of its methyl ether.

The direct chlorination of 4-hydroxybenzophenone in acetic acid solution gave 3 : 5-*dichloro*-4-*hydroxybenzophenone*; under all the conditions tried, the same product was obtained.

The reaction of 4-hydroxybenzophenone with bromine could be regulated, and 3-bromo- and 3 : 5-dibromo-4-hydroxybenzophenone were obtained when the ketone, dissolved in acetic acid, was treated with the appropriate quantity of bromine. The same dibromo-derivative was obtained when the ketone was shaken with an aqueous bromine solution or treated in alkaline solution with bromine.

The iodination of 4-hydroxybenzophenone in alkaline solution yielded the 3-*iodo*-derivative; treatment with iodine monochloride in acetic acid solution gave 3 : 5-*di-iodo*-4-*hydroxybenzophenone.*

A single nitro-group was introduced into 4-hydroxybenzophenone by treating the ketone with nitric acid in glacial acetic acid solution at 50° or by merely dissolving it in cold nitric acid. Solution in nitric acid at 40° gave 3 : 5-dinitro-4-hydroxybenzophenone. Attempts to obtain higher substitution products seemed to result in partial oxidation.

The direct chlorination of the methyl ether could be controlled and 3-*chloro*- and 3 : 5-*dichloro*-4-*methoxybenzophenone* were isolated.

On bromination of the methyl ether, 3-*bromo*-4-*methoxybenzo-*

phenone was obtained under all conditions which did not involve a demethylation. In contrast to this, the chlorination of the monobromo-derivative proceeded smoothly and 3-*chloro*-5-*bromo*-4-*methoxybenzophenone* was obtained.

The introduction of one atom of iodine was effected with iodine monochloride, and higher iodination products than 3-iodo-4-methoxybenzophenone could not be obtained.

The formation of 3-*nitro*-4-*methoxybenzophenone* took place when the methoxybenzophenone was dissolved in fuming nitric acid. Nitration in a mixture of sulphuric and acetic acids yielded a mixture of dinitro-compounds; the formation of 3 : 3′-*dinitro*-4-*methoxybenzophenone* has been definitely established. A second isomeride is most probably 2′ : 3-dinitro-4-methoxybenzophenone, but this structure is based on a process of elimination of probable products. In addition to these isomerides there was a residue which after repeated crystallisations still seemed to be a mixture.

Trinitration products were obtained when nitration was effected in concentrated sulphuric acid solution. The formation of 3 : 3′ : 5 *trinitro*-4-*methoxybenzophenone* has been definitely established; an isomeride is shown to have two nitro-groups in the 3 : 5-positions and it is suggested that the third nitro-group is in the 2′-position. After the separation of the two pure products, a residue was obtained which could not be further purified.

The most suitable methods for the determination of the structure of the substitution products were: (*a*) oximation and conversion of the oximes into anilides. This procedure was found satisfactory provided not more than one nitro-group was present in the molecule; considerable difficulty was experienced in effecting the oximation of dinitro-derivatives, and the product could not be purified easily. (*b*) Synthesis of the substituted ketone by the Friedel–Crafts reaction was effective in the case of certain of the nitro-derivatives.

Oxidation to a substituted benzoic acid was not very satisfactory, as it was difficult to avoid complete oxidation of the molecule.

A survey of the results obtained shows that in 4-hydroxybenzophenone each ortho-position with respect to the hydroxyl group may be substituted with ease, irrespective of the nature of the substituting groups. Substitution in the opposite nucleus could not be effected before the 3 : 5-positions were filled.

The methyl ether behaves somewhat differently, in that one position only in the ortho-relationship to the methoxyl group is usually substituted. Chlorine behaves abnormally, in that both positions may be substituted by this reagent. On nitration, a second substituent enters the unsubstituted nucleus.

A comparison of these results with those obtained in the diphenyl series shows that in each case the presence of a hydroxyl group promotes substitution in all vacant positions in the ortho-para relationship to this group; the presence of such groups as the halogens or the nitro-group inhibits substitution in the same nucleus. The conversion of the hydroxyl group into the methoxyl group reduces the directive power, and although the first substituent enters in an ortho-position to this group, the second entering group usually goes into the opposite nucleus.

EXPERIMENTAL.

4-Methoxybenzophenone was prepared from anisole and benzoyl chloride by Gattermann's method (*Ber.*, 1890, **23**, 1204).

