104. *Nitration of 4-Chloro- and 4-Hydroxy-quinaldine.*

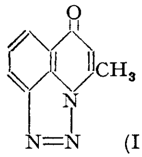
By Barbara E. Halcrow and William O. Kermack.

Nitration of 4-chloroquinaldine yields mainly 4-*chloro*-8-*nitroquinaldine*, along with some of the 5-*nitro*- and the 6-nitro-isomer. The orientation of the 8-nitro-compound has been established by converting it into 4 : 8-dichloroquinaldine, and the 5-nitro-derivative has been converted into the known 5-amino-4-hydroxyquinaldine. The fact that 4-hydroxyquinaldine yields the 3- or the 6-nitro-derivative according as the nitration is carried out in hot concentrated nitric acid or with nitric acid in cold sulphuric acid has been confirmed.

It has been shown (Balaban, J., 1930, 2349) that when 2-hydroxylepidine is nitrated with nitric acid in cold sulphuric acid, the 6-nitro-derivative is formed, whereas, according to Johnston and Hamilton (*J. Amer. Chem. Soc.*, 1941, **63**, 2864) and Krahler and Burger (*ibid.*, 1942, **64**, 2417), the main product of the nitration of 2-chlorolepidine is the 8-nitro-derivative, some of the 6-nitro-compound also being formed. It was thought of interest to investigate the nitration of 4-chloroquinaldine, especially as, if nitration occurred mainly in the 8-position, a promising route would be opened to 8-nitro-4-hydroxyquinaldine. Many unsuccessful attempts had previously been made in this laboratory to obtain this compound from *o*-nitroaniline and ethyl acetoacetate by the general method of Conrad and Limpach, but the presence of the *o*-nitro-group seems to interfere with the reaction.

When 4-chloroquinaldine is nitrated with potassium nitrate in 100% sulphuric acid the product contains three isomeric chloro-nitro-quinaldines. The main product, separated by means of its low solubility in cold 2N-hydrochloric acid, was identified as 4-*chloro*-8-*nitroquinaldine* by conversion into 4-*chloro*-8-*amino*- and thence into 4 : 8-dichloro-quinaldine, identical with the dichloro-compound described by Krahler and Burger (*loc. cit.*). 4-*Chloro*-5-*nitroquinaldine*, separated as the nitrate, was identified by conversion into 5-*nitro*-4-*methoxyquinaldine* and hence through 5-nitro-4-hydroxyquinaldine into 5-amino-4-hydroxyquinaldine, identical with that synthesised by Kermack and Webster (J., 1942, 213). The third isomer, 4-chloro-6-nitroquinaldine, was identical with that of Kermack and Weatherhead (J., 1939, 563).

In some experiments the mixed product obtained after removal of the least basic component, *viz.*, 4-chloro-8-nitroquinaldine, on repeated crystallisation from benzene gave 8-*nitro*-4-*hydroxyquinaldine*, as was proved by converting 4-chloro-8-nitroquinaldine into 8-*nitro*-4-*methoxyquinaldine* and thence into the same 8-nitro-4-hydroxyquinaldine. Reduction of the latter afforded 8-*amino*-4-*hydroxyquinaldine*, which on diazotisation gave a stable, white, crystalline compound, 4-*keto*-1 : 4-*dihydroquinaldine*-1 : 8-*diazoimide* (I) (compare Krahler and Burger for the analogous case of 8-amino-2-hydroxylepidine).



(I.)

Reduction of 4-chloro-8-nitroquinaldine by hydrogen in presence of Raney nickel catalyst (Albert and Ritchie, *J. Proc. Roy. Soc., N.S.W.*, 1940, **74**, 74) yielded 4-chloro-8-aminoquinaldine. Attempts to obtain 4-chloro-2-methyl-*o*-phenanthroline by means of the Skraup reaction on this amino-compound were unsuccessful.

