CCLXXIII.—*Halogen Substitution Products of 4-Aminobenzophenone.*

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According to all accepted theories of substitution, an *op*-directing group controls the type of reaction when in competition with a *m*-directing group, which, however, exerts its general polar influence in reducing the reactivity of the whole molecule. This is substantiated by the present work.

Direct chlorination of 4-aminobenzophenone, with chlorine generated from chloramine-T, gave 3 : 5-dichloro-4-aminobenzophenone; the corresponding acetyl derivative, previously made indirectly by Chattaway (J., 1904, **85**, 340), was obtained in good yield by the action of potassium chlorate and hydrochloric acid on 4-acetamidobenzophenone in glacial acetic acid solution. Its structure has now been confirmed by the conversion of its deamination product, 3 : 5-*dichlorobenzophenone*, into the two corresponding *oximes*, which, by the Beckmann reaction, yielded 3 : 5-*dichlorobenzanilide* and *benz*-3 : 5-*dichloroanilide* respectively, each of these substituted amides being compared directly with synthetic specimens.

3 : 5-Dibromo-4-aminobenzophenone, previously prepared by Clarke and Esselen (*J. Amer. Chem. Soc.*, 1911, **33**, 1135), was readily obtained by the action of bromine, in glacial acetic acid solution, on either 4-aminobenzophenone or 3-*bromo*-4-*aminobenzophenone*. It could not be further brominated to yield any definite product.

At room temperature 4-acetamidobenzophenone was not attacked by bromine in glacial acetic acid solution, but at 100° 3-*bromo*-4-*acetamidobenzophenone* was obtained in quantitative yield. Further bromination to 3 : 5-*dibromo*-4-*acetamidobenzophenone* (yield, 50%) required the action of free bromine at 100°, in presence of pyridine as a catalyst.

Direct iodination of 4-aminobenzophenone, in glacial acetic acid solution, can be carried out by the use of the potassium iodide–dichloramine-T reagent of Bradfield, Orton, and Roberts (J., 1928, 782). At room temperature 3-*iodo*-4-*aminobenzophenone* was obtained quantitatively, and, by warming this with a further proportion of the iodinating reagent, 3 : 5-*di-iodo*-4-*aminobenzophenone* was obtained in good yield. Its structure was verified by conversion to 3 : 5-*di-iodobenzophenone*, which was synthesised by a direct method.

4-Acetamidobenzophenone, in contrast, could not be iodinated even at 100°.

3-Bromo-4-aminobenzophenone on iodination, and 3-iodo-4-aminobenzophenone on bromination, both yielded the same product, *viz.*, 3-*bromo*-5-*iodo*-4-*aminobenzophenone*. This has the same melting point as its 3 : 5-dibromo-analogue, and, as there is no depression of m. p. on mixing these two substances in different proportions, they are probably isomorphous. Their *diacetyl* derivatives, however, are distinctly different in physical properties.

The nitration of 4-acetamidobenzophenone has also been attempted under various conditions, but the compound resisted substitution except under conditions which also caused some decomposition of the benzophenone ring system (compare Elion, *Rec. trav. chim.*, 1924, **43**, 867; 1925, **44**, 99).

EXPERIMENTAL.

4-Aminobenzophenone was prepared by condensing together *p*-nitrobenzoyl chloride and thiophen-free benzene with aluminium chloride, and reducing the resulting 4-nitrobenzophenone in alcoholic solution with stannous chloride and hydrochloric acid. Its acetyl derivative (m. p. 153·5°) crystallised most conveniently from dilute acetic acid.

Chlorination of 4-*Acetamidobenzophenone*.—5 G. of 4-acetamidobenzophenone, dissolved in 100 c.c. of glacial acetic acid, were treated with 5 g. of powdered potassium chlorate and 25 c.c. of concentrated hydrochloric acid, and after 24 hours the mixture was poured into water. The reaction product on crystallisation from alcohol yielded 3 : 5-dichloro-4-acetamidobenzophenone (4 g.), m. p. 185° (Found : Cl, 23·2. Calc. : Cl, 23·05%), together with a small quantity of chloranil. Further substitution could not be effected, even by repeating the reaction at 100°.

