660. *Muscarufin. Part I. The Action of Diazotised Anthranilic Acid on 1,4-Benzoquinones.*

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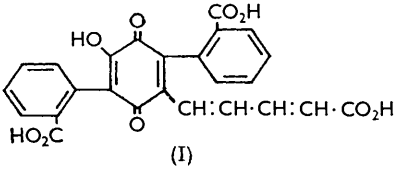
The action of diazotised anthranilic acid on 1,4-benzoquinone and its chloro-, 2,5-dichloro- and 2,6-dichloro-derivatives affords mono- and diarylated quinones, chlorine usually being replaced.

MUSCARUFIN, the pigment of the cap of *Amanita muscaria* (Linn.) Fries, was assigned structure (I) by Kögl and Erxleben.[1] No synthesis has been reported, although several less complex 2,5-diphenyl-1,4-benzoquinones occurring in fungi have been prepared relatively simply.[2] A synthesis of muscarufin (I) has now been undertaken, involving introduction of *o*-carboxyphenyl groups into appropriate 2-(4-carboxybuta-1,3-dienyl)-1,4-benzoquinones.



(I)

1,4-Benzoquinones have been arylated (*a*) by the Friedel–Crafts reaction,[3] (*b*) by decomposition of diazonium salts in alkaline solution,[4] and (*c*) by use of *N*-nitrosoacylamines.[5] Preliminary experiments indicated that method (*b*) was the most appropriate to the present case. The only instances of its use with diazotised anthranilic acid

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[1] Kogl and Erxleben, *Annalen*, 1930, **479**, 11.

[2] See Thomson, " Naturally Occurring Quinones," Butterworths, London, 1957.

[3] Pummerer *et al.*, *Ber.*, 1922, **55**, 3105; 1927, **60**, 1439; 1933, **66**, 792; Browning and Adams, *J. Amer. Chem. Soc.*, 1930, **52**, 4098; Schildneck and Adams, *ibid.*, 1931, **53**, 2373.

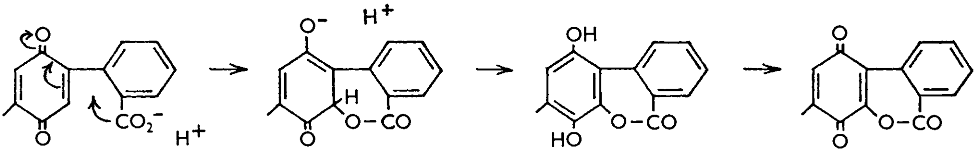
[4] Akagi, *J. Pharm. Soc. Japan*, 1942, **62**, 129, 191, 199.

are those reported by Gunther,[5] who did not investigate the products, and by Bohlmann [6] who obtained an amorphous substance from a reaction with 1,4-benzoquinone, converted by further reactions into crystalline products. We have studied the action of this reagent on 2,5-dichloro-1,4-benzoquinone. By analogy with the syntheses of polyporic acid and atromentin from this quinone we expected *o*-carboxyphenylation at the unsubstituted 3- and 6-position: however, reaction proceeded by replacement of chlorine. This prompted repetition of the reaction with 1,4-benzoquinone, chloro-1,4-benzoquinone, and 2,6-dichloro-1,4-benzoquinone. The reactions with benzoquinone were carried out by two methods; the first is essentially that of Kvalnes, involving use of sodium acetate buffer, and the second, originated by Schimmelschmidt,[7] uses an excess of sodium hydrogen carbonate. The second method demands a water-soluble quinone and therefore could not be applied to the chloroquinones.

2,5-Dichloro-1,4-benzoquinone (XI) with 1 or 2 mols. of diazotised anthranilic acid yielded the orange 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone (VIII) and a yellow, chlorine-free compound, insoluble in common organic solvents. The latter gave a purple solution in alkali whence acidification precipitated 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone (XIV), and it was therefore the dilactone (VI). These products indicate a stepwise replacement of chlorine, with subsequent ring closure of the disubstituted compound.

