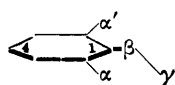


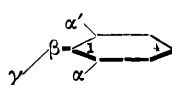
13. 2-Chloro-3 : 5-dinitro-4-chloromethyl- and 2 : 4 : 6-Tribromo-3-bromomethyl-benzoic Acids and Attempts to resolve them.

By A. WEISSBERGER, H. BACH, and E. STRASSER.

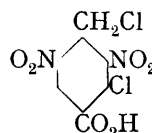
THE existence of enantiomorphous molecules of certain derivatives of diphenyl, naphthalene, and similar compounds is due to steric interferences which block the rotation about a single bond (Mills, *Chem. and Ind.*, 1926, **45**, 884; Adams and Yuan, *Chem. Rev.*, 1933, **12**, 261). For the same reason, resolution would be expected with *mononuclear* compounds of the type (I), if differences between α and α' or a substituent in position 3 or 5 removes the symmetry about the 1 : 4 axis, and if the mutual transformation of (Ia) and (Ib) is sufficiently hindered by blocking of the rotation of $\beta - \gamma$ about the link to the ring. Attempts to realise such cases have been described by Adams and his collaborators (*J. Amer. Chem. Soc.*, 1928, **50**, 2499; 1930, **52**, 2959; 1933, **55**, 4683) and by Le Fèvre (J., 1933, 977); no resolution, however, could be obtained.* We also were unsuccessful in our experiments, which we began from a somewhat different point of view before the publication of those papers.



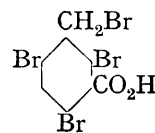
(Ia.)



(Ib.)



(II.)



(III.)

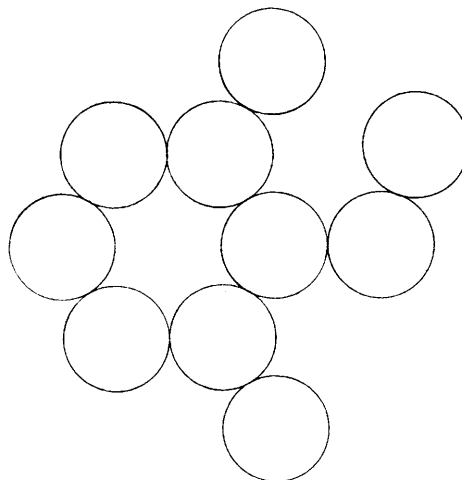
The possibility of resolving a compound of the type under discussion depends on two factors; in addition to the size and position of the groups or atoms α , α' , and γ , the groups whose steric interference inhibits the change of (Ia) into (Ib), there must also be considered

* The possibility of resolving compounds of the type mentioned was in fact investigated in experiments carried out about 50 years ago, the object of which was to examine the constitution of the benzene skeleton (Le Bel, *Bull. Soc. chim.*, 1882, **38**, 98; Lewkowitsch, J., 1888, **53**, 781; V. Meyer, Lühn, and Sudborough, see Meyer-Jacobson, "Lehrbuch," II, 1, p. 63).

the ease with which the groups can slip past one another by distortion from their normal positions. Such distortion should be less probable the smaller the number of bonds involved, unless some special arrangement of the bonds causes a special rigidity. The fig. shows the position through which the molecule must pass for (Ia) to become (Ib), in the case of the simplest mononuclear aromatic system, all the atoms being taken as of the same size (and the angles those of the benzene nucleus and the regular tetrahedron). Obviously interference is to be expected only if the atoms involved are of greater volume, or if they carry charges of the same sign, where the electrical repulsion has the effect of increasing their apparent volume (Weissberger and Sängewald, *Physikal. Z.*, 1929, **30**, 792).

The first substance investigated was 2-chloro-3 : 5-dinitro-4-chloromethylbenzoic acid (II). The efforts to resolve this acid by means of salt formation with optically active bases in the usual way were unsuccessful. As it seemed possible that the acid after liberation from the base racemised too quickly to be detected in the active form, this result was controlled by comparison of the rotatory power of the salts themselves with the activity of the corresponding salts of 3-chloro-2 : 6-dinitro-*p*-toluic acid; no differences exceeding the limits of error were observed.