3 : 5-Dichloro-4-aminobenzophenone was prepared both by the hydrolysis of its acetyl derivative with alcoholic hydrochloric acid and by direct chlorination of 4-aminobenzophenone as follows : To a solution of 4-aminobenzophenone (5 g.) in glacial acetic acid (100 c.c.) were stirred in 2 equivs. (14 g.) of chloramine-T, followed shortly by excess (15 c.c.) of concentrated hydrochloric acid. After 4 hours the mixture was poured into dilute sulphurous acid, the precipitate collected, washed with dilute alkali, and recrystallised from alcohol. From either method of preparation, the base formed matted flocculent needles, m. p. 135° (Chattaway, *loc. cit.*, gives 137°, corr.), but could also be obtained in a compact prismatic form by very slow crystallisation.

3 : 5-*Dichlorobenzophenone*, obtained from the base by elimination of the amino-group in the usual manner, crystallised from methyl alcohol in needles, m. p. 65° (Found : Cl, 28·1. $C_{13}H_8OCl_2$ requires Cl, 28·3%). By refluxing for 8 hours a solution of the ketone (4 g.) in alcohol (100 c.c.) with hydroxylamine hydrochloride (4 g.) and excess of potassium hydroxide (10 g.), a mixture of oximes was produced, which was isolated by removing the alcohol, pouring the residue into water, and neutralising the product. Separation into two pure substances was effected by fractional crystallisation from solutions in dilute methyl and ethyl alcohols.

(i) The less soluble *α-oxime* crystallised in plates or fine needles, m. p. 137° (Found : Cl, 26·5. $C_{13}H_9ONCl_2$ requires Cl, 26·65%); on treatment with phosphorus pentachloride in dry ethereal solution, it was converted quantitatively into 3 : 5-*dichlorobenzanilide*, which was also synthesised from aniline and 3 : 5-dichlorobenzoic acid, and crystallised from dilute alcohol in needles, m. p. 148° either alone or in admixture with that prepared from the oxime (Found : Cl, 26·55. $C_{13}H_9ONCl_2$ requires Cl, 26·65%).

(ii) The *β-oxime* of 3 : 5-dichlorobenzophenone formed over 70% of the mixed oximes; it crystallised in prisms, m. p. 118° (Found : Cl, 26·7%), and on treatment with phosphorus pentachloride as above, it yielded a gummy product which, by fractional crystallisation from dilute methyl alcohol, was separated into some 3 : 5-dichlorobenzanilide, together with *benz*-3 : 5-*dichloroanilide*. This substance was also prepared by the benzoylation (Schotten–

Baumann) of 3 : 5-dichloroaniline, and crystallised in plates or, by slow cooling, in needles of m. p. 148·5° (Found : Cl, 26·6%). The product obtained from the oxime melted at 146—148° as did also a mixture of this with the pure synthetic material.

3-*Bromo*-4-*acetamidobenzophenone*.—5 G. of 4-acetamidobenzophenone and 10 g. of powdered anhydrous sodium acetate were heated for 6 hours at 100° with 50 c.c. of a 10% solution of bromine in glacial acetic acid, and the mixture was then poured into water. The bromination *product* (yield, theoretical) crystallised from slightly diluted methyl alcohol in fine matted needles, m. p. 106° (corr.) (Found : Br, 25·4. $C_{15}H_{12}O_2NBr$ requires Br, 25·5%). The corresponding *base*, obtained by hydrolysis of the acetyl derivative with alcoholic hydrochloric acid, crystallised from alcohol in plates, m. p. 158°, and from dilute alcohol in needles (Found : Br, 28·95. $C_{13}H_{10}ONBr$ requires Br, 29·0%); its *benzoyl* derivative crystallised from alcohol in elongated plates, m. p. 124° (Found : Br, 21·2. $C_{20}H_{14}O_2NBr$ requires Br, 21·05%).

