

343. *Reactivity of the Methylene Group in Derivatives of Phenylacetic Acid.*

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Investigation of the effect of the number and positions of nitro-groups in derivatives of diphenylmethane upon the reactivity of the methylene group (Parkes and Morley, J., 1936, 1478) has now been followed by examination of a number of derivatives of phenylacetic acid and related substances. Nitrous acid is without action upon the methylene group even when two nitro-groups are present in the nucleus, but solutions of diazonium salts react readily. No action occurs with either reagent when a single nitro-group is present; the presence of a nitro- and an amino-group together causes the methylene group to be reactive to a slight extent towards nitrous acid; but diazonium salts attack only the amino-group. Similar results were observed with the corresponding derivatives of oxindole.

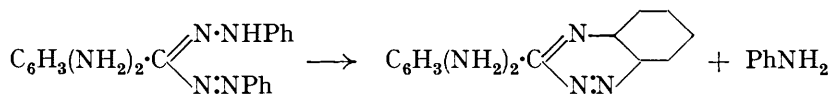
THE behaviour of methyl 2:4-dinitrophenylacetate towards benzenediazonium chloride was first described by V. and A. Meyer (*Ber.*, 1888, **21**, 1307; 1889, **22**, 320), who found that coupling occurred in a manner analogous to the action with acetoacetic ester (*Ber.*, 1877, **10**, 2075). They also observed that there was no action with methyl 2-nitro- or

4-nitro-phenylacetate. These observations have now been extended and a series of such coupled compounds prepared, and the action of bromine upon them has been studied.

Bromination of methyl benzeneazo-2 : 4-dinitrophenylacetate yielded ω -bromo-2 : 4-dinitrobenzaldehyde-*p*-bromophenylhydrazone. Presumably methyl *p*-bromobenzeneazo-2 : 4-dinitrophenylacetate was first formed, but it could not be isolated.

The action of diazonium salt solutions upon 2 : 4-dinitrophenylacetic acid itself yielded brilliant scarlet *formazyl* compounds analogous to those obtained by v. Pechmann (*Ber.*, 1892, **25**, 3175) and by Bamberger and Wheelwright (*ibid.*, p. 3201).

Boiling hydrochloric acid was without effect on the formazyl compounds derived from 2 : 4-dinitrophenylacetic acid, but this was probably due to their insolubility in hydrochloric acid : when the substances were rendered soluble by reduction of the nitro-groups to amino-groups, boiling with hydrochloric acid caused the formation of benzotriazines, the formazyl structure of the compounds thus being confirmed (cf. Bamberger and Wheelwright, *loc. cit.*) :



Reduction of 2 : 4-dinitrophenylacetic acid by ammonium sulphide yields a nitro-amino-derivative which Gabriel and Meyer (*Ber.*, 1881, **14**, 824) suggested was the 2-nitro-4-amino-compound on the ground that, if the nitro-group in the 2-position had been reduced, ring closure would have taken place with the formation of 6-nitro-oxindole. This structure has now been confirmed by oxidation of the nitroaminophenylacetic acid to 2-nitro-4-aminobenzoic acid, and also by the isolation (*inter alia*) of 2-nitro-*p*-toluidine from the products of the decomposition of the nitroaminophenylacetic acid by heat.

Gabriel and Meyer (*loc. cit.*) also investigated the action of nitrous acid on hot solutions of 2-nitro-4-aminophenylacetic acid and isolated various *isonitroso*-compounds. The action in the cold has now been investigated, and as diazotisation was expected to occur, cuprous chloride was added to replace the diazonium group by chlorine : 4-chloro-2-nitrobenzaldehyde and 4-chloro-2-nitrophenylacetic acid resulted. Even in the cold, therefore, the methylene group in this compound is attacked by nitrous acid.

The action of bromine on 2-nitro-4-aminophenylacetic acid yielded a mixture of mono- and di-bromo-derivatives, the separation of which proved difficult owing to their close resemblance in properties. The monobromo-derivative was shown to be 5-bromo-2-nitro-4-aminophenylacetic acid by oxidation of its acetyl compound to the corresponding benzoic acid, and it is therefore concluded that the dibromo-derivative has the bromine atoms in the 5- and 3-positions.

Gabriel and Meyer (*loc. cit.*), by reduction of 2 : 4-dinitrophenylacetic acid with tin and hydrochloric acid, obtained 6-amino-oxindole, and by diazotisation in alcohol with amyl nitrite isolated the corresponding *isonitroso*-diazonium salt. In the present work it was hoped to confine the attack to the amino-group by using nitrous acid in the cold. The diazo-group was replaced by chlorine as before, and a mixture resulted from which 6-chloroisonitroso-oxindole was isolated. A considerable quantity of 6-chloro-oxindole was also formed, but could not be isolated pure.

