

**588.** *A New Synthesis of Arsonic Acids. Part II.\* Coupling of  $\alpha\beta$ -Unsaturated Carbonyl Compounds with Diazotised Arsanilic Acid and 4-Amino-2-nitrophenylarsonic Acid.*

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4-Hydroxy-3-nitrocinnamic acid and diazotised arsanilic acid give 4'-hydroxy-3'-nitrostilbene-4-arsonic acid. 4-Hydroxycinnamic acid and diazotised 4-amino-2-nitrophenylarsonic acid give 4'-hydroxy-3-nitrostilbene-4-arsonic acid.

THE arsonic acids described in Part I\* contain neither amino- nor nitro-groups. For therapeutic purposes it seemed desirable to prepare hydroxynitro-arsonic acids which could then be reduced to the corresponding amino-compounds. Meerwein, Buchner, and van Emster (*J. pr. Chem.*, 1939, **152**, 237) failed in attempts to couple *p*-nitrocinnamic acid with diazo-compounds. l'Ecuyer, Turgotte, Giguère, Olivier, and Roberge succeeded in coupling *m*- (*Canad. J. Res.*, 1947, **25**, 575) and *p*-nitrocinnamic acid (*ibid.*, 1948, **26**, 70) with various diazo-compounds by using large amounts of acetone to keep the nitrocinnamic acids in solution. In order to obtain the 3-amino-4-hydroxy-configuration present in many of the organic arsenicals, 4-hydroxy-3-nitrocinnamic acid was prepared. Its melting point is given by Einhorn and Grabfield (*Annalen*, 1888, **243**, 374) as 198° but by Johnson and Kohmann (*J. Amer. Chem. Soc.*, 1915, **37**, 166) as 223°. The acid has now been synthesised by a Doebner condensation on 4-hydroxy-3-nitrobenzaldehyde, which was prepared by nitration of *p*-hydroxybenzaldehyde (Paal, *Ber.*, 1895, **28**, 2415). After recrystallisation from alcohol, an acid of m. p. 221—223° was obtained.

l'Ecuyer *et al.* (*loc. cit.*) obtained 10% of stilbenes by coupling *m*- and *p*-nitrocinnamic acids with various diazotised amines. Unfortunately, diazotised arsanilic acid does not couple as well as the amines used by the Canadian workers. The yield of 4'-hydroxy-3'-nitrostilbene-4-arsonic acid is only about 2%; the main product is azobenzene-4 : 4'-diarsonic acid (Karrer, *Ber.*, 1912, **45**, 2362; Fichter and Elkind, *Ber.*, 1916, **49**, 246).

Coupling with 4-amino-2- or -3-nitrophenylarsonic acid was then considered. The latter, when diazotised and buffered with sodium acetate, exchanges the nitro- for a hydroxy-group (Benda, *Ber.*, 1911, **44**, 3579; D.R.-P. 243,648) and is therefore useless. The 2-nitro-acid is described only in D.R.-P. 267,307 (*Chem. Zentr.*, 1913, II, 2067). Its diazo-solution with *p*-hydroxycinnamic acid gave the expected 4'-hydroxy-3-nitrostilbene-4-arsonic acid but the yield was poor.

#### EXPERIMENTAL

M. p.s are uncorrected.

*4-Hydroxy-3-nitrobenzaldehyde* (cf. Paal, *Ber.*, 1895, **28**, 2415).—*p*-Hydroxybenzaldehyde, m. p. 114—116° (24.4 g.), nitric acid (15 g.; *d* 1.48), and acetic acid (100 g.) were gently warmed until reaction set in, and cooled with ice-water when the reaction became violent. On cooling, 4-hydroxy-3-nitrobenzaldehyde crystallised (12 g., 37%). Recrystallisation from alcohol gave material of m. p. 143—144°.

