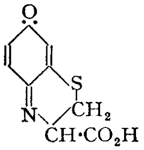
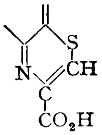
408. *Addition Reactions of Quinones. Part I. The Reaction of Cysteine and Thiourea and its Derivatives with Some Quinones.*

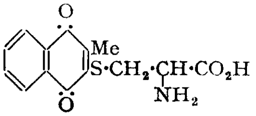
By H. Burton and (Mrs.) S. B. David.

The formation of additive compounds from various quinones and cysteine, thiourea, and *N*-arylthiourea is investigated. Under suitable conditions *S*-2 : 5-dihydroxyphenylthiourea undergoes hydrolysis to a hydroxybenzothioxolone which can be hydrolysed further to mercaptoquinol.

It has long been known that the simple quinones will dehydrogenate amino-acids, especially in an alkaline medium. We were particularly interested to know whether an amino-acid such as cysteine could be made to add, under suitable conditions, to the quinone molecule since one of us has postulated (cf. *J. Soc. Dyers & Col.*, 1950, **66**, 474) that this type of addition may occur during the formation of naturally occurring melanins. Preliminary experiments with cysteine and benzo- or 1 : 4-naphtha-quinone showed that under a variety of experimental conditions highly coloured products were produced.

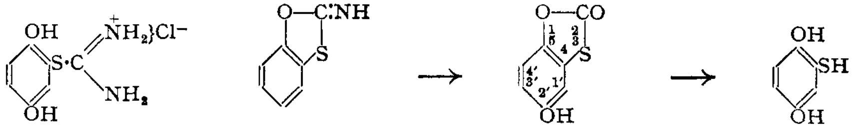

(I)


(I*a*)


(II)

Such products appeared to be mixtures but it seemed to us that, in an acidic medium, condensation of a *S*-benzoquinonylcysteine, if initially produced, to a thiazine of type (I) by loss of water between the amino-group of the side-chain and the adjacent quinone oxygen atom might possibly occur. It is also possible for (I) to undergo dehydrogenation to the true thiazine (cf. I*a*) if an excess of the quinone is present at any stage of the reaction. We were able to show that 2-methyl-1 : 4-naphthaquinone (2 mols.) with cysteine (1 mol.) in a slightly acid medium gave the highly coloured *S*-3-methyl-1 : 4-naphthaquinon-2-ylcysteine (II) : the compound had the correct analytical composition and the expected properties. Reductive acetylation of (II) gave a colourless non-acidic product which did not react with dilute alkali carbonate solution : its high carbon content suggested that loss of carbon dioxide occurred during its formation and we suggest that the product may be entirely or, more probably, partly a reduced thiazine derivative (cf. above).

We had carried out many experiments with thiourea and various quinones in acidic media especially, when our attention was drawn to a statement by Schubert (*J. Amer. Chem. Soc.*, 1947, **69**, 712) that in aqueous hydrochloric acid benzoquinone and thiourea gave the colourless hydrochloride of a 1 : 1-additive compound, whilst 2-methyl-1 : 4-naphthaquinone gave the hydrochloride of an anhydro-derivative of a 1 : 1-additive compound. We have not been able to confirm the latter observation : we find that the above quinones, tolu-2 : 5-quinone, and 1 : 2- and 1 : 4-naphthaquinone all give genuine 1 : 1 additive compound hydrochlorides although in one case the salt was hydrated. It seemed extremely probable that the hydrochloride from benzoquinone and thiourea was, as suggested by Schubert (*loc. cit.*), *S*-2 : 5-dihydroxyphenylthiuronium chloride (III) and not the isomeric *N*-2 : 5-dihydroxyphenyl derivative, but no proof of the structure was given. We have been able to prove the structure in a very simple manner since *S*-2 : 5-dihydroxyphenylthiuronium acetate undergoes hydrolysis in boiling aqueous acetic acid to give a good yield of 2′-hydroxy-4 : 5-benzothioxol-2-one (V) which was presumably



