# 630. *Some Alkylquinoline-5 : 8-quinones.*

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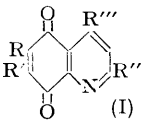
The synthesis from alkyl-amino- and alkyl-hydroxy-quinolines of 6- and 7-alkylquinoline-5 : 8-quinones, as far as the butyl compounds, is described.

The action of hydroxylamine and alkali on certain alkylnitroquinolines gave moderate to poor yields of alkyl-amino-nitroquinolines.

The bacteriostatic properties of the quinoline-5 : 8-quinones are reported.

Very few compounds of the type (I) have been described. Fischer and Renouf (*Ber.*, 1884, **17**, 1644) obtained quinoline-5 : 8-quinone, and Noelting and Trautmann (*Ber.*, 1890, **23**, 3671) prepared the monoximes of (I; R′ = R″ = R‴ = H, R = Me) and (I; R = R″ = R‴ = H, R′ = Me). By an indirect method Zincke and Muller (*Annalen*, 1891, **264**, 201) obtained (I; R″ = R‴ = H, R = OH, R′ = Cl), whilst more recently 6-methylquinoline-5 : 8-quinone was prepared and found to be almost devoid of antihæmorrhagic properties (Christiansen and Dolliver, *J. Amer. Chem. Soc.*, 1941, **63**, 1470; Ansbacher, *Proc. Soc. Exp. Biol. N.Y.*, 1941, **46**, 421). In the course of antitubercular studies Graef, Fredericksen, and Burger (*J. Org. Chem.*, 1946, **11**, 257) synthesised (I; R = R′ = H, R‴ = Me, R″ = $[CH_2]_{10}\cdot CO_2H$).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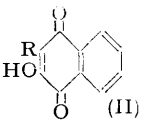
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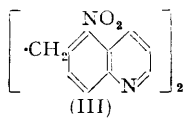
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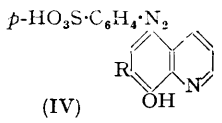
(IV)

In view of the importance of naturally occurring naphtha-1 : 4-quinones, the known antimalarial properties of 2-alkyl-3-hydroxynaphtha-1 : 4-quinones (II) (Fieser and his co-workers, *J. Amer. Chem. Soc.*, 1948, **70**, 3151 *et seq.*), and the possible significance of quinonoid derivatives for the antimalarial action of certain quinoline compounds (Schönhöfer, *Z. physiol. Chem.*, 1942, **274**, 1; Drake and Pratt, *J. Amer. Chem. Soc.*, 1951, **73**, 544; Elderfield, " Heterocyclic Compounds," Vol. IV, p. 198, Wiley, 1952), we undertook a study of quinoline-5 : 8-quinones. We describe here a number of 6- and 7-alkylquinoline-5 : 8-quinones.

Two routes to quinoline-5 : 8-quinones were examined. One proceeded from 5- or 8-aminoquinolines, the other from 5- or 8-hydroxyquinolines (in some cases obtained from the amines). The former method proved the better.

Satisfactory procedures for coupling benzenediazonium chloride with aminoquinolines were devised by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1920, **42**, 2278) and Renshaw, Friedman, and Gajewski (*ibid.*, 1939, **61**, 3322). The latter workers found 5-aminoquinoline to couple at both the 6- and the 8-position. Guided by this experience we coupled diazotised sulphanilic acid with a number of 6-alkyl-5- and 7-alkyl-8-aminoquinolines (Long and Schofield, *J.*, 1953, 2350) in acetic acid: in these cases *ortho*-coupling is impossible, and the *p*-amino-azo-compounds were obtained in almost quantitative yields. These products were reduced by stannous chloride to the corresponding 6- or 7-alkyl-5 : 8-diaminoquinolines, which were immediately oxidised with potassium dichromate. In this manner 2-, 6-, and 7-methyl-, 6- and 7-ethyl-, 6-propyl-, and 6- and 7-butyl-quinoline-5 : 8-quinone were readily obtained in yields varying from 27 to 75%. In an attempt to estimate the yields of diamines formed from the azo-compounds in the cases of the three monomethyl compounds, the solid products were isolated. As expected, these rapidly darkened, and after some months gave very poor yields of quinones by dichromate oxidation. The toluene-*p*-sulphonamido-derivatives of these diamines could only be obtained in poor yields.

