Anthraquinone Dyes. Part IV.[1] Nitration of 2-(3-Chloro-4-methylbenzoyl)benzoic Acid

By **J. Arient, J. Šlosar, V. Štěrba,*** and **K. Obruba,** Research Institute of Organic Syntheses, Pardubice, Rybitví, Czechoslovakia

The principal product of the nitration of 2-(3-chloro-4-methylbenzoyl)benzoic acid is 2-(3-chloro-4-methyl-6-nitrobenzoyl)benzoic acid, formed in 70—80% yield. In addition, 10—15% of 2-(3-chloro-4-methyl-2-nitrobenzoyl)- and 2-(3-chloro-4-methyl-5-nitrobenzoyl)-benzoic acid are formed. This result is in disagreement with a semiquantitative estimate, based on sigma constants, from which 2-(3-chloro-4-methyl-5-nitrobenzoyl)-benzoic acid would be the principal reaction product expected. In a study of the nitration of 2-(3-chloro-4-methylbenzoyl)benzoic acid, authentic specimens of 1,4-dichloro-2-methyl-, 1,2-dichloro-3-methyl-, and 2,3-dichloro-1-methyl-derivatives of anthraquinone were prepared.

In the preceding Paper we reported that in the nitration of 2-(4-methyl-3-nitrobenzoyl)benzoic acid a second nitro-group is introduced into one of the two aromatic rings with the formation of a complex mixture containing substantial amounts of both mono- and tri-nitro-derivatives of toluoylbenzoic acid in addition to the isomeric dinitro-compounds. If the corresponding 3-halogeno-substituted benzoyl derivative is nitrated [for example, 2-(3-chloro-4-methylbenzyol)benzoic acid], the ring which contains the methyl group is much less deactivated than the 3-nitro-derivative and is therefore nitrated preferentially. Since both carbonyl and methyl groups direct further electrophilic substitution to position 5 and the chloro-substituent to positions 2 and 6, it would be expected that the 5-nitro-derivatives would be the principal reaction product. The same conclusion follows from a semiquantitative estimate based on values of sigma constants proposed by Brown.[2]

Iodine-catalysed chlorination of 2-*p*-toluoylbenzoic acid with chlorine in acetic acid gave a high yield of 2-(3-chloro-4-methylbenzoyl)benzoic acid (I), which was subsequently nitrated with a mixture of nitric and sulphuric acids. The nitration proceeded very smoothly and the reaction was complete soon after 1 mol. of nitric acid had been added. Its course may be easily followed, *e.g.*, by polarography. If 1 mol. of nitric acid is used, virtually no dinitro-derivative is formed.

Reduction of the nitrochloro-derivative (II) afforded the aminochloro-acid (III), which in acid media (acetic–hydrochloric acids) forms a cyclic imide, sparingly soluble in the usual solvents. A Sandmeyer reaction converted the aminochloro-acid (III) to the corresponding dichloro-derivative (IV), which was identified, contrary to our initial expectations, as 2-(3,6-dichloro-4-methylbenzoyl)benzoic acid by its melting point and mixed melting point with an authentic specimen prepared by the condensation of 2,5-dichlorotoluene with phthalic anhydride. The structure was further confirmed by cyclisation to 1,4-dichloro-2-methylanthraquinone (XII) which was again compared with an authentic specimen.

The directing influence of chlorine on the nitration of 2-(3-chloro-4-methylbenzoyl)benzoic acid is apparently stronger than the combined effects of the carbonyl and methyl groups since the nitro-group enters predominantly (70—80%) at position 6 with the formation of 2-(3-chloro-4-methyl-6-nitrobenzoyl)benzoic acid (II).

The mother-liquor after crystallisation of the crude chloronitrotoluoylbenzoic acid (II) contains 30—35% of product, essentially a mixture of isomeric chloronitrotoluoylbenzoic acids (II), (VI), and (VIII).

