[Contribution from the Chemistry Department, Marischal College,
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STUDIES IN THE JUGLONE SERIES. I. SOME HALOGEN DERIVATIVES AND THEIR REACTION WITH ANILINE

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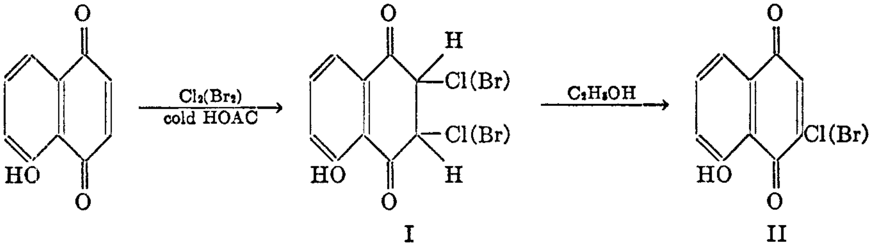
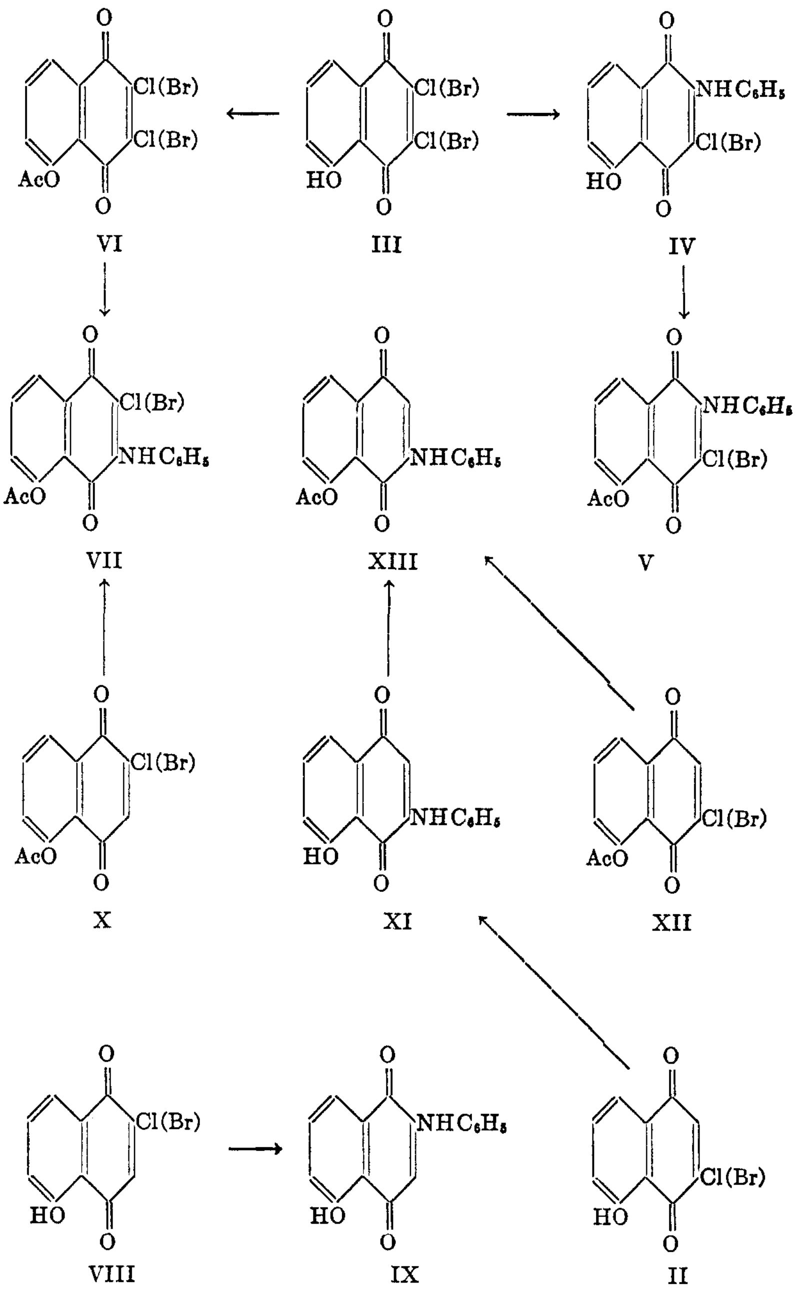
Juglone was first isolated by Vogel and Reischauer (1) in 1856, from fresh walnut shells (*Juglans regia*), where it occurs as an α-hydrojuglone. In 1885 it was shown by Bernthsen and Semper (2) to have the structure 5-hydroxy-1,4-naphthoquinone, which was confirmed two years later by the same authors when they synthesized juglone by chromic acid oxidation of 1,5-dihydroxynaphthalene (3). The chemistry of juglone has not been greatly expanded since that time, and the derivatives which have been obtained are, in many cases, of uncertain constitution. Thus the preparation, by two different methods, of the acetates of 2-chloro- and 2-bromo-juglone is reported in the literature. The brief descriptions accorded to these compounds however, are not in agreement, the difference in melting point amounting to 10° in the case of the bromo derivative, and since the structure of these substances was only assumed by one group of workers, it seemed desirable to verify their identity. In the course of this work it was observed that the constitutions assigned to a number of halogenojuglones in the literature were not well established and certain of these have also been re-examined.