It seemed that 5 : 8-diaminoquinolines, the immediate precursors of quinones in the above work, might be obtained by another method. Recently Huisgen (*Annalen*, 1947, **559**, 101) and Colonna and Montanari (*Gazzetta*, 1951, **81**, 744) obtained aminonitro-

quinolines in moderate to very good yields by the action of hydroxylamine and alkali on nitroquinolines (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273). By applying the conditions of Colonna and Montanari (*loc. cit.*) to 6-methyl-5-nitroquinoline, we obtained 8-amino-6-methyl-5-nitroquinoline (30—35%), unchanged starting material, and variable amounts of a sparingly soluble amorphous product. By varying the proportions of reactants it was possible to maintain the yield of nitro-amine, raise the recovery of starting material, and decrease the amount of amorphous material. We were not able to isolate a salt of the type described by Meisenheimer and Patzig (*Ber.*, 1906, **39**, 2533). Purification of the amorphous material gave a compound which from analysis, and by analogy with the experiments of Huisgen (*loc. cit.*), is possibly 1 : 2-di-(5-nitro-6-quinolyl)ethane (III). However, the action of methanolic potassium hydroxide on 6-methyl-5-nitroquinoline, hydroxylamine being absent, gave a different, unidentified product, evidently not encountered by Bogert and Fisher (*J. Amer. Chem. Soc.*, 1912, **34**, 1569) who described a similar reaction.

Whilst the above reaction provided a useful method of preparing 8-amino-6-methyl-5-nitroquinoline, its application to 6-ethyl-5- and 7-methyl-8-nitroquinoline gave only poor yields of the nitro-amines, and the method failed with 6-butyl-5-nitroquinoline. Since these are instances of nucleophilic substitution the generally adverse influence of alkyl groups is readily understood. 8-Amino-6-methyl- and 8-amino-6-ethyl-5-nitroquinoline were reduced to diamines, which were oxidised to quinoline-5 : 8-quinones. Having regard to the ready availability of 6-methyl-5-nitroquinoline, the sequence of reactions described represents a useful method for obtaining small quantities of 6-methylquinoline-5 : 8-quinone.

For the method based on hydroxyquinolines, 8-hydroxyquinoline is readily available, and the process of nitrosation (Lippmann and Fleissner, *Monatsh.*, 1889, **10**, 794) followed by treatment with iron filings and very dilute hydrochloric acid, whereby 5 : 8-dihydroxyquinoline is formed (Matsumara and Sone, *J. Amer. Chem. Soc.*, 1931, **53**, 1406), was recommended by Fieser and Martin (*ibid.*, 1935, **57**, 1840). However, like Moness and Christiansen (*J. Amer. Pharm. Assoc.*, 1934, **23**, 228) we found the product difficult to purify, and the large volume of reaction solution made the method impracticable.

Fischer and Renouf (*loc. cit.*) originally prepared quinoline-5 : 8-quinone by coupling 8-hydroxyquinoline with diazotised sulphanilic acid, reducing the resulting azo-compound, and oxidising 5-amino-8-hydroxyquinoline. Christiansen and Dolliver (*loc. cit.*) similarly obtained the 6-methylquinone from 5-hydroxy-6-methylquinoline. The method suffers from the inacessibility of homologues of 5- and 8-hydroxyquinoline. Cavallito and Haskell (*J. Amer. Chem. Soc.*, 1944, **66**, 1166) prepared 5-hydroxy- from 5-amino-quinoline, but gave no experimental details. Our own experiments with 5-aminoquinoline, and also attempts to repeat Noelting and Trautmann's preparation of 5-hydroxy- from 5-amino-6-methylquinoline (*Ber.*, 1890, **23**, 3654), realised only poor yields of the hydroxy-compounds. 8-Hydroxy-7-methylquinoline is directly available (Long and Schofield, *loc. cit.*), but an attempt to prepare it from 8-amino-7-methylquinoline gave no phenolic material. Our experience in these experiments is similar to that of other workers (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 550; Price, Snyder, and Heyningen, *J. Amer. Chem. Soc.*, 1946, **68**, 2589; Fieser and Hershberg, *ibid.*, 1940, **62**, 1640; Cook, Heilbron, Hey, Lambert, and Spinks, *J.*, 1943, 404), which indicates difficulties in utilising diazotised aminoquinolines. We prepared 7-allyl-8-hydroxyquinoline by a slight modification of the method of Mander Jones and Trikojus (*Proc. Roy. Soc., N.S.W.*, 1932, **66**, 300), and by a similar process obtained 6-allyl-5-hydroxyquinoline from 5-hydroxyquinoline. The allyl compounds were reduced to hydroxy-propylquinolines.

