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STUDIES IN THE JUGLONE SERIES. II. HYDROXY AND HYDROXYHALOGENO DERIVATIVES

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It was shown in Part I (1) that the structures assigned by previous workers to certain halogen derivatives of juglone were incorrect. A search of the literature has revealed a number of other derivatives of unknown or uncertain constitution, and these have now been investigated.

A hydroxyjuglone was obtained by Mylius (2) by oxidation of juglone, or better, α-hydrojuglone, in alkaline solution, and also by acid hydrolysis of dimethylaminojuglone. The products obtained had very similar physical properties and it was concluded that they were identical. The position of the hydroxyl group was not indicated.[1] Repetition of this work yielded the compounds described by Mylius, but a mixed melting point determination showed a marked depression,[2] and the non-identity of these substances was clearly shown by the preparation of their diacetates, whose melting points differed by 15°. The structure of these two substances has now been established by hydrolysis of 2- and 3-anilinojuglone to give the corresponding hydroxyjuglones, which were compared with Mylius' substances. The product obtained by oxidation of juglone was found to be identical with 3-hydroxyjuglone, and the compound derived from dimethylaminojuglone proved to be 2-hydroxyjuglone. This also establishes the structure of the dimethylamino derivative, and of the anilino derivative obtained by Mylius by reaction of 3-hydroxyjuglone with aniline (2). 3-Hydroxyjuglone is best prepared from 3-chlorojuglone by reaction with sodium hydroxide, but the 2-isomer cannot be obtained in this way. A hydroxyjuglone was also obtained by Fieser and Dunn (4) by Thiele acetylation of juglone to give a tetraacetoxynaphthalene, followed by hydrolysis and oxidation. On repeating this, the product obtained was found to be identical with 3-hydroxyjuglone. The tetraacetoxynaphthalene is therefore the 1,3,4,5-isomer.

By reaction of 2,3-dichloro- and 2,3-dibromo-juglone with sodium hydroxide (5, 6), one halogen atom is replaced, and the chloro product was regarded by Wheeler, Dawson, and McEwen (5) as 3-chloro-2-hydroxyjuglone. 2,3-Dichlorojuglone reacts with aniline to give 2-anilino-3-chlorojuglone (1), acid hydrolysis of which should yield the chlorohydroxy compound of Wheeler *et al.* This was not the case, however, and a new chlorohydroxyjuglone was isolated. The two isomers were also obtained by chlorination of 2- and 3-hydroxyjuglone and could therefore be identified. It was thus confirmed that the product obtained by hydrolysis of the anilino derivative was 3-chloro-2-hydroxyjuglone,

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[1] Certain workers (3, 13), have regarded the compound obtained by the oxidation method as 2-hydroxyjuglone.

[2] Liebermann (9) in 1877, appears to have been the first to record the use of mixed melting point determinations, but Mylius (1885) seems to have overlooked this.

whilst the compound formed by reaction of 2,3-dichlorojuglone with sodium hydroxide was 2-chloro-3-hydroxyjuglone. The corresponding bromohydroxyjuglones were derived from 2,3-dibromojuglone, and were readily converted to chlorohydroxyjuglones by the action of alcoholic hydrochloric acid. According to Wheeler and Naiman (6) crystallization of 2-bromo-3-hydroxyjuglone from aqueous alcohol yields a red monohydrate. This has not been investigated but it may be mentioned that all the halogenohydroxyjuglones so far examined form yellow to orange solutions in alcohol, which become red on addition of water, and similarly, alcoholic solutions of their diacetates, which are pale yellow, redden when diluted with water. In all cases, addition of a trace of mineral acid restores the yellow color. 2- and 3-Hydroxyjuglones do not behave in this way.