2-Chloro- and 2-bromo-juglone were first obtained by Wheeler and Scott (4) by treating juglone in cold glacial acetic acid solution with the appropriate halogen to yield a dihalide addition product (I), which readily splits off a molecule of halogen acid on warming with alcohol. It is clear that the halogen atom in the monohalogenojuglone so obtained may be located at either position 2 or position 3, and in fact a mixture of two isomers would be anticipated. Wheeler and co-workers however, obtained only one isomer in each case, and this they assumed to be the 2-halogeno derivative. The acetates were derived in the usual way. The acetate of 2-bromojuglone was also prepared by Carter, Race, and Rowe (6) by chromic acid oxidation of 2,4-dibromo-5-acetoxy-1-naphthol, a method which admits of no ambiguity, and Thomson (7) has shown that the acetate of 2-chlorojuglone can be obtained in the same way from 2,4-dichloro-5-acetoxy-1-naphthol. These compounds have now been prepared by both



methods, and it has been found that the acetates of Wheeler and Scott (XII) are different from those of Carter *et al.*, and of Thomson (X), the latter yielding on hydrolysis 2-chloro- and 2-bromo-juglones (VIII) different from those of Wheeler and Scott (II). Hence the products obtained by elimination of a molecule of halogen acid from juglone dichloride and dibromide must be the 3-chloro- and 3-bromo-juglones (II). 3-Halogenojuglones have been obtained in this way in high yield but no trace of the 2-isomers has been found, and if formed at all must be in negligible amounts. This exclusive formation of the 3-isomers is rather surprising and must be ascribed to the effect of the hydroxyl group in the benzenoid ring. It may be noted in this connection that Fieser and Dunn (8) observed that the presence of hydroxyl groups in the benzenoid ring of α-naphthoquinone had a marked influence on the additive power of the ethylenic linkage in the quinonoid ring.

Further chlorination of both 2- and 3-chlorojuglone yields 2,3-dichlorojuglone, whilst further bromination of the two bromo compounds yields 2,3-dibromojuglone, which, as was shown by Wheeler and Naiman (5) is readily converted by alcoholic hydrochloric acid to the 2,3-dichloro compound. These reactions firmly establish the constitutions of the 2,3-dihalogenojuglones.

By direct bromination of juglone, Wheeler and Scott (4) obtained a tribromo derivative. One of the bromine atoms was reactive, due, it was thought, to its position para to the hydroxyl group, and the compound was therefore regarded as 2,3,8-tribromojuglone (9). The same compound has now been obtained by further bromination of 2,3-dibromojuglone and 2,6-dibromojuglone, and its structure is therefore 2,3,6-tribromojuglone. The reactions of this compound will be considered further in a subsequent paper.

2,3-Dichlorojuglone (III) reacts readily with aniline and certain other arylamines, with replacement of one of the chlorine atoms, and it was assumed by Wheeler, Dawson, and McEwen (10) that the products were 2-arylamino-3-chlorojuglones (IV). It is known that reaction of 2,3-dichlorojuglone acetate (VI) with aniline affords 3-anilino-2-chlorojuglone acetate (VII) since the same compound can be obtained by reaction of aniline with 2-chlorojuglone acetate (X) (7). Comparison of this acetate (VII) with the acetate (V) of (IV) has shown that these are different compounds which thus confirms the structure originally assigned to (IV). It therefore appears that in 2,3-dichlorojuglone the chlorine atom at position 2 is reactive, whereas in 2,3-dichlorojuglone acetate the chlorine atom at position 3 is reactive. Similarly reaction of 2,3-dibromojuglone with aniline affords 2-anilino-3-bromojuglone, but if the reaction is preceded by acetylation of the hydroxyl group, the product is the acetate of 3-anilino-2-bromojuglone.