A portion of this mixture which was esterified with diazomethane and chromatographed, showed three separate spots, one of which corresponded to methyl 2-(3-chloro-4-methyl-6-nitrobenzoyl)benzoate.

Most of the mixture of the acids was reduced, subjected to the Sandmeyer reaction, and cyclised to a mixture of dichloroanthraquinones. Thin-layer chromatography

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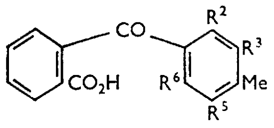
* Present Address: Department of Organic Chemistry, The Institute of Chemical Technology, Pardubice.

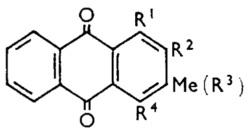
[1] Part III, J. Arient, J. Šlosar, V. Štěrba, and K. Obruba, preceding Paper.

[2] H. C. Brown and Y. Oktamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.

(t.l.c.) afforded 1,2-dichloro-3-methylanthraquinone (XIII) [from the chloronitrotoluoylbenzoic acid (VI)] which was identical with authentic specimen prepared from 2,3-dichlorotoluene (by mixed m. p.).



(I; $R^2 = R^5 = R^6 = H$, $R^3 = Cl$)
(II; $R^2 = R^5 = H$, $R^3 = Cl$, $R^6 = NO_2$)
(III; $R^2 = R^5 = H$, $R^3 = Cl$, $R^6 = NH_2$)
(IV; $R^2 = R^5 = H$, $R^3 = R^6 = Cl$)
(V; $R^2 = R^3 = Cl$, $R^5 = R^6 = H$)
(VI; $R^2 = NO_2$, $R^3 = Cl$, $R^5 = R^6 = H$)
(VII; $R^2 = R^3 = NH_2$, $R^5 = R^6 = H$)
(VIII; $R^2 = R^6 = H$, $R^3 = Cl$, $R^5 = NO_2$)
(IX; $R^2 = R^6 = H$, $R^3 = R^5 = NH_2$)
(X; $R^2 = R^6 = H$, $R^3 = R^5 = Cl$)
(XI; $R^2 = R^5 = H$, $R^3 = R^6 = HN_2$)



(XII; $R^1 = R^4 = Cl$, $R^2 = H$)
(XIII; $R^1 = R^2 = Cl$, $R^4 = H$)
(XIV; $R^2 = R^4 = NH_2$, $R^1 = H$)
(XV; $R^1 = Me$, $R^2 = R^3 = Cl$)

The third component of the mother-liquor was assumed to be 2-(3-chloro-4-methyl-5-nitrobenzoyl)-benzoic acid (VIII). To confirm this, a mixture of the chloronitrotoluoylbenzoic acids from the mother-liquor was heated in an autoclave with ammonia and freshly precipitated copper. After sulphide reduction the resultant mixture of diaminotoluoylbenzoic acids was cyclised by boiling with acetic acid. 2,3-Diamino-(VII) and 3,6-diamino- (XI) substituted 2-(4-methylbenzoyl)benzoic acids were converted to cyclic imides, while the acid (IX) gave 1,3-diamino-2-methylanthraquinone (XIV). The cyclisation products were treated with alkali and the imides hydrolysed and dissolved. 1,3-Diamino-2-methylanthraquinone was identified by t.l.c. The amount of 2-(3-chloro-4-methyl-5-nitrobenzoyl)benzoic acid (VIII) present in the nitration mixture is probably larger than would be expected on the basis of the amount of anthraquinone (XIV) isolated. This acid has chlorine in the *meta* position to the nitro-group and its replacement is therefore not easy. An experiment performed under milder conditions afforded only a trace amount of the diaminoathraquinone (XIV).

Alkaline fission of acid (II) and the dichloro-derivatives (V) and (X) leads to 2,5-, 2,3-, and 2,6-dichlorotoluene, respectively. The dichlorotoluenes were identified by means of gas chromatography.