With some simplification, Fischer and Renouf's method (*loc. cit.*) for preparation of quinoline-5 : 8-quinone from 8-hydroxyquinoline proved satisfactory. We describe below some experiments made to determine the effect of varying the amount of reagent used to oxidise the intermediate 5-amino-8-hydroxyquinoline. By similar procedures we also obtained 6- and 7-methyl- and 7-propylquinoline-5 : 8-quinone. Although 7-allyl-8-hydroxyquinoline readily coupled with diazotised sulphanilic acid and the resulting azo-compound appeared to be reduced normally, we could not obtain a quinone in this case.

Finally, 2 : 4-dimethylquinoline-5 : 8-quinone was obtained by demethylating 5 : 8-dimethoxy-2 : 4-dimethylquinoline and oxidising the product.

The quinolinequinones were yellow-brown crystalline compounds, with a characteristic pungent odour. In both the 6- and the 7-alkyl series the melting point decreased with increasing size of the alkyl group. 6-Butylquinoline-5 : 8-quinone decomposed rapidly in the air. The quinones were quickly decomposed by alkali.

| Compound (I) | Haemolytic *Streptococcus* | *Staph. aureus* | *B. coli* |
|---|---|---|---|
| R = R′ = R″ = R‴ = H | 0·5 | 5 | 20 |
| R′ = R″ = R‴ = H, R = Me | ,, | ,, | ,, |
| R = R″ = R‴ = H, R′ = Me | 0·02 | ,, | 10 |
| R′ = R″ = R‴ = H, R = Et | 20 | 30 | 50 |
| R = R″ = R‴ = H, R′ = Et | 10 | 30 | 100 |
| R′ = R″ = R‴ = H, R = Pr | 5 | 20 | 50 |
| R = R″ = R‴ = H, R′ = Pr | 0·05 | 5 | 50 |
| R = R″ = R‴ = H, R′ = Bu | 5 | 20 | 50 |
| R = R′ = R‴ = H, R″ = Me | 2 | >20 | >20 |
| (IV; R = allyl) | 20 | 20 | 50 |
| (IV; R = Pr) | ,, | ,, | >50 |
| 6-Methyl-5 : 8-di(toluene-*p*-sulphonamido)quinoline | >10 | >10 | >10 |
| 7-Methyl-5 : 8-di(toluene-*p*-sulphonamido)quinoline | >Saturated | >Saturated | >Saturated |

> indicates that the compound was not inhibitory in saturated solution at pH 7·5.

The bacteriostatic properties of a number of the above compounds were examined. For the tabulated figures, which are the concentrations in mg./100 c.c. which prevented visible growth in Hedley Wright broth overnight at 37°, we are indebted to Drs. A. T. Fuller and F. Hawking of the National Institute for Medical Research. It is interesting that 7-alkylquinoline-5 : 8-quinones are more active than the 6-isomers, and that an alkyl group with an odd number of carbon atoms produces a substantial increase in activity compared with even-numbered members. The high activity shown *in vitro* by some of the compounds was not maintained *in vivo* : neither the quinones nor the azo-compounds were effective against *P. berghei* or *T. equiperdum in vivo*.

## Experimental

The m. p.s (decomp.) of the quinones were determined by immersing the specimens in a bath about 20° below the approximately determined figure, and raising the temperature rapidly. Ethereal extracts were dried with anhydrous $Na_2SO_4$.

*Hydroxyquinolines.*—*5-Hydroxyquinoline.* 5-Aminoquinoline (28·5 g.) in hydrochloric acid (55 c.c. of concentrated acid in 100 c.c. of water) was treated with aqueous sodium nitrite (14 g. in 50 c.c.) at 0—5°. Much tar was formed. The solution was slowly added to boiling hydrochloric acid (300 c.c. of concentrated acid in 1 l. of water). Neutralisation with sodium carbonate gave a sludge which was extracted with ether. The red extract was decolorised with large quantities of charcoal. Removal of the ether left a white solid (2·5 g.), m. p. 218°.