3-Bromo-4-aminobenzophenone, on treatment with bromine in glacial acetic acid solution, yielded 3 : 5-dibromo-4-aminobenzophenone of m. p. 148° alone or mixed with a specimen prepared directly by the action of bromine on 4-aminobenzophenone in glacial acetic acid solution. The latter substance is identical with the bromination product of Clarke and Esselen (*loc. cit.*), who gave m. p. 146°; its *diacetyl* derivative, prepared by boiling it for 6 hours with an excess of equal volumes of acetic acid and acetic anhydride, crystallised from alcohol in plates, m. p. 137° (Found : Br, 36·6. $C_{17}H_{13}O_3NBr_2$ requires Br, 36·45%).

3 : 5-*Dibromo*-4-*acetamidobenzophenone*.—5 G. of 3-bromo-4-acetamidobenzophenone, 10 g. of anhydrous sodium acetate, and 1 c.c. of pyridine were intimately mixed together, 3 c.c. of bromine were added slowly, and the mixture was heated at 100° for 3 hours, more bromine being added from time to time in small portions till there was no further reaction. The *dibromo*-compound was separated from the reaction mixture in 50% yield by repeated crystallisation from both methyl and ethyl alcohol, and formed colourless needles, m. p. 214° (Found : Br, 40·4. $C_{15}H_{11}O_2NBr_2$ requires Br, 40·3%). On prolonged hydrolysis with alcoholic hydrobromic acid it yielded 3 : 5-dibromo-4-aminobenzophenone, m. p. 148°, its structure thus being established.

3 : 5-*Dibromobenzophenone*, obtained by the elimination of the amino-group from 3 : 5-dibromo-4-aminobenzophenone in the usual manner, crystallised from methyl alcohol in colourless plates, m. p. 75° (Found : Br, 47·2. $C_{13}H_8OBr_2$ requires Br, 47·05%).

3-*Iodo*-4-*aminobenzophenone*.—To a solution of 10 g. of 4-aminobenzophenone in 100 c.c. of glacial acetic acid, were added 1½ equivs. of iodinating reagent, previously prepared by adding 10 g. of finely powdered potassium iodide, with stirring, to a solution of 8 g. of dichloramine-T in 100 c.c. of glacial acetic acid; after 5 hours the solution was poured into dilute sodium sulphite solution. The product (yield, theoretical) crystallised from methyl alcohol in plates, m. p. 177° (Found : I, 39·2. $C_{13}H_{10}ONI$ requires I, 39·3%); its *benzoyl* derivative crystallised from acetone in clusters of prisms, m. p. 162° (Found : I, 29·9. $C_{20}H_{14}O_2NI$ requires I, 29·7%).

3 : 5-*Di-iodo-4-aminobenzophenone*, obtained by warming together on the water-bath for ½ hour a solution of 3-iodo-4-aminobenzophenone in glacial acetic acid and slightly more than an equivalent quantity of the iodine monochloride reagent, crystallised from acetone in prismatic needles, m. p. 153° (Found : I, 56·3. $C_{13}H_9ONI_2$ requires I, 56·5%); its *diacetyl* derivative, obtained by boiling the base for 6 hours with acetic anhydride, crystallised from alcohol in plates, m. p. 187° (Found : I, 47·6. $C_{17}H_{13}O_3NI_2$ requires I, 47·7%).

4-Acetamidobenzophenone was not attacked by the iodine monochloride reagent after 6 hours' treatment at 100°.

3 : 5-Di-iodobenzophenone was obtained from the corresponding base by elimination of the amino-group in the usual manner, and its structure was established by the following synthesis.

