402. *The Reduction of* p-*Quinones with Lithium Aluminium Hydride.*

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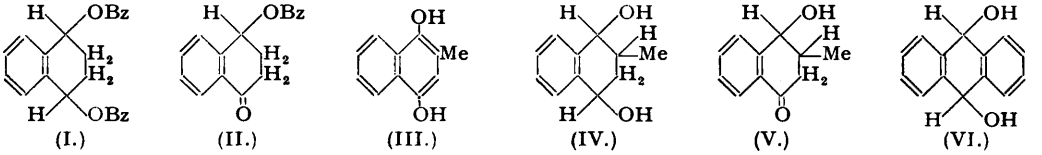
Reduction of 1 : 4-naphthaquinone with lithium aluminium hydride yields 1 : 2 : 3 : 4-tetrahydro-1 : 4-dihydroxynaphthalene and 1 : 2 : 3 : 4-tetrahydro-4-hydroxy-1-ketonaphthalene, but that of 2-methyl-1 : 4-naphthaquinone (menaphthone) gives 1 : 2 : 3 : 4-tetrahydro-4-hydroxy-1-keto-3-methylnaphthalene, and 1 : 2 : 3 : 4-tetrahydro-1 : 4-dihydroxy-2-methylnaphthalene. The reduction of anthraquinone gives 9 : 10-dihydro-9 : 10-dihydroxyanthracene in good yield. This dihydrodihydroxyanthracene appears to be a hitherto undescribed isomer.

Injection of naphthalene, anthracene, or phenanthrene into animals is followed by the excretion of *trans*-1 : 2-glycols (Booth and Boyland, *Biochem. J.*, 1949, **44**, 361; Boyland and Wolf, *ibid.*, 1950, **47**, 64). Such *trans*-glycols identical with the metabolites were synthesised by reduction of the corresponding *o*-quinones with lithium aluminium hydride (Booth, Boyland, and Turner, *J.*, 1950, 1188). Additional evidence for the *trans*-configuration was obtained by optical resolution of the synthetic 9 : 10-dihydro-9 : 10-dihydroxyphenanthrene (Booth, Boyland, and Turner, *J.*, 1950, 2808). In view of the reduction of *o*-quinones to glycols it seemed of interest to extend the reaction to *p*-quinones.

Reduction of 1 : 4-naphthaquinone with excess of lithium aluminium hydride appeared to give a 1 : 2 : 3 : 4-tetrahydro-1 : 4-dihydroxynaphthalene, a viscous oil which was characterised as the dibenzoate (I), and a keto-alcohol characterised as the benzoate (II) and the 2 : 4-dinitrophenylhydrazone.

Reduction of 2-methyl-1 : 4-naphthaquinone gave different neutral alcoholic products according to the conditions (see Table), although the main product of the reaction was the quinol (III). The dihydroxy-derivative (IV) on dehydration gave 2-methylnaphthalene and is the saturated dialcohol corresponding to the biologically active quinone. The saturation of the 2 : 3-bond in this reaction is analogous to the 1 : 4-addition of hydrogen to dibenzoylethylenes by lithium aluminium hydride (Lutz and Gillespie, *J. Amer. Chem. Soc.*, 1950, **72**, 2002).

In an attempt to avoid the hydrogenation of the 2 : 3-bond the reduction was carried out with less lithium aluminium hydride. Under these conditions a keto-alcohol (V) was isolated. The proposed structure is advanced because the compound has (i) a functional keto-group, (ii) an alcoholic hydroxyl group, and (iii) absorption spectra resembling that of acetophenone (Fig. 1), and also because it yields 3-methyl-1-naphthol on dehydration with acid.



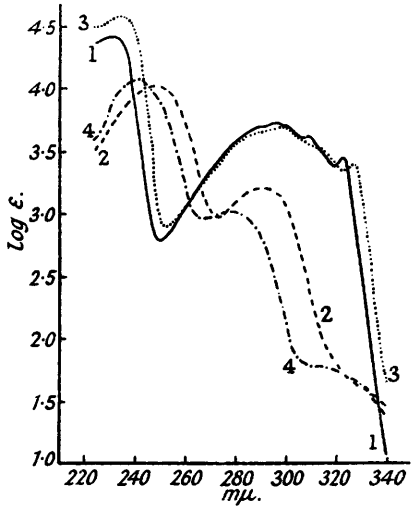
When the reduction was carried out with 1 g. of lithium aluminium hydride and 10 g. of methylnaphthaquinone the only neutral product isolated was the keto-alcohol (V), whether the reaction was carried out at −10°, 25°, or the boiling point of ether. When twice as much lithium aluminium hydride was employed the main neutral product of the reaction depended on the temperature and solvent employed: thus reaction at −10° in ether generally gave the best yields of the keto-alcohol (V), but at 10° in tetrahydrofuran yielded the dihydric alcohol (IV) with a small amount of the keto-alcohol (V); at higher temperatures with the larger quantity of reductant in ether or tetrahydrofuran the first product to crystallise was (IV) but small amounts of (V) were also produced.