Bromination of juglone with excess bromine affords 2,3,6-tribromojuglone (1). The behavior of this compound was studied by Wheeler *et al.* (7, 8), who found that reaction with sodium hydroxide, hydrochloric acid, aniline, and other amines, replaced only one bromine atom. They argued that one bromine atom must therefore have a different environment from the other two, and hence it must be the bromine atom in the benzenoid ring which is involved in the above reactions. However, as was found later by Wheeler and his co-workers, 2,3-dichloro- and 2,3-dibromo-juglone behave in the same way (5, 8), and it has now been shown that the labile bromine atoms of tribromojuglone are in the quinonoid ring. Thus, the product obtained by reaction of 2,3,6-tribromojuglone with sodium hydroxide was also formed by further bromination of 2-bromo-3-hydroxyjuglone, and its structure is consequently 2,6-dibromo-3-hydroxyjuglone (I). The constitutions of certain reduction products derived from this compound now call for correction: in particular the compound obtained by reduction with zinc dust in alkaline solution, regarded by Wheeler *et al.* as 1,4,5,8-tetrahydroxynaphthalene (8),[3] is the 1,3,4,5-isomer. The anilino derivative obtained by reaction of 2,3,6-tribromojuglone with aniline yielded on acid hydrolysis a dibromohydroxyjuglone different from that already described. This was also obtained by bromination of 3-bromo-2-hydroxyjuglone and its structure is thus 3,6-dibromo-2-hydroxyjuglone, the anilino derivative being 2-anilino-3,6-dibromojuglone (II).

Wheeler and Naiman (6) readily converted 2,3-dibromojuglone into 2,3-dichlorojuglone by warming with a large excess of alcoholic hydrochloric acid, but by a similar treatment of 2,3,6-tribromojuglone using an even larger excess of hydrochloric acid, Wheeler and Scott (7) obtained a product which, surprisingly, they considered to be a dibromomonochlorojuglone. This claim was supported by a complete elementary analysis of the compound, and also of the acetyl derivative, although it may be noted that in the latter case the halogen figures were derived from insufficient data (8). On repeating this work, a compound was obtained which was undoubtedly that described by Wheeler and Scott but analysis showed it to be a dichloromonobromojuglone.[4] This would be expected by

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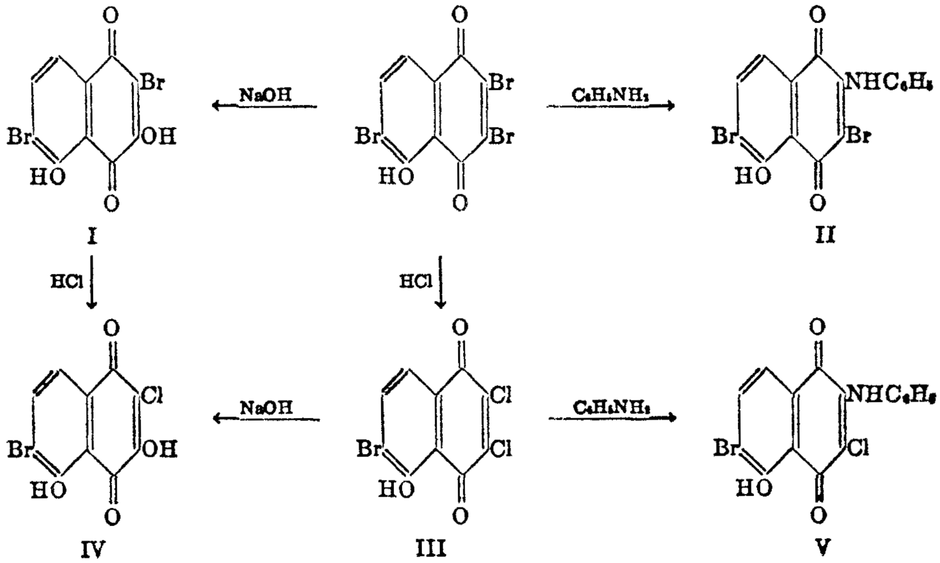
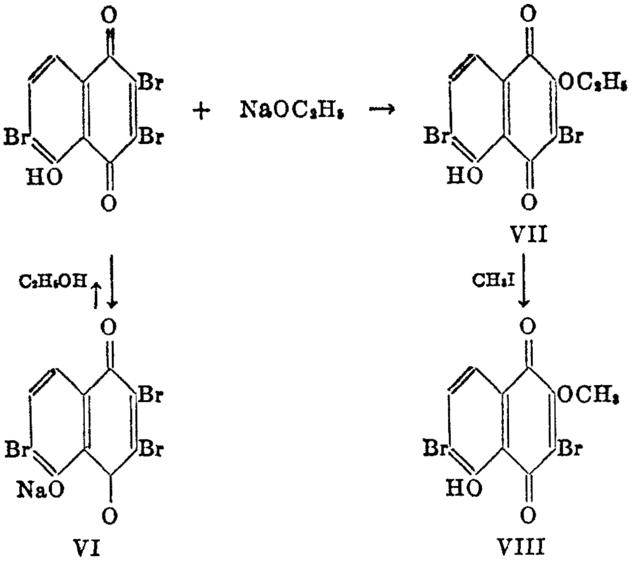
[3] This structure has already been shown to be incorrect by Dimroth and Roos (11).