4-*Hydroxybenzophenone*.—The hydrolysis of all the methyl ethers was effected as follows: 5 G. of the ether and 20 c.c. of 48% hydrobromic acid were dissolved in acetic acid and refluxed for about 12 hours. Part of the acetic acid was then removed, and the residue poured into water. The acid was neutralised with ammonia, the product taken up in ether, and the hydroxy-ketone shaken out with a 10% solution of sodium hydroxide and reprecipitated with sulphuric acid. 4-Hydroxybenzophenone separated from dilute methyl alcohol in prisms, m. p. 135°.

4-Acetoxybenzophenone was prepared by acetylation in pyridine solution. It crystallised from dilute methyl alcohol in needles, m. p. 81° (Found: C, 74·8; H, 5·1. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%).

3-*Chloro*-4-*methoxybenzophenone* was obtained when 4-methoxybenzophenone was treated with chlorine (slightly less than 1 mol.) in a cold solution of acetic acid. It separated from methyl alcohol in prisms, m. p. 98° (Found: Cl, 14·5. $C_{14}H_{11}O_2Cl$ requires Cl, 14·4%). On further chlorination in acetic acid solution, 3:5-dichloro-4-methoxybenzophenone (m. p. 74°) was obtained. The mono-derivative must therefore have been substituted in the 3-position.

3 : 5-*Dichloro*-4-*methoxybenzophenone*.—Into a solution of 10 g. of 4-methoxybenzophenone and 10 g. of fused sodium acetate in glacial acetic acid chlorine was passed until the gain in weight was 7 g. After some hours, the solution was poured into water. The product crystallised from alcohol in colourless needles, m. p. 74°. The same product was obtained by chlorination of the molten ketone in the presence of iodine or by chlorination in boiling carbon tetrachloride solution (Found: Cl, 25·2. $C_{14}H_{10}O_2Cl_2$ requires Cl, 25·3%).

The α-*oxime* was prepared by adding 10 g. of potassium hydroxide and 4·5 g. of hydroxylamine hydrochloride, each dissolved in the minimum quantity of water, to 6 g. of the dichloro-ketone dissolved in 100 c.c. of alcohol. The mixture was refluxed for 6 hours, the alcohol in part removed, and the residue poured into water and neutralised with dilute hydrochloric acid. The oxime separated from alcohol in needles, m. p. 146° (Found : Cl, 23·9. $C_{14}H_{11}O_2NCl_2$ requires Cl, 24·0%).

3 : 5-*Dichloro-4-methoxybenzanilide.*—4 G. of the oxime, in dry ethereal solution, were treated with 7·5 g. of phosphorus pentachloride. After 12 hours, water was cautiously added and the ethereal layer was separated, washed, and dried. The *anilide*, after removal of the ether, crystallised from alcohol in pale yellow needles, m. p. 154° (Found : Cl, 23·95. $C_{14}H_{11}O_2NCl_2$ requires Cl, 24·0%).

On hydrolysis of the anilide (5 g.) with 20 c.c. of 10% hydrochloric acid for 6 hours at 140°, aniline and 3 : 5-*dichloroanisic acid* were obtained. 3 : 5-Dichloroanisic acid, prepared by the direct chlorination of anisic acid, crystallised from alcohol; m. p. 202° (Found : Cl, 32·05. $C_8H_6O_3Cl_2$ requires Cl, 32·1%). The acid was converted into the acid chloride, and the crude product added to a pyridine solution of aniline. The anilide thus obtained had m. p. 154°, alone or mixed with that prepared from the oxime.

3 : 5-*Dichloro-4-hydroxybenzophenone* was obtained from the methyl ether or by passing 5 g. of chlorine into a solution of 5 g. of 4-hydroxybenzophenone and 10 g. of sodium acetate in 100 c.c. of acetic acid and keeping the mixture for some hours. The product crystallised from methyl alcohol in needles, m. p. 148° (Found : Cl, 26·6. $C_{13}H_8O_2Cl_2$ requires Cl, 26·6%).

3-*Bromo-4-methoxybenzophenone.*—A solution of 5 g. of 4-methoxybenzophenone and 5 g. of sodium acetate in acetic acid was heated with 4·5 g. of bromine at 100° for 6 hours. The product separated from alcohol in needles, m. p. 94°. The same product was formed by bromination in the cold, in bright sunlight, or by heating together an intimate mixture of 5 g. of the ketone, 5 g. of sodium acetate, 4 g. of bromine, and 0·5 g. of pyridine (Found : Br, 27·5. $C_{14}H_{11}O_2Br$ requires Br, 27·5%).

