sponding anhydride. In preparing the anhydride, 0.50 g. of the hydrated acid was heated at 125° for fifteen minutes. The residue crystallized at once on cooling in ice and was purified by subliming at 100° and 1 mm. onto an ice-cooled receiver seeded with a crystal of the solid. The anhydride collected as a hard white crystalline mass; yield 0.40 g., m. p. 37–37.5°.

Anal. Calcd. for $C_6H_5O_4Cl$: C, 40.79; H, 2.85; OC_2H_5, 25.52. Found: C, 40.70; H, 3.08; OC_2H_5, 25.23.

Hydrolysis of III.—In one preparation of III as described above, only 300 cc. of alcohol was distilled from the reaction mixture, and in the ether extract there was consequently a considerable quantity of alcohol and water. The alcohol and water were removed as a fore-run in vacuum, but the high boiling ester obtained in this preparation (40 g.) was not III but was ethyl oxalochloroacetate, produced from III by hydrolysis of the acetal linkage. This strongly acidic enolic ester was completely soluble in sodium bicarbonate solution, from which it was reprecipitated by acids, and had b. p. 127–128° (9 mm.).

Anal. Calcd. for $C_8H_{11}O_5Cl$: OC_2H_5, 40.47. Found: OC_2H_5, 40.62.

The ester was identified completely by comparison with an authentic specimen prepared as by Wislicenus,[5] except that 200 cc. of ether was used as a solvent instead of 1 mole; yield 72%, b. p. 127–128° (9 mm.).[6] The known and unknown esters yielded identical condensation products with *m*-cresol, ethyl 3-chloro-7-methylcoumarin 4-carboxylate,[7] m. p. and mixed m. p. 150–151°. The samples also gave identical copper salts with aqueous copper acetate,[5] m. p. and mixed m. p. 178–179°. III could also be hydrolyzed to ethyl oxalochloroacetate in a more orthodox manner; 14.83 g. (0.05 mole) was dissolved in 50 cc. of alcohol and 1 cc. of concd. hydrochloric acid and 42 cc. of water were added. After standing for twelve hours 30 cc. more of water was added and the solution refluxed for ten minutes, cooled, added to 100 cc. of ice water and the ester extracted five times with ether. The ether was distilled and the residue dissolved in sodium bicarbonate solution. The solution was extracted with ether to remove any neutral material, then acidified with dilute sulfuric acid and again extracted five times with ether. After drying over sodium sulfate the product was distilled; yield of ethyl oxalochloroacetate 6.0 g., b. p. 127–128° (9 mm.). This sample gave a copper salt and condensation product with *m*-cresol identical with those described above.

Source of III.—In order to determine if ethyl chloroethoxyacetate, $C_2H_5OCHClCOOC_2H_5$, might be the precursor of III, 33.3 g. (0.2 mole) of this ester[8] was added to a solution of 2.3 g. of sodium in 60 cc. of absolute alcohol. The reaction mixture was treated in the manner described for the preparation of III. The only product obtained was 29 g. of ethyl diethoxyacetate, b. p. 85–87° (17 mm.). In a similar manner, 31.4 g. (0.2 mole) of ethyl dichloroacetate was added to a solution of 4.6 g. of sodium in 125 cc. of absolute alcohol, to which 35.2 g. (0.2 mole) of ethyl diethoxyacetate had been added. Only 6 g. of III was obtained on distillation of the product, the remainder being ethyl diethoxyacetate plus some recovered ethyl dichloroacetate. Since the yield of III from ethyl dichloroacetate is not increased by the presence of an excess of ethyl diethoxyacetate, it appears improbable that interaction of these two esters is responsible for the formation of III.

Summary

The reaction of ethyl dichloroacetate with alcoholic sodium ethoxide gives a small yield of ethyl diethoxyacetate plus larger quantities of ethyl oxalochloroacetate diethyl acetal. The latter compound loses alcohol readily on heating, giving ethyl α-chloro-β-ethoxymaleate, from which the corresponding substituted maleic acid and anhydride have been prepared.

