CCCXXX.—*The Nitration and Bromination of 4-Methylbenzophenone.*

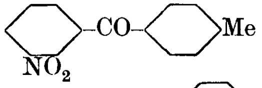
By William Blakey and Harold Archibald Scarborough.

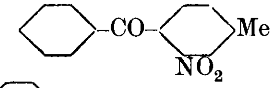
It has been shown (J., 1927, 2865) that the influence of a methoxyl group, in the 4-position, in the benzophenone series is to direct the first entering substituent into the 3-position; and that further substitution leads to the 3′- and the 5-positions being occupied successively. The halogens, which are usually classed with the methoxyl group since their ortho-para directive power is also to be ascribed to a conjugative effect, behave in the benzophenone series in a different manner, in that the first entering substituent goes into the unsubstituted nucleus (compare Kunckel, *Ber.*, 1904, **37**, 3485; Montagne, *Ber.*, 1916, **49**, 2262). It thus seemed of interest to investigate the behaviour of the methyl group, the least active of the ortho-para directive series, and compare it with that of the methoxyl group and of a halogen.

In an investigation of the products of nitration of phenyl-*p*-tolylmethane, Zincke and Milne (*Ber.*, 1872, **5**, 685) showed that a nitro-derivative of 4-methylbenzophenone was formed; and in a further communication, Zincke and Plascuda (*Ber.*, 1874, **7**, 983) described the preparation of the mono-, di-, and tri-nitro-derivatives of the ketone, ascribing the structure 3′-nitro-4-methylbenzophenone (I) to the first because it was oxidised by chromic anhydride in glacial acetic acid solution to *m*-nitrobenzoic acid.

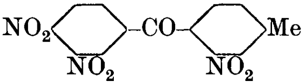
A synthesis of 3′-nitro-4-methylbenzophenone, from *m*-nitrobenzoyl chloride and toluene, was carried out by Limpricht and Lenz (*Annalen*, 1895, **286**, 324), but neither this compound nor its derivatives had the properties ascribed to them by Zincke and Plascuda. Basing their opinion upon the product of oxidation, Limpricht and Lenz reassigned to the alleged substance (I) the structure 2-nitro-4-methylbenzophenone (II); further, they suggested that the continued nitration of 3′-nitro-4-methylbenzophenone yielded 2 : 3′-dinitro-4-methylbenzophenone, and that 3′-nitro-, 4′-nitro-, 2 : 3′-, and 2 : 4′-dinitro-4-methylbenzophenones all gave the same trinitro-compound (III).

(I.)





(II.)



(III.)

The evidence upon which these structures are based seems to be very slender, and, moreover, appears to be contrary to the rules of substitution; the matter was therefore re-investigated.

The nitration of 4-methylbenzophenone, in fuming nitric acid solution, yielded 3-*nitro*-4-*methylbenzophenone*, of which the constitution was established by condensing 3-nitro-*p*-toluoyl chloride with benzene. Under the same conditions, 3′-nitro-4-methylbenzophenone was converted into 3 : 3′-*dinitro*-4-*methylbenzophenone*; the same product was also obtained when 3-nitro-4-methylbenzophenone was nitrated in cold sulphuric acid solution. Further, 4′-nitro-4-methylbenzophenone yielded 3 : 4′-*dinitro*-4-*methylbenzophenone*, since on partial reduction and deamination 3-nitro-4-methylbenzophenone resulted.

The continued nitration of 3 : 3′-dinitro-4-methylbenzophenone in sulphuric acid solution, at 80°, yielded 3 : 3′ : 5-*trinitro*-4-*methylbenzophenone*, which was also obtained when the product of condensation of 3 : 5-dinitro-*p*-toluoyl chloride and benzene was nitrated in sulphuric acid solution, the assigned structure being thus established. Further nitration of 3 : 4′-dinitro-4-methylbenzophenone with a slight excess of nitric acid and in sulphuric acid solution gave 3 : 4′ : 5-*trinitro*-4-*methylbenzophenone*, whereas by use of a large excess of nitric acid at 80°, 3 : 3′ : 4′ : 5-*tetranitro*-4-*methylbenzophenone* was obtained. The proof of the structure of these compounds depends largely upon their reactions with *p*-nitrosodimethylaniline and with piperidine.