Oximation of the ketone was carried out in the manner previously described. The *α-oxime* crystallised from alcohol in plates, m. p. 164° (Found : Br, 26·0. $C_{14}H_{12}O_2NBr$ requires Br, 26·15%). It was transformed into 3-*bromo-4-methoxybenzanilide*, which separated from alcohol in needles, m. p. 170° (Found : Br, 26·15. $C_{14}H_{12}O_2NBr$ requires Br, 26·15%). This anilide on hydrolysis yielded aniline and 3-bromoanisic acid and was prepared from the amine and the acid chloride.

The *β-oxime*, which remained in the mother-liquor, was precipitated with water. It separated from 30% aqueous alcohol in needles, m. p. 111·5° (Found : Br, 26·1. $C_{14}H_{12}O_2NBr$ requires Br, 26·15%). This oxime formed about 60% of the mixed oximes. On transformation, *benzo-3-bromo-4-methoxyanilide* was obtained, which crystallised from alcohol in needles, m. p. 156° (Found : Br, 26·25. $C_{14}H_{12}O_2NBr$ requires Br, 26·15%). The anilide on hydrolysis gave 3-bromoanisidine (m. p. 56°) and was prepared from the amine and benzoyl chloride.

3-Bromo-4-hydroxybenzophenone was obtained by the hydrolysis of the methyl ether or by direct bromination of the ketone in acetic acid solution. It crystallised from alcohol in glistening needles, m. p. 183° (Found : Br, 28·75. Calc. for $C_{13}H_9O_2Br$: Br, 28·9%).

3-*Chloro-5-bromo-4-methoxybenzophenone* was obtained by leading chlorine into a glacial acetic acid solution of 5-bromo-4-methoxybenzophenone and fused sodium acetate, and precipitated after some hours by pouring the product into water. It separated from methyl alcohol in needles, m. p. 92° (Found : 0·1496 g. gave 0·1520 g. of silver halides. Calc. weight, 0·1523 g.). The structure assigned depends upon the fact that in no case has chlorine been introduced into the unsubstituted ring.

3 : 5-Dibromo-4-hydroxybenzophenone resulted from (*a*) direct bromination of the ketone in acetic acid solution (compare Hantzsch, *Ber.*, 1906, **39**, 3094; Kostanecki, *Ber.*, 1907, **40**, 3662); (*b*) the addition of a 5% solution of bromine in potassium bromide to the ketone dissolved in an excess of dilute potassium hydroxide, the temperature being kept below 5°; and (*c*) by shaking the ketone with bromine water. The product separated from alcohol in needles, m. p. 155°.

The same product was obtained when an intimate mixture of fused sodium acetate and 4-methoxybenzophenone was treated with bromine in a sealed tube at 140°.

3-*Iodo-4-methoxybenzophenone*.—10 G. of 4-methoxybenzophenone, dissolved in 100 c.c. of acetic acid, were treated with 12 g. of iodine monochloride. After 2 days, the mixture was poured into water, and the colour discharged with sulphur dioxide. The semi-solid mass crystallised from alcohol in needles, m. p. 81° (Found : I, 37·3. $C_{14}H_{11}O_2I$ requires I, 37·6%).

The *α-oxime* crystallised from alcohol in needles, m. p. 182° (Found : I, 35·9. $C_{14}H_{12}O_2NI$ requires I, 36·0%). On conversion of this oxime, 3-*iodo-4-methoxybenzanilide* was obtained, which separated from alcohol in faintly yellow needles, m. p. 206° (Found : I, 35·9. $C_{14}H_{12}O_2NI$ requires I, 36·0%). The anilide on hydrolysis yielded aniline and 3-iodoanisic acid. The acid separated from alcohol in needles, m. p. 240° (Found : I, 45·55. Calc. for $C_8H_7O_3I$: I, 45·65%). A specimen of the acid was prepared from *p*-cresol for comparison.

The β-*oxime*, precipitated from the mother-liquor on addition of water, crystallised from 30% alcohol in needles, m. p. 135° (Found : I, 35·8%). This oxime, on conversion, yielded *benz*-3-*iodo*-4-*methoxyanilide*, which crystallised from alcohol in needles, m. p. 164° (Found : I, 35·9. $C_{14}H_{12}O_2NI$ requires I, 36·0%). On hydrolysis, the anilide yielded 3-iodoanisidine, which separated from alcohol–light petroleum in needles, m. p. 75° (Found : I, 51·1. Calc. for C_7H_8ONI : I, 51·0%).