Reaction of chloro-1,4-benzoquinone (VII) with 2 mols. of diazotised anthranilic acid led to the same products. Reaction with 2,6-dichloro-1,4-benzoquinone (XV) gave 2-*o*-carboxyphenyl-6-chloro-1,4-benzoquinone (XII) and 2,6-di-*o*-carboxyphenyl-1,4-benzoquinone (XVI). The compounds (VIII), (IX), and (XVI) were recovered unchanged on acidification of their solutions in dilute alkali; they do not possess the lactone structure of (VI). Direct replacement of chlorine is indicated; the only " normal " arylation occurs where positions 5 and 6 are unsubstituted.

The dilactone (VI) is also produced by reaction of diazotised anthranilic acid with 1,4-benzoquinone (see below). It seems probable that 2,5-di-*o*-carboxyphenyl-1,4-benzoquinone is its precursor, and it is significant that the latter has not been found among the products of any reaction in which it might be formed. It is suggested that the dilactone (VI) is produced from 2,5-di-*o*-carboxyphenyl-1,4-benzoquinone by a double process of nucleophilic addition to the β-C atom of the αβ-unsaturated ketone system, followed by prototropic change and aerial oxidation, as illustrated.



The dilactone (VI), on reductive acetylation, formed the diacetate (X) which yielded 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone (XIV) on treatment with alkali. The latter reaction involves hydrolysis to 2′,3′,5′,6′-tetrahydroxy-*p*-terphenyl-2,2″-dicarboxylic acid which is not isolated owing to its rapid aerial oxidation. The quinone (XIV) forms the dilactone (VI) when heated above 300°, as reported by Nilsson,[8] who prepared the quinone by an Ullmann reaction.

Diazotised anthranilic acid (2 mols.) with benzoquinone in the presence of excess of sodium acetate yielded a mixture from which 2′,5′-diacetoxybiphenyl-2-carboxylic acid was obtained by reductive acetylation. Hydrolysis and oxidation of this compound yielded

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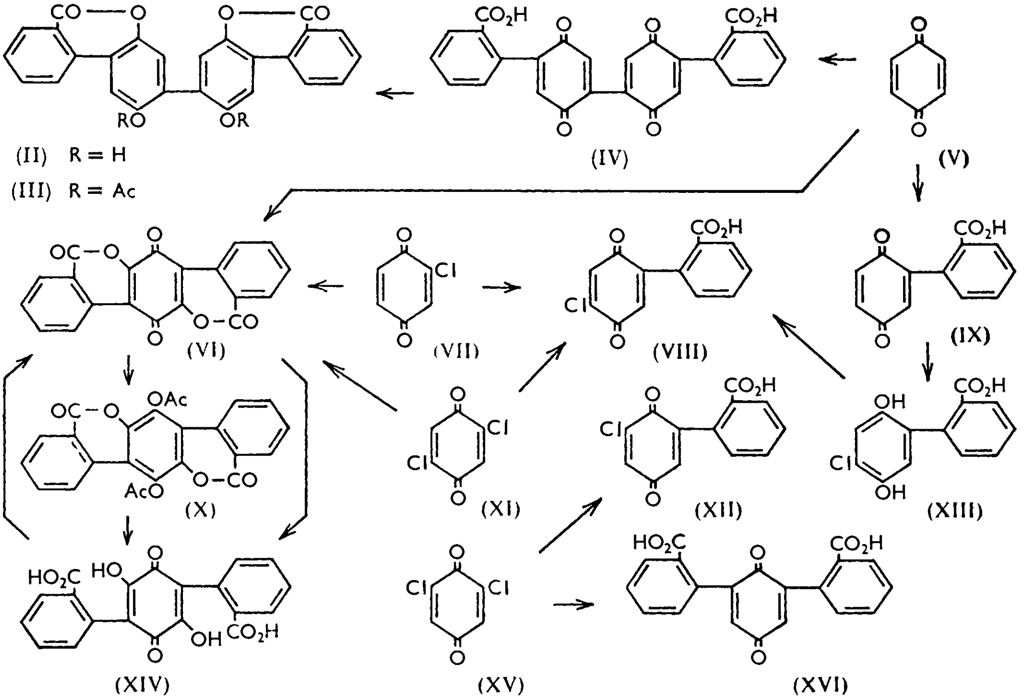
[5] Gunther, G.P. 679,976; Kvalnes, *J. Amer. Chem. Soc.*, 1934, **56**, 2478; Asano and Kameda, *J. Pharm. Soc. Japan*, 1939, **59**, 768; Ghigi, *Boll. sci. Fac. Chim. ind. Bologna*, 1944—1947, **5**, 38; Wieland and Heymann, *Annalen*, 1935, **514**, 145.