*5-Allyloxyquinoline.* Allyl bromide (3·8 g.) was added dropwise to a stirred, refluxing solution of potassium (1·25 g.) and 5-hydroxyquinoline (4·5 g.) in absolute methanol (18 c.c.). Refluxing was continued for 5 hr., methanol was removed, sodium hydroxide solution was added, and the red solution was extracted with ether. Distillation of the crude product (3·9 g.) gave colourless *5-allyloxyquinoline* (3 g.), b. p. 120—124°/0·7 mm. (Found : C, 76·7; H, 6·6. $C_{12}H_{11}ON$ requires C, 77·8; H, 6·0%). The *picrate* formed yellow needles, m. p. 168—170° (Found : C, 52·7; H, 3·3. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%), from acetone. In a similar way 8-hydroxyquinoline (120 g.) gave 8-allyloxyquinoline (103 g.), b. p. 158—160°/2 mm.

*6-Allyl-5-hydroxyquinoline.* When the above ether (2 g.) was heated a purple-black colour developed which became progressively darker. At 200° rearrangement was complete. The product solidified on cooling, and trituration with ether gave *6-allyl-5-hydroxyquinoline* (1·8 g.), which formed needles, m. p. 161° (Found : C, 77·6; H, 5·8. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%), from methanol. The *picrate* formed yellow needles, m. p. 222° (decomp.) (Found : C, 51·9; H, 3·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%), from acetone–aqueous methanol. By the method of Mander Jones and Trikojus (*loc. cit.*) 8-allyloxyquinoline (47 g.) gave 7-allyl-8-hydroxyquinoline (45 g.), b. p. 120°/0·5 mm.

*5-Hydroxy-6-propylquinoline.* The allyl compound (0·7 g.), 5% palladium–charcoal (0·35 g.)

and methanol (20 c.c.) were shaken with hydrogen. Reaction was rapid, and filtration and concentration, followed by the addition of water, gave the substantially pure product (0·68 g.). From aqueous methanol 5-*hydroxy*-6-*propylquinoline* formed plates, m. p. 178—179° (Found : C, 76·6; H, 7·1. $C_{12}H_{13}ON$ requires C, 76·9; H, 7·0%). Its *picrate* separated from acetone–aqueous methanol as fine yellow needles, m. p. 231° (decomp.) (Found : C, 52·3; H, 3·9. $C_{12}H_{13}ON,C_6H_3O_7N_3$ requires C, 52·0; H, 3·9%).

8-*Hydroxy*-7-*propylquinoline*. The allyl compound (30 g.), palladium–charcoal (3 g.) and methanol (300 c.c.) gave in the usual way 8-*hydroxy*-7-*propylquinoline* (26·3 g.), b. p. 147—149°/5—6 mm. (Found : C, 77·0; H, 7·0%), which solidified at 0°. The *picrate* crystallised from methanol as yellow needles, m. p. 168—169° (Found : C, 52·6; H, 3·8%).

*Hydroxy*-p-*sulphophenylazoquinolines*.—(i) In preliminary experiments a vigorously stirred solution of the hydroxyquinoline in aqueous sodium hydroxide (1 equiv.) was treated with sulphanilic acid (1 equiv.) in hydrochloric acid (2 equivs.), and then a solution of sodium nitrite (1 equiv.) was added at 5°. Next morning the azo-compound was collected. In this way azo-compounds were obtained from 8-hydroxy- (100%), 5-hydroxy-6-methyl- (86%), and 8-hydroxy-7-methyl-quinoline (97%; in this case some alcohol was used to obtain complete dissolution of the hydroxyquinoline).

(ii) The hydroxyquinolines were more soluble in acid than in alkali, and in subsequent work we employed a mixture of an aqueous solution of sulphanilic acid with one of the quinoline in hydrochloric acid (1 equiv.). Frequently a crystalline suspension was formed at 5°, but this did not affect the diazotisation. The temperature of diazotisation was not critical, equal success being achieved at 20°. This method gave 90—98% yields of the azo-compound from 8-hydroxy-, 7-*allyl*-8-*hydroxy*- [crimson needles (Found : C, 58·2; H, 4·5. $C_{18}H_{15}O_4N_3S$ requires C, 58·2; H, 4·1%) from pyridine], and 8-*hydroxy*-7-*propyl*-*quinoline* [dark red needles (Found : C, 55·7; H, 4·6. $C_{18}H_{17}O_4N_3S,H_2O$ requires C, 55·5; H, 4·9%) from pyridine].

