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I. DIRECTIVE EFFECTS IN THE SUBSTITUTION OF NAPHTHOQUINONES

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Summary

The reaction of dimethylamine with 5-methoxy-1,4-naphthoquinone gives approximately equal amounts of the two possible substitution products and with 6-methyl-1,4-naphthoquinone followed by acid hydrolysis 2-hydroxy-6-methyl-1,4-naphthoquinone is the principal product. Similar treatment of 5-methyl-1,4-naphthoquinone gives mostly 3-hydroxy-5-methyl-1,4-naphthoquinone. The isomer, 2-hydroxy-5-methyl-1,4-naphthoquinone, has been prepared by another method. The product of Thiele-Winter addition of acetic anhydride to juglone is shown to be a mixture of the two possible isomers, but authentic 1,3,4,5-tetra-acetoxynaphthalene has been prepared from 3,5-dihydroxy-1,4-naphthoquinone. The reaction of acetic anhydride with plumbagin gives three compounds, the composition of the mixture depending on the time of contact. Juglone and plumbagin have been selectively brominated in the 6-position and certain other halogen derivatives of these quinones have been prepared. The preparation of 3-chloro-5-hydroxy-2-methyl-1,4-naphthoquinone provides a new route by which droserone may be obtained from plumbagin.

I. Introduction

Substitution reactions in the quinonoid ring of juglone and some of its derivatives are known to be influenced by the nature of the substituents already present in the benzenoid ring. Usually one of the two possible isomeric products predominates, and in many cases exclusive formation of one isomer has been claimed. Cooke and Segal (1950) and Thomson (1951*a*) have attempted to account for these results in terms of electronic effects relayed from the 5-substituent.

The isolation of only one isomer from substitutions of juglone acetate is not readily explained since no strong specific activation or deactivation would be expected from the 5-acetoxy-group. However, in some cases the reported yield of substitution product is only moderate and the formation of substantial amounts of the second isomer is not excluded. The ready hydrolysis of the acetoxy-group is a factor which may confuse the issue in some cases, and in particular it limits the investigation of substitution by bases. It was therefore considered necessary to determine the effects of other substituents which would be expected to give results similar to those of the acetoxy-group.

(*a*) *Reaction with Dimethylamine*

The reaction of dimethylamine with 5-methoxy-1,4-naphthoquinone and with 5- and 6-methyl-1,4-naphthoquinone has been studied. The methoxy-

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and methyl substituents were chosen for their stability and because they would be more likely to give specific directive effects of the kind previously claimed for the acetoxy-group.

No attempt was made to isolate the primary products of substitution but the crude dimethylaminoquinones were hydrolysed to the corresponding hydroxyquinones. The latter are generally more readily purified, and the orientation of substituents is more readily determined.

The two isomeric products from 5-methoxy-1,4-naphthoquinone were apparently formed in approximately equal amounts, but they could not be separated easily. However, after demethylation the known 2,5-dihydroxy-1,4-naphthoquinone was obtained, while the action of diacetyl peroxide gave a mixture of products from which 2-methyl-3-hydroxy-5-methoxy-1,4-naphthoquinone was readily separated.

Only one pure compound was obtained from 5-methyl-1,4-naphthoquinone, but there was some evidence of the presence of a small amount of the other isomer. The product was evidently 3-hydroxy-5-methyl-1,4-naphthoquinone since it was not identical with 2-hydroxy-5-methyl-1,4-naphthoquinone prepared from 5-methyl-1-tetralone by the general method of Buu-Hoï and Cagniant (1942).

From 6-methyl-1,4-naphthoquinone only the known 2-hydroxy-6-methyl-1,4-naphthoquinone was isolated, but again there was some evidence of the formation of small amounts of the other isomer.

These results suggest that the acetoxy-group should not have any strong directive effect in substitution reactions of this type. However, the predominant formation of one isomer from each of the methylnaphthoquinones is in accord with the earlier suggestions concerning the effect of a predominantly electron-releasing substituent.