The anilide was prepared from *o*-anisidine by the following stages : *o*-anisidine was converted into *o*-iodoanisole and nitrated in glacial acetic acid solution. The 2-iodo-4-nitroanisole thus obtained was reduced to the amine, which was treated with benzoyl chloride in pyridine.

3-*Iodo*-4-*hydroxybenzophenone* was obtained on the hydrolysis of the methyl ether or by treating an alkaline solution of 4-hydroxybenzophenone with a 5% solution of iodine in potassium iodide. The product separated from methyl alcohol in plates, m. p. 184° (Found : I, 39·05. $C_{13}H_9O_2I$ requires I, 39·2%).

3 : 5-*Di-iodo*-4-*hydroxybenzophenone*.—5 G. of the hydroxyketone together with 10 g. of sodium acetate were dissolved in 100 c.c. of acetic acid and treated with 9 g. of iodine monochloride. After 12 hours, the mixture was poured into water; the precipitate obtained crystallised from alcohol in feathery needles, m. p. 145° (Found : I, 57·6. $C_{13}H_8O_2I_2$ requires I, 57·7%).

3-*Nitro*-4-*methoxybenzophenone*.—A solution of 5 g. of 4-methoxybenzophenone in 50 c.c. of nitric acid (*d* 1·5) was kept for 12 hours, and then poured on ice; the semi-solid product crystallised from alcohol in yellow needles, m. p. 105° (Found : N, 5·5. $C_{14}H_{11}O_4N$ requires N, 5·45%).

An oxime was obtained when 17 g. of the nitro-compound dissolved in alcohol were treated with 14 g. of hydroxylamine hydrochloride and 11·5 g. of potassium hydroxide, each dissolved in the minimum quantity of water. A red coloration appeared in the solution and acetic acid was added until the colour became yellowish-green. After refluxing for 3 hours, the oxime was extracted in the usual way. The α-*oxime*, after repeated crystallisations from alcohol, separated in yellow plates, m. p. 179° (Found : N, 10·3. $C_{14}H_{12}O_4N_2$ requires N, 10·3%). On conversion the oxime yielded 3-*nitro*-4-*methoxybenzanilide*, which separated from alcohol in needles, m. p. 163° (Found : N, 10·3. $C_{14}H_{12}O_4N_2$ requires N, 10·3%). This anilide on hydrolysis gave 3-nitroanisic acid and aniline, and was prepared from the amine and the acid chloride.

3-Nitro-4-hydroxybenzophenone was obtained when (*a*) the methyl ether was hydrolysed, (*b*) 5 g. of 4-hydroxybenzophenone, dissolved in a mixture of 100 c.c. of acetic acid and 20 c.c. of acetic anhydride, were treated with 1·5 c.c. of nitric acid (*d* 1·5), dissolved in 10 c.c. of acetic acid at 50—60°, and (*c*) a solution of 5 g. of the hydroxy-ketone in 100 c.c. of nitric acid (*d* 1·4) was kept at 0° for 2 hours. The product crystallised from methyl alcohol in plates, m. p. 94° (Borsche, *Ber.*, 1917, **50**, 1339, gives m. p. 120—121°) (Found : N, 5·7. Calc. for $C_{13}H_9O_4N$: N, 5·75%).

3 : 5-*Dinitro-4-methoxybenzophenone.*—5 G. of 4-chloro-3 : 5-dinitrobenzophenone (Ullmann, *Annalen*, 1909, **366**, 92), dissolved in dry methyl alcohol, were treated with a solution of 1 g. of sodium in methyl alcohol. After 12 hours, the product was precipitated by pouring the mixture into dilute hydrochloric acid. It separated from methyl alcohol in yellow needles, m. p. 105° (Found : C, 55·5; H, 3·4. $C_{14}H_{10}O_6N_2$ requires C, 55·6; H, 3·3%).

3 : 5-Dinitro-4-hydroxybenzophenone was prepared by Ullmann's method (*loc. cit.*) or by heating a solution of 5 g. of 4-hydroxybenzophenone in 100 c.c. of nitric acid (*d* 1·4) at 40° for 30 minutes. It crystallised from alcohol in yellow needles, m. p. 138° (Found : N, 9·85. Calc. for $C_{13}H_8O_6N_2$: N, 9·75%). The product of direct nitration did not appear to be a single substance, but no other pure compound was isolated.

