

## A NOTE ON THE PREPARATION OF *m*-HYDROXYPHENYLPROPIONIC ACID

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METHODS hitherto used for the preparation of *m*-hydroxyphenylpropionic acid have involved several stages. *m*-Hydroxybenzaldehyde, obtained by reduction of *m*-nitrobenzaldehyde and diazotisation of the amino compound, is converted by a Perkin or Knövenagel condensation into *m*-hydroxycinnamic acid,<sup>1,2</sup> which is then reduced by means of sodium amalgam<sup>3</sup> or catalytic hydrogenation.<sup>2</sup> Alternatively, the *m*-nitrobenzaldehyde is converted into *m*-nitrocinnamic acid, using the Perkin method,<sup>4,5</sup> and reduced to *m*-aminocinnamic acid by stannous chloride in hydrochloric acid,<sup>4,6</sup> diazotised and hydrolysed to *m*-hydroxycinnamic acid,<sup>4</sup> which is then reduced to the phenylpropionic derivative by sodium amalgam.<sup>3</sup>

It is now shown that *m*-nitrocinnamic acid can be reduced to *m*-aminophenylpropionic acid in a single operation, thereby eliminating one stage of the above sequence. Furthermore, the troublesome diazotisation of the very insoluble *m*-aminocinnamic acid is replaced by the straightforward diazotisation of the *m*-aminophenylpropionic acid. The reduction is carried out (a) by catalytic hydrogenation, using Adam's catalyst, (b) by nickel-aluminium alloy in sodium hydroxide solution, using the Schwenk-Papa technique.<sup>7</sup> Hydrogenation at atmospheric pressure using Raney nickel fails to reduce the cinnamic group.

### EXPERIMENTAL

*m*-Nitrobenzaldehyde. This was prepared by nitration of benzaldehyde using the methods of Friedlander and Henriques<sup>8</sup> and Ehrlich,<sup>9</sup> m.pt. 58° C.

*m*-Nitrocinnamic acid. *m*-Nitrobenzaldehyde (20 g.), acetic anhydride (24 ml.) and pyridine (1 ml.) were heated in a 500-ml. round-bottomed flask fitted with a wide air condenser, to 120° C. on a wax bath. Potassium carbonate (3.6 g.) was added as rapidly as possible without the solution foaming over. The temperature was raised to 180° C. and maintained for 25 minutes. The solution was cooled, diluted with water, and the precipitated acid dissolved in dilute ammonia, boiled with charcoal and filtered. The acid was re-precipitated with dilute sulphuric acid, washed, dried and recrystallised twice from ethanol. Yield 16 g., m.pt. 196° C.

*m*-Hydroxyphenylpropionic acid. (a) *Schwenk-Papa Method.* *m*-Nitrocinnamic acid (150 g.) was dissolved in a solution of sodium hydroxide (600 g. in 3 l. of water) in a 5-l. wide-necked flask. The solution was automatically stirred at 90° C. and nickel-aluminium alloy (450 g.) added in small portions, care being taken to avoid foaming. The contents of the flask were then boiled for 2 hours and filtered whilst hot. The precipitate of nickel was washed with 100-ml. quantities of hot water, about 500 ml. being required to remove all the amino acid. The filtrate and washings, whilst still warm, were acidified by running in a mixture of

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concentrated sulphuric acid (1.25 l.) and water (2 l.) with continuous stirring. The mixture was heated until all the precipitated aluminium hydroxide had redissolved, cooled to 5° C. and diazotised with sodium nitrite (30 g.) dissolved in water (50 ml.). After 15 minutes, urea was added until no nitrite could be detected, and the solution boiled as rapidly as possible with the addition of copper sulphate solution (30 ml.) as catalyst. When evolution of nitrogen had ceased, the flask was cooled and the solid matter, consisting of a mixture of *m*-hydroxyphenylpropionic acid and tar, was filtered out. The filtrate was extracted with ether and the mixture of tar and acid was washed with ether, in which the tar was insoluble. The bulked ether extract was evaporated, and the residue, after solution in ethanol and treatment with charcoal, gave 90 g. of brown crystals, which recrystallised from benzene/ligroin or chloroform in the form of light brown crystals. Yield 83 g. (65 per cent.), m.pt. 112° C. (Lit. 111° to 112.5° C.).

*Benzyl ether.* From sodium derivative and benzyl chloride in ethanol. M.pt. 84.5° C. Colourless plates. Found: C, 75.23; H, 5.96.  $C_{16}H_{16}O_3$  requires C 75.00; H, 6.25 per cent.

(b) *Catalytic hydrogenation—Adam's catalyst.* Ethyl *m*-nitrocinnamate (10 g.), suspended in ethanol (150 ml.) containing Adam's catalyst (0.2 g.), was hydrogenated at atmospheric pressure and room temperature. Six equivalents of hydrogen were taken up rapidly (within an hour) and a further 2 equivalents in 24 hours. The ethanol was removed, the product dissolved in acid, diazotised and boiled as above. The ester was extracted with ether and after solution in ethanol and treatment with charcoal, evaporated to give an oily residue, which was hydrolysed giving 7 g. of *m*-hydroxyphenylpropionic acid, m.pt. 112.5° C. Benzyl ether, m.pt. 84.5°. Mixed m.pt. with product from (a), 84.5° C.

(c) *Catalytic hydrogenation—Raney nickel.* Method as (b), using glacial acetic acid as solvent, Raney nickel catalyst (0.5 g.) and hydrogenating at 95° C. and atmospheric pressure. Six equivalents were absorbed in 5 hours, after which absorption ceased. The product, treated as above, gave 5 g. of *m*-hydroxycinnamic acid, m.pt. 191° C. Mixed m.pt. with material prepared by method of Ingold and Piggot,<sup>4</sup> 191° C.

### SUMMARY

By an adaptation of the Schwenk-Papa method, or by catalytic hydrogenation, *m*-nitrocinnamic acid is reduced to *m*-aminophenylpropionic acid, which is converted without isolation into *m*-hydroxyphenylpropionic acid. Advantages are claimed for this method.

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