It seemed possible that previous reports of the formation of only one isomer from juglone acetate may have been due in some cases to the difficulty of separating and purifying the products. This does account for at least one such claim, as the following results show.

(*b*) *Thiele-Winter Addition Reaction*

Fieser and Dunn (1937) and Thomson (1951*a*) have reported that the addition of acetic anhydride to juglone acetate gives only one product, and Thomson claimed that this was 1,3,4,5-tetra-acetoxynaphthalene. It has now been found that this product actually consists of approximately equal amounts of the two possible isomers. Hydrolysis and oxidation gave a considerable amount of 2,5-dihydroxy-1,4-naphthoquinone, which was isolated as the diacetate. Pure 1,3,4,5-tetra-acetoxynaphthalene has now been obtained by the reductive acetylation of 3,5-dihydroxy-1,4-naphthoquinone. A mixture of equal amounts of the two pure tetra-acetoxynaphthalenes had the melting point previously reported for the addition product.

The reaction of plumbagin, 2-methyl-5-hydroxy-1,4-naphthoquinone, with acetic anhydride has also been studied. Three products were obtained, but the proportions varied with the conditions. Brief treatment gave principally

plumbagin acetate, but longer reaction times produced the Thiele-Winter addition product, 1,3,4,5-tetra-acetoxy-2-methylnaphthalene, and/or another compound which has not been identified. Hydrolysis of the leucotetra-acetate followed by oxidation gave droserone. Since this work was completed the results of a similar study by Asano and Hase (1943) have become available.

(*c*) *Halogen Derivatives of Juglone and Plumbagin*

It was expected that addition of chlorine or bromine to plumbagin would give a 2,3-dihalide from which 3-chloro- or 3-bromoplumbagin could be obtained by elimination of hydrogen halide. These reactions have long been known to occur with juglone. It was found, however, that the addition of the halogens to plumbagin was slow, and subsequent elimination of hydrogen halide gave mixtures. With excess chlorine in acetic acid, followed by heating with sodium acetate, two products were obtained. One was the expected 2-methyl-3-chloro-5-hydroxy-1,4-naphthoquinone, and the other was presumably 2-methyl-3,6-dichloro-5-hydroxy-1,4-naphthoquinone. As Thomson (1949) has shown that the former can be hydrolysed to droserone, this completes another method for obtaining this pigment from plumbagin. In a similar manner 2-methyl-3-bromo-5-hydroxy-1,4-naphthoquinnoe was also obtained.

When brominated in glacial acetic acid in the presence of anhydrous sodium acetate, juglone gave a monobromo-derivative different from 2- or 3-bromojuglone. This product was evidently 5-hydroxy-6-bromo-1,4-naphthoquinone because it gave 2,3,6-tribromojuglone on further bromination. Similar results were obtained with plumbagin, and the product was presumably 2-methyl-5-hydroxy-6-bromo-1,4-naphthoquinone. Analogous substitutions with chlorine could not be obtained.

5-Hydroxy-8-chloro-1,4-naphthoquinone, prepared by condensation of *p*-chlorophenol, or *p*-bromophenol, with maleic anhydride in a melt of aluminium chloride and sodium chloride, was different from the product described by Gomez (1935), who used the same method of preparation.

II. Experimental

Melting points are corrected and were observed in Pyrex capillaries. Microanalyses by Dr. W. Zimmermann and assistants.

