

**661.** *Muscarufin. Part II.\** 2-(4-Carboxybuta-1,3-dienyl)-1,4-benzoquinones.

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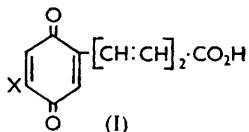
Syntheses of several 5-phenylpenta-2,4-dienoic acids are described. From these 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinone and its 5-chloro-derivative have been prepared.

2-(4-CARBOXYBUTA-1,3-DIENYL)-1,4-BENZOQUINONE (I; X = H) and its 5-chloro-derivative (I; X = Cl) were required as intermediates in a synthesis of muscarufin. No method for the direct introduction of a pentadienoic acid side-chain into 1,4-benzoquinone has been described. Appropriately substituted 5-phenylpenta-2,4-dienoic acids, which can be converted into the desired quinones, have therefore been prepared. Many methods could be used to make such compounds. Bohlmann<sup>1</sup> has shown the limitations of the Reformatsky reaction between benzaldehydes and  $\gamma$ -bromocrotonic esters; this method was therefore rejected in favour of a two-stage preparation *via* the cinnamaldehyde. The most appropriate cinnamaldehydes, *viz.*, the 2- and 3-hydroxy- and 2,5-dihydroxy-aldehyde, cannot be made from the corresponding benzaldehydes by condensation with

\* Part I, preceding paper.

<sup>1</sup> Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.

acetaldehyde in appreciable yield unless the hydroxyl groups are masked, *e.g.*, by formation of the methoxymethyl ethers<sup>2</sup> or glycosides.<sup>3</sup> Overall yields are poor even when this expedient is used. Nitrosalicylaldehydes condense with acetaldehyde,<sup>4</sup> but the resulting nitrocoumaraldehydes are difficult to purify and the yields are *ca.* 5%. Hydroxybenzaldehydes were not investigated further as starting materials. Reactions of nitro- and chloronitro-benzaldehydes with acetaldehyde gave cinnamaldehydes in the following yields: *m*-nitro- 55%, *p*-nitro- 72%,



4-chloro-3-nitro- 72%, and 4-chloro-2-nitro- 73%. The intermediate aldols were dehydrated by means of acetic anhydride without isolation. 2-Nitrocinnamaldehyde was obtained by nitration of cinnamaldehyde in 55% yield.<sup>5</sup>

Four methods of converting the cinnamaldehydes into phenylpentadienoic acids were examined: (a) condensation with acetone, followed by oxidation; (b) the Perkin reaction; (c) condensation with malonic acid; and (d) condensation with pyruvic acid, followed by oxidation. Only method (d) gave acceptable yields.

The 5-(nitrophenyl)penta-2,4-dienoic acids were reduced to amino-compounds by ferrous hydroxide in aqueous ammonia. Diazotisation and replacement of the diazonium group by hydroxyl took place in 50–60% yield, except with the 3-amino-4-chloro-compound which gave only a 2% yield of the phenol, probably as a result of loss through diazo-oxide formation.

Potassium nitrosodisulphonate oxidises many phenols to quinones<sup>6</sup> and was used by Bohlmann<sup>7</sup> in the preparation of 2-(4-carboxybuta-1,3-dienyl)-5-methoxy-1,4-benzoquinone (I; X = OMe), but it failed to oxidise the phenols prepared in the present work. Small yields of benzoquinones were obtained by coupling the phenols with diazotised aniline, reduction to *p*-aminophenols, and oxidation. The Elbs persulphate oxidation converted 5-*m*-hydroxyphenylpenta-2,4-dienoic acid into the dihydroxy-compound in moderate yield; the 5-*o*-hydroxyphenylpenta-2,4-dienoic acids, however, gave poor yields of quinols and much resin. Ferric chloride was used to complete the oxidation to quinones.

On treatment with hydrogen chloride in chloroform, 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinone gave 2-(4-carboxybuta-1,3-dienyl)-5-chloroquinol, identical with the product of the Elbs oxidation of 5-(4-chloro-2-hydroxyphenyl)-2,4-pentadienoic acid.

#### EXPERIMENTAL

4-Chloro-3-nitrocinnamaldehyde.—(i) 4-Chlorocinnamaldehyde (4 g.) was added to concentrated sulphuric acid (50 ml.) containing sodium nitrate (1.5 g.) at 0°. The mixture was allowed to attain room temperature (18°) and set aside for 3 hr., then poured on crushed ice (500 g.). The precipitate recrystallised from alcohol, to give almost colourless needles of 4-chloro-3-nitrocinnamaldehyde (2.8 g.), *m. p.* 140° (Found: C, 51.4; H, 2.95; N, 6.4; Cl, 16.5. C<sub>9</sub>H<sub>6</sub>O<sub>3</sub>NCl requires C, 51.2; H, 2.8; N, 6.6; Cl, 16.5%).