The bromination of 4-methylbenzophenone, which was effected by dissolving the compound in a large excess of dry bromine, gave 3-*bromo*-4-*methylbenzophenone*, the structure being established by a synthesis of the compound from 3-bromo-*p*-toluoyl chloride and benzene, and also by reducing 3-nitro-4-methylbenzophenone to the amine and replacing the amino-group by bromine. Under the same conditions 3′- and 4′-nitro- and 3′ : 5′-*dinitro*-4-*methylbenzophenones* were brominated and in each case the bromine atom entered the 3-position. In the first two cases the products were reduced to the corresponding amino-compounds, and removal of the amino-group yielded 3-bromo-4-methylbenzophenone, thus establishing the constitutions.

The nitration of 4′-chloro-4-methylbenzophenone, in nitric acid solution, gave an almost quantitative yield of 4′-*chloro*-3-*nitro*-4-*methylbenzophenone*, which was also obtained when 3-nitro-*p*-toluoyl chloride was condensed with chlorobenzene. Further nitration, in sulphuric acid solution, yielded 4′-*chloro*-3 : 3′-*dinitro*-4-*methylbenzophenone* of which the structure was established by condensing 4-chloro-3-nitrobenzoyl chloride with toluene and nitrating the product by fuming nitric acid. Continued nitration, in sulphuric acid solution at 60°, gave 4′-*chloro*-3 : 3′ : 5-*trinitro*-4-*methylbenzophenone*; the same compound was obtained on nitration of 4′-*chloro*-3 : 5-*dinitro*-4-*methylbenzophenone*, which was itself prepared by condensing 3 : 5-dinitro-*p*-toluoyl chloride with chlorobenzene, whereby the structure was established.

On bromination of 4′-chloro-4-methylbenzophenone in excess of dry bromine, 4′-*chloro*-3-*bromo*-4-*methylbenzophenone* was formed in quantitative yield; its structure was established by reducing 4′-chloro-3-nitro-4-methylbenzophenone to the amine and then replacing the amino-group by bromine.

The results show that the methyl group exerts a marked directive influence, and that the first substituent enters in the ortho-position to this group. The presence of one or two nitro-groups or a chlorine atom in the phenyl nucleus does not appear to affect the position taken up by the entering substituent. The second entering substituent goes to the 3′-position, and the presence of a substituent in the 3-position of the tolyl nucleus would appear to inhibit further substitution in this nucleus. The third entering substituent occupies the 5-position whatever the nature of the substituents previously introduced. The formation of a single product on the further substitution of 4′-chloro-4-methylbenzophenone was to be expected from a consideration of the substitution products of 4-chloro- and of 4-methyl-benzophenone.

A comparison between the behaviour of the methyl and the methoxyl groups shows that they are alike in that the sequence in which substituents enter is the same, with one exception, and the methods by which these substituents are introduced are similar. They differ in that on di- and tri-substitution the methyl group leads to only one isolable isomeride, whereas with the methoxyl group at least two isomerides are obtained.

EXPERIMENTAL.

4-Methylbenzophenone was prepared from benzoyl chloride and toluene according to the method described by Meyer (*Monatsh.*, 1907, **28**, 1223); it separated from light petroleum in plates, m. p. 56°.

3-*Nitro*-4-*methylbenzophenone*.—This was obtained (*a*) from 4-methylbenzophenone by dissolving it in nitric acid (*d* 1·5) and allowing the solution to stand for 1 hour, or (*b*) from 3-nitro-*p*-toluic acid by conversion into the acid chloride, with excess of thionyl chloride, and condensation with benzene in the presence of aluminium chloride; it crystallised from acetic acid or from alcohol in faintly yellow plates, m. p. 129° (Found : N, 5·95. $C_{14}H_{11}O_3N$ requires N, 5·8%).