*Amino*-p-*sulphophenylazoquinolines*.—A solution of sulphanilic acid, sodium hydroxide, and sodium nitrite (1 equiv. of each) was poured into ice and hydrochloric acid (2 equivs.). The resulting suspension was immediately added to a vigorously stirred and cooled solution of the alkyl-aminoquinoline in dilute acetic acid. The dark red suspension was treated with sodium acetate. Next morning the purple solid was collected. Azo-compounds in 90—100% yield were thus obtained from 8-amino-2-methyl-, 5-amino-6-methyl-, 8-amino-7-methyl-, 5-amino-6-ethyl-, 8-amino-7-ethyl-, 5-amino-6-propyl-, 5-amino-6-butyl-, and 8-amino-7-butyl-quinoline.

*Quinoline*-5 : 8-*quinones*.

*From Hydroxy*-p-*sulphophenylazoquinolines*.—The azo-compound was added slowly to a boiling solution of stannous chloride (2·3 equivs.) in hydrochloric acid (2 c.c. of concentrated acid per 1 g. of stannous chloride). Boiling was continued until the initial colour had disappeared. Frequently yellowish-brown crystals separated. The mixture was diluted with boiling water, and hydrogen sulphide was passed in for several hours. After filtration the solution was oxidised directly.

Aliquot parts of the aminophenol solution were vigorously agitated with a solution of potassium dichromate in sulphuric acid (1 c.c. of concentrated acid and 10 c.c. of water per 1 g. of potassium dichromate). The resulting dark red solution was extracted with chloroform. Removal of the solvent provided the quinone. In the following Table the number of atom-equivs. of oxygen is calculated by assuming that the aminophenol was formed quantitatively.

| | Azo-compound (g.) | Aminophenol soln. (c.c.) | $K_2Cr_2O_7$ (g.) | Atom-equivs. of $O_2$ | Yield (g.) | Yield (%) |
|---|---|---|---|---|---|---|
| Quinoline-5 : 8-quinone [1] | 22·7 | 200 | 4·2 | 0·6 | 3·35 | 30 [2] |
| | ,, | ,, | 8·4 | 1·2 | 3·25 | 29·5 |
| | 56·2 | 3500 | 25·0 | 1·5 | 7·30 | 27 |
| | 68·1 | 1500 | 37·8 | 1·8 | 8·90 | 27 |
| | 22·7 | 400 | 16·8 | 2·4 | 3·3 | 30 |
| | ,, | 450 | 21·0 | 3·0 | 3·0 | 27 |
| 7-Propylquinoline-5 : 8-quinone [1] | 13·0 | 700 | 9·8 | 3·0 | 4·9 | 68 |
| | 4·6 | 250 | 4·5 | 3·7 | 1·4 | 55 |
| | ,, | 340 | 6·7 | 5·5 | 1·45 | 57 |
| | ,, | 400 | 7·4 | 8·9 | 1·5 | 58·5 |

[1] See below for properties. [2] This material was highly impure and rapidly decomposed.

In the same way 5-hydroxy-6-methyl-8-*p*-sulphophenylazoquinoline (2 g.) with potassium dichromate (4 g.) in 3N-sulphuric acid (50 c.c.), and 8-hydroxy-7-methyl-5-*p*-sulphophenylazo-

quinoline (5·15 g.) with potassium dichromate (5 g.), gave the corresponding quinones (0·38 g. and 1·37 g.) (see below).