These unexpected results led to an examination of the reaction of the monohalogenojuglones and their acetates with aniline. 2-Chloro- and 2-bromojuglone (VIII), and 3-chloro- and 3-bromo-juglone (II), all react with elimination of the halogen atom to form the corresponding 2- and 3-anilinojuglones (IX), (XI). One of these corresponds to the anilinojuglone obtained by Mylius (11) from hydroxyjuglone, but their identity has not yet been established. Attempts to make an anilinojuglone by direct reaction of juglone and aniline failed, in contrast to α-naphthoquinone (12) and 5-chloro and 5-bromo-naphthoquinone (13), which readily form anilino derivatives. The acetates of the 2-halogenojuglones (X) yield 3-anilino-2-halogenojuglone acetates (VII), but in the case of the acetates of the 3-halogenojuglones (XII) the halogen atom is again eliminated to give the acetate of 3-anilinojuglone (XIII), the bromo compound forming, in addition, a small amount of 2-anilino-3-bromojuglone acetate (V). The product obtained from the reaction of 3-chlorojuglone acetate and aniline appeared to be very similar to that obtained from the corresponding bromo compound but it was not found possible to isolate 2-anilino-3-chlorojuglone acetate.

It is clear from the behavior of these compounds that the substituent in the benzenoid ring has a pronounced influence on the reaction taking place in the quinonoid ring; when the benzenoid ring is unsubstituted, as in 2-chloro- and 2-bromo-1,4-naphthoquinone, the halogen atom is not replaced and reaction with aniline affords 3-anilino-2-chloro- or -bromo-1,4-naphthoquinone (14). On the other hand 2,6-dichloro-1,4-naphthoquinone reacts with aniline to give 2-anilino-6-chloro-1,4-naphthoquinone (15), and 2,6-dibromo- and 2,6,8-tribromo-juglone yield 2-anilino-6-bromo- and 2-anilino-6,8-dibromo-juglone respectively (16). From the information at present available it appears, therefore, that with the exception of the acetoxyl group at position 5, substitution in the benzenoid ring favors halogen replacement in the quinonoid ring, but until more data have been obtained it is difficult to find any comprehensive explanation of these anomalous reactions.

EXPERIMENTAL[1, 2, 3]

Where identity is specified this was established by mixed m.p.

3-Chloro- and 3-bromo-juglone (II). These were prepared by the method of Wheeler and Scott (4) and the improved method of Wheeler and Naiman (5). The dihalide addition products were converted to the monohalogenojuglones most expeditiously by boiling one part dihalide with six parts alcohol for three or four minutes until crystals began to separate. The suspension was then cooled and the crystals collected. 3-Chlorojuglone was obtained in 83% yield from the dichloride; orange needles from alcohol, m.p. 166°. The acetate crystallized from alcohol in yellow plates, m.p. 147°. 3-Bromojuglone was obtained in 98% yield from the dibromide; orange-brown leaflets or needles from glacial acetic acid, m.p. 172°. The acetate crystallized from alcohol in yellow plates, m.p. 151.5°. (Wheeler and Scott report m.p. 166°, and acetate, m.p. 148°.)

Wheeler and co-workers prepared the acetates of several halogenojuglones by heating with a large excess of acetic anhydride for several hours. This lengthy procedure is not necessary. The acetates are readily prepared by boiling one part halogenojuglone with two or three parts acetic anhydride, containing a trace of concentrated sulfuric acid, for one minute. The acetyl derivatives separate rapidly on cooling.

2-Chloro- and 2-bromo-juglone (VIII). 2-Chlorojuglone acetate was prepared by oxidation of 2,4-dichloro-5-acetoxy-1-naphthol according to the procedure of Wheeler and Mattox (17), who erroneously regarded the substance as the acetate of 8-chlorojuglone (7); yellow needles, m.p. 143°. A mixture with the acetate of 3-chlorojuglone had m.p. 116–120°. Hydrolysis with alcoholic hydrochloric acid yielded 2-chlorojuglone, orange-brown plates from alcohol, m.p. 112°.

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[1] Melting points are uncorrected.

[2] Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford, and Dr. J. W. Minnis of Edinburgh.

[3] The author is indebted to Imperial Chemical Industries Ltd., Dyestuffs Division, for a gift of 1,5-dihydroxynaphthalene, from which juglone was prepared.