It seemed desirable to reinvestigate the nitration of 4-hydroxyquinaldine, for Conrad and Limpach (*Ber.*, 1887, **20**, 950) state that it yields the 3-nitro-derivative, whereas Kermack and Weatherhead (*loc. cit.*) found that it nitrates in the 6-position. The explanation lies in the fact that Conrad and Limpach used hot, concentrated nitric acid, whereas Kermack and Weatherhead carried out nitration in cold concentrated sulphuric acid. The two nitro-derivatives are very similar: both are unmelted at 400°, and dissolve readily in sodium hydroxide solution and ammonia, though in dilute ammonia the 3-nitro-compound appears somewhat more readily soluble. They are, however, readily distinguishable on conversion into the corresponding 4-chloronitroquinaldines by the action of phosphorus oxychloride and pentachloride. 4-Chloro-3-nitroquinaldine melts at 93—94° (Conrad and Limpach, *Ber.*, 1888, **21**, 1981), and 4-chloro-6-nitroquinaldine at 142° (Kermack and Weatherhead, *loc. cit.*). The mixed m. p. of these isomers showed marked depression, so it is certain that they are distinct. It would seem that in the concentrated sulphuric acid the hydroxyquinaldine exists in the form of its salt, with the result that nitration in the 3-position of the positively charged pyridine ring is inhibited, whilst the 6-position can still undergo activation by electromeric shift of electrons from the hydroxy-group to the carbon atom in position 6. In concentrated nitric acid, which contains many water molecules, sufficient amounts of the base apparently exist in the uncombined state to allow nitration in the 3-position to be the predominating reaction. In neither case does the 8-nitro-derivative appear to be formed.

Experimental.

Nitration of 4-*Chloroquinaldine*.—The base (45 g.) was dissolved in 100% sulphuric acid (298 g.), the solution being kept cold in a freezing mixture, and potassium nitrate (35 g.) added gradually with mechanical stirring. After standing overnight at room temperature, the reaction mixture was poured on ice and basified with sodium hydroxide. The precipitated yellow solid was filtered off and washed.

4-*Chloro*-8-*nitroquinaldine*.—The yellow solid obtained above was heated to boiling in 2N-hydrochloric acid (200 c.c.), the solution filtered immediately from a small residue, and diluted with its own volume of water. The yellow solid deposited crystallised from alcohol as yellow needles (12·5 g.), m. p. 111—113° (Found: C, 53·9; H, 2·9. $C_{10}H_7O_2N_2Cl$ requires C, 53·9; H, 3·1%), sparingly soluble in water, insoluble in sodium hydroxide and N-hydrochloric acid. The *compound* is partly soluble in cold 2—3N- and completely soluble in 4—10N-hydrochloric acid. It is soluble in benzene, but insoluble in ligroin and light petroleum.

4-*Chloro*-8-*aminoquinaldine*.—4-Chloro-8-nitroquinaldine (3 g.) was dissolved with warming in alcohol (45 c.c.) in a stout bottle, and Raney nickel catalyst sludge (3—4 c.c.) added. The bottle was evacuated, and hydrogen led in with vigorous shaking till absorption (about 1 l.) was complete. The catalyst was filtered off, and the alcoholic solution evaporated to dryness; the grey *substance* obtained crystallised from alcohol as yellow plates (1·5 g.), m. p. 108—110° (Found : C, 62·0; H, 4·9. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7%), soluble in benzene, acetone, ether, ligroin or hydrochloric acid, insoluble in water and sodium hydroxide. The compound gives a positive diazo-test. It shows a marked blue fluorescence in organic solvents, but none in dilute hydrochloric acid.

4 : 8-*Dichloroquinaldine*.—4-Chloro-8-aminoquinaldine (0·5 g.), water (2·5 c.c.), and concentrated hydrochloric acid (1 c.c.) were cooled in a freezing mixture, and a solution of sodium nitrite (0·25 g.) in water (2 c.c.) added slowly with stirring. The diazotised solution was added slowly to a suspension of cuprous chloride (from cupric chloride 0·15 g., water 0·15 c.c., concentrated hydrochloric acid 0·5 c.c., and copper 0·07 g.). Nitrogen was given off, and the mixture was warmed gently to 30° till frothing ceased. On basification and steam-distillation, a white solid was obtained; crystallised from light petroleum, this had m. p. 81—82°, mixed m. p. with 4 : 8-dichloroquinaldine (m. p. 84°) prepared from *o*-chloroaniline, 83—84°. Krahler and Burger (*loc. cit.*) give m. p. 87°.