Nitrous acid was found not to attack the methylene group in 6-acetamido-oxindole, and the same negative result was obtained also with 2-nitro-4-acetamidophenylacetic acid, showing that the methylene group is only reactive to nitrous acid when the amino-group is free to react also with the nitrous acid. Similarly the methylene group in 6-acetamido-oxindole was found not to couple with diazonium salts.

The action of stannous chloride on 2 : 4-dinitrophenylacetic acid always gave a mixture of about 75% of unchanged acid and 25% of 6-nitro-oxindole, although widely varying conditions were used. Separation of this mixture proved impracticable.

Borsche and Meyer have already shown that the methylene group in 6-nitro-oxindole is reactive to nitrous acid (*Ber.*, 1921, **54**, 2844), so the coupling with diazonium salts was attempted, and 6-nitro-3-*p*-bromobenzeneazo-oxindole was readily isolated.

The results of investigations on methylene group reactivity are summarised in the following table.

Substance.	Reagent.		
	Nitrous acid.	Diazonium salts.	Aldehydes.
2 : 4-Dinitrophenylacetic acid	No action	Formazyl compounds	Couple ¹
Methyl 2 : 4-dinitrophenylacetate ...	No action	Couple	
2-Nitro-4-aminophenylacetic acid ...	Partial attack	Attack NH ₂ group	
2-Nitro-4-acetamidophenylacetic acid ...	No action		
4-Chloro-2-nitrophenylacetic acid ...	No action	No action	
Oxindole	Attacked ²	Couple ³	Couple ⁴
6-Nitro-oxindole	Attacked ⁵	Couple	
6-Amino-oxindole	Partial attack	Attack NH ₂ group	Couple, ⁶ alk. on NH ₂ , acid on CH ₂
6-Acetamido-oxindole	No action	No action	
2 : 4-Dinitrotoluene	No action	No action	

¹ Pschorr, *Ber.*, 1896, **29**, 496. ² Baeyer and Knop, *Annalen*, 1866, **140**, 34. ³ Roux and Martinet, *Rev. Gén. Matières Colorantes*, 1923, **28**, 152. ⁴ Hansen, *Ann. Chim.*, 1924, **1**, 94. ⁵ Borsche and Meyer, *Ber.*, 1921, **54**, 2844. ⁶ N. Kishi, *J. Pharm. Soc., Japan*, 1927, **96**, 677.

EXPERIMENTAL.

2 : 4-Dinitrophenylacetic acid was prepared by Gabriel and Meyer's method (*loc. cit.*), but since it was found to decompose very readily in presence of alkali (even boiling with sodium acetate solution giving a quantitative yield of 2 : 4-dinitrotoluene in a short time), it was recrystallised from hot water made slightly acid with sulphuric acid. The *benzyl* ester separated from alcohol in long, pale yellow needles, m. p. 98° (Found : N, 9·2. C₁₅H₁₂O₆N₂ requires N, 9·0%).

Methyl p-Chlorobenzeneazo-2 : 4-dinitrophenylacetate.—A mixture of 12 g. of methyl 2 : 4-dinitrophenylacetate, 300 c.c. of alcohol, and 100 g. of sodium acetate was cooled in ice, and the diazonium solution obtained from 6·3 g. of *p*-chloroaniline, dissolved in 40 c.c. of dilute hydrochloric acid, added. After 7 hours, the *product* was collected and recrystallised from alcohol, forming orange needles, m. p. 155° (Found : Cl, 9·3. C₁₅H₁₁O₆N₄Cl requires Cl, 9·3%). The following were obtained similarly and crystallised from alcohol : *methyl p-bromobenzeneazo-2 : 4-dinitrophenylacetate*, golden-yellow silky plates, m. p. 182° (Found : Br, 18·9. C₁₅H₁₁O₆N₄Br requires Br, 18·9%); *methyl 2' : 4'-dichlorobenzeneazo-2 : 4-dinitrophenylacetate*, golden-yellow plates, m. p. 181° (Found : Cl, 17·55. C₁₅H₁₀O₆N₄Cl₂ requires Cl, 17·2%); *methyl 2' : 4'-dibromobenzeneazo-2 : 4-dinitrophenylacetate*, golden-yellow plates, m. p. 199° (Found : Br, 30·0. C₁₅H₁₀O₆N₄Br₂ requires Br, 31·8%).