2-Bromojuglone acetate was prepared by oxidation of 2,4-dibromo-5-acetoxy-1-naphthol as described by Carter *et al.* (6), yellow needles, m.p. 158°. A mixture with the acetate of 3-bromojuglone had m.p. 124–126°. 2-Bromojuglone was obtained by hydrolysis with alcoholic sulfuric acid. Hydrolysis with hydrochloric acid yields 2-chlorojuglone, which is in consonance with the known lability of the bromine atoms in 3-bromo- and 2,3-dibromojuglone. A solution of 2 g. of 2-bromojuglone acetate in 80 cc. of alcohol was refluxed for one hour with a solution of 4 cc. of concentrated sulfuric acid in 20 cc. of water. The crystals which separated on cooling were recrystallized twice from acetone and finally from ligroin (b.p. 50–60°); orange-red prisms, m.p. 136°; yield, 87%.

Anal. Calc'd for $C_{10}H_5BrO_3$: C, 47.4; H, 2.0; Br, 31.6.
Found: C, 47.5; H, 2.2; Br, 31.9.

2,3-Dichlorojuglone (III). A solution of either 2- or 3-chlorojuglone in a little glacial acetic acid containing a 50% excess of chlorine was heated for three hours on the steam-bath. Crystals of 2,3-dichlorojuglone separated on cooling. Recrystallization from alcohol gave golden-brown needles, m.p. 154°.

2,3-Dibromojuglone (III). This was prepared in the same manner as the dichloro compound from either 2- or 3-bromojuglone. Recrystallization from alcohol yielded golden-brown needles, m.p. 169°.

2,3,6-Tribromojuglone. This was obtained by direct bromination of juglone by the method of Wheeler and Scott (4), who regarded it as the 2,3,8-isomer, and also by bromination of 2,3-dibromojuglone and 2,6-dibromojuglone (6, 16). To a hot solution of 0.8 g. of dibromojuglone in 10 cc. of glacial acetic acid, was added a solution of 0.2 cc. of bromine in 2 cc. of glacial acetic acid. After warming for three hours on the water-bath the solution was allowed to cool, when red needles were deposited. These had m.p. 172° which was not raised by further crystallization. The identical product was obtained from all three sources, each yielding an identical acetate, yellow needles, m.p. 188°. (Wheeler and Scott report m.p. 170°, and acetate, m.p. 186°.)

2-Anilino-3-chlorojuglone acetate (V). A solution of 0.8 g. of 2-anilino-3-chlorojuglone (10) in 8 cc. of pyridine was refluxed for one hour with 2.5 cc. of acetic anhydride, cooled, and poured onto crushed ice. The red precipitate so obtained was collected and recrystallized twice from alcohol; fine rust-red needles, m.p. 183°; yield, 88%.

Anal. Calc'd for $C_{18}H_{12}ClNO_4$: C, 63.2; H, 3.5; Cl, 10.4; N, 4.1.
Found: C, 63.5; H, 3.6; Cl, 10.3; N, 4.2.

3-Anilino-2-chlorojuglone acetate (VII). This was prepared by reaction of aniline with the acetates of 2-chloro- and 2,3-dichloro-juglone (7); red needles, m.p. 172°. A mixture with (V) had m.p. 150–153°.

2-Anilino-3-bromojuglone (IV). To 0.8 g. of 2,3-dibromojuglone dissolved in 70 cc. of alcohol, 0.25 cc. of aniline was added, and the solution refluxed for twenty minutes. The orange solution rapidly became a dark violet-brown and crystals deposited on cooling. Recrystallization from acetone yielded dark violet needles (ruby by transmitted light), m.p. 215°; yield, 60%.

Anal. Calc'd for $C_{16}H_{10}BrNO_3$: C, 55.8; H, 2.9; Br, 23.25; N, 4.1.
Found: C, 56.15; H, 3.0; Br, 22.6; N, 4.3.

2-Anilino-3-bromojuglone acetate (V). A solution of 0.6 g. of 2-anilino-3-bromojuglone in 10 cc. of pyridine was warmed on the steam-bath with 1.5 cc. of acetic anhydride for ten minutes, and set aside for twenty-four hours. Crushed ice was then added to the solution to precipitate a red crystalline solid which had m.p. 203°. Recrystallization from glacial acetic acid afforded light red needles, m.p. 205°; yield, 80%.

Anal. Calc'd for $C_{18}H_{12}BrNO_4$: C, 56.0; H, 3.1; Br, 20.7; N, 3.6.
Found: C, 55.9· H, 2.8; Br, 20.2; N, 3.7.

3-Anilino-2-bromojuglone acetate (VII). A solution of 0.4 g. of 2,3-dibromojuglone acetate in 20 cc. of alcohol was refluxed with 0.1 cc. of aniline, the orange solution rapidly becoming deep red. After one hour the solution was concentrated to 10 cc. and allowed to cool. The red solid which deposited was crystallized twice from alcohol to yield red needles, m.p. 162°; yield, 51%.

