

48. Preparation of Iodinated Mono- and Di-phenyl-acetic and -propionic Acids.

By JEAN W. BARNETT, F. A. ROBINSON, and BARBARA M. WILSON.

The preparation of nine iodinated derivatives of mono- and di-phenyl-acetic and -propionic acids is described.

3 : 5-Di-iodo- and **3 : 4 : 5-tri-iodo-phenylacetic acid** were prepared from **3 : 5-di-iodo-4-amino-phenylacetic acid**. This was obtained by iodination of *p*-aminophenylacetic acid (*Org. Synth.*, Coll. Vol. I, 44) by a method analogous to that used for the preparation of **3 : 5-di-iodo-4-aminobenzoic acid** by Wheeler and Liddle (*Amer. Chem. J.*, 1920, 42, 456). Replacement of the amino-group of **3 : 5-di-iodo-4-aminophenylacetic acid** by hydrogen proved unexpectedly difficult, the usual methods yielding black tars. Satisfactory results were eventually obtained by adding a solution of the diazonium salt to a cold alcoholic suspension of cuprous oxide (cf. Hodgson and Turner, *J.*, 1942, 748). The amino-group was readily replaced by iodine by the standard method.

3 : 5-Di-iodo-2-hydroxyphenylacetic acid was prepared by iodination of *o*-hydroxyphenylacetic acid with iodine in potassium iodide.

3 : 5-Di-iodo-4-hydroxydiphenylacetic acid was prepared by iodination of *p*-hydroxydiphenylacetic acid, obtained by the method of Bistrzycki and Flatau (*Ber.*, 1895, 28, 987). This method gave unsatisfactory results unless very pure mandelic acid was used as the starting material. Even then, crystallisation was very slow.

3 : 5-Di-iodo-2-hydroxydiphenylacetic acid was prepared by iodination of *o*-hydroxydiphenylacetic acid, which is known in the form of its lactone, 3-phenylisocoumaranone (Bistrzycki, *Ber.*, 1897, 30, 124). This was converted into the acid by heating with sodium hydroxide and then iodinated by treatment with iodine in potassium iodide solution. Attempts to convert the resulting acid into the corresponding di-iodoisocoumaranone were unsuccessful.

α -Phenyl- β -3 : 5-di-iodophenyl- and **α -phenyl- β -3 : 4 : 5-tri-iodophenyl-propionic acid** were obtained from **α -phenyl- β -(3 : 5-di-iodo-4-aminophenyl)propionic acid** by methods analogous to those used in the preparation of the iodo-phenylacetic acids. Iodination of **α -phenyl- β -*p*-aminophenylpropionic acid** with 4 moles of iodine monochloride gave **α -phenyl- β -(3 : 5-di-iodo-4-aminophenyl)propionic acid**, but with 2 moles of iodine monochloride the product was mainly the mono-iodo-derivative.

α -Phenyl- β -(3 : 5-di-iodo-2-hydroxyphenyl)propionic acid was obtained as follows. Catalytic hydrogenation of 3-phenylcoumarin with Raney nickel gave 3-phenyl-3 : 4-dihydrocoumarin; this was described by Späth and Galinovsky (*Ber.*, 1937, 70, 235), but the method of preparation was not disclosed. The coumarin was converted into the hydroxy-acid, and iodinated in potassium iodide solution. The resulting acid was converted into **6 : 8-di-iodo-3-phenyl-3 : 4-dihydrocoumarin** by heating at the melting point in a high vacuum.

α -Phenyl- β -(3 : 5-di-iodo-4-hydroxyphenyl)ethane was prepared from **α -phenyl- β -*p*-hydroxyphenylethane**, obtained as a product of the reduction of **α -phenyl- β -*p*-hydroxyphenylacrylonitrile** by means of sodium amalgam. **α -Phenyl- β -*p*-methoxyphenylethane** had previously been prepared by a similar method from **α -phenyl- β -*p*-methoxyphenylacrylonitrile** (Freund and Remse, *Ber.*, 1890, 23, 2859), and the hydroxy-derivative prepared from it by demethylation (*Ber.*, 1901, 34, 3081). The direct preparation of **α -phenyl- β -*p*-hydroxyphenylethane** from **α -phenyl- β -*p*-hydroxyphenylacrylonitrile** has not, however, been previously described.

EXPERIMENTAL.

All the iodo-compounds described below melted with decomposition.