On reduction of this compound with tin and hydrochloric acid, decomposition of the tin double salt with 30% sodium hydroxide solution, and extraction of the free base with ether, 3-*amino*-4-*methylbenzophenone* was obtained; it separated from methyl alcohol in needles, m. p. 109° (Found : N, 6·7. $C_{14}H_{13}ON$ requires N, 6·65%). The *hydrobromide* separated from its solution in dilute acid in long needles, m. p. 130° (Found : HBr, 27·5. $C_{14}H_{13}ON,HBr$ requires HBr, 27·7%); the *acetyl* derivative, formed by refluxing the base for 6 hours with a mixture of acetic acid and acetic anhydride, crystallised from methyl alcohol in needles, m. p. 108° (Found : C, 76·05; H, 5·95. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 5·95%).

3-*Bromo*-4-*methylbenzophenone*.—This was obtained (*a*) when 3-amino-4-methylbenzophenone was diazotised and treated with cuprous bromide; (*b*) when 4-methylbenzophenone was dissolved in dry bromine and the solution allowed to stand in sunlight for 2 days, the excess of bromine being removed in a current of air and by treatment with sulphurous acid; and (*c*) when 3-bromo-*p*-toluic acid was converted into the acid chloride and condensed with benzene in the presence of aluminium chloride. It separated from methyl alcohol in needles, m. p. 107° (Found: Br, 29·1. $C_{14}H_{11}OBr$ requires Br, 29·1%).

3 : 3′-*Dinitro*-4-*methylbenzophenone*.—5 G. of 3-nitro-4-methylbenzophenone were dissolved in 10 c.c. of sulphuric acid and 5 c.c. of acetic acid, treated with 2 c.c. of nitric acid (*d* 1·5), and the solution allowed to stand for 2 days. A mixture of di- and tri-nitro-derivatives was precipitated on pouring into water, and the more soluble dinitro-compound was isolated by repeated extractions with small quantities of methyl alcohol. The same product, 3 : 3′-*dinitro*-4-*methylbenzophenone*, was obtained when 3′-nitro-4-methylbenzophenone was dissolved in nitric acid (*d* 1·5) and the solution allowed to stand for 2 hours. It crystallised from methyl alcohol in

faintly yellow plates, m. p. 135° (Limpricht and Lenz, *loc. cit.*, give m. p. 125°) (Found : N, 9·8. $C_{14}H_{10}O_5N_2$ requires N, 9·8%).

3 : 5-*Dinitro*-4-*methylbenzophenone*.—5 G. of 3 : 5-dinitro-*p*-toluic acid were refluxed with an excess of thionyl chloride, the excess was removed, and the residue dissolved in 100 c.c. of benzene; 10 g. of aluminium chloride were added gradually, and the reaction completed on the water-bath. 3 : 5-*Dinitro*-4-*methylbenzophenone* crystallised from alcohol in small, yellow plates, m. p. 109° (Found : N, 9·8. $C_{14}H_{10}O_5N_2$ requires N, 9·8%).

5-*Nitro*-3-*amino*-4-*methylbenzophenone*, prepared from this compound by reduction with hydrogen sulphide in alcoholic ammonia solution, crystallised from alcohol in deep orange needles, m. p. 157° (Found : N, 11·0. $C_{14}H_{12}O_3N_2$ requires N, 10·95%).

3 : 3′ : 5-*Trinitro*-4-*methylbenzophenone*.—When 3 : 5-dinitro-4-methylbenzophenone, dissolved in sulphuric acid, was treated with an excess of nitric acid (*d* 1·5) and the solution allowed to stand for some days at room temperature, or when 3-nitro-, 3′-nitro-, or 3 : 3′-dinitro-4-methylbenzophenone was further nitrated under similar conditions, 3 : 3′ : 5-*trinitro*-4-*methylbenzophenone* was obtained; it separated from acetic acid in pale yellow needles, m. p. 173° (Found : N, 12·55. $C_{14}H_9O_7N_3$ requires N, 12·65%).

3 : 4′-*Dinitro*-4-*methylbenzophenone*.—This was prepared by dissolving 4′-nitro-4-methylbenzophenone in an excess of nitric acid (*d* 1·5) and allowing the solution to stand for 2 hours; it separated from alcohol in faintly yellow plates, m. p. 130° (compare Limpricht and Lenz, *loc. cit.*).