We next worked with 2 : 4 : 6-tribromo-3-bromomethylbenzoic acid (III). This would be expected to be more suitable because the substituent γ is bromine of slightly greater radius than chlorine, and because the groups α and α' are also bromine atoms. Unlike the nitro-group, the bromine atom, because of its higher symmetry, cannot turn out of the way of the interfering group by rotation about the bond to the nucleus, and further the electric field, which should increase its effective volume with respect to the interfering bromine atom of the methyl group, is homogeneous in all directions round the axis formed by the bond to the ring. Repulsion of a negatively charged atom by the nitro-group, however, would only be expected in a position where it is faced by an oxygen atom.



The attempts to resolve this acid—which contains the bromine atom in the *p*-position to the bromomethyl group because it is more easily prepared than the acid without it—with optically active bases were, however, a failure. No difference could be observed between the rotatory power of the salts, as far as these proved to be formed by salt formation of the carboxylic group, and those of the corresponding acid with no substituent in the methyl group. The conditions of salt formation needed care, since under some conditions the bromine atom in the side chain reacted more readily than the precipitation of the ordinary salt proceeded, even in solvents where the reactivity of this bromine atom would be expected to be small (Menschutkin, *Z. physikal. Chem.*, 1890, **6**, 41; Grimm, Ruff, and Wolff, *ibid.*, 1931, *B*, **13**, 301). The carboxyl group seems to be markedly affected by the two bromine atoms in the *o*-positions to it.

Further investigation on the line pointed out in this paper should attempt another increase of α and of γ , the enclosure of the carboxyl or another reactive group between two substituents being avoided if possible.

EXPERIMENTAL.

3-Chloro-*p*-toluidine was prepared according to Blanksma (*Rec. trav. chim.*, 1906, **25**, 370). *p*-Nitrotoluene (350 g.), in boiling alcohol (1500 c.c.) and hydrochloric acid (3000 c.c., *d* 1.19), was reduced with stannous chloride (1700 g.) in hydrochloric acid (2000 c.c., *d* 1.19), added slowly. Boiling was continued for 1 hour, the mixture made alkaline, *p*-toluidine and 3-chloro-*p*-toluidine driven over by steam, transformed into the hydrochlorides (350 g.) and subjected to

steam-distillation. Only 3-chloro-*p*-toluidine went over; some which remained with the more basic *p*-toluidine also went over after addition of an amount of caustic soda equivalent to the base already driven out. Yield, 97 g. (26.8% of the theoretical), b. p. 225—226°, m. p. 6—7°.

3-Chloro-*p*-toluonitrile was prepared according to Claus and Davidsen (*J. pr. Chem.*, 1889, 39, 491). 3-Chloro-*p*-toluidine (140 g.) in water (200 c.c.), hydrochloric acid (*d* 1.19, 400 c.c.), and ice (800 g.), was diazotised with sodium nitrite (70 g., in water, 230 c.c.). This solution was quickly added with mechanical stirring to a boiling cuprous cyanide mixture (prepared from 500 g. of copper sulphate; Henle, "Org. Chem. Prakt.," 2nd ed., 1927, p. 148), and boiling continued for 10 minutes. Steam-distillation, followed by recrystallisation from alcohol, yielded 90 g. (60%), m. p. 60—61°.

2-Chloro-4-chloromethylbenzonitrile.—3-Chloro-*p*-toluonitrile (20 g.) and phosphorus pentachloride (30 g.) were heated for 5 hours in a large sealed tube at 200°; the mixture was then poured on ice, and the solid dried and recrystallised 5—7 times from light petroleum (b. p. 40—60°), giving 7.6 g. of colourless needles, m. p. 68—69.5° (Found: Cl, 38.1. $C_8H_5NCl_2$ requires Cl, 38.1%). The position of the newly introduced chlorine was proved by the production of chlorine ion on boiling with alcoholic potassium hydroxide solution; it was determined according to Schultze (*Ber.*, 1884, 17, 1675) (Found: ionised Cl, 19.05; calc., 19.07%).

Treatment of fused 3-chloro-*p*-toluonitrile with chlorine in light was not a convenient method of preparation: a product, m. p. 67—69°, was isolated which contained three chlorine atoms.