| Quinoline-5 : 8-quinone | Azo-compound (g.) | Vol. of diamine soln. (l.) | $K_2Cr_2O_7$ (g.) | Atom-equivs. of $O_2$ | Yield (g.) | Yield (%) |
|---|---|---|---|---|---|---|
| 2-Methyl- ..... | 13·3 | 0·4 | 10·5 | 3·3 | 1·8 | 27 |
| 6-Methyl- ..... | ,, | ,, | 21·0 | 6·6 | 1·5 | 22 |
| 6-Methyl- ..... | 5·8 | 0·44 | 6·5 | 4·0 | 0·8 | 28 |
| | ,, | ,, | ,, | ,, | 1·0 | 34 |
| 7-Methyl- ..... | 11·5 | 0·4 | 9·8 | 3·0 | 2·6 | 45 |
| | 16·1 | 0·5 | 8·4 | 2·0 | 3·0 | 37 [1] |
| | ,, | 0·6 | 12·6 | 3·0 | 2·6 | 32 [1] |
| | ,, | 0·7 | 16·8 | 4·0 | 2·3 | 28 [1] |
| 6-Ethyl- ..... | 27·5 | 3·0 | 22·5 | 3·0 | 10·3 | 73 |
| 7-Ethyl- ..... | 6·7 | 1·0 | 5·3 | ,, | 2·4 | 68·5 |
| | 20·0 | 3·0 | 15·9 | ,, | 6·6 | 63·5 [2] |
| 6-Propyl- ..... | 6·2 | 1·0 | 3·2 | 2·0 | 1·7 | 50·5 |
| | ,, | ,, | 4·9 | 3·0 | 1·6 | 47·5 |
| | 18·6 | 3·0 | 14·7 | ,, | 2·7 | 27 [2] |
| 6-Butyl- ..... | 23·4 | 2·0 | 9·6 | 2·0 | 4·5 | 34 |
| 7-Butyl- ..... | 6·2 | 1·0 | 2·0 | ,, | 0·9 | 44 [2] |
| | ,, | ,, | 3·0 | 3·0 | 1·15 | 56 [2] |
| | 18·5 | 3·0 | 9·0 | ,, | 4·6 | 75 |

[1] Experiments with an old specimen of diamine hydrochloride. [2] In these experiments a brownish-black colour was produced in the drying agent when the chloroform extract was dried. The specimen of $Na_2SO_4$ used proved to be slightly alkaline.

| Quinoline-5 : 8-quinone | Method of prepn.[1] | Solvent [2] | Cryst. form | M. p. | Formula | Analysis, % Found C | Found H | Reqd. C | Reqd. H |
|---|---|---|---|---|---|---|---|---|---|
| Parent compound | A | a | Brown needles | 113—115° (decomp.) [3] | — | — | — | — | — |
| 2-Methyl- | B | ,, | Light brown needles | 135 (decomp.) | $C_{10}H_7O_2N$ | 69·5 | 4·15 | 69·4 | 4·1 |
| 6-Methyl- | A & B | ,, | Brown needles | 177—180 (decomp.) [4] | ,, | 69·9 | 4·1 | ,, | ,, |
| 7-Methyl- | ,, | ,, | Pale yellow rods | 175—180 (decomp.) | ,, | 69·3 | 4·1 | ,, | ,, |
| 2 : 4-Dimethyl- | C | ,, | Yellow-brown needles | 156 (decomp.) | $C_{11}H_9O_2N$ | 70·4 | 4·9 | 70·6 | 4·85 |
| 6-Ethyl- | B | ,, | Yellow-brown flakes | 135—137 (decomp.) | ,, | 70·3 | 4·7 | ,, | ,, |
| 7-Ethyl- | ,, | ,, | Brown prisms | 123—125 (decomp.) | ,, | 70·4 | 5·3 | ,, | ,, |
| 6-Propyl- | ,, | b | Brown feathers | 68—70 | $C_{12}H_{10}O_2N$ | 71·5 | 6·0 | 71·6 | 5·5 |
| 7-Propyl- | A | a | Ochre crystals | 75—78 | ,, | 70·7 | 4·9 | ,, | ,, |
| 6-Butyl | B | b | Fawn powder | 49—50 [5] | $C_{13}H_{13}O_2N$ | 71·1 | 5·7 | 72·5 | 6·15 |
| 7-Butyl- | B | ,, | Greenish-brown | 67—88 | ,, | 72·5 | 5·6 | ,, | ,, |

[1] (A) From hydroxyquinolines. (B) From aminoquinolines. (C) See separate description. [2] (a) Benzene–ligroin (b. p. 60—80°); (b) ether–light petroleum (b. p. 40—60°). [3] Fischer and Renouf (*loc. cit.*) gave m. p. 110—120° (decomp.). [4] Christiansen and Dolliver (*loc. cit.*) gave m. p. 167—168°. [5] This compound decomposed rapidly in air.

