425. *The Synthesis of 3'-Methyl-4'-nitrobiphenylcarboxylic Acids by the Reaction of 3-Methyl-4-nitrobenzenediazonium Acetate with Methyl Benzoate.*

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Reaction of 3-methyl-4-nitrobenzenediazonium acetate with methyl benzoate gives the three isomeric methyl 3'-methyl-4'-nitrobiphenylcarboxylic acids. The isomers were reduced and hydrolysed to the amino-acids, whose structures were determined by oxidation of the acetamido-acids to the corresponding benzenedicarboxylic acids.

REACTION of 3-methyl-4-nitrobenzenediazonium acetate with methyl benzoate has been carried out primarily to obtain methyl 3'-methyl-4'-nitrobiphenyl-2-carboxylate for conversion into the amino acid which was required for comparison with metabolites of 2',3-dimethyl-4-biphenylylamine.

Aromatic esters react with arenediazonium salts to give diaryls, as described by Gomberg and his co-workers [1,2] but only in the case of the reaction with ethyl benzoate, reported by Hey,[3] have the three isomers predicted by Hey and Waters [4] been isolated. After reaction [2] of sodium benzenediazoate and methyl benzoate only the 4-isomer was isolated, but for the reaction with ethyl phthalate Butterworth *et al.*[5] suggested that the 3-isomer might have been formed in addition to the 4-phenylphthalic acid.

The present communication reports the reaction between diazotised 4-nitro-*m*-toluidine and methyl benzoate in the presence of sodium acetate, as described by Elk, Haworth, and Hey [6] as these experimental conditions would be expected to give the best yields of biaryls from bases containing a *p*-nitro-group. The three isomeric methyl 3'-methyl-4'-nitrobiphenylcarboxylates were isolated and were then reduced catalytically to the amino-esters. The structures of these have been determined by hydrolysis, followed by oxidation of the acetamido-acids to the corresponding benzenedicarboxylic acids with chromium trioxide. The oxidation of the 2-carboxylic acid did not give phthalic acid, in agreement with the fact that this acid undergoes complete degradation on oxidation by chromium trioxide.[7] This acetamido-acid gave 4'-acetamidobiphenyl-2,3'-dicarboxylic acid on oxidation with potassium permanganate.

EXPERIMENTAL

Infrared spectra were obtained by using sodium chloride discs with the Perkin–Elmer Infracord spectrophotometer model 137.

Paper Chromatography.—Descending chromatograms on Whatman no. 1 paper were used with the following solvent systems: (A) butan-1-ol–2N-ammonia (2 : 1 : 1); (B) butan-1-ol–propan-1-ol–2N-ammonia (2 : 1 : 1); (C) butan-1-ol–propan-1-ol–water (2 : 1 : 1); (D) butan-1-ol–acetic acid–water (12 : 3 : 5). The R_F values are tabulated.

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[1] Gomberg and Bachmann, *J. Amer. Chem. Soc.*, 1924, **46**, 2339.

[2] Gomberg and Pernett, *J. Amer. Chem. Soc.*, 1926, **48**, 1372.

[3] Hey, *J.*, 1934, 1966.

[4] Hey and Waters, *J.*, 1948, 882.

[5] Butterworth, Heilbron, Hey, and Wilkinson, *J.*, 1938, 1386.

[6] Elks, Haworth, and Hey, *J.*, 1940, 1284.

[7] "The Chemistry of Carbon Compounds," Vol. III, ed. E. H. Rodd, Elsevier, Amsterdam, 1956, p. 843.

Chromatographic results ($100R_F$) (for solvents A—D see text).

	A	B	C	D
Me 3′-methyl-4′-nitrobiphenyl-3-carboxylate	94	88	88	88
4′-Amino-3′-methylbiphenyl-3-carboxylic acid	20	22	54	83
4′-Acetamido-3′-methylbiphenyl-3-carboxylic acid	27	30	58	86
Product from alkali treatment of 1st compound	O	O	15	83
Me 3′-methyl-4′-nitrobiphenyl-2-carboxylate	92	88	88	90
4′-Amino-3′-methylbiphenyl-2-carboxylic acid	19	21	41	82
4′-Acetamido-3′-methylbiphenyl-2-carboxylic acid	30	33	47	87
Product from alkali treatment of 2nd ester above	02	04	16	84
Me 3′-methyl-4′-nitrobiphenyl-4-carboxylate	84	80	86	88
4′-Amino-3′-methylbiphenyl-4-carboxylic acid	17	16	49	83
4′-Acetamido-3′-methylbiphenyl-4-carboxylic acid	23	23	49	86
Product from alkali treatment of 3rd ester above	O	O	12	78
4′-Aminobiphenyl-2,3′-dicarboxylic acid	02	02	16	84
4′-Acetamidobiphenyl-2,3′-dicarboxylic acid	05	06	21	85
Phthalic acid	02	04	32	73
Isophthalic acid	02	03	20	86
Terephthalic acid	O	02	10	82

O = Origin.