(III) (IV) (V) (VI)

formed by way of 2 : 5-dihydroxyphenyl thiocyanate and the imino-thioxole (IV). The possibility of a rearrangement of the type, $R\cdot NH\cdot C(SH){:}NH_2^+\}Cl^- \rightleftharpoons NH\cdot C(SR){:}NH_2^+\}Cl^-$ (R = acyl), investigated by Dixon and Taylor (*J.*, 1920, **117**, 720) is not excluded but it appears to us to be unlikely since in (III) R is aryl and not acyl. We find that (V) gives a monoacetate and is stable to hot dilute sulphuric acid and zinc–dilute sulphuric acid, but is rapidly hydrolysed by alkali hydroxide. In the presence of air a dark brown solution is rapidly formed, but in the absence of oxygen the solution remains colourless and an almost quantitative yield of mercaptoquinol (VI) results.

Compounds of types (IV) have been claimed (F.P. 852,020 : cf. Kaufmann, "Newer Methods of Preparative Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 379) to result when suitably constituted dihydric phenols are treated with thiocyanating agents; they are stated to be hydrolysed by acids to compounds of type (V). The example quoted by Kaufmann (*op. cit.*) appears to us to be an improbable one : the compound formed from resorcinol would undoubtedly be 3′-hydroxy-4 : 5-benzothioxol-2-one and not the 1′-hydroxy-derivative.

Inconclusive results were obtained (see Experimental) when (III) was hydrolysed in more acidic or in alkaline media. The formation of coloured products under such conditions does not however warrant Schubert's description of the hydrochlorides as unstable compounds : we have kept specimens for several years without any decomposition having taken place.

We have not had the opportunity to investigate the hydrolysis of the other *S*-dihydroxyarylthioureas to see if the formation of compounds of type (V) is general, since one of us can no longer participate in the work.

We have also found that benzoquinone will react with *N*-1- and -2-naphthylthioureas in aqueous hydrochloric acid, forming thiuronium salts; experiments with *N*-phenylthiourea indicated addition both to benzoquinone and to 1 : 4-naphthaquinone but the results were very variable.

EXPERIMENTAL

S-3-*Methyl*-1 : 4-*naphthaquinon*-2-*ylcysteine* (II).—A solution of cysteine hydrochloride (1·6 g.) and sodium acetate trihydrate (1·4 g.) in water (*ca.* 8 c.c.) was mixed with a solution of 2-methyl-1 : 4-naphthaquinone (3·44 g.) in methanol (90 c.c.), and the mixture kept in a stoppered flask at *ca.* 35° for 60 hours, during which a greenish-black solid (2 g.) separated. This was filtered off and washed first with aqueous methanol and finally with water; the dried material did not melt below 280°. It dissolved in cold aqueous sodium carbonate, giving a green solution which became purple when heated, in cold aqueous sodium hydroxide to a deep purple solution, and in boiling acetic acid to a red solution. It could not be recrystallised satisfactorily but the analytical data indicated that it was S-3-*methyl*-1 : 4-*naphthaquinon*-2-*ylcysteine* (Found : C, 57·6; H, 4·1; N, 4·65; S, 10·8. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·5; N, 4·8; S, 11·0%).

A mixture of the above compound (2 g.), acetic acid (7·5 c.c.), acetic anhydride (15 c.c.), and zinc dust (6 g.) was refluxed for 8 hours, then filtered whilst still hot, and the filtrate added to crushed ice. The solid which separated was filtered off and washed with dilute sulphuric acid, and then with water. Crystallisation of the air-dried material from benzene–methanol gave almost colourless needles of a *substance*, m. p. *ca.* 125° after softening from 100° (Found : C, 67·4; H, 6·3%), which were insoluble in aqueous sodium carbonate and slightly soluble in cold dilute sodium hydroxide (probably because of hydrolysis of the acetoxy-group present).