The vitamin-K activity of these new water-soluble derivatives has been determined by Dr. Inger Kruse and Professor Henrik Dam at the Department of Biology, Polytechnic Institute, Copenhagen, by the method of assay described by Dam, Kruse, and Søndergaard (*Acta Physiol. Scandinavica*, 1951, **22**, 238). 1 : 2 : 3 : 4-Tetrahydro-1 : 4-dihydroxy-2-methylnaphthalene (IV) injected in aqueous solution had 1/16 of the activity of menaphthone injected in oil (mean result of 5 determinations, 1 μg. of IV ≡ 0·062 μg. of menaphthone). The

keto-alcohol (V) had only 1/23 of the activity when tested in the same way (mean result of 5-determinations, 1 μg. of V ≡ 0·044 μg. of menaphthone).

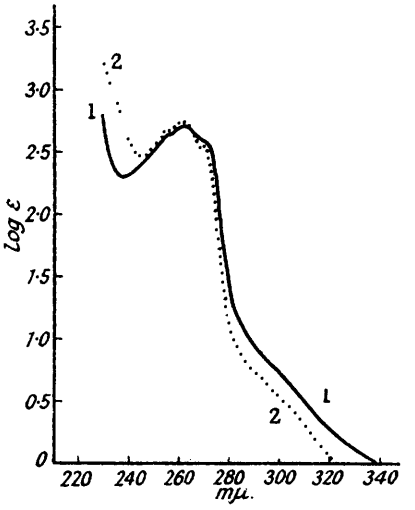
The 9 : 10-dihydro-9 : 10-dihydroxyanthracene (VI) obtained on reduction of anthraquinone was dimorphic, forming needles, m. p. 140° and plates, m. p. 137°. Both these forms appeared to be different from the compound, m. p. 195°, obtained by reduction of anthracene photo-oxide (Dufraisse and Houpillart, *Compt. rend.*, 1937, **205**, 740). They also appear to be different from the product obtained by alkaline hydrolysis of the benzoate (Prevost, *ibid.*, 1935, **200**, 408). The structure ascribed to our compound (VI) is supported by the close resemblance of the absorption spectra to that of 9 : 10-diethyl-9 : 10-dihydro-9 : 10-dihydroxyanthracene (prepared by the action of ethylmagnesium iodide on anthraquinone) (Fig. 2). Both crystalline forms had the same absorption spectra when dissolved in alcohol.

FIG. 1.



(1), *α-Naphthol.* (2), 1 : 2 : 3 : 4-*Tetrahydro*-1-*hydroxy*-4-*keto*-2-*methylnaphthalene.* (3), *Dehydration product of* (3). (4), *Aceto-phenone.*

FIG. 2.



(1), 9 : 10-*Diethyl*-9 : 10-*dihydro*-9 : 10-*dihydroxy-anthracene.* (2), 9 : 10-*Dihydro*-9 : 10-*di-hydroxyanthracene.*

The results show that whereas 9 : 10-anthraquinone is reduced smoothly by lithium aluminium hydride to a dihydric alcohol (dihydrodihydroxyanthracene), naphthaquinone and 2-methylnaphthaquinone give large amounts of quinols and other products, and we have been unable to reduce the naphthaquinones to alcohols without reducing the 2 : 3-bond.

EXPERIMENTAL.

Reduction of 1 : 4-*Naphthaquinone.*—Naphthaquinone (20 g.) was extracted in the Soxhlet apparatus with ether (300 ml.; dried over sodium) containing lithium aluminium hydride (4 g.). The quinone dissolved in about 2 hours. The ether was cooled to 0° and technical ether (200 ml.) and then water followed by 2N-sulphuric acid were added to decompose excess of lithium aluminium hydride and the complex. The ethereal layer was separated, washed with water and then with 2N-sodium hydroxide containing sodium dithionite to remove unchanged quinone and phenolic material, and again with water, dried (Na_2SO_4), and evaporated to dryness. A red oil (6·5 g.), very soluble in ether, alcohol, and benzene, but insoluble in light petroleum (b. p. 40—60°), remained. The oil did not crystallise from ether or benzene– or *cyclo*hexane–light petroleum. The dried oil was dissolved in dry pyridine (15 ml.), and benzoyl chloride added (12 g.). The mixture was set aside for 24 hours at room temperature. Water (100 ml.) was added and the oil extracted with ether; the combined extracts were washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water. The ether was evaporated, giving an oil (16 g.) which crystallised from alcohol; after 3 days in the cold, plates of irregular shape and m. p. 175—185° separated. As fractional crystallisation was unsuccessful, half of the total amount of the red oil (8 g.) consisting of mixed benzoates in benzene–*cyclo*hexane (1 : 19) was passed through an alumina column (25 × 4 cm.) prepared in the same solvent. Two bands were formed. Elution with benzene–*cyclo*hexane (3 : 7) removed material (0·3 g.) which after crystallisation from alcohol gave 1 : 4-*dibenzoyloxy*-1 : 2 : 3 : 4-*tetrahydronaphthalene* as elongated plates, m. p. 181—183° (Found: C, 77·1; H, 5·7. $C_{24}H_{20}O_4$ requires C, 77·5; H, 5·4%).