Authentic 2-(3,6-dichloro-4-methylbenzoyl)benzoic acid required for identification purposes as well as 1,4-dichloro-2-methyl- and 1,2-dichloro-3-methyl-derivatives of anthraquinone were prepared by the Friedel–Crafts condensation of phthalic anhydride with 2,3- and 2,5-dichlorotoluene and the subsequent cyclisation of the resulting dichlorotoluoylbenzoic acids.

While 2-(3,6-dichloro-4-methylbenzoyl)benzoic acid is the sole condensation product, condensation of phthalic anhydride with 2,3-dichlorotoluene yields a mixture of two acids, whose cyclisation leads to a mixture of 1,2-dichloro-3-methyl- (XIII) and 2,3-dichloro-1-methyl- (XV) derivatives of anthraquinone, which can be resolved by chromatography on a preparative scale. 2,3-Dichloro-1-methylanthraquinone (XV) isolated from the first fractions contained trace amounts of 1,2-dichloro-3-methylanthraquinone, which were converted by heating with sodium sulphite and carbonate to a water soluble sulphonic acid and thus removed. The last chromatographic portions afforded pure isomer (XIII).

EXPERIMENTAL

2-(3-*Chloro*-4-*methylbenzoyl*)*benzoic Acid* (I).—*p*-Toluoylbenzoic acid (200 g., 0·83 mole) was dissolved in 95% acetic acid (900 ml.) and iodine (1 g.) was added. A stream of chlorine was passed through the stirred mixture at 75—80° at such a rate that a small fraction was evolved with the hydrogen chloride formed; the chlorination was complete after 7 hr. Most of the product crystallised on cooling and was filtered off, washed with 80% acetic acid, dried under reduced pressure, and recrystallised from toluene (2 l.) (184 g., 81%), m. p. 180·5—181·5° (lit.,[3] 175°). The purity of the product was checked by a determination of its equivalent weight and by fusion with potassium hydroxide at 300—350°. G.l.c. of the resulting distillate revealed less than 1% of toluene.

Nitration of 2-(3-*Chloro*-4-*methylbenzoyl*)*benzoic Acid*.—2-(3-Chloro-4-methylbenzoyl)benzoic acid (110 g., 0·4 mole) was dissolved in concentrated sulphuric acid (350 ml.), cooled to 5°, and a mixture of concentrated sulphuric acid (120 ml.) and 65% nitric acid (29 ml., 0·42 mole) was added dropwise at 5—10°. After 10 min. the reaction mixture was poured on ice to give crystalline 2-(3-*chloro*-4-*methyl*-6-*nitrobenzoyl*)*benzoic acid* (II) (79 g.), m. p. 177—178° (acetic acid) (Found: C, 56·3; H, 3·35; Cl, 11·5; N, 4·2. $C_{15}H_{10}ClNO_5$ requires C, 56·35; H, 3·1; Cl, 11·1; N, 4·4%).

The mother-liquor was reduced to 150 ml., and water (300 ml.) was added; the crystalline mixture of nitrochlorotoluoylbenzoic acids which formed was filtered off (43 g.).

Methyl Nitrochlorotoluoylbenzoates.—The crystalline nitrochlorotoluoylbenzoic acid (II) (0·2 g.), prepared as described above, was dissolved in hot methanol, cooled to 0°, and an ethereal solution of diazomethane was added until clearly in excess; the solvents were removed by distillation. T.l.c. of the ester on alumina with hexane–acetone (7 : 1) showed no impurities under u.v. light.

The mixture of nitrochlorotoluoylbenzoic acids (0·2 g.) obtained from the mother-liquor after crystallisation of the main product (II) was subjected to the same procedure. The chromatogram showed three intense spots, the largest having the same R_F as the methyl esters of the acid (II).