*4-Hydroxy-3-nitrocinnamic Acid*.—4-Hydroxy-3-nitrobenzaldehyde (m. p. 140—142°; 20.8 g.) and malonic acid (31 g.) in dry pyridine (100—150 c.c.) were heated on the boiling water-bath until dissolved, and a few drops of piperidine were added. Evolution of carbon dioxide was rapid and after 2 hours the mixture was boiled over a naked flame for 20 minutes. After cooling, it was poured into an ice-cold 17% hydrochloric acid (400 c.c.). The 4-hydroxy-3-nitrocinnamic acid precipitated was purified by dissolution in sodium hydrogen carbonate solution, recovered, dried, and digested with acetone (150 c.c.). The insoluble material, recrystallised from alcohol, melted at 221—223° (Johnson and Kohmann give m. p. 223°) (yield : 18.8 g., 65.7%) (Found : N, 6.8. Calc. for C<sub>9</sub>H<sub>7</sub>O<sub>5</sub>N : N, 6.7%).

*4'-Hydroxy-3'-nitrostilbene-4-arsonic Acid*.—To arsanilic acid (10.85 g.) in a solution of sodium hydrogen carbonate (4.2 g.) in water (90 c.c.) was added sodium nitrite (3.65 g.) in water (10 c.c.), and the mixture was dropped into cooled 25% hydrochloric acid (32 c.c.). The clear diazonium solution was added to a solution made from 4-hydroxy-3-nitrocinnamic acid

\* Part I, *J.*, 1951, 1943.

(10.45 g.) in acetone (550 c.c.) and sodium chloroacetate (35 g.) in water (25 c.c.). After the pH had become adjusted to about 5, the solution was yellow, and the temperature approx. 16°. The colour changed to red, the solution was warmed on the water-bath to 20—22°, and a solution of cupric chloride (10 g.) in water (10 c.c.) was added dropwise. Gas evolution set in and a reddish precipitate began to be formed. The gas evolution lasted for about 20 minutes. After a few hours, the precipitate was filtered off, washed with acetone, air-dried, and then dissolved in 2*N*-sodium hydroxide (100 c.c.). The alkaline solution was filtered from copper hydroxide and acidified with hydrochloric acid. The brown precipitate was filtered off, dried, and digested with cold dilute sodium hydrogen carbonate solution in which the greater part was soluble. The 4'-hydroxy-3'-nitrostilbene-4-arsonic acid remaining undissolved was recrystallised from acetic acid and alcohol, from which it crystallised in clusters of yellow needles (*ca.* 2%) which did not melt at 300° (Found: C, 46.3, 45.9; H, 3.4, 3.5; As, 20.8; N, 3.8. C<sub>14</sub>H<sub>12</sub>AsO<sub>6</sub>N requires C, 46.0; H, 3.3; As, 20.5; N, 3.8%). It gave a red sodium salt.

The material soluble in cold bicarbonate solution was reprecipitated with hydrochloric acid. It consisted chiefly of azobenzene-4 : 4'-diarsonic acid (see Part I).

4'-Hydroxy-3-nitrostilbene-4-arsonic Acid.—4-Amino-2-nitrophenylarsonic acid (12.26 g.) was dissolved in a solution of sodium hydrogen carbonate (3.8 g.) in water (80 c.c.) to which was added sodium nitrite (3.6 g.) in water (10 c.c.). This solution was diazotised as above with 25% hydrochloric acid (32 c.c.). The clear solution was then poured into a solution of *p*-hydroxycinnamic acid (8.2 g.) in acetone (200 c.c.) to which sodium chloroacetate (17.5 g.) had been added. Gas evolution set in almost at once and became violent. Cupric chloride (5 g.) in water (10 c.c.) was added dropwise. The gas evolution lasted for approx. 30 minutes. A brownish precipitate separated which was filtered off, air-dried, digested with *N*-sodium hydroxide (50 c.c.), and filtered from the copper hydroxide. The alkaline solution was acidified with cold hydrochloric acid, and the precipitate filtered off, dried, and digested with a small amount of sodium hydrogen carbonate solution in which the greater part dissolved. 1.3 G. remained undissolved and were recrystallised from glacial acetic acid from which the 4'-hydroxy-3-nitrostilbene-4-arsonic acid separated in reddish needles and rods which did not melt at 300° (Found: C, 45.9, 46.1; H, 3.5, 3.4; As, 20.7; N, 4.1%).

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