[4] The acetate had m.p. 172° whereas Wheeler and Andrews record m.p. 159.5–160°. Several other discrepancies in melting point of this order have been observed. See experimental section of this paper and (10).

analogy with 2,3-dibromojuglone, and the dichloromonobromo structure was supported by the preparation and analysis of a number of derivatives. Replacement of one halogen atom invariably yielded monobromomonochloro derivatives (IV),





(V), and the structure 6-bromo-2,3-dichlorojuglone (III) was established by its reaction with sodium hydroxide, which yielded a bromochlorohydroxyjuglone (IV) identical with that obtained by treatment of 2,6-dibromo-3-hydroxyjuglone (I) with alcoholic hydrochloric acid. Attempts to prepare 6-bromo-2,3-dichlorojuglone by bromination of 2,3-dichlorojuglone under a variety of conditions were unsuccessful. This recalls the failure of Wheeler, Dawson, and McEwen (5) to chlorinate 2,3-dichlorojuglone, in marked contrast to the ease with which juglone takes up three atoms of bromine.

In this series, compounds possessing identical structures but different halogen atoms frequently have similar melting points, and mixtures of the two usually melt at intermediate temperatures; in such cases a mixed melting point determination is an unreliable criterion of identity. This applies particularly to halogenohydroxyjuglones and their diacetates. Examples are given in Table I.

The structures of two further compounds remain to be elucidated. Wheeler and Andrews (8) attempted to prepare tribromojuglone ethers by interaction of ethyl and methyl iodides with the sodium salt of tribromojuglone in alcoholic solution, but the reaction products contained only two atoms of bromine, the third being replaced by a hydroxyl group, and the compounds were regarded as 5-alkoxy-8-hydroxy-2,3-dibromo-1,4-naphthoquinones. The elimination of bromine, it was explained, was due to the action of the alcohol. Previously, Wheeler and Scott (7) had reported that tribromojuglone remained unchanged after boiling with alcohol for six hours, but Wheeler and Andrews claimed that an alcoholic solution of tribromojuglone gave a precipitate with silver nitrate after boiling for an unspecified time. The formation of alkoxyhydroxydibromonaphthoquinones has now been confirmed, but boiling alcohol has no effect on tribromojuglone, the latter being recovered unchanged after eighteen hours boiling. However the sodium salt of tribromojuglone reacts with ethyl and also with methyl alcohol to give the same ethoxy- and methoxy-hydroxydibromonaphthoquinones as Wheeler and Andrews obtained by reaction with alcoholic ethyl and

