275. *Naturally Occurring Quinones. A New Synthesis of Plumbagin and a Note on the Structure of β-Hydroplumbagin.*

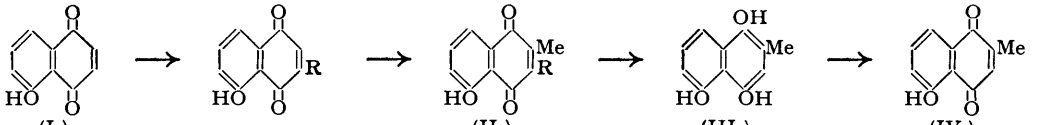
By R. H. Thomson.

Plumbagin (IV) has been synthesised from 3-carboxymethylthio-2-methyljuglone (II; R = $S{\cdot}CH_2{\cdot}CO_2H$) by hydrogenolysis with Raney nickel followed by oxidation. β-Hydroplumbagin is shown to be 2 : 3-dihydro-5-hydroxy-2-methyl-1 : 4-naphthaquinone (VI).

To complete earlier work (*J.*, 1950, 1737) on the structure of β-hydrojuglone and other known compounds of the series, plumbagin has now been synthesised and converted into β-hydroplumbagin.

Plumbagin (IV) occurs in various *Plumbago* and *Drosera* species but is not readily available from natural sources in this country. It was first obtained synthetically by Saenz de Buruaga and Verdú (*Anal. Fís. Quím.*, 1934, **32**, 830) by oxidation of 2-methyl-1 : 4-naphthaquinone with Caro's acid, but the product was mixed with much unchanged starting material and an unidentified compound. The structure (IV) was established by Fieser and Dunn (*J. Amer. Chem. Soc.*, 1936, **58**, 572), who converted *m*-toluoyl chloride into the desired 6-methyl-1-tetralone, from which plumbagin was ultimately obtained in very low overall yield. Shortly afterwards a more convenient synthesis, from 2-methyl-1 : 5-dinitronaphthalene, was achieved by Dieterle and Kruta (*Arch. Pharm.*, 1936, **274**, 457), although the final yield was not recorded.

The present synthesis from juglone (I) is outlined below; unsuccessful attempts to prepare plumbagin by direct alkylation of juglone have already been reported (*J.*, 1949, 1277).



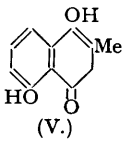
(I.) (II.) (III.) (IV.)

Initially, efforts were made to debrominate 3-bromo-2-methyljuglone (II; R = Br) by reduction with hydrogen and a palladium–barium sulphate catalyst in glacial acetic acid in the presence of sodium acetate, followed by immediate oxidation of the α-hydroplumbagin (III) so

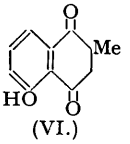
obtained. This was not successful, although trial experiments with 3-bromojuglone yielded small amounts of bromine-free quinone. The acetate of (II; R = Br) and the corresponding triacetate obtained by reductive acetylation were also tried, but only traces of the appropriate plumbagin derivatives were isolated.