(ii) 4-Chloro-3-nitrobenzaldehyde (41 g.) was dissolved in acetaldehyde (95 ml.) cooled to 4°. 2% Sodium hydroxide solution (15 ml.) was added dropwise to the stirred solution at 7–10° during 30 min. Acetic anhydride (60 ml.) was added, the excess of acetaldehyde was distilled off, and the solution was boiled under reflux for 45 min. The mixture was poured into 2N-hydrochloric acid (400 ml.), then heated at 100° for 1 hr., cooled, and kept overnight. The precipitate was filtered off and recrystallised from ethanol to give 4-chloro-3-nitrocinnamaldehyde (31 g.), *m. p.* and mixed *m. p.* 140°.

4-Chloro-2-nitrocinnamaldehyde (76%) was similarly obtained, as pale yellow needles (from 50% acetic acid), *m. p.* 117°, from 4-chloro-2-nitrobenzaldehyde (Found: C, 51.1; H, 3.0; N, 6.5; Cl, 16.4%).

<sup>2</sup> Hoering and Baum, G.P. 209,608; Pauly and Wascher, *Ber.*, 1923, **56**, 603.

<sup>3</sup> Tiemann, *Ber.*, 1885, **18**, 3482.

<sup>4</sup> Miller and Kinkelin, *Ber.*, 1887, **20**, 1933.

<sup>5</sup> Davey and Gwilt, *J.*, 1955, 1385.

<sup>6</sup> Teuber *et al.*, *Chem. Ber.*, 1953, **86**, 1036; 1955, **88**, 802.

<sup>7</sup> Bohlmann and Kritzer, *Chem. Ber.*, 1957, **90**, 1512.

5-(*Nitrophenyl*)penta-2,4-dienoic Acids.—(i) 2-Nitrocinnamaldehyde (24.5 g.) was dissolved in ethanol (200 ml.) and water (100 ml.). The mixture was cooled to 5°, and aqueous sodium hydroxide (9 g. in 100 ml.) was added, followed by pyruvic acid (15 g.) during 30 min. at <18°. The mixture was stirred for a further 6 hr. at 18°, then filtered, and the residue of sodium 2-nitrocinnamylidenepyruvate was washed with ethanol (until the washings were colourless) and dried (yield, 20.7 g.). 6-*o*-Nitrophenyl-2-oxohexa-3,5-dienoic acid was obtained by acidification of an aqueous solution of the sodium salt; it formed yellow plates, m. p. 186°, from ethanol (Found: C, 58.4; H, 3.6; N, 5.4.  $C_{12}H_9O_5N$  requires C, 58.3; H, 3.6; N, 5.7%). The sodium salt (19 g.) in water (1 l.) was treated with 30% hydrogen peroxide (13 ml.). After it had been stirred for 3 hr., the mixture was acidified with hydrochloric acid, and the colourless precipitate of 5-*o*-nitrophenylpenta-2,4-dienoic acid (14.1 g.), m. p. 218°, was filtered off, washed with water, and dried.

By the same procedure were prepared: 6-*m*-nitrophenyl-, yellow plates (from ethanol), m. p. 171° (Found: C, 58.5; H, 3.6; N, 5.6%), 6-(4-chloro-3-nitrophenyl)-, yellow needles (from 50% ethanol), m. p. 191° (Found: C, 51.0; H, 2.8; N, 4.95; Cl, 12.5%), 6-(4-chloro-2-nitrophenyl)-2-oxohexa-3,5-dienoic acid, yellow needles (from 50% ethanol), m. p. 176° (decomp.) (Found: C, 51.2; H, 2.6; N, 4.8; Cl, 12.3.  $C_{12}H_8O_5NCl$  requires C, 51.2; H, 2.8; N, 5.0; Cl, 12.6%); 5-*m*-nitrophenyl-, pale yellow needles (from acetic acid), m. p. 242° (48% yield from *m*-nitrocinnamaldehyde), 5-(4-chloro-2-nitrophenyl)-, needles (from alcohol), m. p. 238° (44%) (Found: C, 52.1; H, 3.0; N, 5.2; Cl, 14.1.  $C_{11}H_8O_4NCl$  requires C, 52.1; H, 3.2; N, 5.5; Cl, 14.0%), and 5-(4-chloro-3-nitrophenyl)-penta-2,4-dienoic acid, yellow needles (from aqueous acetic acid), m. p. 232° (54%) (Found: C, 53.2; H, 3.2; N, 5.4; Cl, 14.0%).