*From Amino-*p*-sulphophenylazoquinolines.*—The azo-compounds were reduced in the way described above. Except in the cases of the three monomethyl compounds, the solutions were partly freed from tin and oxidised immediately. When the diluted reduction solution from 5-amino-6-ethyl-8-*p*-sulphophenylazoquinoline was treated with hydrogen sulphide and filtered, the filtrate was colourless. The tin sulphide contained small red crystals, and repeated extraction with boiling water gave the characteristic red diamine solution. Subsequently, all sulphide residues were similarly treated. Details of these experiments and of the *products* are tabulated above.

The residues obtained by evaporating hydrochloric acid solutions of 5 : 8-diamino-2- and -6-methylquinoline were dissolved in pyridine and treated with toluene-*p*-sulphonyl chloride. Much heat was evolved, and next morning the solutions were poured into iced hydrochloric acid. The solutions of the precipitates in aqueous sodium hydroxide were decolorised and acidified. 2-*Methyl-*, prisms, m. p. 194° (Found : C, 59·6; H, 4·8. $C_{24}H_{23}O_4N_3S_2$ requires C, 59·6; H, 4·8%), and 6-*methyl-*5 : 8-*di*(*toluene*-p-*sulphonamido*)*quinoline*, small needles, m. p. 186° (Found : C, 59·75; H, 4·9%), from aqueous methanol, were obtained.

*Miscellaneous experiments.*

*Reaction of 6-Methyl-5-nitroquinoline with Hydroxylamine.*—The best yield of 8-amino-6-methyl-5-nitroquinoline was obtained as follows : The nitro-compound (11·5 g.), hydroxylamine hydrochloride (50 g.), and absolute alcohol (200 c.c.) were stirred and refluxed whilst a solution of potassium hydroxide (100 g.) in absolute alcohol (500 c.c.) was added slowly. Refluxing was continued for 6 hr. The mixture was poured on ice and the product was collected next morning. The solid was repeatedly extracted with benzene, and on cooling of the concentrated extracts the amine (5·3 g.; m. p. 190—192°) separated. *8-Amino-6-methyl-5-nitroquinoline* formed short, orange-red needles, m. p. 192—193° (Found : C, 58·8; H, 4·2. $C_{10}H_9O_2N_3$ requires C, 59·0; H, 4·5%), from benzene. The *semipicrate* formed orange needles, m. p. 177—180° (decomp.) (Found : C, 48·1; H, 3·4. $C_{10}H_9O_2N_3,\frac{1}{2}C_6H_3O_7N_3$ requires C, 49·1; H, 3·3%).

In another experiment, carried out similarly but at 70° for 3 hr., the nitroquinoline (2 g.), hydroxylamine hydrochloride (5 g.), potassium hydroxide (10 g.), and absolute alcohol (140 c.c.) gave, as the sole product, benzene-insoluble material (1·3 g.; m. p. 282—283°). Recrystallised from acetic anhydride this formed soft, pale yellow-green needles, m. p. 282—285° (Found : C, 63·1; H, 3·5; N, 12·2. $C_{20}H_{14}O_4N_4$ requires C, 64·1; H, 3·8; N, 15·0%). Various conditions gave mixtures of starting material, nitro-amine, and amorphous material (for details see R. Long, Thesis, London, 1953).

*Action of Alkali on 6-Methyl-5-nitroquinoline.*—The nitro-compound (1 g.), potassium hydroxide (2 g.), and alcohol (20 c.c.) were refluxed for 2·5 hr. A dark brown colour was immediately produced, and small crystals (0·4 g.), m. p. 277—278°, separated. These were collected after the addition of water. From acetic anhydride the product formed golden needles, m. p. 312—315° (decomp.) (Found : C, 71·1; H, 2·9%). The same material (Found : C, 71·8; H, 3·1%) appeared to arise on crystallisation from a large volume of benzene.