Attention was then turned to thio-ether derivatives. Addition of thiols to juglone yields 3-substituted derivatives, but the corresponding plumbagin derivatives were prepared preferably from 3-chloro-2-methyljuglone. Model experiments showed that hydrogenolysis of 3-alkyl- and -aryl-thiojuglones with Raney nickel and subsequent oxidation to juglone was feasible, although yields were poor. However no plumbagin was obtained from 2-methyl-3-*p*-tolylthiojuglone (II; R = *p*-Me·C_6H_4·S) by this method, and 1 : 4 : 5-triacetoxy-2-methyl-3-*p*-tolylthionaphthalene yielded only trifling amounts of α-hydroplumbagin triacetate. The difficulty appeared to arise in the oxidation stage, and to avoid this the solution of α-hydroplumbagin obtained by hydrogenolysis was boiled with acid stannous chloride solution to convert the α- into the more stable β-isomer (cf. α- and β-hydrojuglones, *J.*, 1950, 1737). With 3-ethylthio-2-methyljuglone (II; R = EtS) this procedure yielded at first a new yellow compound, m. p. 164°. Similarly, an attempt to obtain β-hydrojuglone from 3-ethylthiojuglone afforded another new yellow substance, m. p. 181°. These compounds (which are at present under investigation) contain more hydrogen than would the expected hydroquinones, and by reduction of the reaction time and the amount of Raney nickel, their formation was largely avoided (the hydroquinones are not reduced by boiling acid stannous chloride solution). The isolation of β-hydroplumbagin at this stage was not pursued. Plumbagin was finally obtained by hydrogenolysis of 3-carboxymethylthio-2-methyljuglone (II; R = S·CH_2·CO_2H), the resulting α-hydroplumbagin being transferred to acid stannous chloride solution, and, after removal of the yellow compound, oxidised with hydrogen peroxide.

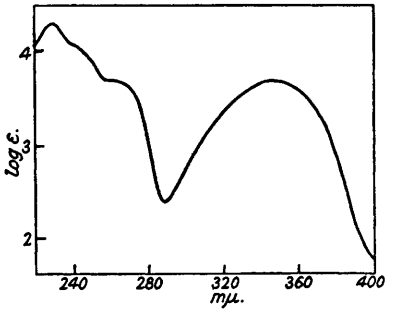
β-Hydroplumbagin was prepared by fusion of the α-isomer. As the compound formed only a monophenylsemicarbazone, Olay (*Rev. Acad. cienc. Madrid*, 1935, **32**, 384) tentatively proposed the monoketo-structure (V). Although all attempts to prepare dicarbonyl derivatives have



(V.)



(VI.)



failed, no enolic group at $C_{(1)}$ could be detected. The compound dissolves slowly in cold dilute alkali regenerating the α-isomer, but Zerewitinoff estimation indicated only one active hydrogen atom. Spectroscopic examination of β-hydroplumbagin showed clearly that it has the structure (VI). The infra-red spectra of both a crystalline sample and a dilute carbon tetrachloride solution show no free hydroxyl band in the 3600-cm.$^{-1}$ region whereas two carbonyl bands are present at 1695 cm.$^{-1}$ and 1645 cm.$^{-1}$. Furthermore the ultra-violet absorption spectrum (figure) is almost identical with that of β-hydrojuglone.

Experimental.

3-Bromo-2-methyljuglone.—This was prepared from 3-bromojuglone (4·38 g.) and acetyl peroxide (2·3 g.) in glacial acetic acid (36 c.c.) as described for the corresponding chloro-compound (*J.*, 1949, 1278). 3-Bromo-2-methyljuglone crystallised from alcohol in fine orange needles, m. p. 118° (yield 18·5%) (Found: C, 49·35; H, 2·8; Br, 29·6. $C_{11}H_7O_3Br$ requires C, 49·45; H, 2·6; Br, 29·95%). The *acetate* separated from aqueous alcohol in yellow rods, m. p. 152° (Found: C, 50·1; H, 2·8; Br, 25·65. $C_{13}H_9O_4Br$ requires C, 50·5; H, 2·9; Br, 25·85%). Reductive acetylation of the quinone with zinc dust, acetic anhydride, and 2 drops of triethylamine yielded 1 : 4 : 5-*triacetoxy*-3-*bromo*-2-*methylnaphthalene* which crystallised from alcohol in short needles, m. p. 191° (Found: C, 51·65; H, 3·55; Br, 20·1. $C_{17}H_{15}O_6Br$ requires C, 51·65; H, 3·8; Br, 20·2%).