(*a*) *Reaction of Dimethylamine with Naphthoquinones.*—(i) 5-Methoxy-1,4-naphthoquinone was prepared as described by Thomson, Race, and Rowe (1947) and was allowed to react with excess dimethylamine under the conditions used by Anslow and Raistrick (1939) for a similar reaction. However, better yields were obtained when the reaction mixture contained no alcohol. The crude product was hydrolysed by heating for 30 min. on a water-bath with concentrated hydrochloric acid, and the mixture was then diluted and extracted continuously with ether. The hydroxyquinones were extracted from the ether with 5% aqueous sodium carbonate and then precipitated with hydrochloric acid. Yield 42%. The crude product was a mixture of the two isomers which could not be easily separated. Part of the mixture was therefore demethylated with $NaAlCl_4$ as previously described by Cooke and Segal (1950). The crude orange-red product was sublimed in a vacuum and then acetylated to give 2,5-diacetoxy-1,4-naphthoquinone, m.p. 152 °C., alone or mixed with an authentic specimen. Another portion of the mixture was treated with diacetyl peroxide as described by Cooke and Segal (1950), and from the mixed isomers 2-methyl-3-hydroxy-5-methoxy-1,4-naphthoquinone was readily separated. It had m.p. 171–172 °C., not depressed by an authentic specimen.

(ii) 5-Methyl-1,4-naphthoquinone was prepared from benzoquinone and piperylene by the diene synthesis. The general conditions of Fieser (1948) were used. The initial addition product was not isolated but was rearranged with acidified stannous chloride to give *1,4-dihydroxy-5,8-dihydro-5-methylnaphthalene* which separated from aqueous ethanol in colourless needles, m.p. 147 °C. (Found : C, 74·5 ; H, 6·7%. Calc. for $C_{11}H_{12}O_2$: C, 75·0 ; H, 6·8%).

The two stage oxidation of this product gave a 95% conversion to 5-methyl-1,4-naphthoquinone, yellow needles from aqueous acetone, m.p. 122·5–123 °C. Herzenberg and Ruhemann (1927) reported m.p. 102–103° C. and Veselý *et al.* (1929) gave m.p. 121–122 °C. for products prepared by different methods (Found : C, 76·6 ; H, 4·7%. Calc. for $C_{11}H_8O_2$: C, 76·7 ; H, 4·7%).

The reaction of this product with dimethylamine was studied under the conditions used by Plimpton (1880) for 1,4-naphthoquinone. The resulting product was hydrolysed by heating on a water-bath for 45 min. with a mixture of equal volumes of ethanol and concentrated hydrochloric acid. Most of the alcohol was then evaporated and, after dilution with water, the mixture was extracted continuously with ether. The product was recovered as described above and fractionally crystallized from aqueous ethanol. The major product, evidently *3-hydroxy-5-methyl-1,4-naphthoquinone*, formed yellow needles, changing to prisms, m.p. 175–176 °C. (Found : C, 70·1 ; H, 4·3%. Calc. for $C_{11}H_8O_3$: C, 70·2 ; H, 4·3%). The smaller more soluble fraction, m.p. ~134 °C., appeared to contain some of the isomeric compound.

2-Hydroxy-5-methyl-1,4-naphthoquinone was prepared from 5-methyl-1-tetralone by the general method of Buu-Hoï and Cagniant (1942). The product formed pale yellow needles from aqueous methanol, m.p. 145–146 °C. (Found : C, 69·9 ; H, 4·4%. Calc. for $C_{11}H_8O_3$; C, 70·2 ; H, 4·3%).

(iii) 6-Methyl-1,4-naphthoquinone, prepared from benzoquinone and isoprene by the modified diene synthesis of Fieser (1948), crystallized from aqueous acetone as yellow needles, m.p. 91–92 °C. Bendz (1951) reports m.p. 90–91 °C. (Found : C, 76·9 ; H, 4·7%. Calc. for $C_{11}H_8O_2$: C, 76·7 ; H, 4·7%). This compound was allowed to react with dimethylamine as described for the isomer, and the crude product was hydrolysed to give the hydroxynaphthoquinone in 55% yield. This was mostly 2-hydroxy-6-methyl-1,4-naphthoquinone, golden-yellow leaflets from benzene, m.p. 198 °C. Fieser, Hartwell, and Seligman (1936) reported m.p. 199 °C. (Found : C, 70·3 ; H, 4·3%. Calc. for $C_{11}H_8O_3$: C, 70·2 ; H, 4·3%). The methyl ether had m.p. 166·5–167·5 °C. Fieser, Hartwell, and Seligman reported m.p. 167–167·5 °C. No other pure product could be isolated from the more soluble fractions, but small quantities of the isomer may have been present.