(ii) 2-Nitrocinnamaldehyde (6 g.) was added during 6 hr. to refluxing acetic anhydride (60 ml.) and anhydrous sodium acetate (6 g.). The mixture was heated for a further 18 hr., then poured into water (500 ml.) and set aside. The solid was filtered off and boiled with a 10% solution (100 ml.) of sodium carbonate. The solution was filtered and acidified with dilute sulphuric acid; the precipitate was filtered off and recrystallised from ethanol, giving 5-*o*-nitrophenylpenta-2,4-dienoic acid (2.2 g.), m. p. 218°.

By the same procedure 5-*m*-nitrophenyl-, m. p. 242°, 5-(4-chloro-2-nitrophenyl)-, m. p. 238°, and 5-(4-chloro-3-nitrophenyl)-penta-2,4-dienoic acid, m. p. 232°, were obtained in yields of 24, 25, and 18% respectively.

(iii) 2-Nitrocinnamaldehyde (10 g.), malonic acid (5 g.), and pyridine (6 g.) were heated at 100° for 6 hr., then poured into 2*N*-hydrochloric acid (100 ml.). The deposited solid was washed with water and dissolved in 10% sodium carbonate solution (150 ml.); the solution was filtered and acidified with dilute sulphuric acid. The precipitated *o*-nitrophenylpenta-2,4-dienoic acid recrystallised from ethanol as almost colourless needles (4.9 g., 40%), m. p. 218°. Yields of other 5-substituted penta-2,4-dienoic acids obtained by this method were: *m*-nitro-, 36%; 4-chloro-2-nitro-, 16%; and 4-chloro-3-nitro-, 17%.

6-Arylhexas-3,5-dien-2-ones and 1,9-Diarylnona-1,3,6,8-tetraen-5-ones.—2-Nitrocinnamaldehyde (20 g.) was warmed with ethanol (680 ml.) and water (120 ml.) until a clear solution was formed. This was cooled to 20°, and acetone (20 g.) was added, followed by 10% sodium hydroxide solution, with stirring, until the solution was alkaline to litmus. The mixture was stirred for 2 hr. at 20°, and the precipitate was filtered off, washed with water, dried, and recrystallised from ethanol to give pale yellow needles of 1,9-diphenylnona-1,3,6,8-tetraen-5-one (11.4 g.), m. p. 208°. The filtrate was poured into water (2 l.) and set aside for 14 hr. The precipitated 6-arylhexas-3,5-dien-2-one was filtered off, washed with water, dried, and recrystallised from ethanol, forming pale yellow needles (4.4 g.), m. p. 73°.

Similarly were obtained the 6-*m*-nitrophenyl (3.0 g. from 20 g.), m. p. 100.5°, yellow needles (from ethanol) (Found: C, 66.2; H, 5.0; N, 6.4.  $C_{12}H_{11}O_3N$  requires C, 66.4; H, 5.1; N, 6.45%), and 1,9-*di*-*m*-nitrophenyl (14.2 g.), m. p. 199°, yellow needles (from ethanol) (Found: C, 66.8; H, 4.3; N, 7.2.  $C_{21}H_{16}O_5N_2$  requires C, 67.0; H, 4.25; N, 7.45%), 6-(4-chloro-2-nitrophenyl) (2.8 g. from 24 g.) m. p. 112°, pale yellow needles (from ethanol) (Found: C, 57.0; H, 4.3; N, 5.5; Cl, 13.9.  $C_{12}H_{10}O_3NCl$  requires C, 57.25; H, 4.0; N, 5.6; Cl, 14.1%), and 1,9-*di*-(4-chloro-2-nitrophenyl) (1.0 g.), m. p. 246°, yellow needles (from acetic acid) (Found: C, 56.4; H, 3.2; N, 6.3; Cl, 15.7.  $C_{21}H_{14}O_5N_2Cl_2$  requires C, 56.6; H, 3.15; N, 6.3; Cl, 15.95%), 6-(4-chloro-3-nitrophenyl) (0.8 g. from 24 g.), m. p. 124°, pale yellow needles (from ethanol) (Found: C, 57.1; H, 4.2; N, 5.5; Cl, 14.0%), and 1,9-*di*-(4-chloro-3-nitrophenyl) compound (2.4 g.), m. p. 239°, pale yellow needles (from ethanol) (Found: C, 56.5; H, 2.9; N, 6.2; Cl, 15.85%).