Compounds with aromatic amino-groups were detected on paper chromatograms by diazotisation with 0·5% aqueous sodium nitrite and 0·5N-hydrochloric acid, followed by spraying with a solution of a 0·5% solution of 1- or 2-naphthol in a 4% solution of sodium hydroxide in 50% aqueous ethanol. The compounds were also detected by spraying with 0·5% ethanolic *p*-dimethylaminobenzaldehyde containing hydrochloric acid (1%), or a 0·5% solution of *p*-dimethylaminocinnamaldehyde in 90% ethanol containing 5% of hydrochloric acid. The last two spray reagents were also used to detect acetamido-compounds, the colours appearing overnight. Compounds with an aromatic nitro-group were also detected with these spray reagents by first reducing the nitro-group with a titanous chloride spray.

The isomeric phthalic acids were detected by spraying the paper with a mixture of Methyl Red (0·1%) in ethanol (1 vol.) with 0·667M-phosphate buffer (pH 7·0) (2 vols.).

Diazotisation and coupling with the alkaline naphthols produced orange or red spots with amino-compounds. *p*-Dimethylaminobenzaldehyde gave colours ranging from pale yellow to deep orange; *p*-dimethylaminocinnamaldehyde gave colours from pink to dark blue. Methyl Red solution gives red spots on a pale yellow background with aromatic acids.

Reaction of 3-*Methyl*-4-*nitrobenzenediazonium Acetate with Methyl Benzoate.*—4-Nitro-*m*-toluidine (150 g.) was diazotised in hydrochloric acid (200 ml.), ice (350 g.), and water (75 g.) with sodium nitrite (70 g.) in water (200 g.). The mixture was filtered and methyl benzoate (1 l.) and hydrated sodium acetate (300 g.) were added. The filtrate was stirred for 20 hr. during which the temperature rose to 25°; it was then heated at 80° for a further 2 hr. The organic phase was separated and washed with water, the excess of methyl benzoate distilled off under reduced pressure and the residual oil triturated with ether (300 ml.), yielding a pale brown powder which crystallised from chloroform to give the isomer of m. p. 176° (16 g.). The ether was evaporated and yielded a gum which was extracted with boiling methanol (2 × 500 ml.). The methanol extract was allowed to cool, filtered, and evaporated. The residual oil was distilled under reduced pressure and the fraction boiling at 180—190°/0·7 mm. collected. In methanol this gave pale yellow crystals, m. p. 96° (21 g.). Concentration of the mother-liquors, followed by cooling in carbon dioxide–acetone, gave a third isomer, m. p. 80° (2·5 g.).

Each isomer (100 mg.) of methyl 3′-methyl-4′-nitrobiphenylcarboxylate was heated for 4 hr. at 100° with potassium hydroxide (2 g.) in water (1 g.), to produce the corresponding aminobiphenyldicarboxylic acids by hydrolysis and rearrangement. The hydrolysates were neutralised and compared with authentic 4-aminobiphenyl-2′,3-dicarboxylic acid by paper chromatography with the four solvent systems described above. Only the ester of m. p. 96° gave this acid.

4′-*Acetamido*-3′-*methylbiphenyl*-3-*carboxylic Acid.*—The isomer of m. p. 80° was recrystallised from benzene to yield pale yellow needles of *methyl* 3′-*methyl*-4′-*nitrobiphenyl*-3-*carboxylate* (Found: C, 65·9; H, 5·0; N, 5·4. $C_{14}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%). Catalytic reduction of this (1·6 g.) in benzene with Adams catalyst, followed by heating with 4N-hydrochloric acid (250 ml.) at 100° for 60 min., gave 4′-amino-3′-methylbiphenyl-3-carboxylic acid

(850 mg.) which was converted by acetic anhydride in pyridine into the *4′-acetamido-acid*, m. p. 240°, plates (from aqueous ethanol) (Found: C, 71·15; H, 5·6; N, 5·2. $C_{16}H_{15}NO_3$ requires C, 71·4; H, 5·6; N, 5·2%).