2-(2-*Amino*-5-*chloro*-4-*methylbenzoyl*)*benzoic Acid*.—A solution of the nitrochlorotoluoylbenzoic acid (II) (36 g., 0·11 mole) in ethanol (140 ml.) was added in portions into a vigorously stirred and boiling mixture of water (300 ml.), ethanol (65 ml.), acetic acid (6 ml.), and iron filings (40 g.). After the reduction was complete the reaction mixture was made alkaline by the addition of a solution of sodium

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[3] G.P. 540,408; Frdl. XVIII, p. 540.

carbonate (20 g.); the iron oxides were removed by filtration. The filtrate was acidified with acetic acid to give pale yellow crystals of 2-(*2-amino-5-chloro-4-methylbenzoyl)-benzoic acid* (27·3 g., 83%), m. p. 303—304° (acetic acid) (Found: C, 62·4; H, 4·25; Cl, 12·45; N, 4·8. $C_{15}H_{12}ClNO_3$ requires C, 62·2; H, 4·15; Cl, 12·25; N, 4·85%).

2-(3,6-*Dichloro*-4-*methylbenzoyl)benzoic Acid*.—(*a*) A hot solution of the aminochlorotoluoylbenzoic acid (III) (36 g., 0·125 mole) in ethanol was heated with a 10% solution of sodium hydroxide; the sodium salt of the amino-acid crystallised on cooling and was separated and dried under reduced pressure. The sodium salt (37·4 g., 0·12 mole) and sodium nitrite (8·5 g., 0·125 mole) was dissolved in water (100 ml.) and added portionwise to a stirred mixture of crushed ice (200 g.) and concentrated hydrochloric acid at 10°; after 30 min., sulphamic acid was added in order to destroy the small excess of nitrous acid present. The reaction mixture was poured into a stirred solution of cuprous chloride [prepared by reduction of $CuSO_4,5H_2O$ (175 g.) according to Fieser [4]] in concentrated hydrochloric acid (240 ml.). After the evolution of nitrogen ceased, the reaction mixture was heated to 60°. The following day, the 2-(3,6-*dichloro*-4-*methylbenzoyl)benzoic acid* (IV) which had separated was filtered off (21 g., 57%), m. p. 181·5—182·5 (toluene) (Found: C, 58·3; H, 3·3; Cl, 23·85. $C_{15}H_{10}Cl_2O_2$ requires C, 58·3; H, 3·25; Cl, 22·95%).

(*b*) Aluminium chloride (13·3 g.) was added over a period of 30 min. to a mixture of 2,5-dichlorotoluene (16·1 g., 0·1 mole) and phthalic anhydride (7·4 g., 0·05 mole) after which the reaction mixture was slowly heated to 100° and kept at this temperature for 12 hr. The melt solidified on cooling and after cautious decomposition with concentrated hydrochloric acid, water (150 ml.) was added. Unchanged dichlorotoluene was removed by steam distillation and a sample of the organic phase of the distillate was examined by gas chromatography and gave confirmation that no isomerisation of dichlorotoluene occurred during the reaction. The brown product was boiled twice with sodium carbonate solution and the combined alkaline extracts were acidified with hydrochloric acid. The crude acid was crystallised from toluene and then from acetic acid, to give of 2-(3,6-dichloro-4-methylbenzoyl)benzoic acid (3·2 g.), m. p. 179—180°.

1,4-*Dichloro*-2-*methylanthraquinone*.—A solution of the dichlorotoluoylbenzoic acid (IV) (13·5 g.) in conc. sulphuric acid (300 ml.) was heated to 90° for 6 hr. and then to 105° for 2 hr. After cooling, the reaction mixture was poured on ice, and the precipitated yellowish-brown dichloromethylanthraquinone was filtered off and washed with water; unchanged acid was extracted with dilute ammonia, to leave 1,4-dichloro-2-methylanthraquinone (XII) (7·6 g., 68%), m. p. 188—189° (acetic acid). A pure specimen was obtained by chromatography on a column of alumina (benzene), m. p. 190·5—191·5° (ethyl acetate) (lit.,[5] 185—186°) (Found: C, 61·9; H, 2·75; Cl, 24·4. Calc. for $C_{15}H_8Cl_2O_2$: C, 61·9; H, 2·75; Cl, 24·35%).