3 : 5-*Dinitrobenzophenone*, prepared by condensation of 3 : 5-dinitrobenzoyl chloride with benzene in the presence of aluminium chloride, crystallised from alcohol in pale yellow prisms, m. p. 131° (Found : N, 10·4. $C_{13}H_8O_5N_2$ requires N, 10·3%). On reduction with hydrogen sulphide in alcoholic ammonia solution it yielded 3-*nitro-5-aminobenzophenone*, which crystallised from dilute alcohol in orange needles, m. p. 130° (Found : N, 11·5. $C_{13}H_{10}O_3N_2$ requires N, 11·6%); this base also crystallised from benzene in plates, and could occasionally be isolated in a form of m. p. 146°. Its *diacetyl* derivative, obtained by refluxing it with acetic anhydride, crystallised from dilute alcohol in long, pale yellow needles, which melted sharply at 191° after sintering at 115—125° (Found : N, 8·6. $C_{17}H_{14}O_5N_4$ requires N, 8·6%). The powdered base, suspended in concentrated hydrochloric acid, was diazotised at 0° by the addition of powdered sodium nitrite, and after ½ hour the mixture was poured into a concentrated potassium iodide solution and warmed on the water-bath till all reaction had ceased. The solid product, after repeated crystallisation from acetone and from alcohol, formed orange-yellow prisms, m. p. 118° of 5-*iodo-3-nitrobenzophenone* (Found : I, 35·6. $C_{13}H_8O_3NI$ requires I, 35·9%), and when this was reduced in alcoholic solution with stannous chloride and

hydrochloric acid, 3-amino-5-iodobenzophenone was obtained. The latter, without isolation in the pure state, was converted by the normal method into 3 : 5-*di-iodobenzophenone* (Found : I, 58·6. $C_{13}H_8OI_2$ requires I, 58·5%), which crystallised from methyl alcohol in prisms, m. p. 91° alone or mixed with the deamination product of di-iodo-4-aminobenzophenone; on being boiled with hydroxylamine hydrochloride in excess of alcoholic potash solution it yielded benzophenone oxime (m. p. 140°), the iodine having been eliminated from the aromatic nucleus. The di-iodobenzophenone, however, did not react with piperidine at 100°.

3-*Bromo*-5-*iodo*-4-*aminobenzophenone*, which crystallised from acetone in needles, was obtained (*a*) by warming on the water-bath for ½ hour a solution of 3-bromo-4-aminobenzophenone in glacial acetic acid with 1½ equivs. of iodine monochloride reagent, prepared as previously described, and pouring the product into water, or (*b*) by warming 3-iodo-4-aminobenzophenone, dissolved in glacial acetic acid, with a slight excess of bromine. The product from either method of preparation, as also their mixture, melted at 148° [Found, for ratio of mixed silver halides to substance taken, by Carius's method : (*a*), 1·056, (*b*), 1·052; by Stepanow's method : (*b*), 1·047. $C_{13}H_9ONBrI$ requires ratio, 1·052]. The m. p. of this substance, however, was not depressed after its admixture, in various proportions, with 3 : 5-dibromo-4-aminobenzophenone (m. p. 148°, also).

3-*Bromo*-5-*iodo*-4-*diacetamidobenzophenone*, prepared by refluxing the base for 6 hours with acetic anhydride, crystallised from alcohol in plates, m. p. 161°, not isomorphous with the corresponding dibromo-derivative (Found, for ratio of mixed silver halides to substance taken : 0·865. $C_{17}H_{13}O_3NBrI$ requires ratio, 0·869).

Nitration of 4-acetamidobenzophenone with fuming nitric acid in cold glacial acetic acid solution did not occur, even if acetic anhydride or concentrated sulphuric acid were added to the reaction mixture. At higher temperatures, or in the absence of a solvent, some decomposition set in and no pure product could be isolated.

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