(5) Wislicenus, *Ber.*, **43**, 3529 (1910).
(6) The properties of this ester are being further investigated.
(7) Dey, *J. Chem. Soc.*, **107**, 1649 (1915).
(8) Mylo, *Ber.*, **44**, 3213 (1911).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of Plumbagin

BY L. F. FIESER AND J. T. DUNN

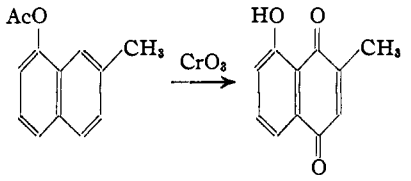
Investigations of the active principle responsible for the various medicinal qualities attributed to roots of the plants *Plumbago europaea*, *P. zeylonica*, and *P. rosea* date from Dulong's[1] isolation of the substance plumbagin in a fairly pure condition in 1828. Except for occasional references to the preparation of the substance by steam distillation[2] or solvent extraction[3] of the plumbago root, or the Indian drug "Chita," the problem received little attention for a full century. Since 1928 the structure of plumbagin has been in part elucidated by the work of Indian and Spanish investigators, but the reports are in some cases contradictory and the evidence is still incomplete.

Roy and Dutt[4] recognized the quinone-like character of the yellow pigment, established the presence of an acidic hydroxyl group, and ob-

(1) Dulong, *J. pharm. chim.*, **14**, 441 (1828).
(2) Flückiger, *N. Handwörterb. Chem.*, **5**, 723 (1890).
(3) Wefers Bettink, *Rec. trav. chim.*, **8**, 319 (1889).
(4) Roy and Dutt, *J. Indian Chem. Soc.*, **5**, 419 (1928).

tained naphthalene and β-methylnaphthalene on distillation of the substance over zinc dust. Their proposed empirical formula later was shown to be incorrect, however, and their statements that plumbagin forms a dioxime and that it yields cinnamic acid as one product of oxidation apparently are in error. The correct formula, $C_{11}H_8O_3$, was established by A. Madinaveitia and Gallego,[5] who noted a similarity in the solubility and color of the complex copper and nickel salts to those of juglone and suggested that plumbagin is a methyl derivative of juglone (5-hydroxy-1,4-naphthoquinone). Their statement that a further oxidation product is a methylhydroxyphthalic acid is not consistent with later evidence.

For comparison with plumbagin, de Buruaga[6] prepared a compound believed to have the structure of 2-methyl-8-hydroxy-1,4-naphthoquinone (II). This was obtained by the oxidation of the



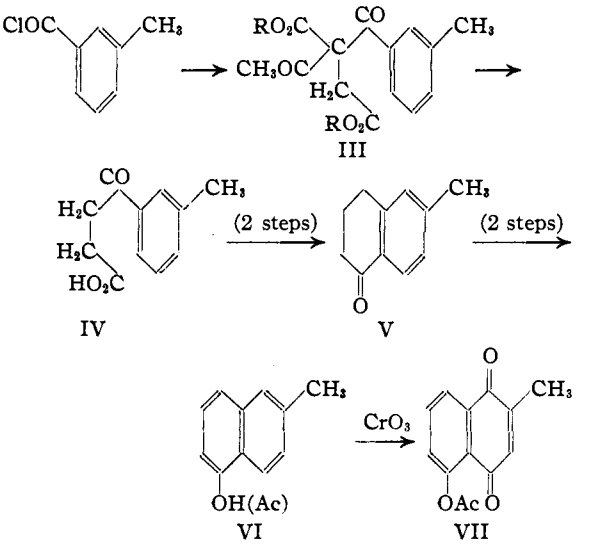
I II

acetyl derivative of a methylnaphthol prepared from a product of the sulfonation of β-methylnaphthalene with chlorosulfonic acid.[7] The reaction product proved to be an isomer of plumbagin, but since no evidence was presented as to the structure of the starting material, de Buruaga's conclusion that plumbagin is not the 8-hydroxy derivative of 2-methyl-1,4-naphthoquinone was hardly justified. Indeed this structure (II) was later suggested for the pigment by J. Madinaveitia[8] because of the similarity of the absorption spectrum to that of juglone and because of the formation of only a monoxime.

The synthetic preparation of a substance which proved to be identical with plumbagin was accomplished by de Buruaga and Verdú,[9] who obtained a hydroxy-2-methyl-1,4-naphthoquinone by the oxidation of 2-methyl-1,4-naphthoquinone with Caro's acid. While this observation does not fix the position of the hydroxyl group, it limits the number of possible structures. The ability of plumbagin to form complexes with metal salts (and with boro-acetic anhydride) indicates that the hydroxyl group occupies a position close to a carbonyl group, and since the substance is not identical with phthiocol[10] it must be either the 5- or the 8-derivative of 2-methyl-1,4-naphthoquinone.