*5 : 8-Diamino-6-methylquinoline and its Oxidation.*—8-Amino-6-methyl-5-nitroquinoline (3 g.), palladium–charcoal (0·5 g.), and warm methanol (500 c.c.) were shaken with hydrogen. Reduction was complete only after 2 days. Filtration and evaporation gave a greenish-black residue (2·6 g.), which from benzene formed golden blades of *5 : 8-diamino-6-methylquinoline*, m. p. 161—163° (Found : C, 68·3; H, 6·3. $C_{10}H_{11}N_3$ requires C, 69·3; H, 6·4%). Its *picrate* crystallised from methanol–acetone as felted, tan needles, m. p. 197—200° (decomp.) (Found : C, 49·1; H, 3·8. $C_{10}H_{11}N_3,C_6H_3O_7N_3,C_3H_6O$ requires C, 49·6; H, 4·4%). The crude diamine (2 g.) in 6N-sulphuric acid (60 c.c.) gave, in the usual way with potassium dichromate (6·8 g. in 70 c.c. of water), 6-methylquinoline-5 : 8-quinone (0·5 g.).

The nitro-amine (8 g.), with stannous chloride (27·2 g.) and concentrated hydrochloric acid (56 c.c.) at 95° for 3 hr. gave a crystalline salt, which when dissolved in water (2·5 l.) and oxidised with potassium dichromate (24 g. in 275 c.c. of 4N-sulphuric acid) provided the quinone (3·55 g.).

*5-Amino-7-methyl-8-nitroquinoline.*—7-Methyl-8-nitroquinoline (5 g.), hydroxylamine hydrochloride (20 g.), and absolute ethanol (200 c.c.) were refluxed and treated slowly with potassium hydroxide (40 g.) in ethanol (200 c.c.). After refluxing for 8 hr. the mixture was poured into water, and the precipitate (3·6 g.) collected. This material (2·5 g.) was repeatedly crystallised from benzene, *5-amino-7-methyl-8-nitroquinoline* being obtained as yellowish-orange prisms (0·55 g.), m. p. 207—208° (Found : C, 58·9; H, 4·55. $C_{10}H_9O_2N_3$ requires C, 59·0; H, 4·5%).

*8-Amino-6-ethyl-5-nitroquinoline.*—In the same way 6-ethyl-5-nitroquinoline (10 g.), hydroxylamine hydrochloride (40 g.), and absolute ethanol (100 c.c.) gave with potassium hydroxide (80 g.) in absolute ethanol (200 c.c.) a crude product (2·95 g.) which could not be purified by crystallisation. Passage in benzene over alumina gave a bright orange middle band of *8-amino-6-ethyl-5-nitroquinoline* (1·1 g.) which formed crimson needles, m. p. 128—129° (Found : C, 60·9; H, 4·7. $C_{11}H_{11}O_2N_3$ requires C, 60·8; H, 5·1%), from ether.

The nitro-amine (0·4 g.), with palladium–charcoal (0·1 g.) in methanol (10 c.c.), was very slowly reduced. The crude diamine so obtained, in 4N-sulphuric acid (10 c.c.), was oxidised with potassium dichromate (0·5 g.) in water (10 c.c.), giving 6-ethylquinoline-5 : 8-quinone (0·25 g.).

*5 : 8-Dimethoxy-2 : 4-dimethylquinoline.*—2 : 5-Dimethoxyaniline (18 g.) and acetylacetone (13 g.) were refluxed for ½ hr., after which concentrated sulphuric acid (0·5 c.c.) was added carefully. After ¼ hr. more of refluxing the mixture was poured into concentrated sulphuric acid (150 c.c.), and the solution was warmed at 95° for ¼ hr. The cooled, diluted solution was basified, and the precipitate crystallised from ethyl acetate, giving crystals (6 g.), m. p. 104—107° (Lions, Perkin, and Robinson gave m. p. 107°).

*2 : 4-Dimethylquinoline-5 : 8-quinone.*—The above product (1 g.) and hydrobromic acid (*d* 1·48; 5 c.c.) were refluxed for 5 hr. The suspension formed on cooling was diluted and

neutralised with ammonia, and extracted with ether. The tacky product recovered from the ether was treated in 5N-hydrochloric acid (10 c.c.) with excess of aqueous ferric chloride solution (10%). From the deep-red solution chloroform removed 2 : 4-*dimethylquinoline*-5 : 8-*quinone* (0·35 g.) (see Table).

The authors are indebted to the Medical Research Council for a maintenance grant to one of them (R. L.), and to Imperial Chemical Industries Limited and the Council of University College, Exeter, for financial support.

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[*Received, June* 1*st*, 1953.]