Elution of the column was continued with 2 : 3, 1 : 1, 3 : 2, 7 : 3, and 4 : 1 mixtures of benzene and *cyclo*hexane; concentration of the eluate from the last solvent mixture yielded a solid residue (3·0 g.)

which, after recrystallisation from ethanol and *cyclo*hexane, still appeared to be a mixture (m. p. 75—82°). A portion of this material (1·0 g.) was passed through another column of alumina (3 × 17 cm.) prepared in *cyclo*hexane. Elution with *cyclo*hexane–benzene yielded 1 : 4-dibenzoyloxy-1 : 2 : 3 : 4-tetrahydronaphthalene (0·01 g.) and then *4-benzoyloxy-1 : 2 : 3 : 4-tetrahydro-1-ketonaphthalene* (0·5 g.) which, crystallised from *cyclo*hexane, had m. p. 94—95° and gave a violet colour with *m*-dinitrobenzene in alcoholic potash (Found : C, 76·5; H, 5·5. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%).

The monobenzoate gave, by the standard method, a 2 : *4-dinitrophenylhydrazone*, which after two crystallisations from benzene formed reddish-orange needles, m. p. 215—216° (decomp.) (Found : C, 61·8; H, 4·3; N, 12·8. $C_{23}H_{18}O_6N_4$ requires C, 61·9; H, 4·1; N, 12·55%).

1 : 2 : 3 : 4-*Tetrahydro*-1 : *4-dihydroxy-2-methylnaphthalene*.—2-Methyl-1 : 4-naphthaquinone (10 g.) was dried *in vacuo* and then added slowly down the condenser to a solution of lithium aluminium hydride (2 g.) in ether (200 ml.; sodium-dried) under reflux. The solution was boiled for 30 minutes and then cooled. Ether (50 ml.; technical), water (5 ml.), and then 2N-sulphuric acid (20 ml.) were added slowly. The ethereal solution was extracted successively with 10N-sulphuric acid (2 × 10 ml.), water (10 ml.), and 2N-sodium hydroxide (four times). The ethereal solution was dried (NaOH) and evaporated to dryness. The residue was recrystallised twice from benzene, to give 1 : 2 : 3 : 4-*tetrahydro*-1 : 4-*dihydroxy-2-methylnaphthalene* (IV) (0·45 g.), m. p. 182°, soluble in hot water, alcohol, benzene, and chloroform (Found : C, 73·9; H, 8·1. $C_{11}H_{14}O_2$ requires C, 74·1; H, 7·9%).

This alcohol (0·15 g.) in pyridine (2 ml.), with acetic anhydride (2 ml.) overnight, gave the *diacetate*, which crystallised from benzene–light petroleum in white needles, m. p. 115—117° (Found : C, 68·9; H, 6·9. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9%).

Dehydration of 1 : 2 : 3 : 4-*Tetrahydro*-1 : 4-*dihydroxy-2-methylnaphthalene*.—The dialcohol (0·45 g.) was distilled with 5N-hydrochloric acid (80 ml.). 2-Methylnaphthalene (0·26 g.) distilled over and was purified by sublimation at 60°/1 mm.; it had m. p. (alone or with an authentic specimen) 33—34°. The picrate, prepared in acetone, had m. p. (alone or mixed with authentic specimen) 113—114°.

The dialcohol was recovered unchanged from attempted methylations with (*a*) methyl sulphate and sodium hydroxide, (*b*) methyl iodide, and (*c*) diazomethane.

Attempted chromatographic analysis on alumina of the dialcohol did not reveal the presence of more than one substance.

1 : 2 : 3 : 4-*Tetrahydro*-1-*hydroxy*-4-*keto*-2-*methylnaphthalene* (V).—2-Methyl-1 : 4-naphthaquinone (10 g.) was dissolved in dry ether (750 ml.) at −10° and an ethereal solution of lithium aluminium hydride (2 g.) run in during 30 minutes. The reaction mixture was worked up in the usual way and the neutral product after recrystallisation gave the *keto-alcohol* (0·69 g.), m. p. 96—98° (Found : C, 75·0; H, 7·3. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·9%).