S-2 : 5-*Dihydroxyphenylthiuronium chloride* (III).—This was prepared in 72% yield essentially by Schubert's method (*loc. cit.*); the purified colourless compound became red at 150° and after progressive blackening decomposed at 160° (Found: C, 38·5; H, 4·4; N, 12·3; Cl, 15·8; S, 14·5. Calc. for $C_7H_9O_2N_2ClS$: C, 38·1; H, 4·1; N, 12·7; Cl, 16·1; S, 14·5%).

The following thiuronium salts were prepared by shaking a mixture of thiourea (3 g.), the appropriate quinone (1 g.), and alcohol (10 c.c.) in 2N-hydrochloric acid (4 c.c.) until complete dissolution occurred, and then leaving the mixture at 0° for at least 3 days. The almost colourless solid products which had then separated were purified by dissolving them in the minimum amount of cold water, stirring the solution with a little charcoal, filtering, and adding concentrated hydrochloric acid (one-quarter of the total volume) to the filtrate; the colourless products which then separated were filtered off and dried in an ordinary desiccator over calcium chloride.

S-2 : 5-*Dihydroxy*-4-*methylphenylthiuronium chloride* (from tolu-2 : 5-quinone), decomp. 185—195° (Found: C, 40·9; H, 4·9; N, 11·6; Cl, 14·9; S, 13·8. $C_8H_{11}O_2N_2ClS$ requires C, 40·9; H, 4·7; N, 11·9; Cl, 15·1; S, 13·6%).

S-1 : 4-*Dihydroxy*-2-*naphthylthiuronium chloride hydrate* (from 1 : 4-naphthaquinone), decomp. 170—180° (Found: C, 45·9; H, 4·7; N, 9·9; Cl, 11·9; S, 11·0; H_2O, by loss at room temp./high vac. over P_2O_5, 6·4. $C_{11}H_{11}O_2N_2ClS,H_2O$ requires C, 45·8; H, 4·5; N, 9·7; Cl, 12·3; S, 11·1; H_2O, 6·2%).

S-3 : 4-*Dihydroxy*-1-*naphthylthiuronium chloride* (from 1 : 2-naphthaquinone), decomp. 215—218° (Found: C, 48·5; H, 4·3; N, 10·3; Cl, 13·2; S, 11·8. $C_{11}H_{11}O_2N_2ClS$ requires C, 48·8; H, 4·1; N, 10·3; Cl, 13·1; S, 11·8%).

S-1 : 4-*Dihydroxy*-3-*methyl*-2-*naphthylthiuronium chloride* (from 2-methyl-1 : 4-naphthaquinone), blackens at 250° (Found: C, 51·4; H, 4·5; N, 9·35; Cl, 12·2; S, 11·0. $C_{12}H_{13}O_2N_2ClS$ requires C, 50·6; H, 4·6; N, 9·8; Cl, 12·5; S, 11·2%). No evidence for the formation of an anhydro-compound (Schubert, *loc. cit.*) was obtained.

2′-*Hydroxy*-4 : 5-*benzothioxol*-2-*one* (V).—A solution of *S*-2 : 5-dihydroxyphenylthiuronium chloride (2·2 g.) and anhydrous sodium acetate (0·8 g.) in water (4 c.c.) and acetic acid (10 c.c.) was boiled under reflux for 2 hours. The cooled solution was diluted with water, and the resulting white precipitate filtered off and washed with water. The *thioxolone* (1·3 g.) separated from alcohol in colourless needles, m. p. 170—171° (Found: C, 50·1; H, 2·5; S, 18·9%; *M*, 154. $C_7H_4O_3S$ requires C, 50·0; H, 2·4; S, 19·0%; *M*, 168).

The thioxolone was recovered unchanged after treatment with boiling concentrated hydrochloric acid until dissolution occurred, and it was not appreciably altered by treatment with zinc dust in boiling aqueous ethyl-alcoholic sulphuric acid during 5 hours.

Acetylation with acetic anhydride and a little 72% perchloric acid gave 2′-*acetoxy*-4 : 5-*benzothioxol*-2-*one*, colourless needles (from benzene or ethyl alcohol), m. p. 88° (Found: C, 51·5; H, 2·7; S, 15·2. $C_9H_6O_4S$ requires C, 51·4; H, 2·9; S, 15·2%), in almost quantitative yield.