The acetamido-acid (100 mg.) was heated under reflux with a 10% (w/v) solution of chromium trioxide in 90% aqueous acetic acid and gave isophthalic acid (30 mg.), m. p. 320°. The infrared spectrum and properties on paper chromatograms were indistinguishable from those of authentic isophthalic acid.

4′-Acetamido-3′-methylbiphenyl-2-carboxylic Acid.—The isomer of m. p. 96° was recrystallised from methanol, to yield *methyl 3′-methyl-4′-nitrobiphenyl-2-carboxylate* as needles (Found: C, 66·2; H, 4·7; N, 5·0%). Reduction and hydrolysis of this compound (2·7 g.) as above gave *4′-amino-3′-methylbiphenyl-2-carboxylic acid* (1·4 g.), needles (from aqueous ethanol), m. p. 209° (Found: C, 74·05; H, 6·2; N, 6·0. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·8; N, 6·2%). The derived *acetamido-acid*, needles, m. p. 188° (Found: C, 71·0; H, 5·9; N, 5·1%), was oxidised with chromium trioxide as above, but no phthalic acid was detected. Oxidation with potassium permanganate gave 4′-acetamidobiphenyl-2,3′-dicarboxylic acid, m. p. 247°, identical in infrared spectrum with the compound described below.

4′-Acetamido-3′-methylbiphenyl-4-carboxylic Acid.—The isomer of m. p. 176° was recrystallised from benzene, to give *methyl 3′-methyl-4′-nitrobiphenyl-4-carboxylate*, needles, m. p. 176, (Found: C, 66·4; H, 4·5; N, 4·9%). Reduction and hydrolysis as above gave 4′-amino-3′-methylbiphenyl-4-carboxylic acid, m. p. 214°, whose *sodium salt* crystallised from water as needles (Found: C, 65·1; H, 5·1; N, 5·4; Na, 8·9; loss on drying, 4·1. $C_{14}H_{12}NNaO_2,\frac{1}{2}H_2O$ requires C, 65·1; H, 5·0; N, 5·4; Na, 8·9%; loss on drying 3·4%).

The acid afforded *4′-acetamido-3′-methylbiphenyl-4-carboxylic acid*, needles (from ethanol), sublimed at 320° (Found: C, 71·1; H, 5·6; N, 5·1%), which was oxidised by chromium trioxide to terephthalic acid (40 mg. from 100 mg.), sublimes at *ca.* 300°, identical with authentic terephthalic acid as regards paper chromatography in four solvent systems and infrared spectroscopy.

4′-Acetamidobiphenyl-2,3′-dicarboxylic Acid.—This compound was prepared by heating *N*-acetyl-2′,3-dimethyl-4-biphenylylamine (3·1 g.) under reflux with a solution of potassium permanganate (12 g.) and hydrated magnesium sulphate (30 g.) in water (250 ml.) for 3 hr. After filtration the solution was treated with sulphur dioxide. The precipitate was collected, washed with water, and dissolved in sodium hydrogen carbonate solution. The solution was filtered and acidified to give the *dicarboxylic acid* (2·5 g.) which recrystallised from ethanol as pale yellow needles, m. p. 247° (Found: C, 63·8; H, 4·5; N, 4·7. $C_{16}H_{13}NO_5$ requires C, 64·2; H, 4·4; N, 4·7%). This compound was heated under reflux with 4N-hydrochloric acid for 3 hr., which afforded *4′-aminobiphenyl-2,3′-dicarboxylic acid*, pale yellow needles (from aqueous ethanol), m. p. 274° (sinters at 230°) (Found: C, 65·15; H, 4·5; N, 5·6. $C_{14}H_{11}NO_4$ requires C, 65·4; H, 4·3; N, 5·45%). Recrystallisation from 4N-hydrochloric acid gave the *hydrochloride* as needles, m. p. 240° (decomp.) (Found: C, 57·6; H, 4·3; N, 4·5. $C_{14}H_{12}ClNO_4$ requires C, 57·3; H, 4·1; N, 4·8%).

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