3 : 4 : 5-Tri-iodophenylacetic Acid.—*p*-Aminophenylacetic acid (10.5 g.) was dissolved in excess of dilute hydrochloric acid and exactly two equivalents of iodine monochloride were added with shaking. A brown precipitate formed after 16 hours and was filtered off; m. p. 205—206°. Yield, 16.4 g. (58%). After recrystallisation from a large volume of boiling acetone and then from pyridine, **3 : 5-di-iodo-4-aminophenylacetic acid** was obtained in colourless needles, m. p. 220—221°; the m. p. was unchanged after further recrystallisation from pyridine (Found : C, 24.9; H, 1.80; N, 3.58; I, 65.0. $C_8H_7O_2NI_2$ requires C, 23.8; H, 1.74; N, 3.47; I, 63.0%). The compound was sparingly soluble in acetone, practically insoluble in alcohol and in ether.

3 : 5-Di-iodo-4-aminophenylacetic acid (3.5 g.) was diazotised by addition of solid sodium nitrite to an ice-cold solution in concentrated sulphuric acid. After 2 hours at 0°, the dark solution was poured on ice, and potassium iodide solution (9 g. in 20 ml. of water) added, giving a brown precipitate. The mixture was heated on the water-bath until no more nitrogen was evolved (about 1 hour). The product was then poured into saturated sodium hydrogen sulphite solution and the precipitated **3 : 4 : 5-tri-iodophenylacetic acid** was filtered off, washed with water, and recrystallised from acetone; m. p. 219—220°. Yield, 3.5 g. (78%). After two recrystallisations from acetone, the product was obtained in pale yellow needles, m. p. 224—225°, readily soluble in ether, in alcohol, and in acetone, but insoluble in water (Found : C, 18.9; H, 0.99; I, 74.6. $C_8H_5O_2I_3$ requires C, 18.7; H, 0.97; I, 74.1%).

3 : 5-Di-iodophenylacetic Acid.—**3 : 5-Di-iodo-4-aminophenylacetic acid** (3.5 g.) was diazotised as described above. After 2 hours at 0°, the solution of the diazonium salt was poured on ice and the clear ice-cold solution was added to a suspension of cuprous oxide (2 g.) in cold alcohol (150 ml.). Immediate evolution of nitrogen took place and, when this had slackened, the mixture was refluxed until no more nitrogen was given off ($\frac{1}{2}$ hour). The product was poured into one volume of water, and after 16 hours the precipitate was filtered off (together with cuprous oxide) and extracted with ether, in which the precipitate was readily soluble (the starting material was insoluble in ether). The ethereal extracts were washed with sodium thiosulphate solution and then with water, dried (Na_2SO_4), and evaporated to dryness. The residue was crystallised from boiling absolute alcohol and then from toluene. It formed pale yellow needles, m. p. 195—196°. Further recrystallisation from toluene caused no change in m. p. (Found : C, 25.0; H, 1.76. $C_8H_6O_2I_2$ requires C, 24.7; H, 1.55%). The compound was readily soluble in alcohol, in ether, and in boiling toluene, but insoluble in light petroleum and in water.

3 : 5-Di-iodo-2-hydroxyphenylacetic Acid.—Iodination of *o*-hydroxyphenylacetic acid (6 g.) dissolved in excess of *N*-sodium hydroxide solution, by addition with stirring of $2\frac{1}{2}$ equivalents of iodine in 25% aqueous potassium iodide solution, gave a dark solution, from which the crude **3 : 5-di-iodo-2-hydroxyphenylacetic acid** was precipitated by pouring into sodium hydrogen sulphite solution. This precipitate was extracted twice with ether, and the extracts were washed once with water, dried (Na_2SO_4), and evaporated to a small bulk; **3 : 5-di-iodo-2-hydroxyphenylacetic acid** then crystallised as needles, m. p. 163—164°. Yield, 6.5 g. (41%). It was recrystallised from absolute alcohol; m. p. 164—165° (Found : C, 23.8; H, 1.67; I, 63.4. $C_8H_6O_3I_2$ requires C, 23.8; H, 1.49; I, 62.8%). The compound was readily soluble in alcohol and in ether but insoluble in light petroleum and in water.

3 : 5-Di-iodo-4-hydroxydiphenylacetic Acid.—*p*-Hydroxydiphenylacetic acid (5 g.) was dissolved in *N*-sodium hydroxide (100 ml.) and iodinated by addition of $2\frac{1}{2}$ equivalents of iodine in 25% potassium iodide solution (150 ml.) with stirring. After $\frac{1}{2}$ hour, it was worked up as described for the preparation of **3 : 5-di-iodo-2-hydroxyphenylacetic acid**. The residue was crystallised from boiling toluene, yielding 5 g. of **3 : 5-di-iodo-4-hydroxydiphenylacetic acid** as a micro-crystalline powder, m. p. 192°. The mother liquors gave a further 2.1 g., m. p. 190°. Total yield, 67%. Two further recrystallisations of the first crop from toluene gave crystals, m. p. 193—194° (Found : I, 52.5. $C_{14}H_{10}O_3I_2$ requires I, 52.9%). The substance was readily soluble in alcohol, in ether, and in boiling toluene, but insoluble in light petroleum and in water.