Mercaptoquinol (VI).—2′-Hydroxy-4 : 5-benzothioxol-2-one (2·5 g.) was dissolved in oxygen-free 2N-sodium hydroxide (25 c.c.) in a nitrogen atmosphere and the solution boiled for 1 hour in a stream of oxygen-free nitrogen: no sodium sulphide was present in the solution (negative test with sodium nitroprusside). The solution was allowed to cool in nitrogen to room temperature and was then acidified with 2N-sulphuric acid whereupon evolution of some carbon dioxide occurred. The solution was then saturated with sodium sulphate and extracted thrice with ether; the ethereal extracts were evaporated immediately in a vacuum-desiccator (P_2O_5), and the resulting solid (2·2 g.) crystallised from chloroform–ethyl acetate (10 : 1), giving almost colourless, flat prisms, m. p. 118° (Found: C, 50·4; H, 4·2; S, 22·7. Calc. for $C_6H_6O_2S$: C, 50·7; H, 4·2; S, 22·5%), of mercaptoquinol. The compound was identical (m. p. and mixed m. p.) with that prepared by Alcalay's method (*Helv. Chim. Acta*, 1947, **30**, 578), and was further characterised by oxidation with iodine in ether–chloroform to bis-2 : 5-dihydroxyphenyl disulphide, m. p. 179—180° (cf. Jacini, *Gazzetta*, 1947, **77**, 252).

In our hands Alcalay's method for the preparation of mercaptoquinol gave a product (m. p. 114°) which appeared to be contaminated with a small amount of a persistent impurity; four or five recrystallisations were necessary to raise the m. p. to 118°.

Hydrolysis of *S*-2 : 5-dihydroxyphenylthiuronium chloride with boiling hydrochloric acid under varying conditions usually gave red products (cf. Schubert, *loc. cit.*); in one case some impure quinol, identified by conversion into its diacetate, was obtained.

Hydrolysis with boiling N-sodium hydroxide invariably led to dark solutions. Crystalline, nitrogen-free materials containing a high proportion of sulphur (*e.g.*, Found: S, 21·3%) were often isolated after acidification; these were obviously impure oxidation products of mercaptoquinol.

Reaction of Benzoquinone with N-*Arylthioureas.*—Benzoquinone (1 g.) was added to a solution of the *N*-arylthiourea (5 g.) in the minimum volume of 50% aqueous alcohol to which was added 25% of its volume of concentrated hydrochloric acid. The mixture was stirred for 1—2 days at room temperature, then filtered, and the filtrate kept at 0° until no further solid material separated. The solid thereby obtained was not completely soluble in cold water; addition of concentrated hydrochloric acid to the filtrate gave the microcrystalline hydrochlorides of the appropriate addition products. *S*-2 : 5-Dihydroxyphenyl-*N*-1-naphthylthiuronium chloride was obtained as a *monohydrate*, m. p. 140° (orange melt) (Found : C, 56·0; H, 4·6; N, 7·8; Cl, 9·4; S, 8·8. $C_{17}H_{15}O_2N_2ClS,H_2O$ requires C, 56·0; H, 4·7; N, 7·7; Cl, 9·7; S, 8·8%).

S-2 : 5-*Dihydroxyphenyl*-N-2-*naphthylthiuronium chloride* was obtained as a buff-coloured powder, m. p. *ca.* 200° (decomp.) (Found : N, 8·1; Cl, 10·0. $C_{17}H_{15}O_2N_2ClS$ requires N, 8·1; Cl, 10·2%).

N-Phenylthiourea gave very variable results. In some cases little or no reaction occurred whilst under apparently identical conditions products of m. p. 165—175° (decomp.), containing variable amounts of ionisable chlorine, were obtained. Similar variable reactions occurred between *N*-phenylthiourea and 1 : 4-naphthaquinone.

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