ω-Bromo-2 : 4-dinitrobenzaldehyde-p-bromophenylhydrazone.—5 G. of methyl benzeneazo-2 : 4-dinitrophenylacetate were dissolved in 20 c.c. of boiling acetic acid, and 1 g. of sodium acetate added, followed by a solution of 4·8 g. of bromine in 20 c.c. of acetic acid. The mixture was poured into water, and the yellow solid recrystallised from acetic acid. It formed bright yellow plates, m. p. 176°, and was identified by comparison with an authentic specimen prepared by brominating 2 : 4-dinitrobenzaldehydephenylhydrazone (Chattaway and Adamson, *J.*, 1931, 2792).

Formazyl-2 : 4-dinitrobenzene.—20 G. of 2 : 4-dinitrophenylacetic acid were mixed with 250 g. of sodium acetate and 20 c.c. of water. To this mixture, cooled in ice, the diazonium chloride solution obtained from 17 g. of aniline was added. After 8 hours the *solid* was filtered off and recrystallised from acetic acid, forming crimson micro-needles, m. p. 198° (Found : N, 21·3. C₁₉H₁₄O₄N₆ requires N, 21·5%).

The following were prepared similarly : *pp'-Dibromoformazyl-2 : 4-dinitrobenzene*, bright crimson plates (from ethyl acetate), m. p. 220° (Found : N, 15·4; Br, 29·7. C₁₉H₁₂O₄N₆Br₂ requires N, 15·3; Br, 29·2%); *2' : 2'' : 4' : 4''-tetrachloroformazyl-2 : 4-dinitrobenzene*, deep red, microcrystalline powder (from acetone), m. p. 206° (darkening at 150°) (Found : Cl, 28·4. C₁₉H₁₀O₄N₆Cl₄ requires Cl, 27·0%); *2' : 2'' : 4' : 4''-tetrabromoformazyl-2 : 4-dinitrobenzene*, deep red micro-crystals (from ethyl acetate), m. p. 201° (darkening at 150°) (Found : Br, 43·1. C₁₉H₁₀O₄N₆Br₄ requires Br, 45·0%).

6 (or 7)-Bromo-3-2' : 4'-diaminophenyl-1 : 2 : 4-benzotriazine.—15 G. of *pp'*-dibromoformazyl-2 : 4-dinitrobenzene were suspended in 150 c.c. of concentrated hydrochloric acid, and 60 g. of tin added. After refluxing for several hours, the solution was filtered and evaporated until the tin salt began to crystallise. This was recrystallised from dilute hydrochloric acid and decomposed with aqueous ammonia; steam-distillation then removed *p*-bromoaniline. The

residue was cooled, made alkaline with aqueous ammonia, and repeatedly extracted with ether. The red ethereal solution on evaporation left a very small quantity of a grey powder, which crystallised from alcohol in almost colourless plates, m. p. 180° (darkening at 160°) (Found : N, 22.1; Br, 24.8. $C_{13}H_{10}N_2Br$ requires N, 22.15; Br, 25.3%).

2-Nitro-4-aminophenylacetic Acid.—The deep violet solution of 50 g. of 2:4-dinitrophenylacetic acid in 400 c.c. of freshly prepared aqueous ammonium sulphide was mechanically stirred while hydrogen sulphide was passed in. After 1½—2 hours' stirring, when a sample had given a satisfactory result, the solution was boiled for 5—6 hours, cooled, filtered, and acidified with hydrochloric acid. The 2-nitro-4-aminophenylacetic acid crystallised from water in orange-red flat needles, m. p. 185°. The reduction was very uncertain, and often yielded only a tar even after the sample had given a successful result.

The *acetyl* compound had m. p. 205° (Found : N, 11.5. $C_{10}H_{10}O_5N_2$ requires N, 11.8%), and the *benzoyl* compound, m. p. 223° (Found : N, 9.15. $C_{15}H_{12}O_5N_2$ requires N, 9.3%).

Action of Heat.—2-Nitro-4-aminophenylacetic acid (3—4 g.) was heated at 190° for a few minutes, and the resultant tar boiled with water. The solid that separated on cooling crystallised from water in yellow micro-crystals of 2-nitro-4-2'-nitro-4'-aminophenylacetamidophenylacetic acid, m. p. 213°, soluble in alkali solution and reprecipitated by acids (Found : N, 15.0. $C_{16}H_{14}O_7N_4$ requires N, 14.9%).

When the temperature was allowed to rise to 270°, the mixture obtained, on extraction with boiling water, yielded this yellow powder and 2-nitro-*p*-toluidine. The latter was identified by comparison with an authentic specimen (Noelting and Collin, *Ber.*, 1884, 17, 263).