3-*Nitro*-4′-*amino*-4-*methylbenzophenone*.—A warm solution of 10 g. of 3 : 4′-dinitro-4-methylbenzophenone in a mixture of 200 c.c. of alcohol and 10 c.c. of ammonia (*d* 0·880) was treated with hydrogen sulphide until saturated; after removal of a part of the alcohol, the residue was poured into dilute hydrochloric acid, heated, and filtered. An unstable hydrochloride separated on cooling. The free *base* was liberated with ammonia; it crystallised from methyl alcohol in yellow plates, m. p. 164° (Found : N, 11·0. $C_{14}H_{12}O_3N_2$ requires N, 10·95%). On removal of the amino-group in the usual manner, 3-nitro-4-methylbenzophenone (m. p. 129°) was obtained.

3 : 4′ : 5-*Trinitro*-4-*methylbenzophenone*.—5 G. of 4′-nitro-4-methylbenzophenone, dissolved in 20 c.c. of sulphuric acid, were treated with 4 c.c. of nitric acid (*d* 1·5), the solution was kept for 24 hours, and the reaction completed on the water-bath. The product crystallised from acetic acid in pale yellow needles, m. p. 160° (Found : N, 12·7. $C_{14}H_9O_7N_3$ requires N, 12·65%). This compound did not react with piperidine, but with *p*-nitrosodimethylaniline in alcoholic solution it yielded a light brown, amorphous powder which could not be

obtained in a sufficiently pure state for analysis. When the trinitro-compound was reduced with hydrogen sulphide in alcoholic ammonia solution, and the product worked up in the manner previously described, 3-*nitro*-4′ : 5-*diamino*-4-*methylbenzophenone* was obtained; it separated from dilute acetone in orange plates, m. p. 202° (Found : N, 15·2. $C_{14}H_{13}O_3N_3$ requires N, 15·5%). 3-Nitro-4-methylbenzophenone was obtained on the removal of the amino-groups, thus suggesting that one of these groups was present in each nucleus.

3 : 3′ : 4′ : 5 - *Tetranitro* - 4 - *methylbenzophenone*.—When either 3 : 4′-dinitro- or 3 : 4′ : 5-trinitro-4-methylbenzophenone was dissolved in a mixture of equal volumes of sulphuric and nitric acids and heated on the water-bath for 6 hours, 3 : 3′ : 4′ : 5-*tetranitro*-4-*methylbenzophenone* was obtained; it separated from acetic acid in small, yellow prisms, m. p. 187° (Found : N, 14·9. $C_{14}H_8O_9N_4$ requires N, 14·9%). This compound reacted with piperidine, with boiling alcoholic ammonia, and with sodium methoxide, but in each case the product was a brown powder which could not be recrystallised from any of the usual solvents.

3 - *Bromo* - 3′ - *nitro* - 4 - *methylbenzophenone* was obtained when 3′-nitro-4-methylbenzophenone was treated with an excess of dry bromine; it separated from alcohol in faintly yellow plates, m. p. 124° (Found : Br, 24·85. $C_{14}H_{10}O_3NBr$ requires Br, 25·0%). On reduction with stannous chloride in alcoholic hydrogen chloride solution, 3-*bromo*-3′-*amino*-4-*methylbenzophenone* was obtained, which crystallised from dilute methyl alcohol in yellow needles, m. p. 94° (Found : Br, 27·6. $C_{14}H_{12}ONBr$ requires Br, 27·6%); deamination yielded 3-bromo-4-methylbenzophenone (m. p. 107°).

3′ : 5′-*Dinitro*-4-*methylbenzophenone*, prepared by condensation of 3 : 5-dinitrobenzoyl chloride with toluene in the presence of aluminium chloride, crystallised from methyl alcohol in faintly yellow plates, m. p. 134° (Found : N, 9·8. $C_{14}H_{10}O_5N_2$ requires N, 9·8%); on treatment with an excess of dry bromine, this yielded 3-*bromo*-3′ : 5′-*dinitro*-4-*methylbenzophenone*, which separated from alcohol or acetic acid in faintly yellow needles, m. p. 173° (Found : N, 7·7. $C_{14}H_9O_5N_2Br$ requires N, 7·65%). The structure of the latter compound follows from its analogy with 3-bromo-3′-nitro-4-methylbenzophenone.