In connection with other work in progress on hydroxynaphthoquinones, we attempted to synthesize both of the above quinones by methods which would leave no doubt as to their structures. 7-Methyl-1-naphthol was prepared from β-*p*-toluylpropionic acid by cyclization and dehydrogenation through the bromo compound, according to Krollpfeiffer and Schäffer.[11] On oxidizing the acetyl derivative (I) and steam distilling the product, we obtained both 2-methyl-8-hydroxy-1,4-naphthoquinone (II) and its acetyl compound. The melting points of the hydroxy quinone, the naphthol, and the acetylnaphthol are the same as those recorded by de Buruaga, and consequently the structures assumed by this investigator are correct.

For the synthesis of 2-methyl-5-hydroxy-1,4-naphthoquinone, β-*m*-toluylpropionic acid (V) was prepared by the general method of Mrs. G. M. Robinson,[12] *m*-toluyl chloride being condensed with acetyl diethyl succinate and the product (III) being submitted to hydrolysis. The keto acid was reduced and the tolylbutyric acid was cyclized to V through the acid chloride. Dehy-



(5) A. Madinaveitia and Gallego, *Anales soc. españ. fis. quím.*, **26**, 263 (1928).
(6) De Buruaga, *ibid.*, **31**, 185 (1933).
(7) Dziewoński and Wulffsohn, *Bull. intern. acad. Polonaise*, **A**, 143 (1929).
(8) J. Madinaveitia, *Rev. acad. cienc. Madrid*, **31**, 617 (1934).
(9) De Buruaga and Verdú, *Anales españ. fis. quím.*, **32**, 830 (1934).
(10) Anderson and Newman, *J. Biol. Chem.*, **103**, 197 (1933).
(11) Krollpfeiffer and Schäffer, *Ber.*, **56**, 620 (1923).
(12) Mrs. G. M. Robinson, *J. Chem. Soc.*, 745 (1930).

drogenation of the ketone was accomplished through the α-bromo derivative, and the acetylmethylnaphthol was oxidized with chromic anhydride in the cold. The chief reaction product, easily isolated from the mixture by steam distillation, was the acetyl derivative of a methylhydroxy-α-naphthoquinone. The ring closure of α-*m*-tolylbutyric acid conceivably can occur at either the ortho or para position with respect to the methyl group, but only in the latter case can the naphthol give a para quinone of the composition found. Consequently the structure of the oxidation product is unambiguously established as that of 2-methyl-5-acetoxy-1,4-naphthoquinone, VII. The direct alkaline hydrolysis of VII proceeded poorly, but the hydroxy compound was readily obtained by reductive acetylation, hydrolysis of the triacetyl hydroquinone and oxidation. The synthetic 2-methyl-5-hydroxy-1,4-naphthoquinone was found to be identical with plumbagin. The sample used for comparison was extracted by Dr. Tummin-Katti[13] and supplied by him to Dr. M. S. Newman of this Laboratory for comparison with phthiocol. The natural and synthetic materials were also compared through the acetyl derivatives and the triacetylhydroquinones. Contrary to some statements in the literature, pure plumbagin (m. p. 78–79°) was found to be yellow tinged with orange; the acetyl derivative is yellow and melts at 117–118°, not "yellow, m. p. 138°"[4] or "red, m. p. 115°,"[5]

Like other quinones having hydroxyl groups in the vicinity of the ketonic oxygen atoms, plumbagin forms a colored boroacetate complex with Dimroth's reagent.[14] Added to a solution of boroacetic anhydride in acetic anhydride, the quinone produces an orange-red coloration which becomes brilliant red on warming. 2-Methyl-8-hydroxy-1,4-naphthoquinone behaves in a similar manner, whereas the acetyl derivatives of the quinones give only yellow solutions. Juglone produces a brilliant red coloration at room temperature. 2-Hydroxy-1,4-naphthoquinone gives a brilliant yellow color at 25° and an orange-yellow color at 60°, while with phthiocol the color changes from orange to red on warming. It is interesting that 6-hydroxy-1,2-naphthoquinone, like morpholquinone,[15] apparently forms a complex (amphiquinonoid form?), for it produces an orange-red coloration in the reagent at 25°.

(13) Tummin-Katti and Patwardhan, *J. Indian Inst. Sci.*, **A15**, 9 (1932).