Oxidation.—4 G. of 2-nitro-4-acetamidophenylacetic acid, 500 c.c. of water, 8 g. of magnesium sulphate, and 15 g. of potassium permanganate were refluxed together for 7 hours. The nitroacetamidobenzoic acid which separated on evaporation and acidification was refluxed with caustic potash solution, and the resulting 2-nitro-4-aminobenzoic acid recrystallised from water. It was identical with an authentic specimen prepared by the similar oxidation of 2-nitro-*p*-toluidine.

Action of nitrous acid. 8 G. of 2-nitro-4-aminophenylacetic acid were ground with 80 c.c. of dilute hydrochloric acid, cooled in ice, and 5 g. of sodium nitrite added with stirring. This solution was added to ice-cold cuprous chloride solution. The mixture was submitted to steam-distillation. The oil in the distillate, after solidifying, crystallised from light petroleum (b. p. 40—60°) in bunches of white needles, m. p. 65°, identified as 4-chloro-2-nitrobenzaldehyde by comparison with an authentic specimen (Sachs and Kempf, *Ber.*, 1902, 35, 1234; 1903, 36, 3300). The pale brown substance left after the steam-distillation crystallised from benzene in needles, m. p. 163°, identified as 4-chloro-2-nitrophenylacetic acid by the isolation of 4-chloro-2-nitrotoluene from the products of decomposition by heat.

5-Bromo- and 3:5-Dibromo-2-nitro-4-aminophenylacetic Acid.—3 G. of 2-nitro-4-aminophenylacetic acid were suspended in 15 c.c. of acetic acid, a large excess of bromine in acetic acid added, the mixture kept at 60° for a few minutes and poured into water, and the solid obtained recrystallised several times from acetic acid. Analysis showed it to be a mixture of about 94% of the dibromo- and about 6% of the monobromo-compound. The mixture similarly obtained when 1 mol. of bromine was used contained about 80% of the monobromo-compound. Separation was effected after acetylation. The *dibromo-acetyl* compound was isolated readily and recrystallised from acetic acid, m. p. 240° (decomp.) (Found : Br, 40.8. $C_{10}H_8O_5N_2Br_2$ requires Br, 40.4%). The monobromo-acetyl compound could not be obtained quite pure. The position of the bromine atom in it was established as follows : 5-bromo-2-nitro-*p*-toluidine (Claus and Herbabny, *Annalen*, 1892, 265, 367) was acetylated, and the product oxidised by means of potassium permanganate in presence of magnesium sulphate. 5-Bromo-2-nitro-4-acetamidobenzoic acid, which separated on acidification, crystallised from water in colourless needles, m. p. 246°. The same substance, m. p. 245°, was obtained by the similar oxidation of the slightly impure monobromonitroacetamidophenylacetic acid.

6-Amino-oxindole.—This was obtained by Gabriel's method (*loc. cit.*). The *acetyl* derivative formed pinkish plates, m. p. 324° (Found : N, 14.6. $C_{10}H_{10}O_2N_2$ requires N, 14.7%), and the *benzoyl* derivative white micro-needles, m. p. 273° (Found : N, 11.0. $C_{15}H_{12}O_2N_2$ requires N, 11.1%), both from acetic acid.

6-Chloroisoxinoso-oxindole.—A solution of 5 g. of 6-amino-oxindole in 100 c.c. of alcohol and 50 c.c. of dilute hydrochloric acid was diazotised with 10 g. of amyl nitrite. The brown precipitate formed exploded on heating (compare Gabriel, *loc. cit.*). 2 G. of this substance were mixed with 30 c.c. of dilute hydrochloric acid cooled in ice, and added to cold cuprous chloride solution. After boiling, a brown precipitate was formed, which was suspended in water, aerated

to oxidise any cuprous chloride, and washed with hydrochloric acid and water. The 6-chloro-isonitroso-oxindole separated from dilute acetic acid as a red-brown powder, m. p. 240° (Found : Cl, 17.9. $C_8H_5O_2N_2Cl$ requires Cl, 18.0%).

6-Nitro-3-p-bromobenzeneazo-oxindole.—2.5 G. of 6-nitro-oxindole (Marschalk, *Ber.*, 1912, 45, 282) were mixed with 100 g. of sodium acetate and 20 c.c. of water and cooled in ice while the diazonium chloride solution obtained from 5 g. of *p*-bromoaniline was added. After 7 hours the yellow solid was filtered off; it separated from acetic anhydride as an orange powder, m. p. 281° (decomp.) (Found : Br, 21.6. $C_{14}H_9O_3N_4Br$ requires Br, 22.1%).

The authors thank Mr. W. G. Alway for help with the experimental work.

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[Received, September 22nd, 1938.]