5-Chloro-2-nitro-*p*-toluonitrile.—Treatment of 3-chloro-*p*-toluonitrile with nitration acid (2 parts of HNO_3 , *d* 1.4, and 3 parts of H_2SO_4) for 30 minutes at 60° gave a neutral compound, m. p. 91.5—92.5° after recrystallisation from alcohol (Found: C, 49.05; H, 2.15; N, 14.1. Calc.: C, 48.9; H, 2.6; N, 14.3%). Yield, 90%. According to the analysis and m. p., and m. p. of the acid, 180°, obtained by saponification with 70% sulphuric acid, the compound is 5-chloro-2-nitro-*p*-toluonitrile, which was prepared by Claus and Davidsen (*Annalen*, 1891, 265, 345) from 5-chloro-2-nitro-*p*-toluidine by the Sandmeyer reaction.

3-Chloro-2 : 6-dinitro-*p*-toluic Acid.—3-Chloro-*p*-toluonitrile (2 g.) was dissolved in concentrated sulphuric acid (16 g.) and nitric acid (4 g., *d* 1.52) and heated in a water-bath. A violent reaction ensued and an acid was precipitated, m. p. 229—230.5° after recrystallisation from 60% alcohol and 235—237° after recrystallisation from xylene. The same substance was obtained by the corresponding treatment of 5-chloro-2-nitro-*p*-toluonitrile and is identical with that prepared by Claus and Davidsen (*loc. cit.*) by nitration of the corresponding acids.

2-Chloro-3 : 5-dinitro-4-chloromethylbenzoic Acid.—2-Chloro-4-chloromethylbenzonitrile (3.7 g.) was added to a mixture of concentrated sulphuric acid (30 g.) and nitric acid (7.5 g., *d* 1.52) and slowly heated in a water-bath. (The reaction sometimes goes on smoothly and is completed after a few minutes at 100°; sometimes, however, it becomes very violent and must be stopped by cooling.) The dinitro-acid was collected after cooling, washed with a little ice-water (yield, 3.7 g., m. p. 185—189°), and recrystallised three times from 25% alcohol, giving faintly yellow needles, m. p. 195—197°, 198—200° (corr.*) [Found: C, 32.3; H, 1.4; N, 9.6; Cl, 24.0; *M*, in dioxan (Weissberger and Bach, *J. pr. Chem.*, 1930, 127, 262), 303. $C_8H_4O_6N_2Cl_2$ requires C, 32.5; H, 1.4; N, 9.5; Cl, 24.0%; *M*, 295]. The positions of the nitro-groups are obviously 3 : 5, since the substituents already present and the first entering nitro-group uniformly direct subsequent substituents into these positions and the entrance of two nitro-groups in *o*-positions to each other seems impossible under the conditions of preparation.

2 : 4 : 6-Tribromo-*m*-toluonitrile.—2 : 4 : 6-Tribromo-*m*-toluidine (68 g.) was dissolved in concentrated sulphuric acid (160 g.) and poured on ice to get it into an easily diazotisable form; most of the acid was then neutralised by addition, with cooling, of a solution of 80 g. of sodium hydroxide (80 g.) in water (200 c.c.). 2 Hours after diazotisation (sodium nitrite, 15 g., in water, 50 c.c.), the solution was filtered and dropped into a solution prepared from hydrated copper sulphate (70 g.), water (700 c.c.), and potassium cyanide (125 g.) at 90°. The precipitate was collected when cool, and extracted with boiling alcohol (2 × 400 c.c.). The alcoholic solutions were diluted with water (800 c.c.), whereupon the nitrile crystallised. Recrystallisation from ligroin gave 34 g. of colourless crystals, m. p. 122—123° (123—124°, corr.) after further recrystallisation from ligroin or cyclohexane (Found: C, 27.0; H, 1.4; Br, 67.7. $C_8H_4NBr_3$ requires C, 27.1; H, 1.1; Br, 67.8%).

2 : 4 : 6-Tribromo-*m*-toluamide.—2 : 4 : 6-Tribromo-*m*-toluonitrile (8 g.) and 66% hydrobromic acid (15 c.c.) were heated in a sealed tube for 14 hours at 160—180°. The product was filtered, washed with water, and triturated with dilute sodium hydroxide solution to remove

* Corrected according to Berl and Kullmann, *Ber.*, 1927, 60, 811.

the acid; on acidification, 2 : 4 : 6-tribromo-*m*-toluic acid (0.35 g.) separated. The residue was dried, extracted with light petroleum, which removed 2 : 4 : 6-tribromotoluene (0.1 g.), and recrystallised from 50% alcohol, giving 6.5 g. of colourless crystals, m. p. 199—200°, 202—203° (corr.) (Found : C, 26.0; H, 1.8; Br, 64.3. $C_8H_6ONBr_3$ requires C, 25.8; H, 1.6; Br, 64.5%). This method of saponification was used with regard to the eventual necessity of saponification of the nitrile brominated in the side chain.