Lactam of Aminochlorotoluoylbenzoic Acid.—A solution of the aminochlorotoluoylbenzoic acid (III) (4 g.) in acetic acid (100 ml.) and hydrochloric acid (0·2 ml.) was boiled for 10 min. On cooling, white crystals of the *lactam* of acid (III) separated in near quantitative yield, m. p. 303·5—304·5° (acetic anhydride–toluene) (Found: C, 66·05; H, 3·75; Cl, 13·45; N, 5·20. $C_{15}H_{10}ClNO_2$ requires C, 66·35; H, 3·7; Cl, 13·05; N, 5·15%).

Alkaline Hydrolysis of 2-(3,6-*Dichloro*-4-*methylbenzoyl)-benzoic Acid*.—2-(3,6-Dichloro-4-methylbenzoyl)benzoic acid (1·2 g.) was heated with a (1 : 1) mixture of sodium hydroxide and potassium hydroxide (2 g.) in a small retort at 300—350° for 20 min. 2,5-Dichlorotoluene distilled; the water was separated and the product (0·45 g.) was dried (KOH); the compound was identical (g.l.c.) with an authentic specimen of 2,4-dichlorotoluene.

Condensation of 2,3-*Dichlorotoluene with Phthalic Anhydride*.—The condensation was carried out as described for 2,5-dichlorotoluene, and the product crystallised from toluene; the resulting dichlorotoluoylbenzoic acid (3·8 g.) had a m. p. 160—170°.

Cyclisation of a Mixture of Dichlorotoluoylbenzoic Acid.—2-(3,6-Dichloro-4-methylbenzoyl)benzoic acid was cyclised and worked up as described for the dichlorotoluoylbenzoic acid (IV) prepared from toluoylbenzoic acid, to give 1,4-*dichloro*-2-*methylanthraquonine*, m. p. 89—190° (Found: C, 62·15; H, 3·0; Cl, 24·4. $C_{15}H_8Cl_2O_2$ requires C, 61·9; H, 2·75; Cl, 24·35%).

Dichlorotoluoylbenzoic acid, prepared by the condensation of 2,3-dichlorotoluene with phthalic anhydride, was cyclised in the same manner and the resulting mixture of 2,3-dichloro-1-methyl- and 1,2-dichloro-3-methyl-anthraquinones (2 g.) was chromatographd on alumina with benzene. The first fractions (0·6 g.), which after crystallisation from ethyl acetate melted at 175—190°, were heated at 130° under pressure with a solution of sodium sulphite (0·5 g.) and sodium carbonate (0·1 g.) in water (10 ml.) for 10 hr. Unchanged 2,3-dichloro-1-methylanthraquinone (0·45 g.) was filtered off and washed with hot water; after crystallisation (ethyl acetate) it melted at 179—180°.

The last chromatographic portion (0·45 g.) melted at 204—205·5° after a crystallisation (benzene). Further crystallisation (ethyl acetate) afforded almost colourless *crystals* (0·35 g.), m. p. 207—208° (Found: C, 61·8; H, 2·85; Cl, 24·5. $C_{15}H_8Cl_2O_2$ requires C, 61·9; H, 2·75; Cl, 24·37%).

A mixture of chloronitrotoluoylbenzoic acids (10 g.), from the mother-liquor after crystallisation of crude chloronitrotoluoylbenzoic acid, was reduced with iron filings. After reduction, the filtrate was taken almost to dryness, acetic and hydrochloric acids added (1 : 1), and the amino-group diazotised with sodium nitrite. The solution of the resultant diazonium salt was poured into an excess of cuprous chloride in hydrochloric acid and the resulting dichlorotoluoylbenzoic acids cyclised; the dichloromethylanthraquinones formed were chromatographed as described for the dichlorotoluoylbenzoic acid prepared from phthalic anhydride and 2,3-dichlorotoluene. After recrystallisations from benzene and ethyl acetate the final chromatographic fraction melted at 205—207° and was identical with an authentic specimen of 1,2-dichloro-3-methylanthraquinone (mixed m. p.).