3-*Bromo*-4′-*nitro*-4-*methylbenzophenone*, prepared from 4′-nitro-4-methylbenzophenone in the manner previously described, crystallised from alcohol in faintly yellow plates, m. p. 119° (Found : Br, 24·85. $C_{14}H_{10}O_3NBr$ requires Br, 25·0%); on reduction with stannous chloride in alcoholic hydrogen chloride solution, 3-*bromo*-4′-

amino-4-*methylbenzophenone* was formed: faintly yellow needles, m. p. 162°, from methyl alcohol (Found: N, 5·0. $C_{14}H_{12}ONBr$ requires N, 4·9%). Deamination yielded 3-bromo-4-methylbenzophenone (m. p. 107°).

4′-*Chloro*-3-*nitro*-4-*methylbenzophenone*, obtained when *p*-chlorobenzoyl chloride was condensed with toluene in the presence of aluminium chloride, and the product (m. p. 128°) dissolved in excess of nitric acid (*d* 1·5) and allowed to stand for 12 hours, separated from methyl alcohol in long needles, m. p. 98°. It was also obtained when 3-nitro-4′-amino-4-methylbenzophenone was diazotised and treated with cuprous chloride (Found: N, 5·15. $C_{14}H_{10}O_3NCl$ requires N, 5·1%). Reduction of this nitro-compound in the usual manner gave 4′-*chloro*-3-*amino*-4-*methylbenzophenone*, which crystallised from methyl alcohol in faintly yellow prisms, m. p. 142° (Found: N, 5·6. $C_{14}H_{12}ONCl$ requires N, 5·7%).

4′-*Chloro*-3′-*nitro*-4-*methylbenzophenone* was prepared by dissolving 4-chloro-3-nitrobenzoyl chloride in toluene in the presence of aluminium chloride; it separated from methyl alcohol in heavy yellow prisms, m. p. 121° (Found: N, 5·2; Cl, 12·85. $C_{14}H_{10}O_3NCl$ requires N, 5·1; Cl, 12·9%).

4′-*Chloro*-3 : 3′-*dinitro*-4-*methylbenzophenone* was obtained when the foregoing compound was dissolved in nitric acid (*d* 1·5) and the solution allowed to stand for 24 hours; or when 4′-chloro-3-nitro-4-methylbenzophenone, dissolved in sulphuric acid, was treated with a slight excess of nitric acid. In the latter case, the product was a mixture of di- and tri-nitro-compounds. The substance crystallised from methyl alcohol or dilute acetone in yellow prisms, m. p. 131° (Found: N, 8·75. $C_{14}H_9O_5N_2Cl$ requires N, 8·75%).

4′-*Chloro*-3 : 5-*dinitro*-4-*methylbenzophenone*, resulting from the condensation of 3 : 5-dinitro-4-toluoyl chloride and chlorobenzene in presence of aluminium chloride, crystallised from alcohol or acetic acid in yellow plates, m. p. 118° (Found: N, 8·8. $C_{14}H_9O_5N_2Cl$ requires N, 8·75%).

4′-*Chloro*-3 : 3′ : 5-*trinitro*-4-*methylbenzophenone* was obtained when 3′-nitro- or 3 : 3′- or 3 : 5-dinitro-4′-chloro-4-methylbenzophenone was dissolved in a mixture of sulphuric and nitric acids and the solution gently warmed or allowed to stand for some days at the ordinary temperature; it separated from acetic acid in heavy, yellow needles, m. p. 182° (Found: N, 11·45. $C_{14}H_8O_7N_3Cl$ requires N, 11·5%).

4′-*Chloro*-3-*bromo*-4-*methylbenzophenone* was prepared by dissolving 4′-chloro-4-methylbenzophenone in dry bromine, and by treating a diazotised solution of 4′-chloro-3-amino-4-methylbenzophenone with cuprous bromide; it crystallised from alcohol in needles, m. p. 122° (0·1756 G. gave 0·1885 g. of silver halides. $C_{14}H_{10}OClBr$ requires 0·1880 g.).

THE UNIVERSITY CHEMICAL LABORATORIES,
CAMBRIDGE.

[*Received, July 4th,* 1928.]