[6] Bohlmann, *Chem. Ber.*, 1957, **90**, 1519.

[7] Schimmelschmidt, *Annalen*, 1950, **566**, 184.

[8] Nilsson, *Acta Chem. Scand.*, 1956, **10**, 1377.

2-*o*-carboxyphenyl-1,4-benzoquinone (IX). A reaction in which equimolecular proportions were used gave 2-*o*-carboxyphenyl-1,4-benzoquinone directly in better yield. The latter was converted into 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone by treatment with hydrogen chloride, followed by oxidation. When arylation of unsubstituted 1,4-benzoquinone was carried out by the Schimmelschmidt procedure a red amorphous solid was obtained. This was converted by reduction and subsequent boiling with alkali into a yellow crystalline compound of empirical formula $C_{13}H_7O_4$, reduction and reductive acetylation of which gave colourless crystalline compounds of empirical formulæ $C_{13}H_7O_3$ and $C_{15}H_9O_4$ respectively. The yellow compound is a quinone-acid, and structures (IV), (II), and (III) are suggested for these three products.



EXPERIMENTAL

*2,5-Di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone Dilactone* (VI).—A solution of 1,4-benzoquinone was prepared by warming to 60° a mixture of quinol (11 g.), potassium bromate (6·1 g.), 2N-sulphuric acid (3 ml.), and water (100 ml.). Cooling gave a fine suspension. A paste prepared by grinding anthranilic acid (26·4 g.) with concentrated hydrochloric acid (50 ml.) and water (80 ml.) was cooled to 0° and treated with an ice-cold solution of sodium nitrite (14·5 g.) in water (175 ml.) with stirring. Saturated sodium acetate solution was added until the solution became alkaline to Congo Red; the mixture was then added all at once to the stirred benzoquinone suspension at 5°. Nitrogen was evolved and a precipitate was formed. Foaming was controlled by pentyl alcohol. The mixture was stirred for 45 min., set aside for 1 hr., and filtered. The precipitate was dried and extracted with boiling acetic acid, the major portion dissolving. The residue was recrystallised from anisole, yielding yellow plates of 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone dilactone (0·65 g.), m. p. >400° (Found: C, 69·6; H, 2·1. Calc. for $C_{20}H_8O_6$: C, 69·8; H, 2·3%).

2′,5′-Dihydroxybiphenyl-2-carboxylic Acid.—The crude precipitate (15 g.) from the reaction described above was heated with acetic anhydride (75 ml.) and anhydrous sodium acetate (4 g.) under reflux for 1 hr., during which zinc dust (3 g.) was added in small portions. The mixture was filtered and the residue was washed with acetic acid. The washings were combined with the filtrate and poured into water (300 ml.), an oil separating which solidified and was recrystallised four times from acetic acid and twice from ethanol to give *2′,5′-diacetoxybiphenyl-2-carboxylic acid* as colourless needles (4·5 g.), m. p. 193° (Found: C, 65·1; H, 4·4. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·4%).

The diacetate was heated with 2N-sulphuric acid (75 ml.) and ethanol (60 ml.) for 2 hr. Crystals which separated on cooling recrystallised from ethanol to give the *dihydroxy-acid* as needles (1·65 g.), m. p. 265° (Found: C, 67·9; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%).

o-*Carboxyphenyl*-1,4-*benzoquinone* (IX).—(i) The preceding acid was added in small portions with stirring to nitric acid (5 ml.; *d* 1·42), then poured into water (50 ml.), forming a precipitate of o-*carboxyphenyl*-1,4-*benzoquinone*, which recrystallised from ethanol as orange needles (0·8 g.), m. p. 243°, with darkening and softening at 235° (Found: C, 68·4; H, 3·2. $C_{13}H_8O_4$ requires C, 68·4; H, 3·5%).