TABLE I

MIXED MELTING POINTS WHICH ARE UNRELIABLE CRITERIA OF IDENTITY

COMPOUND	M.P., °C.	MIXED M.P., °C.
2-Chloro-3-hydroxyjuglone	193	193
2-Bromo-3-hydroxyjuglone	194	
2-Chloro-3-hydroxyjuglone diacetate	147	146–147
2-Bromo-3-hydroxyjuglone diacetate	146	
3-Chloro-2-hydroxyjuglone	224	212–213
3-Bromo-2-hydroxyjuglone	217	
3-Chloro-2-hydroxyjuglone diacetate	157	158–159
3-Bromo-2-hydroxyjuglone diacetate	164	
6-Bromo-2-chloro-3-hydroxyjuglone	255	246–247
2,6-Dibromo-3-hydroxyjuglone	241	
6-Bromo-2-chloro-3-hydroxyjuglone diacetate	170	174–175
2,6-Dibromo-3-hydroxyjuglone diacetate	179	
2-Anilino-6-bromo-3-chlorojuglone	249	245–247
2-Anilino-3,6-dibromojuglone	244	
3-Chlorojuglone	166	169
3-Bromojuglone	172	
3-Chlorojuglone acetate	147	149
3-Bromojuglone acetate	151.5	

methyl iodides. In the preparation using alcoholic methyl iodide, the initial reaction product is the ethyl ether, which is slowly converted to the methyl ether on prolonged boiling. No reaction occurred when the sodium salt was refluxed with methyl iodide alone, or in dioxane solution, showing that the sodium salt does not react directly with methyl iodide. The conversion of the ethyl to the methyl ether, which was also achieved by refluxing a methyl alcoholic solution of the ethyl ether containing a trace of sodium, strongly suggested that the alkoxyl group was attached to the quinonoid ring. This was established conclusively by reaction with aniline, when both ethers gave 2-anilino-3,6-dibromojuglone, and by a facile hydrolysis with sodium hydroxide, which afforded 2-hydroxy-3,6-dibromojuglone. The ethers therefore have the structure 2-alkoxy-3,6-dibromojuglone, the ether group in the quinonoid ring having typical ester-like properties (12). As would be anticipated, the bromine atom at position 3 prevents esterification of 2-hydroxy-3,6-dibromojuglone by the Fischer-Speier method, but the methyl ether was easily obtained by methylation with diazomethane. The formation of the methyl ether by the Wheeler and Andrews method may be visualized as follows: the sodium salt (VI) reacts initially with ethyl alcohol to form tribromojuglone and sodium ethoxide, which further interact, the bromine atom at position 2 being replaced by an ethoxyl group (VII). Finally the ethyl ether reacts with methyl iodide to form the methyl ether (VIII). The trans-etherification (or trans-esterification) is possibly base-catalyzed, but the mechanism has not been studied. With regard to the formation of (VII), a similar reaction occurs when the sodium salt of tribromojuglone is boiled with water, a mixture of tribromojuglone and 2-hydroxy-3,6-dibromojuglone being obtained. Incomplete conversion to the hydroxy derivative is probably due to the low solubility of tribromojuglone in water. The presence of ethyl iodide in the preparation of 2-ethoxy-3,6-dibromojuglone by the Wheeler and Andrews method is superfluous.

EXPERIMENTAL

Microanalyses by Drs. G. Weiler and F. B. Strauss of Oxford. Melting points are uncorrected. Acetyl derivatives were prepared by the method given in Part I (1).

2-Hydroxyjuglone. (a) Hydrolysis of 2-dimethylaminojuglone according to Mylius (2); yield, 74%.

(b) Hydrolysis of 2-anilinojuglone(1). One gram of 2-anilinojuglone was dissolved in 15 cc. of concentrated sulfuric acid, and 15 cc. of water was added cautiously to the deep violet solution. The resulting dark red suspension was refluxed gently for five minutes until the color became dark brown. The mixture was then cooled, diluted with water, and filtered. The solid was extracted with 200 cc. of warm 2% aqueous sodium acetate, and the red extract acidified with dilute sulfuric acid. The yellow precipitate was collected and crystallized from dilute acetic acid; yield, 55%.