(*b*) *Thiele-Winter Reaction with Juglone and Plumbagin.*—(i) *Juglone.* The reaction was repeated as described by Fieser and Dunn (1937), and after many crystallizations the product melted at 154 °C. after softening from 145 °C. The mixture of hydroxyquinones obtained by alkaline hydrolysis of this product was acetylated, and fractional crystallization from benzene-light petroleum (40–60 °C.) readily gave pure 2,5-diacetoxy-1,4-naphthoquinone, m.p. 152–153 °C., not depressed by mixing with an authentic specimen. Reductive acetylation of this material gave 1,2,4,5-tetra-acetoxynaphthalene, m.p. 174 °C., after softening from 167 °C. If allowed to solidify it then melted sharply at 173–174 °C. (cf. Thomson 1951*a*). *1,3,4,5-Tetra-acetoxynaphthalene* was obtained by reductive acetylation of 3,5-dihydroxy-1,4-naphthoquinone. It formed colourless prisms from ethanol, m.p. 167–168 °C. When mixed with an equal amount of 1,2,4,5-tetra-acetoxynaphthalene the m.p. was 154 °C. after softening from 145 °C.

(ii) *Plumbagin.* The quinone (0·1 g.) was dissolved in acetic anhydride (0·8 ml.) and one drop of concentrated sulphuric acid was added. After 24 days, water was added and the dark precipitate purified by sublimation in a vacuum and crystallization from ethanol. The 1,3,4,5-tetra-acetoxy-2-methylnaphthalene formed colourless prisms, m.p. 175·5–176·5 °C. Asano and Hase (1943) reported m.p. 174 °C. (Found : C, 60·7 ; H, 4·9%. Calc. for $C_{19}H_{18}O_8$: C, 61·0 ; H, 4·8%). On hydrolysis with cold methanolic potassium hydroxide, followed by dilution with water and acidification, droserone, m.p. 180–181 °C., was obtained.

When the reaction of acetic anhydride with plumbagin was allowed to proceed for shorter times two other products were obtained in addition to, or instead of, that described above. These products could be separated by fractional sublimation in a vacuum. The more volatile compound

formed large yellow plates from ethanol, m.p. 117–118 °C., and was evidently plumbagin acetate. It could be obtained almost exclusively by reaction at 0 °C. in the presence of only a trace of sulphuric acid, for a time just sufficient to change the colour to yellow. It was never obtained pure under the conditions of Fieser and Dunn (1936), which gave mostly the substance found in the less volatile fraction. This *compound* was sparingly soluble in most solvents, but it crystallized from methyl cellosolve in small colourless needles, m.p. 281–283 °C., uncorr. On standing it rapidly became greenish (Found: C, 67·5; H, 4·4%). This product has not been examined further.

(c) *Halogen Derivatives of Juglone and Plumbagin.*—(i) *5-Hydroxy-6-bromo-1,4-naphthoquinone.* Juglone (0·3 g.) was dissolved in glacial acetic acid (2 ml.) and anhydrous sodium acetate (0·4 g.) was added and well mixed to dissolve as much as possible. A solution of bromine (0·27 g.) in acetic acid (3 ml.) was then added. The flask was stoppered and allowed to stand for 8 days. The precipitated *bromojuglone* was then collected and purified by sublimation in a vacuum and crystallization from light petroleum (90–100 °C.). It formed fine deep orange needles, m.p. 153–154 °C. (Found: C, 47·6; H, 2·2; Br, 31·9%. Calc. for $C_{10}H_5O_3Br$: C, 47·5; H, 2·0; Br, 31·6%).