(14) Dimroth and Faust, *Ber.*, **54**, 3020 (1921); Dimroth, *Ann.*, **446**, 97 (1926).

(15) Fieser, THIS JOURNAL, **51**, 2471 (1929).

Experimental Part

β-*m*-Toluylpropionic Acid.—A solution of 46.3 g. of acetyl diethyl succinate in 50 cc. of absolute ether was added cautiously to an ethereal suspension of 4.8 g. of powdered sodium, and after completion of the reaction the solution was decanted from a little unchanged sodium and treated slowly, while cooling, with a solution of 30 g. of *m*-toluyl chloride in 20 cc. of absolute ether. The separation of sodium chloride appeared to be complete after forty-eight hours and the ethereal solution was then washed with water and with soda solution and dried. The oily condensation product remaining after removal of the ether was stirred mechanically with a solution of 34 g. of potassium hydroxide in 2250 cc. of water for forty-eight hours and the somewhat yellow solution obtained was decanted from a small amount of precipitated material and treated with 175 cc. of concentrated hydrochloric acid. A mixture of the keto acid and *m*-toluic acid soon separated in a nearly colorless condition. A solution of the mixed acids in alcohol was treated with aqueous semicarbazide solution and allowed to stand for two days, and the semicarbazone of the keto acid which separated was recrystallized from alcohol; yield, 13.5 g.; m. p. 191–193°. Seven grams of *m*-toluic acid was recovered from the mother liquor. On boiling the semicarbazone with 70 cc. of 2 *N* hydrochloric acid for a few minutes and cooling the solution, β-*m*-toluylpropionic acid crystallized in a nearly pure condition; yield, 10.5 g. A sample further crystallized from water formed small, colorless plates, m. p. 115–117°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.71; H, 6.30. Found: C, 68.78; H, 6.23.

Anal. (semicarbazone). Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.81; H, 6.07. Found: C, 57.84; H, 5.99.

γ-*m*-Tolylbutyric acid was obtained by the reduction of the keto acid (10 g.) by Martin's modification[16] of the Clemmensen method. After vacuum distillation and crystallization from petroleum ether the substance formed thin, colorless plates melting at 35–36°; yield, 7.6 g. (84%).

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.11; H, 7.92. Found: C, 74.03; H, 8.15.

6-Methyltetralone-1.—Cyclization of the keto acid (7.1 g.) was accomplished through the acid chloride by the procedure of Martin and Fieser.[17] The ketone boiled initially at 129–132° at 5 mm. and was somewhat yellow, but the color was removed by repeated extraction of an ethereal solution with dilute alkali and after a second distillation a colorless liquid was obtained; yield, 5.2 g. (81%).

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.45; H, 7.57. Found: C, 82.15; H, 7.61.

2-Bromo-6-methyltetralone-1.—A solution of 5.5 g. of bromine in 15 cc. of carbon bisulfide was added by drops to a stirred solution of 4.9 g. of the tetralone in 30 cc. of the

(16) E. L. Martin, paper submitted for publication.

(17) Martin and Fieser, "Organic Syntheses," **15**, 77 (1935).

same solvent at 5°. After stirring for an additional half-hour the solvent was removed by evaporation, leaving a thick yellow oil. Once seed had been obtained the oil solidified fairly easily. A portion for analysis was purified by crystallization from petroleum ether. The substance forms clusters of thick, colorless prisms, m. p. 75–76°, but it darkens on standing. It is very irritating to the skin.

Anal. Calcd. for $C_{11}H_{11}OBr$: C, 55.23; H, 4.64. Found: C, 55.44; H, 4.83.

6-Methyl-1-naphthol.—A solution of 7 g. of the crude bromo compound in 46 cc. of freshly distilled diethylaniline was boiled gently for one hour and the dark red solution was acidified with dilute sulfuric acid and extracted with ether. After washing the ethereal solution with sodium acetate solution and with water, the product was recovered and vacuum distilled. The reddish, oily distillate was extracted from an ethereal solution with dilute alkali and the solution was quickly acidified and extracted with ether. Vacuum distillation (b. p. 166–169° at 10 mm.) then gave a product which solidified to a nearly colorless crystalline mass; yield, 3.3 g. (70%, based on the methyltetralone). A sample crystallized from petroleum ether was obtained as long, slender, colorless needles, m. p. 83–84°.