Both preparations yielded identical minute, light orange, needles, m.p. 220° (dec.), and formed identical diacetates which crystallized from methyl alcohol in elongated yellow plates, m.p. 152°.

3-Hydroxyjuglone. (a) Oxidation of α-hydrojuglone in alkaline solution with potassium ferricyanide as described by Mylius (2). The crude product was purified *via* the diacetate; yield, 9%.

(b) Hydrolysis of 3-anilinojuglone (1). A suspension of 0.5 g. of 3-anilinojuglone (finely divided) in 25 cc. of concentrated hydrochloric acid was refluxed for forty-five minutes, during which the reddish-violet color became a dark yellowish brown. After cooling, the suspension was diluted with water, and the solid collected and extracted with petrol (100–120°). The extract was concentrated to small bulk, from which orange plates separated on cooling; yield, 59%.

(c) Thiele acetylation of juglone, followed by hydrolysis and oxidation of 1,3,4,5-tetraacetoxynaphthalene by the method of Fieser and Dunn (4). Juglone acetate separated twice during the acetylation period (ten days at room temperature) and was redissolved by warming; over-all yield, 52%.

(d) To a warm solution of 0.25 g. of 3-chlorojuglone in 20 cc. of alcohol, 10 cc. of 10% aqueous sodium hydroxide was added. The initial violet color rapidly changed to blood-red. After one hour on the water-bath the solution was cooled, diluted with 25 cc. of water, and acidified with dilute sulfuric acid. The reddish orange crystals which precipitated were collected and recrystallized from dilute acetic acid; yield, 79%.

All preparations yielded identical small, light orange plates, m.p. 218–220° (dec. after blackening from 210°), from dilute acetic acid, and formed identical diacetates which crystallized from methyl alcohol in fine pale yellow needles, m.p. 137°. A mixture of 2- and 3-hydroxyjuglone had m.p. 190°.

3-Chloro-2-hydroxyjuglone. (a) To a solution of 0.4 g. of 2-anilino-3-chlorojuglone in 6 cc. of concentrated sulfuric acid, 4 cc. of water was added cautiously. The suspension so obtained was refluxed gently for five minutes until the red color had disappeared. The resulting brown crystalline suspension was cooled, diluted with water, and the product collected and recystallized from glacial acetic acid (charcoal); yield, 90%.

(b) A solution of 0.2 g. of 2-hydroxyjuglone in 4 cc. of glacial acetic acid containing 0.1 g. of chlorine was warmed on the water-bath for three hours, cooled, and poured into 50 cc. of cold water containing a little sulfuric acid. The yellow precipitate obtained was collected and crystallized from glacial acetic acid; yield, 67%.

(c) A solution of 0.2 g. of 3-bromo-2-hydroxyjuglone in 6 cc. of alcohol was warmed on the water-bath for one hour with 1.0 cc. of concentrated hydrochloric acid. Crystals of the chloro compound separated on cooling; yield, 90%.

All preparations yielded identical small glistening orange plates, m.p. 224°.

Anal. Calc'd for $C_{10}H_5ClO_4$: C, 53.45; H, 2.3; Cl, 15.8.
Found: C, 53.3; H, 2.3; Cl, 15.6.

All products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 157°.

3-Bromo-2-hydroxyjuglone. (a) Hydrolysis of 2-anilino-3-bromojuglone was carried out as described for the corresponding chloro compound.

(b) To a solution of 0.26 g. of 2-hydroxyjuglone in 10 cc. of glacial acetic acid, 0.065 cc. of bromine was added, and the solution warmed on the water-bath for two hours. Crystals separated on cooling, and were recrystallized from glacial acetic acid; yield, 71%.