2 : 4 : 6-Tribromo-*m*-toluic Acid.—To the amide (17 g.), dissolved in concentrated sulphuric acid (200 c.c.) and cooled with ice, a solution of sodium nitrite (15 g.) in water (40 c.c.) was added by means of a capillary which reached to the bottom of the bottle (Gattermann, *Ber.*, 1899, **32**, 1118). The mixture was slowly heated to 90°, kept for 4 hours at this temperature, then poured on ice, and filtered. The residue was dissolved in 0.5*N*-sodium hydroxide, and the filtered solution treated with hydrochloric acid. The *acid* obtained separated from 50% methyl alcohol as colourless needles, sintering at about 160°, m. p. 187.5—188.5°, 190.5—191.5° (corr.). Investigation under the hot-stage microscope showed that the sintering is due to polymorphism (Found : C, 25.9; H, 1.6; Br, 64.1. $C_8H_5O_2Br_3$ requires C, 25.75; H, 1.3; Br, 64.3%).

2 : 4 : 6-Tribromo-3-bromomethylbenzoic Acid.—The introduction of bromine into the methyl group was carried out according to Helferich and Gootz (*Ber.*, 1932, **65**, 407). 2 : 4 : 6-Tribromo-*m*-toluic acid (13.3 g.) was dissolved in alcohol-free chloroform (350 c.c.), finely powdered sodium bicarbonate (3 g.) added, and then a solution of bromine (5.9 g.) in chloroform (50 c.c.). This mixture was mechanically stirred and, the outside of the bottle being cooled by a stream of air, insulated with a 500 watt lamp till it was colourless. After evaporation of the chloroform the residue was recrystallised from benzene, yielding 12.2 g. (76%) of colourless needles, m. p. 180.5—181.5°, 183.5—184.5° (corr.). This *acid* too is polymorphous; faint sintering occurs at about 160° and a sample introduced into the melting-point apparatus at 175° melted completely, but solidified after a short time at the same temperature and then exhibited the melting point noted above (Found : C, 21.6; H, 1.1; Br, 70.5. $C_8H_4O_2Br_4$ requires C, 21.6; H, 0.9; Br, 70.8%).

Attempted Resolutions.—The salts of 2-chloro-3 : 5-dinitro-4-chloromethylbenzoic acid with brucine, in alcohol and alcohol-chloroform, strychnine, quinine, and quinidine, in alcohol, were prepared by mixing solutions of equivalent amounts of the acid and the base in such concentrations that about one half of the salts crystallised on standing. These crystallisates showed, in chloroform or in acetone solution, no other activities than the corresponding salts of the 3-chloro-2 : 6-dinitro-*p*-toluic acid.

The salt of 2 : 4 : 6-tribromo-3-bromomethylbenzoic acid with brucine which was quickly precipitated (about one half of the total) from acetone or benzene solution on scratching showed no other rotatory power, in chloroform, than that of 2 : 4 : 6-tribromo-*m*-toluic acid. From alcohol, the whole of the salt was precipitated, either quickly on scratching or slowly without; it also showed no different activity. If the crystallisation from acetone, benzene, or dioxan proceeded slowly, the precipitates exhibited other (positive) rotatory powers. They proved to be hydrobromides of bases which were formed by condensation involving the bromomethyl group and could not be decomposed by shaking with acid under conditions where the salts with the same rotatory powers as those of the acid with no bromine in the side chain were decomposed. This decomposition also required a rather long treatment; obviously the decomposition of the salts is hindered by the proximity of the bromines to the carboxyl group.

Corresponding observations were made with coniine (in ether, amyl ether and acetone), quinine (in acetone, alcohol, benzene), and morphine (in acetone, alcohol-acetone and dioxan-acetone), at the ordinary and at low temperatures (freezing mixture, carbon dioxide snow).

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