(ii) Experiment (i) was repeated with half the quantity of anthranilic acid. The precipitate was separated and dried. A small portion was extracted with light petroleum ether (b. p. 100—120°), the extract yielding crystals on cooling. The bulk of the precipitate was dissolved in acetic acid (100 ml.). Seeding afforded a solid which recrystallised from ethanol, giving orange needles of the quinone (8·4 g.) m. p. 243°.

2,5-*Di*-o-*carboxyphenyl*-3,6-*dihydroxy*-1,4-*benzoquinone* (XIV).—The dilactone (VI) (0·5 g.) was heated in methanol (35 ml.) and 2N-aqueous sodium hydroxide (35 ml.) for 15 min., after which the methanol was allowed to evaporate. The purple solution was acidified with hydrochloric acid; the colour was discharged and 2,5-di-*o*-carboxyphenyl-3,6-dihydroxy-1,4-benzoquinone was precipitated. This was recrystallised three times from dioxan, forming yellow needles, which became orange in air owing to loss of dioxan of crystallisation (0·33 g.), m. p. >400° (Found: C, 63·0; H, 2·6. Calc. for $C_{20}H_{12}O_8$: C, 63·2; H, 3·2%). Attempted recrystallisation from acetic acid gave the quinone dilactone (VI).

*2′,5′-Diacetoxy-3′,6′-dihydroxy-*p*-terphenyl-2,2″-dicarboxylic Dilactone* (X).—The dilactone (VI) (0·5 g.) was heated under reflux for 30 min. with acetic anhydride (5 ml.), zinc dust (0·2 g.), and anhydrous sodium acetate (0·1 g.). The mixture was filtered hot; it deposited the *dilactone* (X) on cooling. This recrystallised from *o*-dichlorobenzene as colourless needles (0·46 g.), m. p. 363° (decomp.) (Found: C, 67·0; H, 3·0. $C_{24}H_{14}O_8$ requires C, 67·0; H, 3·3%), dissolving in warm alcoholic alkali to a purple solution, whence acidification precipitated the acid (XIV).

2-o-*Carboxyphenyl*-5-*chloro*-1,4-*benzoquinone* (VIII).—(i) A slow stream of hydrogen chloride was bubbled into a solution of *o*-carboxyphenyl-1,4-benzoquinone (0·5 g.) in chloroform (100 ml.) for 10 min. The precipitated 2-o-*carboxyphenyl*-5-*chloroquinol* recrystallised from ethanol as colourless needles (0·45 g.), m. p. 251° (Found: C, 59·2; H, 3·18; Cl, 13·6. $C_{13}H_9O_4Cl$ requires C, 59·0; H, 3·4; Cl, 13·4%). The quinol (0·2 g.), when warmed with 2N-sulphuric acid (0·2 ml.), water (10 ml.), and potassium bromate (0·15 g.), became red and rapidly yielded 2-o-*carboxyphenyl*-5-*chloro*-1,4-*benzoquinone*, which recrystallised from acetone as orange needles (0·15 g.), m. p. 263°, with sublimation (Found: C, 59·4; H, 2·4; Cl, 13·4. $C_{13}H_7O_4Cl$ requires C, 59·4; H, 2·7; Cl, 13·5%).

(ii) A vigorously stirred solution of chloro-1,4-benzoquinone (VII) (14·2 g.) in ethanol (100 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 27·1 g. of acid) containing excess of sodium acetate. After 1 hr. the precipitate was separated, washed with ethanol (200 ml.), and heated under reflux with acetone (100 ml.). The insoluble portion was recrystallised three times from anisole to yield the dilactone (VI) as yellow plates, m. p. >400° (Found: C, 69·7; H, 2·3%). Concentration of the acetone solution gave crystals of 2-*o*-carboxyphenyl-5-chloro-1,4-benzoquinone, which recrystallised from acetone as orange needles (3·1 g.), m. p. 263°, undepressed by admixture with the product from (i).