Anal. Calcd. for $C_{11}H_{10}O$: C, 83.49; H, 6.38. Found: C, 83.32; H, 6.52.

2-Methyl-5-acetoxy-1,4-naphthoquinone.—Acetylation of 2-methyl-5-naphthol with acetic anhydride and sodium acetate gave a substance which is liquid at room temperature and which boiled at about 124° at 2 mm. A solution of 2 g. of the acetyl derivative in 16 cc. of glacial acetic acid was stirred at 0° and treated with 5.5 g. of chromic anhydride in 14 cc. of 80% acetic acid. After twelve hours at 0° the solution was allowed to stand at room temperature for sixty hours and then mixed with water and steam distilled. The oxidation product was extracted with ether from a large volume of yellow distillate, and after removing acids by washing with sodium bicarbonate solution the ethereal solution was evaporated and the reddish-yellow, oily residue was distilled in vacuum and crystallized repeatedly from alcohol. 2-Methyl-5-acetoxy-1,4-naphthoquinone was obtained as large yellow needles melting at 117–118°; yield, 150 mg.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.79; H, 4.38. Found: C, 67.79; H, 4.17.

2-Methyl-1,4,5-triacetoxynaphthalene.—A mixture of 100 mg. of the above acetyl compound with zinc dust, fused sodium acetate, and acetic anhydride was boiled gently until the solution was colorless. After filtering and adding water, the triacetyl derivative slowly solidified. Crystallized from water it formed colorless plates, m. p. 125–126°; yield, 120 mg. (88%).

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.54; H, 5.10. Found: C, 64.46; H, 5.37.

2-Methyl-5-hydroxy-1,4-naphthoquinone.—The triacetyl compound (100 mg.) was hydrolyzed with boiling 5% sodium hydroxide solution containing a trace of sodium hydrosulfite in a nitrogen atmosphere, and the solution was acidified with excess dilute sulfuric acid, cooled to 0°, and treated all at once with a solution of 0.2 g. of potassium dichromate. The hydroxyquinone separated as small needles and on being crystallized from dilute alcohol it formed long, orange-yellow needles melting at 78–79°; yield about 40 mg.

Comparison with Plumbagin.—The natural plumbagin as received was dull orange and melted at 75–78°, the sample apparently having deteriorated on storage. Mixtures with the synthetic quinone showed no depression. A small sample of the natural pigment was acetylated by adding a very small quantity of concentrated sulfuric acid to an ice-cold solution of the material in acetic anhydride, allowing the solution to stand at room temperature for one hour, and removing the excess anhydride in ice water. The product was obtained as yellow microcrystals and on crystallization it formed yellow needles melting at 117–118° and giving no depression when mixed with the synthetic preparation. The triacetyl hydroquinone was prepared as above and was likewise identical with the sample obtained by synthesis.

Synthesis of 2-Methyl-8-hydroxy-1,4-naphthoquinone.—β-*p*-Toluylpropionic acid was prepared by the Friedel and Crafts reaction of succinic anhydride with toluene and the remaining steps were carried out as above. The properties and yields were as follows:

	M. p., °C.	Yield, %
β-*p*-Toluylpropionic acid	124–126	94.5
γ-*p*-Tolylbutyric acid	60–61	92.3
7-Methyltetralone-1	Liq.	79
7-Methyl-1-naphthol	108–109	40
Acetyl-7-methyl-1-naphthol	38–39	..
2-Methyl-8-hydroxy-1,4-naphthoquinone	157–158	8.4
2-Methyl-8-acetoxy-1,4-naphthoquinone	115–116	15.7

The dehydrogenation of 7-methyltetralone-1 with sulfur and with selenium was investigated but the results were much less satisfactory than by the bromination procedure. On steam distillation of the reaction mixture resulting from the oxidation of acetyl-7-methyl-1-naphthol, the free hydroxyquinone crystallized almost completely from the distillate and the acetyl derivative was obtained on extracting the mother liquor with ether.

2-Methyl-8-acetoxy-1,4-naphthoquinone.—The neutral oxidation product crystallizes from alcohol as long, pale yellow needles, m. p. 115–116°. An identical product was obtained on acetylating the acidic oxidation product by the method described for plumbagin.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.79; H, 4.38. Found: C, 67.52; H, 4.61.

Summary

The 5- and the 8-hydroxy derivatives of 2-methyl-1,4-naphthoquinone have been synthesized by methods which establish their structures. The former substance is identical with natural plumbagin.

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