The keto-alcohol (0·18 g.), set aside in pyridine (2 ml.) with acetic anhydride (2 ml.) overnight, afforded the *acetate* which crystallised from *cyclo*hexane and then had m. p. 120—121° (Found : C, 71·0; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·5%).

Dehydration of Keto-alcohol (V).—The keto-alcohol (0·56 g.) was distilled with 5N-hydrochloric acid (100 ml.) in 80 minutes. The solid in the distillate was filtered off and gave 3-methylnaphthol (0·4 g., 80%), m. p. 88—90°, solidifying and remelting at 90—91·5°. The product, which was easily soluble in alkali, gave a white precipitate with ferric chloride, a pink colour with diazotised sulphanilic acid, a mauve colour with diazotised *p*-nitroaniline, and a green colour with sodium hypochlorite. Schotten–Baumann treatment gave a benzoate which, crystallised twice from ethanol (yield, 0·18 g. from 0·316 g.), had m. p. 85—86° (Found : C, 82·0; H, 5·4. Calc. for $C_{18}H_{14}O_2$: C, 82·3; H, 5·4%). Tishler, Fieser, and Wendler (*J. Amer. Chem. Soc.*, 1940, **62**, 2866) report m. p. 75—76° for the benzoate.

The keto-alcohol (0·50 g.) was treated with lithium aluminium hydride (0·10 g.) in boiling dry ether for 60 minutes. The neutral alcohol fraction was isolated and yielded 0·40 g. (78%) of 1 : 2 : 3 : 4-tetrahydro-1 : 4-dihydroxy-2-methylnaphthalene, m. p. (alone and mixed with authentic specimen) 181—182°.

The keto-alcohol (0·176 g.), by the standard procedure, gave a 2 : *4-dinitrophenylhydrazone* (0·20 g.), as red needles, m. p. 235—237°, soluble in benzene, alcohol, chloroform and ether (Found : C, 57·6; H, 4·3; N, 15·9. $C_{17}H_{16}O_5N_4$ requires C, 57·3; H, 4·5; N, 15·7%).

Main products from 10 *g. of* 2-*methyl*-1 : 4-*naphthaquinone and* (a) 1 *g. or* (b) 2 *g. of* $LiAlH_4$.

Solvent.	Temp.	(*a*) (V),* mg.	(*b*) (IV), mg.	(*b*) (V), mg.
Ether	−10°	440, 380 (mean, 410)	180	690, 470, 590, 760 (mean, 630)
Tetrahydrofuran	−10	300	230, 180 (mean, 205)	nil
Ether	25	420	200	nil
Ether	B. p.	120	100, 300 (mean, 200)	nil
Tetrahydrofuran	B. p.	—	225	nil

* No (IV) was isolated in these experiments.

Reduction of 2-*Methyl*-1 : 4-*naphthaquinone under Different Conditions*.—The yields of neutral alcohol products given by the reduction with lithium aluminium hydride carried out in ether and tetrahydrofuran at different temperatures are shown in the Table. In these experiments the lithium aluminium hydride in ethereal solution was added to a solution of the quinone.

Reduction of Anthraquinone with Lithium Hydride.—Anthraquinone (20·8 g., 0·1 mol.; dried over phosphoric oxide) was extracted in a Soxhlet apparatus with dry ether (250 ml.) containing lithium

aluminium hydride (2·1 g., 10% excess). After 20 hours 3·8 g. of quinone had dissolved. The remaining anthraquinone had a slight odour of benzaldehyde. The ethereal solution was treated as in other reactions and the neutral fraction was crystallised from benzene, to give a crystalline alcohol as needles, but containing some plates (2·8 g.), m. p. 128° preceded by signs of decomposition at 100°.

This experiment was repeated but with freshly redistilled tetrahydrofuran (250 ml.) in place of ether. After 20 hours, 14 g. of quinone were extracted from the Soxhlet thimble. The same neutral solid, 9 : 10-*dihydro*-9 : 10-*dihydroxyanthracene* (VI) (9·6 g.), was isolated. The material, dissolved in warm benzene, was washed with sodium hydroxide solution containing sodium dithionite. After being washed with water and dried (Na_2SO_4), the benzene solution was concentrated *in vacuo* until crystallisation commenced. The product (mainly needles but some plates) had m. p. 130—135° (Found: C, 78·9; H, 6·1. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%). The needles alone melted at 140°. The needles which first separated contained a little anthraquinone but the plates were never contaminated therewith.

The product (mixed forms) in pyridine with benzoyl chloride gave a *dibenzoate* which, crystallised twice from hexane containing a little benzene, had m. p. 127—128° (Found: C, 79·5; H, 5·1. $C_{28}H_{20}O_4$ requires C, 80·0; H, 4·8%).

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