Both preparations yielded identical orange-red needles, m.p. 217°.

Anal. Calc'd for $C_{10}H_5BrO_4$: C, 44.6; H, 1.85; Br, 29.75.
Found: C, 44.45; H, 2.05; Br, 29.6.

Both products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 164°.

2-Chloro-3-hydroxyjuglone. (a) This was obtained by reaction of 2,3-dichlorojuglone with sodium hydroxide as recorded by Wheeler, Dawson, and McEwen (5) who regarded it as 2-hydroxy-3-chlorojuglone.

(b) 3-Hydroxyjuglone was chlorinated in the same manner as 2-hydroxyjuglone.

(c) 2-Bromo-3-hydroxyjuglone was treated with alcoholic hydrochloric acid as described above for the isomeric compound. The product was isolated by dilution with water, and crystallized from carbon tetrachloride.

All preparations yielded clusters of identical orange-brown needles, m.p. 193° from carbon tetrachloride, (Wheeler *et al.* report m.p. 191°) and formed identical diacetates, m.p. 147°, fine yellow needles from alcohol.

2-Bromo-3-hydroxyjuglone. (a) This was obtained by reaction of 2,3-dibromojuglone with sodium hydroxide according to Wheeler and Naiman (6).

(b) 3-Hydroxyjuglone was brominated in the same manner as 2-hydroxyjuglone. The product was isolated by pouring the solution into very dilute sulfuric acid, and crystallized from carbon tetrachloride.

Both preparations yielded identical fine, light orange, needles, m.p. 194° (Wheeler and Naiman record m.p. 192°).

Anal. Calc'd for $C_{10}H_5BrO_4$: C, 44.6; H, 1.85; Br, 29.75.
Found: C, 44.9; H, 1.9; Br, 29.55.

Both products formed identical diacetates which crystallized from alcohol in yellow needles, m.p. 146°.

3,6-Dibromo-2-hydroxyjuglone. (a) 2-Anilino-3,6-dibromojuglone was hydrolyzed with sulfuric acid in the usual way, and the crude product extracted with 2% aqueous sodium acetate; yield, 61%.

(b) A solution of 0.22 g. of 3-bromo-2-hydroxyjuglone in 2.2 cc. of glacial acetic acid was refluxed with 0.2 cc. of bromine for three hours. The crystals which separated on cooling were recrystallized from the same solvent; yield, 58%.

(c) To a hot solution of 0.25 g. of 2-methoxy-(or ethoxy-)3,6-dibromojuglone in 50 cc. of alcohol, 20 cc. of 10% aqueous sodium hydroxide was added. After warming for five minutes on the water-bath, the red solution was cooled, diluted with 70 cc. of water, and acidified with dilute sulfuric acid. The yellow precipitate was crystallized from glacial acetic acid; yield, 60%.

All preparations yielded identical orange needles, m.p. 206°.

Anal. Calc'd for $C_{10}H_4Br_2O_4$: C, 34.5; H, 1.15; Br, 46.0.
Found: C, 34.3; H, 1.5; Br, 45.7.

All products formed identical diacetates, m.p. 176°, yellow needles from alcohol.

2,6-Dibromo-3-hydroxyjuglone (I). (a) This was obtained by reaction of 2,3,6-tribromojuglone with sodium hydroxide by the method of Wheeler and Scott (7).

(b) 2-Bromo-3-hydroxyjuglone was brominated as described for the isomer.

Both preparations yielded golden brown prismatic needles, m.p. 241°, from glacial acetic acid. (Wheeler and Scott, who regarded this compound as 2,3-dibromo-8-hydroxyjuglone, recorded m.p. 236°). Wheeler and Andrews (8) prepared a monoacetate (presumably the 2-acetoxy compound) by boiling the material with a large excess of acetic anhydride for seventeen hours. A diacetate was readily obtained by boiling for one minute with twice its weight of acetic anhydride containing a trace of concentrated sulfuric acid. It crystallized from alcohol in clusters of yellow elongated plates, m.p. 179°.