3′-*Nitro-4-methoxybenzophenone.*—18 G. of *m*-nitrobenzoyl chloride and 10·5 g. of anisole, dissolved in 100 c.c. of carbon disulphide, were treated with 25 g. of aluminium chloride at room temperature, and the reaction completed on the water-bath. The product crystallised from alcohol in faintly yellow needles, m. p. 95° (Found : N, 5·5. $C_{14}H_{11}O_4N$ requires N, 5·45%). On hydrolysis, 3′-nitro-4-hydroxybenzophenone was obtained.

3 : 3′-*Dinitro-4-methoxybenzophenone.*—(*a*) A solution of 5 g. of 3′-nitro-4-methoxybenzophenone in 50 c.c. of nitric acid (*d* 1·5) was kept over-night. (*b*) 15 G. of 4-methoxybenzophenone, dissolved in a mixture of 60 c.c. each of acetic and sulphuric acids, were treated with 10 c.c. of nitric acid (*d* 1·5) below 10°; the product, which was a mixture of isomerides, was crystallised from acetic acid and then repeatedly from alcohol until a pure substance was obtained. (*c*) 5 G. of 3-nitro-4-methoxybenzophenone were nitrated, in solution in a mixture of sulphuric and acetic acids, with 2 c.c. of nitric acid (*d* 1·5). The yield was about 70% of the mixed nitration product.

It separated from alcohol in faintly yellow needles, m. p. 143° (Found : N, 9·3. $C_{14}H_{10}O_6N_2$ requires N, 9·2%).

3 : 3′-*Dinitro-4-hydroxybenzophenone* was obtained on demethylation. It separated from alcohol in faintly green prisms, m. p. 165° (Found : N, 9·8. $C_{13}H_8O_6N_2$ requires N, 9·75%).

The structure of these compounds follows from their method of preparation.

3 : 4′-*Dinitro*-4-*methoxybenzophenone*. — 4′-Nitro-4-methoxybenzophenone (Auwers, *Ber.*, 1903, **36**, 3891) was nitrated by dissolving it in nitric acid (*d* 1·5) and keeping the solution for 12 hours. The product separated from alcohol in small prisms, m. p. 174° (Found : N, 9·3. $C_{14}H_{10}O_6N_2$ requires N, 9·3%).

3 : 3′ : 5-*Trinitro*-4-*methoxybenzophenone*.—(*a*) A solution of 10 g. of 4-methoxybenzophenone in a mixture of equal volumes of sulphuric acid and nitric acid (*d* 1·5) was kept for 2 days. The product was a mixture of isomerides, which were separated by successive crystallisations from acetic acid, toluene, and acetic acid. (*b*) 3 : 5-Dinitro-4-methoxybenzophenone was nitrated under the same conditions and the isomerides were separated. (*c*) 3 : 3′-Dinitro-4-methoxybenzophenone on nitration gave an almost quantitative yield of the trinitro-compound. This isomeride formed about 65% of the crude nitration product and was sparingly soluble in toluene; it separated from acetic acid in prisms, m. p. 184° (Found : N, 12·05. $C_{14}H_9O_8N_3$ requires N, 12·1%). The structure assigned is based on three observations : (1) on prolonged oxidation with chromic anhydride in acetic acid solution, a small quantity of *m*-nitrobenzoic acid (m. p. 140°) was isolated, (2) on further nitration the two dinitro-4-methoxybenzophenones both yielded the same product, and (3) 3 : 3′-dinitro-4-methoxybenzophenone yielded one trinitro-compound only.

2′(?) : 3-*Dinitro*-4-*methoxybenzophenone* was obtained when the 3 : 3′-dinitro-compound had all been removed from the crude nitration product. It was crystallised from toluene and then from acetic acid, separating in needles, m. p. 125° (Found : N, 9·35. $C_{14}H_{10}O_6N_2$ requires N, 9·3%).

2′(?) : 3 : 5-*Trinitro*-4-*methoxybenzophenone* was obtained from the crude nitration products of 4-methoxybenzophenone and of 3 : 5-dinitro-4-methoxybenzophenone. It crystallised from toluene in glistening, light yellow plates, m. p. 142° (Found : N, 12·1. $C_{14}H_9O_8N_3$ requires N, 12·1%).

A definite structure cannot be assigned to these compounds, as all attempts to prepare a pure specimen of 2′-nitro-4-methoxybenzophenone failed. Three out of the four most probable dinitro-4-methoxybenzophenones, however, have been obtained in a state of purity and the dinitro-4-methoxybenzophenone, m. p. 125°, was not identical with any of these compounds.

THE UNIVERSITY CHEMICAL LABORATORIES,
CAMBRIDGE.

[*Received, August* 31*st*, 1927.]