3-Phenylthiojuglone.—(*a*) Juglone (0·87 g.) was dissolved in warm alcohol (40 c.c.), the solution cooled quickly to room temperature, and benzenethiol (0·25 c.c.) added to the suspension. The juglone rapidly dissolved forming a brown solution, followed almost immediately by a yellow-brown crystalline precipitate. The mixture was heated just to the boiling point and allowed to cool. Almost pure

3-phenylthiojuglone separated and was recrystallised from alcohol; it formed orange-yellow needles, m. p. 153° (yield, 80%).

(*b*) A solution of benzenethiol (0·26 c.c.) in alcohol (5 c.c.) containing pyridine (0·2 c.c.) was added to a suspension of 3-chlorojuglone (0·5 g.) in alcohol (30 c.c.). The quinone rapidly dissolved with evolution of heat followed by deposition of 3-phenylthiojuglone. The suspension was heated to the boiling point and the dark-red solution then allowed to cool. The *juglone* which separated was recrystallised from alcohol forming orange-yellow needles, m. p. 153° (yield, 60%) (Found: C, 68·0; H, 3·4. $C_{16}H_{10}O_3S$ requires C, 68·1; H, 3·6%). The *acetate* separated from alcohol in long yellow needles or plates, m. p. 156° (Found: C, 67·0; H, 3·8. $C_{18}H_{12}O_4S$ requires C, 66·7; H, 3·7%). Reductive acetylation of the acetate afforded 1 : 4 : 5-*triacetoxy*-3-*phenylthionaphthalene* which crystallised from aqueous alcohol in small needles, m. p. 131° (Found: C, 64·3; H, 4·3. $C_{22}H_{18}O_6S$ requires C, 64·4; H, 4·4%).

2-*Methyl*-3-p-*tolylthiojuglone*.—A solution of toluene-*p*-thiol (0·8 g.) in alcohol (12 c.c.) containing pyridine (0·53 c.c.) was added to a suspension of 3-chloro-2-methyljuglone (1·45 g.) in alcohol (60 c.c.). The mixture was refluxed for 1 hour and set aside overnight. The crystalline product was collected and recrystallised from alcohol (charcoal) forming clusters of reddish-brown needles, m. p. 126°, of the *juglone* (yield 76%) (Found: C, 70·0; H, 4·8. $C_{18}H_{14}O_3S$ requires C, 69·7; H, 4·5%). The *acetate* formed red needles (from alcohol), m. p. 148° (Found: C, 67·9; H, 4·5. $C_{20}H_{16}O_4S$ requires C, 68·2; H, 4·5%). Reductive acetylation of the quinone gave 1 : 4 : 5-*triacetoxy*-2-*methyl*-3-p-*tolylthionaphthalene* forming small needles (from aqueous acetic acid), m. p. 184° (Found: C, 65·9; H, 5·2. $C_{24}H_{22}O_6S$ requires C, 65·75; H, 5·0%).

3-*Carboxymethylthio*-2-*methyljuglone*.—A solution of 3-chloro-2-methyljuglone (1·93 g.), thioglycollic acid (0·6 c.c.), and pyridine (2·2 c.c.) in alcohol (110 c.c.) was boiled for 2 minutes and then set aside overnight. After acidification with 4N-sulphuric acid, the solution was cooled in an ice-bath, stirred, and diluted with water (400 c.c.). Stirring was continued until the oily precipitate had crystallised. The product was collected, washed, dried, and recrystallised from benzene–light petroleum (charcoal). The *acid* separated in minute bright-red needles, m. p. 168° (yield, 58%) (Found: C, 56·1; H, 3·9. $C_{13}H_{10}O_5S$ requires C, 56·1; H, 3·9%). The *ethyl* ester was obtained by boiling a solution of the acid (0·6 g.) in alcohol (25 c.c.) with concentrated hydrochloric acid (8 c.c.) for 2 minutes. It crystallised from aqueous alcohol in orange-yellow needles, m. p. 94° (Found: C, 58·8; H, 4·7. $C_{15}H_{14}O_5S$ requires C, 58·8; H, 4·6%).