Anal. Calc'd for $C_{14}H_8Br_2O_6$: C, 38.9; H, 1.85; Br, 37.0.
Found: C, 38.95; H, 1.95; Br, 37.2.

6-Bromo-2,3-dichlorojuglone (III). This was obtained by the method of Wheeler and Scott (7) who considered it to be 8-chloro-2,3-dibromojuglone. It crystallized from alcohol in red brown plates, m.p. 152°.

Anal. Calc'd for $C_{10}H_3BrCl_2O_3$: C, 37.3; H, 0.9.
Found: C, 37.5; H, 0.9.

The diacetate crystallized from alcohol in pale yellow needles, m.p. 172°. [Wheeler and Andrews (8) report m.p. 159.5–160°.]

Anal. Calc'd for $C_{12}H_5BrCl_2O_4$: C, 39.6; H, 1.4.
Found: C, 39.3; H, 1.55.

6-Bromo-2-chloro-3-hydroxyjuglone (IV). (a) An alcoholic solution of (III) was treated with excess sodium hydroxide by the usual method, the initial violet solution rapidly becoming blood-red. The product was crystallized from glacial acetic acid.

(b) 2,6-Dibromo-3-hydroxyjuglone was warmed with alcoholic hydrochloric acid in the usual manner. The bromochloro compound separated on cooling.

Both preparations yielded clusters of identical red brown prismatic needles, m.p. 255°, from glacial acetic acid.

Anal. Calc'd for $C_{10}H_4BrClO_4$: C, 39.55; H, 1.3.
Found: C, 39.7; H, 1.55.

Both products formed identical diacetates which separated from alcohol in minute yellow needles, m.p. 170°.

Anal. Calc'd for $C_{14}H_8BrClO_6$: C, 43.35; H, 2.1.
Found: C, 43.3; H, 2.25.

2-Anilino-3,6-dibromojuglone (II). (a) By reaction of 2,3,6-tribromojuglone with aniline according to Wheeler and Andrews (8) who considered it to be 8-anilino-2,3-dibromojuglone.

(b) A solution of 0.2 g. of 2-methoxy-3,6-dibromojuglone in 40 cc. of alcohol was refluxed with 0.1 cc. of aniline for twenty minutes. Crystals of the anilino derivative separated almost as soon as boiling commenced; yield, 94%.

Both products crystallized from methyl ethyl ketone in identical dark violet leaflets, m.p. 244°. (Wheeler and Andrews report m.p. 234.5–235.5°). The same product was obtained from 2-ethoxy-3,6-dibromojuglone.

Anal. Calc'd for $C_{16}H_9Br_2NO_3$: C, 45.4; H, 2.1; N, 3.3.
Found: C, 45.6; H, 2.4; N, 3.1.

2-Anilino-6-bromo-3-chlorojuglone (V). This was obtained from 6-bromo-2,3-dichlorojuglone as for (II) (a). It crystallized from methyl ethyl ketone in dark violet needles, m.p. 249°; yield, 68%.

Anal. Calc'd for $C_{16}H_9BrClNO_3$: C, 50.7; H, 2.4; N, 3.7.
Found: C, 50.6; H, 2.7; N, 3.85.

2-p-Toluidino-3,6-dibromojuglone. This was prepared by the method of Wheeler and Andrews (8). Crystallization from methyl ethyl ketone yielded dark violet rectangular plates, which appear black in the mass, m.p. 224°. (Wheeler and Andrews record m.p. 216–217°).

Anal. Calc'd for $C_{17}H_{11}Br_2NO_3$: C, 46.7; H, 2.5; N, 3.2.
Found: C, 46.8; H, 2.7; N, 3.55.