The *acetyl derivative* formed yellow blades or plates from benzene-light petroleum, m.p. 184–185 °C. (Found: C, 48·6; H, 2·5; Br, 27·8%. Calc. for $C_{12}H_7O_4Br$: C, 48·8; H, 2·4; Br, 27·1%).

(ii) *2,3,6-Tribromojuglone.* The 5-hydroxy-6-bromo-1,4-naphthoquinone (80 mg.) was dissolved in acetic acid (1 ml.) and bromine (0·1 ml.) was added. The mixture was heated for 3 hr. on the water-bath and then cooled. The solid was collected and crystallized from chloroform-light petroleum giving red needles, m.p. 173–175 °C. Thomson (1948) reported m.p. 172 °C. The acetyl derivative formed yellow needles from ethanol, m.p. 188–189 °C. Thomson reported m.p. 188 °C.

(iii) *5-Hydroxy-8-chloro-1,4-naphthoquinone.* Maleic anhydride was condensed with *p*-chlorophenol or *p*-bromophenol as described by Gomez (1935). The product was purified by extraction with light petroleum and, after recovery, by sublimation in a vacuum and finally crystallization from chloroform-light petroleum giving red needles, m.p. 201–202 °C. Gomez reported m.p. 122 °C. (Found: C, 57·2; H, 2·6%. Calc. for $C_{10}H_5O_3Cl$: C, 57·6; H, 2·4%). The acetyl derivative separated from ethanol or benzene-light petroleum in pale yellow needles, m.p. 147–148 °C. Gomez reported m.p. 164 °C. (Found: C, 57·1; H, 2·8; Cl, 14·6%. Calc. for $C_{12}H_7O_4Cl$: C, 57·5; H, 2·8; Cl, 14·2%).

(iv) *2-Methyl-5-hydroxy-6-bromo-1,4-naphthoquinone.* Plumbagin was brominated as described for juglone. The *product* was precipitated with water and purified by sublimation in a vacuum and crystallization from ethanol. It formed deep orange needles, m.p. 183–185 °C. (Found: C, 49·3; H, 2·9; Br, 30·5%. Calc. for $C_{11}H_7O_3Br$: C, 49·5; H, 2·6; Br, 29·9%).

The *acetyl derivative* separated from benzene-light petroleum as yellow prisms, m.p. 135–136 °C. (Found: C, 50·8; H, 3·0; Br, 25·6%. Calc. for $C_{13}H_9O_4Br$: C, 50·5; H, 2·9; Br, 25·8%).

(v) *2-Methyl-3-bromo-5-hydroxy-1,4-naphthoquinone.* The addition of bromine to plumbagin was carried out as described by Thomson (1948) for juglone. The colour faded only slowly over a period of 4 hr., and after boiling the product with ethanol only a small amount of the required product, m.p. 117–118 °C., was isolated. Thomson (1951*b*) reported m.p. 118 °C. for this compound prepared by another method.

(vi) *2-Methyl-3-chloro-5-hydroxy-1,4-naphthoquinone and 2-Methyl-3,6-dichloro-5-hydroxy-1,4-naphthoquinone.* Plumbagin was allowed to react with excess chlorine in acetic acid for 3 hr. The remaining chlorine was then removed by aeration and the mixture was boiled with excess anhydrous sodium acetate. Fractional crystallization of the product from light petroleum gave a less-soluble fraction, the *dichloro-derivative*, which separated in orange-red needles, m.p. 150–151 °C. (Found: C, 51·6; H, 2·6; Cl, 27·6%. Calc. for $C_{11}H_6O_3Cl_2$: C, 51·4; H, 2·3; Cl, 27·6%). The more soluble fraction was finally crystallized from aqueous acetic acid, giving 2-methyl-3-chloro-5-hydroxy-1,4-naphthoquinone as orange-yellow plates, m.p. 123–124 °C Thomson (1949) prepared this compound by another method and reported m.p. 125 °C.

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