(iii) A solution of 2,5-dichloro-1,4-benzoquinone (XI) (18·5 g.) in ethanol (1600 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 27·5 g. of acid) containing excess of sodium acetate. Procedure (ii) led to 5-*o*-carboxyphenyl-2-chloro-1,4-benzoquinone (1·75 g.), m. p. and mixed m. p. 263°, and the dilactone (VI) (0·75 g.) (Found: C, 69·6; H, 2·2%).

2-o-*Carboxyphenyl*-6-*chloro*-1,4-*benzoquinone* (XII) *and* 2,6-*Di*-o-*carboxyphenyl*-1,4-*benzoquinone* (XVI).—A stirred solution of 2,6-dichloro-1,4-benzoquinone (XV) (12·2 g.) in ethanol (800 ml.) was treated at 5° with a solution of diazotised anthranilic acid (from 18·2 g. of acid) containing excess of sodium acetate. The mixture was stirred for 3 hr., after which the brown precipitate was collected, washed with water, dried, and extracted with ethanol (Soxhlet). On cooling, yellow crystals were deposited which, recrystallised from ethanol, gave orange needles of 2-o-*carboxyphenyl*-6-*chloro*-1,4-*benzoquinone* (3·4 g.), m. p. 226° (Found: C, 59·6; H, 2·7; Cl, 13·5. $C_{13}H_7O_4Cl$ requires C, 59·4; H, 2·7; Cl, 13·5%). The residue from the ethanol-extraction crystallised from dioxan, yielding orange-red leaflets of 2,6-*di*-o-*carboxyphenyl*-1,4-*benzoquinone* (1·2 g.), m. p. 399° with softening at 379° (Found: C, 68·6; H, 3·2. $C_{20}H_{12}O_6$ requires C, 69·0; H, 3·5%).

2,2'''-*Dicarboxyquaterphenyl*-2',5' : 2'',5''-*diquinone*.—A solution of *o*-carboxybenzenediazonium chloride prepared from anthranilic acid (70 g.), water (100 ml.), concentrated hydrochloric acid (100 ml.), ice (400 g.), and 40% sodium nitrite solution (70 ml.) was added dropwise with stirring at 5° during 3 hr. to a suspension of 1,4-benzoquinone (21·5 g.) in water (200 ml.) containing sodium hydrogen carbonate (100 g.). The solution was filtered; then acidification with hydrochloric acid gave an amorphous brown precipitate. This material, which could not be crystallised, was warmed with sodium dithionite (25 g.) in 1 : 3 aqueous ethanol (1 l.). The solution was filtered and concentrated to 400 ml.; on cooling, colourless crystals (9·3 g.) separated. Further concentration precipitated a resin. The colourless substance (8 g.) was heated under reflux with 2N-sodium hydroxide (100 ml.) for 1 hr. while air was bubbled through the solution; on cooling and acidification of the solution the *diquinone* crystallised. After three recrystallisations from acetic acid and two from ethanol, it was obtained as yellow plates (5·75 g.), m. p. 389° (Found: C, 68·3; H, 3·3. $C_{26}H_{14}O_8$ requires C, 68·7; H, 3·1%), $\nu_{max.}$ (potassium bromide disc) 1694 (C:O of CO_2H) and 1650 cm.$^{-1}$ (C:O of quinone).

Dilactone (II).—The diquinone (0·5 g.) was heated under reflux for 30 min. with acetic acid (20 ml.) and zinc dust (0·3 g.). The suspension of colourless solid thus formed was decanted from residual zinc and filtered. The solid was washed with water and recrystallised from ethanol and from acetic acid to give the *dilactone* as colourless plates (0·32 g.), m. p. 389° (Found: C, 73·9; H, 3·6. $C_{26}H_{14}O_6$ requires C, 73·9; H, 3·3%). Solutions in alcohol and in acetic acid exhibit a strong violet fluorescence. The *diacetate* (III), prepared by heating the diquinone (0·5 g.) with acetic anhydride and zinc dust, was obtained as colourless needles (0·37 g.) (from acetic acid), m. p. 387° (Found: C, 71·1; H, 3·6. $C_{30}H_{18}O_8$ requires C, 71·1; H, 3·6%).

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