5-(Aminophenyl)penta-2,4-dienoic Acids.—To 5-*o*-nitrophenylpenta-2,4-dienoic acid (2.2 g.) in *N*-ammonia (200 ml.), ferrous sulphate heptahydrate (16.7 g.) in water (50 ml.) was added, the mixture was warmed to 60° for 15 min., with stirring, then filtered, and the precipitate was washed several times with hot water. The filtrate, combined with the washings, was concentrated to 60 ml. The crystals which were deposited were filtered off from time to time, and after the concentrated solution had cooled, recrystallised from ethanol, giving 5-*o*-aminophenylpenta-2,4-dienoic acid as yellow plates (1.7 g.), m. p. 175°. Similarly, 5-*m*-aminophenylpenta-2,4-dienoic acid was obtained as yellow needles (from ethanol), m. p. 178°, in 70% yield.

5-(2-Amino-4-chlorophenyl)penta-2,4-dienoic acid formed yellow needles (from ethanol), m. p. 239° (56% yield) (Found: C, 59.05; H, 4.3; N, 6.4; Cl, 15.9.  $C_{11}H_{10}O_2NCl$  requires C, 59.1; H, 4.5; N, 6.5; Cl, 15.9%) its acetyl derivative crystallised from ethanol as pale yellow needles, m. p. 291° (Found: C, 58.6; H, 4.6; N, 5.2; Cl, 13.0.  $C_{13}H_{12}O_3NCl$  requires C, 58.8; H, 4.4; N, 5.3; Cl, 13.4%). 5-(3-Amino-4-chlorophenyl)penta-2,4-dienoic acid formed yellow needles (from ethanol), m. p. 237° (55%) (Found: C, 58.9; H, 4.5; N, 6.3; Cl, 15.75%) [acetyl derivative, pale yellow needles (from ethanol), m. p. 284° (Found: C, 58.8; H, 4.5; N, 5.5; Cl, 13.25%)].

5-(Hydroxyphenyl)penta-2,4-dienoic Acids.—5-*o*-Aminophenylpenta-2,4-dienoic acid (1.1 g.), sodium carbonate (0.3 g.), and sodium nitrite (0.35 g.) were dissolved in water (50 ml.), and the solution was poured into a stirred mixture of ice (10 g.) and concentrated hydrochloric acid (5 ml.). The mixture was diluted with water (100 ml.) and added at 3–4 drops per min. to a boiling solution of sodium sulphate (250 g.) and concentrated sulphuric acid (5 ml.) in water (200 ml.), which was agitated and kept boiling by introduction of steam. The addition was made through a tube surrounded by a cold-water jacket, which extended almost to the surface of the hydrolysing medium. A few minutes after the addition was complete the solution was cooled and set aside for several hours. The yellow crystalline precipitate was filtered off, washed with water, and recrystallised from acetic acid to give 5-*o*-hydroxyphenylpenta-2,4-dienoic acid as yellow needles (0.6 g.), m. p. 237° (Found: C, 69.7; H, 5.4.  $C_{11}H_{10}O_3$  requires C, 69.5; H, 5.3%). The acetyl derivative crystallised from benzene in colourless needles, m. p. 182° (Found: C, 67.2; H, 5.2.  $C_{13}H_{12}O_4$  requires C, 67.2; H, 5.2%).

The same procedure gave 5-*m*-hydroxyphenyl- (55%), almost colourless needles (from water), m. p. 209° (Found: C, 69.5; H, 4.9%), 5-(4-chloro-2-hydroxyphenyl)- (52%), yellow needles (from acetic acid), m. p. 243° (Found: C, 58.9; H, 4.2; Cl, 15.7.  $C_{11}H_9O_3Cl$  requires C, 58.8; H, 4.0; Cl, 15.8%), and 5-(4-chloro-3-hydroxyphenyl)-penta-2,4-dienoic acid (2%), m. p. 224°, colourless needles from ethanol (Found: C, 59.0; H, 4.2; Cl, 15.8%). The acetyl derivatives, prepared in the usual way, formed needles, m. p. 160° (from benzene) (Found: C, 67.1; H, 5.3.  $C_{13}H_{12}O_4$  requires C, 67.2; H, 5.2%), m. p. 228° (from ethanol) (Found: C, 58.7; H, 4.5; Cl, 13.6.  $C_{13}H_{11}O_4Cl$  requires C, 58.8; H, 4.1; Cl, 13.3%), and m. p. 227° (from benzene) (Found: C, 58.8; H, 4.3; Cl, 13.2%), respectively.