Analysis of the Nitration Products of Chlorotoluoylbenzoic Acid.—2-(3-Chloro-4-methylbenzoyl)benzoic acid (40 g.) was nitrated in the manner described previously. A portion of the resulting crude chloronitrotoluoylbenzoic acid (6 g.) was reduced with iron filings. After reduction, the reaction mixture was made alkaline with sodium carbonate, and the iron oxides removed by filtration. The filtrate was acidified with acetic and hydrochloric acids and taken

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[4] L. F. Fieser, " Experiments in Organic Chemistry," D. C. Heath and Co., 1941, p. 213.

[5] P. Ruggli, and E. Merz, *Helv. Chim. Acta.*, 1929, **12**, 71.

to dryness under reduced pressure. Cyclic imide constantly separated during the latter process and was twice removed by filtration. The residue was redissolved in acetic acid and boiled for 10 min. After cooling, the remainder of the imide which had separated was filtered off.

The cyclic imide, freed from inorganic impurities by boiling with water, and dried at 60—70° to constant weight (3·3 g.), was converted to the sodium salt by boiling with a solution of sodium hydroxide (3 g.) in 20% ethanol (100 ml.). The alcohol was removed by distillation and sodium nitrite (1 g.) was added to the solution after which the mixture was added portionwise to a mixture of acetic acid (50 ml.) and conc. hydrochloric acid (8 ml.) at 0—5°. The excess of sodium nitrite was destroyed by the addition of sulphamic acid and the diazonium salt treated to give the chloro-compound. The crude mixture of dichlorotoluoylbenzoic acids (3·2 g.) was hydrolysed by heating to 300—350° with a mixture of sodium and potassium hydroxides. The mixture of dichlorotoluenes that distilled was analysed by g.l.c. at 110° with a column (2·5 m. × 3 mm.) packed with kieselguhr, impregnated with 10% of Bentonite and 10% of dioctyl phthalate; nitrogen (10 ml./min.) was used as carrier gas. The chromatogram showed peaks due to 2,5- and 2,3-dichlorotoluenes in the ratio 2 : 1 (from integrated areas).

The mother-liquors, after isolation of the cyclic imides, contained uncyclised chloroaminotoluoylbenzoic acids, where were diazotised at 0—5° and worked up as described for the cyclic imides. G.l.c. showed the presence of 2,6- and 2,3-dichlorotoluenes in the approximate ratio 5 : 1. In addition, a smaller amount of 2,5-dichlorotoluene was also present as evidenced by the dissymmetry of the 2,5-dichlorotoluene peak.

Proof of the Structure of 2-(3-*Chloro*-4-*methyl*-5-*nitrobenzoyl)benzoic acid* (XI).—A mixture of chloronitrotoluoylbenzoic acids (5 g.) from the mother-liquor from the crystallisation of crude chloronitrotoluoylbenzoic acid was heated at 185° in an autoclave with 20% ammonia (50 ml.) and freshly reduced copper powder (0·5 g.) for 5 hr. After the inorganic impurities had been removed by filtration, sodium sulphide (5 g.) was added and the mixture was boiled. Acetic acid (100 ml.) was added to 20 ml. of the reaction solution and the mixture was boiled for a further hour; the volume of liquid was now approximately 50 ml. The reaction mixture was made alkaline with an excess of 20% sodium hydroxide solution, boiled briefly, cooled, and extracted with ethyl acetate. The organic extract was taken to dryness and a sample of the residue (0·15 g.) was subjected to t.l.c. on alumina. 1,3-Diamino-2-methylanthraquinone was identified as the principal component from its R_F, colour and comparison with an authentic specimen.

Elemental analyses were carried out under the direction of Ing. L. Synek.

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