3-*Ethylthiojuglone*.—A solution of 3-chlorojuglone (0·4 g.) in alcohol (20 c.c.) containing ethanethiol (0·2 c.c.) and pyridine (0·5 c.c.) was boiled for 1 minute and set aside to crystallise. 3-*Ethylthiojuglone* separated from alcohol in orange needles, m. p. 152° (yield, 36%) (Found: C, 61·55; H, 4·3. $C_{12}H_{10}O_3S$ requires C, 61·55; H, 4·3%). The *acetate* formed fine yellow needles (from alcohol), m. p. 157° (Found: C, 60·7; H, 4·4. $C_{14}H_{12}O_4S$ requires C, 60·85; H, 4·4%). 3-Ethylthiojuglone could not be obtained by addition of ethanethiol to juglone.

3-*Ethylthio*-2-*methyljuglone*.—This was prepared in the usual way from 3-chloro-2-methyljuglone (0·42 g.), ethanethiol (0·2 c.c.), and pyridine (0·5 c.c.) in alcohol (20 c.c.), and isolated by acidification of the solution and dilution with water. 3-*Ethylthio*-2-*methyljuglone* crystallised from aqueous alcohol in fine orange needles, m. p. 85° (yield, 38%) (Found: C, 63·05; H, 5·2. $C_{13}H_{12}O_3S$ requires C, 62·85; H, 4·9%). The *acetate* formed fine yellow needles (from aqueous alcohol), m. p. 91° (Found: C, 62·1; H, 5·15. $C_{15}H_{14}O_4S$ requires C, 62·05; H, 4·85%).

2-*Methyljuglone* (*Plumbagin*).—3-Carboxymethylthio-2-methyljuglone (1·4 g.) in alcohol (70 c.c.) was refluxed with Raney nickel (7 g.) for 10 minutes. After addition of a little "Celite" and a few drops of glacial acetic acid, the hot suspension was filtered rapidly into a solution of stannous chloride (7 g.) in water (252 c.c.) containing concentrated hydrochloric acid (28 c.c.). The nickel residue was extracted four times with boiling alcohol (70 c.c. in all). The alcohol was removed from the combined filtrates by distillation, and the residual acid solution heated with a little charcoal and filtered. After extraction of the pale yellow filtrate with chloroform (4 × 5 c.c.) the aqueous solution of α-hydroplumbagin was cooled in ice, and hydrogen peroxide (16 c.c.; 100 vols.) added. After 1 hour the fine orange crystalline precipitate of plumbagin was collected and dried *in vacuo* (0·49 g.; m. p. 71—73°). Ether-extraction of the filtrate yielded a further small quantity of the quinone, which crystallised from aqueous alcohol in orange-yellow needles, m. p. 77°; total yield 48% (Fieser and Dunn, *loc. cit.*, give m. p. 78—79°; Dieterle and Kruta, *loc. cit.*, give m. p. 77°) (Found: C, 70·05; H, 4·45. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%). The acetate separated from aqueous alcohol in small yellow needles, m. p. 117—118° (Found: C, 68·0; H, 4·4. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·4%). The chloroform extract was dried ($CaCl_2$) and the solvent removed under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 100—120°) afforded fine pale yellow needles, m. p. 164° (*ca.* 5 mg.) (Found: C, 68·9, 68·8; H, 6·6, 6·5%).

1 : 2 : 3 : 4-*Tetrahydro*-5-*hydroxy*-1 : 4-*diketo*-2-*methylnaphthalene* (*β-Hydroplumbagin*).—This was prepared by Madinaveitia and Olay's method (*Anal. Fis. Quim.*, 1933, **31**, 134) of fusing the α-isomer in a vacuum. It formed small, pale-yellow needles, m. p. 87° (the Spanish workers report 86°) (yield, 41%) [Found: C, 69·3; H, 5·1; Active H, 0·40.* Calc. for $C_{11}H_{10}O_3$: C, 69·45; H, 5·3; Active H (one atom), 0·53%].

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* Analysis by Drs. Weiler and Strauss.