5-(2,5-Dihydroxyphenyl)penta-2,4-dienoic Acids.—5-*o*-Hydroxyphenylpenta-2,4-dienoic acid (5.7 g.), dissolved in 10% sodium hydroxide solution (50 ml.), was cooled to 10°. Potassium persulphate (7 g.) in water (250 ml.) was added during 2 hr., with stirring. After 14 hr. the solution was acidified to Congo Red with hydrochloric acid. The precipitate was filtered off. The solution was then made acid to litmus, and heated at 100° for 1 hr., then cooled, and extracted with ether. The extract was dried, and the ether was removed, leaving a solid which recrystallised from acetic acid to give yellow needles of 5-(2,5-dihydroxyphenyl)penta-2,4-dienoic acid (0.4 g.), m. p. 225° (Found: C, 63.8; H, 4.85.  $C_{11}H_{10}O_4$  requires C, 64.1; H, 4.85%).

By the same procedure 5-*m*-hydroxyphenylpenta-2,4-dienoic acid (5.8 g.) gave the same product (1.4 g.). 5-(4-Chloro-2-hydroxyphenyl)- (5.8 g.) gave 5-(4-chloro-2,5-dihydroxyphenyl)penta-2,4-dienoic acid (0.2 g.), yellow needles (from acetic acid), m. p. 254° (Found: C, 54.6; H, 3.6; Cl, 14.8.  $C_{11}H_9O_4Cl$  requires C, 54.9; H, 3.7; Cl, 14.7%).

2-(4-Carboxybuta-1,3-dienyl)-1,4-benzoquinone.—5-(2,5-Dihydroxyphenyl)penta-2,4-dienoic acid (4.2 g.) was treated in water (200 ml.) at 60° with aqueous ferric chloride (11 g. in 200 ml.). After 5 min. the brown precipitate was filtered off, washed with water, and dissolved in hot ethanol (30 ml.). On cooling, the red 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinone crystallised. This recrystallised from ethanol as red needles (2.1 g.), m. p. 166–168° (decomp.) (Found: C, 64.6; H, 4.1.  $C_{11}H_8O_4$  requires C, 64.7; H, 3.9%).

2-(4-Carboxybuta-1,3-dienyl)-5-chloro-1,4-benzoquinone.—(i) By the above procedure 5-(4-chloro-2,5-dihydroxyphenyl)penta-2,4-dienoic acid (2.4 g.) gave 2-(4-carboxybuta-1,3-dienyl)-5-chloro-1,4-benzoquinone as orange needles (1.3 g.) (from ethanol), m. p. 188° (Found: C, 55.1; H, 3.05; Cl, 14.8.  $C_{11}H_7O_4Cl$  requires C, 55.3; H, 2.9; Cl, 14.9%).

(ii) Aniline (0.5 g.) in concentrated hydrochloric acid (1.25 ml.) and water (1.25 ml.) was treated at <5° with sodium nitrite (0.35 g.) in water (1 ml.). After 10 min. it was added slowly to an ice-cold stirred 5-(4-chloro-2-hydroxyphenyl)penta-2,4-dienoic acid (1.15 g.) in 10% sodium hydroxide solution (3.6 ml.) containing sodium carbonate (0.05 g.). The mixture was stirred for 3 hr. at 0—5°; 50% sodium hydroxide solution (2 ml.) was then added, the solution was warmed to 80°, and sodium dithionite solution was added dropwise until the colour was discharged. Aniline was removed in steam, and the residue made acid to Congo Red. The yellow precipitate of 5-(5-amino-4-chloro-2-hydroxyphenyl)-2,4-pentadienoic acid was filtered off, washed with water, dissolved in water (250 ml.), and warmed with ferric chloride (11 g.) and concentrated hydrochloric acid (5 ml.) in water (100 ml.). The precipitate formed was separated and recrystallised twice from ethanol, to give the quinone as orange needles (0.06 g.), m. p. 188°.

(iii) 2-(4-Carboxybuta-1,3-dienyl)-1,4-benzoquinone (1.2 g.) was suspended in chloroform (100 ml.), and hydrogen chloride was bubbled through the mixture for 5 min. After 10 hr. the precipitated 5-(4-chloro-2,5-dihydroxyphenyl)penta-2,4-dienoic acid was filtered off, and recrystallised from acetic acid to give yellow needles (1.05 g.), m. p. and mixed m. p. 254°. Oxidation with ferric chloride, as described previously, gave the quinone as orange needles (0.57 g.) (from alcohol), m. p. 188°.

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