2-p-Toluidino-6-bromo-3-chlorojuglone. This was prepared by the same method as the previous compound. It crystallized from methyl ethyl ketone in dark violet elongated plates, which appear black in the mass, m.p. 251°; yield, 62%.

Anal. Calc'd for $C_{17}H_{11}BrClNO_3$: C, 52.0; H, 2.8; N, 3.6.
Found: C, 52.1; H, 3.0; N, 3.75.

2-Methoxy-3,6-dibromojuglone (VIII). (a) This was prepared by refluxing the sodium salt of 2,3,6-tribromojuglone with alcoholic methyl iodide as described by Wheeler and Andrews (8). The ether separated on cooling. The violet color disappeared much more rapidly than was reported by these workers, possibly because they failed to wash the sodium salt completely free from the sodium carbonate used in its preparation. If the experiment is stopped after two hours, and the solution concentrated to small bulk, the 2-ethoxy derivative separates on cooling; yield, 69%.

(b) A solution of 0.8 g. of the sodium salt of tribromojuglone in 100 cc. of methyl alcohol was boiled under reflux. The violet color rapidly disappeared and crystals began to separate from the solution in ten minutes. After boiling for thirty minutes the red suspension was cooled, and the product collected; yield, 66%.

(c) An ice-cold solution of 0.15 g. of 2-hydroxy-3,6-dibromojuglone in 75 cc. of ether was treated with an ether solution of diazomethane (from 0.5 g. of nitrosomethylurea). Orange crystals separated almost immediately, and after standing in the ice-bath for an hour, these were collected; yield, 66%.

(d) A solution of 0.25 g. of 2-ethoxy-3,6-dibromojuglone in 50 cc. of methyl alcohol containing a trace of sodium, was refluxed for nine hours. The methyl ether separated on cooling; yield, 52%.

All products were recrystallized from alcohol forming identical glistening orange needles, m.p. 211–212°. (Wheeler and Andrews record 209–210°.)

2-Ethoxy-3,6-dibromojuglone (VII). (a) This was prepared as for (VIII) (a) using alcoholic ethyl iodide, according to Wheeler and Andrews (8).

(b) The preparation of (VIII) (b) above was repeated using ethyl alcohol. Reaction was much slower, the solution only becoming red (by reflected light) after three hours. The solution was refluxed for five hours, and concentrated to small bulk. The ethyl ether separated on cooling; yield, 78%.

Both preparations afforded identical fine glistening orange needles, m.p. 139–141°, from alcohol. (Wheeler and Andrews report m.p. 134–136°.)

Further reactions of the sodium salt of 2,3,6-tribromojuglone. (a) A solution of 0.25 g. of the sodium salt in 15 cc. of water was refluxed for three hours. The blue-violet solution became red in one hour, and a brown precipitate appeared. The latter was collected, after cooling; 0.08 g., m.p. 170°. Recrystallization from glacial acetic acid afforded orange-red needles, m.p. 172°, identical with 2,3,6-tribromojuglone. The filtrate was acidified, and the orange precipitate collected; 0.1 g., m.p. 180–190°. After two crystallizations from glacial acetic acid the product formed orange needles, m.p. 206°, identical with 2-hydroxy-3,6-dibromojuglone. Repeating this experiment using 150 cc. of water gave approximately the same result.

(b) A suspension of 0.4 g. of the sodium salt in 6 cc. of dry methyl iodide was boiled under reflux for twelve hours. No visible change occurred, and all the sodium salt was recovered by evaporation of the methyl iodide.

(c) A solution of 0.2 g. of the sodium salt in 40 cc. of dry dioxane was refluxed with 0.2 cc. of methyl iodide for eight hours. There was no change in the blue-violet color and all the sodium salt was recovered on removal of the solvent.

SUMMARY

The constitution of a number of juglone derivatives, hitherto unknown or uncertain, has been determined. The structure of all known juglone compounds is now established.

ABERDEEN, SCOTLAND

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