Anal. Calc'd for $C_{18}H_{12}BrNO_4$: C, 56.0; H, 3.1; Br, 20.7; N, 3.6.
Found: C, 56.3; H, 3.2; Br, 20.5; N, 3.4.

The same compound was also obtained by refluxing a solution of 0.8 g. of 2-bromojuglone acetate in 20 cc. of alcohol with 0.3 cc. of aniline for one hour.

2-Anilinojuglone (IX). A solution of 0.6 g. of 2-chlorojuglone in 30 cc. of alcohol was refluxed for ten minutes with 0.25 cc. of aniline. Crystals began to separate from the solution after four or five minutes. These were collected after cooling, and recrystallized from benzene in dark reddish-violet needles, m.p. 247°; yield, 63%. The same compound was obtained by reaction of 2-bromojuglone with aniline.

Anal. Calc'd for $C_{16}H_{11}NO_3$: C, 72.5; H, 4.2; N, 5.3.
Found: C, 72.6; H, 4.3; N, 5.4.

Acetylation with acetic anhydride in pyridine afforded an acetate separating from alcohol in fine red needles, m.p. 204°.

Anal. Calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.2; N, 4.55.
Found: C, 70.4; H, 4.4; N, 4.25.

3-Anilinojuglone (XI). A solution of 1.2 g. of 3-chlorojuglone in 80 cc. of alcohol was refluxed with 0.6 cc. of aniline for one hour. The dark crystalline solid which separated on cooling was dissolved in 100 cc. of hot acetone, filtered from a little black insoluble material, and concentrated to small bulk. The crystals obtained, when recrystallized from acetone (charcoal) formed small russet leaflets, m.p. 228°; yield, 52%.

Anal. Calc'd for $C_{16}H_{11}NO_3$: C, 72.5; H, 4.2; N, 5.3.
Found: C, 72.35; H, 4.25; N, 5.4.

Acetylation with acetic anhydride in pyridine afforded an acetate (XIII), crystallizing from alcohol in red needles, m.p. 168°.

Anal. Calc'd for $C_{18}H_{13}NO_4$: C, 70.4; H, 4.2; N, 4.55.
Found: C, 70.1; H, 4.25; N, 4.75.

An anilinojuglone is reported by Mylius (11), m.p. 230°, but the identity of these compounds has not yet been established. When attempts were made to prepare an anilinojuglone by refluxing a solution of 1 g. of juglone in 60 cc. of alcohol with 0.5 cc. of freshly distilled aniline, extensive decomposition occurred in a few minutes. A black solid separated, from which nothing could be obtained by solvent extraction. Variation of this procedure had the same result.

Reactions of monohalogenojuglone acetates with aniline. (a) *2-Chloro- and 2-bromojuglone acetates (X).* These give the corresponding 3-anilino-2-chloro- or -bromojuglone acetates (VII) (see above).

(b) *3-Chlorojuglone acetate (XII).* A solution of 1 g. of 3-chlorojuglone acetate in 20 cc. of alcohol was refluxed with 0.4 cc. of aniline for one hour. The solution was then concentrated to half bulk and allowed to stand overnight. Dark red crystals (0.4 g.) were deposited, m.p. 140–143°. Recrystallization from benzene yielded red needles, m.p. 168°, identical with the acetate of 3-anilinojuglone (XIII). Attempts to isolate an anilinochlorojuglone acetate by fractional crystallization and by chromatographic separation were unsuccessful.

(c) *3-Bromojuglone acetate (XII).* A solution of 0.9 g. of 3-bromojuglone acetate in 15 cc. of alcohol was refluxed for one hour with 0.3 cc. of aniline, and then allowed to stand overnight. A dark red solid (0.4 g.) separated from the solution, m.p.147–150°. Crystallization from the minimum amount of glacial acetic acid yielded a small crop (50 mg.) of red needles, m.p. 204°. Hot water was added to the mother liquor and the solution allowed to crystallize. Red needles (0.25 g.) separated, m.p. 162°. Recrystallization of the first crop from glacial acetic acid afforded fine light red needles, m.p. 205°, identical with 2-anilino-3-bromojuglone acetate (V). Recrystallization of the second crop once from dilute acetic acid, and twice from alcohol furnished red needles, m.p. 168°, identical with the acetate of 3-anilinojuglone (XIII).

SUMMARY

Compounds prepared from juglone *via* intermediate addition products and hitherto described as 2-chloro- and 2-bromo-juglone have been re-orientated as 3-chloro- and 3-bromo-juglone.

A tribromo derivative obtained by direct bromination of juglone has been shown to be the 2,3,6- and not the 2,3,8-isomer.

The reactions of aniline with certain halogenojuglones have been investigated.

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