3 : 5-Di-iodo-2-hydroxydiphenylacetic Acid.—3-Phenylisocoumaranone (19 g.) was iodinated in the manner described above by means of iodine in potassium iodide solution, the only difference being that the lactone could be dissolved in sodium hydroxide solution only by warming gently. After being worked up in the usual manner, the residue was crystallised from ether by cautious addition of light petroleum until just cloudy. **3 : 5-Di-iodo-2-hydroxydiphenylacetic acid** separated as a micro-crystalline powder, m. p. 142° (decomp.). Yield, 13.1 g. (33%). For analysis, it was recrystallised from ether-light petroleum, with no change of m. p. (Found : I, 52.7, 52.9. $C_{14}H_{10}O_3I_2$ requires I, 52.9%). The compound was readily soluble in ether and in alcohol, but insoluble in light petroleum and in water.

An attempt to dehydrate the di-iodo-derivative by heating it gradually at 0.002 mm. up to 150° led to complete decomposition, only a deep-violet oil being obtained.

α -Phenyl- β -(3 : 5-di-iodo-4-hydroxyphenyl)ethane.— α -Phenyl- β -*p*-hydroxyphenylacrylonitrile (10 g.) was dissolved in absolute alcohol (200 ml.) and reduced by slow addition of small lumps of sodium (23.3 g.) over a period of $\frac{1}{2}$ hour, followed by prolonged heating on the water-bath until all the sodium had dissolved (ca. $4\frac{1}{2}$ hours). After addition of one volume of water, the solution was concentrated under reduced pressure to small bulk. The residue was extracted thrice with ether, and the extracts were washed twice with dilute hydrochloric acid in order to remove the β -phenyl- γ -*p*-hydroxyphenylpropylamine, formed as a by-product in the reduction. They were finally washed once with water, dried, and evaporated under reduced pressure. The solid residue of α -phenyl- β -*p*-hydroxyphenylethane was recrystallised from aqueous alcohol, giving leaflets, m. p. 99—100° (lit., 100—101°). Yield, 4.7 g., together with a further 600 mg. of lower melting material (93—96°) from the mother liquors. Total yield, 67%.

To a solution of α -phenyl- β -*p*-hydroxyphenylethane (5 g.) in aqueous alcoholic ammonia [120 ml., made by adding 10 ml. of ammonia (*d*, 0.88) and 10 ml. of alcohol to 100 ml. of water], solid iodine (15 g.)

was added with mechanical stirring over a period of 15 minutes. A green solid separated from the solution almost immediately and increased in bulk on standing. The mixture was stirred for $\frac{1}{2}$ hour, and the precipitate was then filtered off, dissolved in hot alcohol, and treated with charcoal; the filtrate was poured into water, whereby a sticky brown solid was precipitated. This was dissolved in ether, and the solution was dried (Na_2SO_4), and evaporated almost to dryness; the residue crystallised slowly; m. p. 80—81°. Yield, 4.5 g. (40%). The crude α -phenyl- β -(3 : 5-di-iodo-4-hydroxyphenyl)ethane was crystallised from ether-light petroleum; m. p. 82—83° (Found : C, 37.3; H, 2.60; I, 55.9. $\text{C}_{14}\text{H}_{12}\text{OI}_2$ requires C, 37.3; H, 2.67; I, 56.4%). The compound was readily soluble in ether and in alcohol, but insoluble in light petroleum and in water.

α -Phenyl- β -3 : 4 : 5-tri-iodophenylpropionic Acid.— α -Phenyl- β -*p*-aminophenylpropionic acid (5 g.) was dissolved in 2*N*-hydrochloric acid (1 l.) by warming on a water-bath and, after filtration from a trace of insoluble material, the cooled liquid was treated with iodine monochloride (15 g.; 4 mols.) in three portions, with continuous shaking during the addition. After 48 hours at 20°, the precipitate which had formed was filtered off and extracted thrice with ether. The extracts were washed in turn once with sodium thiosulphate solution which removed free iodine, and once with water, then dried (Na_2SO_4) and evaporated carefully almost to dryness. On standing, pure α -phenyl- β -(3 : 5-di-iodo-4-aminophenyl)propionic acid crystallised in colourless prisms, m. p. 172—173°. Yield, 5.5 g. (53%). Recrystallisation from alcohol did not raise the m. p. (Found : C, 36.5; H, 2.64; N, 2.99; I, 51.5. $\text{C}_{15}\text{H}_{13}\text{O}_2\text{N}_2\text{I}_2$ requires C, 36.5; H, 2.64; N, 2.84; I, 51.3%). The compound was soluble in ether and in alcohol but insoluble in light petroleum.

α -Phenyl- β -(3 : 5-di-iodo-4-aminophenyl)propionic acid (3.5 g.) was dissolved in concentrated sulphuric acid (15 ml.) and diazotised by addition of solid sodium nitrite (1.85 g.) at 0°. After 15 minutes at 0°, it was poured on 3 vols. of ice, and filtered from a trace of insoluble material. To the ice-cold filtrate potassium iodide solution (11 g. in 20 ml. of water) was added, and the mixture warmed on the water-bath until no more nitrogen was given off and the oil had solidified forming a voluminous black precipitate. This was extracted thrice with ether, washed first with sodium thiosulphate solution to remove iodine, and then with water, dried (Na_2SO_4), and evaporated almost to dryness. α -Phenyl- β -3 : 4 : 5-tri-iodophenylpropionic acid crystallised at once from the concentrated ethereal solution as rectangular leaflets, m. p. 208—209°. Yield, 3.0 g. (70%). It was recrystallised from boiling absolute alcohol; m. p. 211—212°. A further recrystallisation did not raise the m. p. (Found : C, 30.2; H, 1.55; I, 63.0. $\text{C}_{15}\text{H}_{11}\text{O}_2\text{I}_3$ requires C, 29.8; H, 1.82; I, 63.1%).

α -Phenyl- β -3 : 5-di-iodophenylpropionic Acid.— α -Phenyl- β -(3 : 5-di-iodo-4-aminophenyl)propionic acid (3.5 g.) was diazotised and the solution of the diazonium salt treated with alcohol and cuprous oxide in the manner described for the preparation of 3 : 5-di-iodophenylacetic acid. The ethereal extract was evaporated to dryness and the residue taken up in toluene (3 ml.). Crystals of α -phenyl- β -3 : 5-di-iodophenylpropionic acid, m. p. 149—150°, were obtained. Yield, 1.25 g. (37%). Recrystallisation from toluene raised the m. p. to 153—154°, unchanged by a further recrystallisation (Found : C, 37.8; H, 2.70. $\text{C}_{15}\text{H}_{12}\text{O}_2\text{I}_2$ requires C, 37.5; H, 2.51%).

α -Phenyl- β -(3 : 5-di-iodo-2-hydroxyphenyl)propionic Acid.—3-Phenylcoumarin (5 g.) was refluxed with 10% sodium hydroxide solution (50 ml.) until completely dissolved and, after cooling to 20°, it was reduced catalytically with Raney nickel (prepared from 2 g. of alloy). Slightly more than the theoretical amount of hydrogen had been absorbed after 20 hours. The catalyst was filtered off, and the filtrate extracted once with ether. The alkaline solution was acidified and extracted thrice with ether, the extract washed with water, dried, and evaporated to small bulk. Crystallisation was best effected by allowing the concentrated ethereal solution to evaporate slowly at room temperature. When crystals had begun to form, light petroleum was added until a slight permanent cloudiness remained, yielding 3-phenyl-3 : 4-dihydrocoumarin, m. p. 115—116° (lit. 122°). Yield, 4.5 g. (89%).

3-Phenyl-3 : 4-dihydrocoumarin (14 g.) was dissolved in *N*-sodium hydroxide (250 ml.) by warming gently, and the solution treated with iodine (35 g.) in 10% aqueous potassium iodide solution (300 ml.). The mixture was stirred for $\frac{1}{2}$ hour after the addition was completed, and the crude iodinated product precipitated by pouring into concentrated sodium hydrogen sulphite solution. The solid was filtered off, dissolved in ether, and the solution washed with water, dried, and evaporated almost to dryness. Careful addition of light petroleum yielded α -phenyl- β -(3 : 5-di-iodo-2-hydroxyphenyl)propionic acid, m. p. 130—132°. Yield, 14.0 g. (68%). Recrystallisation from toluene raised the m. p. to 141—142° (decomp.).

Attempted dehydration. When the above iodinated hydroxy-acid was heated gradually in an oil-bath to 140° at 0.005 mm., loss of water occurred when the melting point was reached. The temperature was maintained at ca. 145° for 15 minutes, and the mixture cooled and extracted with ether. Washing with sodium bicarbonate solution removed unchanged material. The remaining ethereal extract was washed with sodium thiosulphate solution and water, dried, and evaporated to dryness. The residue was crystallised from toluene, yielding 6 : 8-di-iodo-3-phenyl-3 : 4-dihydrocoumarin, m. p. 141—142° (no decomp.). Mixed m. p. with the original acid, 122—124°. It was insoluble in sodium bicarbonate and in cold sodium hydroxide solution, but dissolved in the latter after prolonged boiling (Found : C, 38.1; H, 2.12; I, 50.2. $\text{C}_{15}\text{H}_{10}\text{O}_2\text{I}_2$ requires C, 37.8; H, 2.10; I, 53.4%).

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