4-*Chloro*-5-*nitroquinaldine*.—The N-hydrochloric acid filtrate from the crude 4-chloro-8-nitroquinaldine was basified with sodium hydroxide. The yellow solid obtained (precipitate X) was warmed in N-nitric acid, and the solution filtered. The filtrate deposited a sticky orange substance which was dissolved with warming in dilute hydrochloric acid. On basification with sodium hydroxide, a precipitate was obtained which crystallised from alcohol as colourless prisms, m. p. 111—113°. The mixed m. p. with 4-chloro-8-nitroquinaldine (m. p. 111—113°) was 82—105°, and that with the 6-nitro-isomer (m. p. 142°) was 90—105° (Found : N, 12·6. $C_{10}H_7O_2N_2Cl$ requires N, 12·6%). 4-*Chloro*-5-*nitroquinaldine* is sparingly soluble in water, soluble in dilute hydrochloric acid, and insoluble in sodium hydroxide. It is soluble in benzene and acetone and slightly soluble in ligroin.

5-*Nitro*-4-*methoxyquinaldine*.—4-Chloro-5-nitroquinaldine (0·5 g.) was added to a solution of sodium (0·1 g.) in methyl alcohol (5 c.c.), and the mixture heated under reflux on the steam-bath for 1—2 hours. The methyl alcohol was evaporated off, and the black residue diluted with water. The dark brown product crystallised from alcohol and then from ligroin as light brown crystals, more being obtained from the aqueous filtrate on concentration; m. p. 164—165° (Found : C, 60·8; H, 4·7. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6%).

5-*Amino*-4-*hydroxyquinaldine*.—5-Nitro-4-methoxyquinaldine (0·1 g.) and 5N-hydrochloric acid (1 c.c.) were heated under reflux for an hour, and the red solution evaporated to a third of its volume. Stannous chloride (0·3 g.) was added, and the mixture heated at 100° for an hour. The crystalline orange-brown precipitate which separated on cooling was filtered off and suspended in hot water. The tin was removed with hydrogen sulphide, and the yellow filtrate evaporated to dryness. The bright yellow residual solid was dissolved in a little water, giving a colourless solution, and basified with a drop of ammonia. The mixture was evaporated to a small volume, and the grey product which separated crystallised from water; m. p. 210—213°, unchanged on admixture with 5-amino-4-hydroxyquinaldine (m. p. 210—213°) prepared according to Kermack and Webster (*loc. cit.*). Both samples of the substance when diazotised and coupled with β-naphthol gave diazo-compounds of the same red shade.

4-*Chloro*-6-*nitroquinaldine*.—After the removal of the nitrate of 4-chloro-5-nitroquinaldine from the N-nitric acid, 4-chloro-6-nitroquinaldine separated on standing in crystals, m. p. 140—142°, and mixed m. p. 141—142°.

8-*Nitro*-4-*methoxyquinaldine*.—4-Chloro-8-nitroquinaldine (10 g.) was added to a solution of sodium (2 g.) in methyl alcohol (100 c.c.), and the mixture heated under reflux for 1—2 hours. Most of the methyl alcohol was removed by distillation and the residue diluted with water. The precipitated solid crystallised from alcohol as long, colourless plates (6·75 g.), m. p. 129—130° (Found : C, 60·7; H, 4·2. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6%), soluble in benzene, acetone, ether, and dilute hydrochloric acid, insoluble in water, sodium hydroxide, and ligroin.

8-*Nitro*-4-*hydroxyquinaldine*.—(1) 8-Nitro-4-methoxyquinaldine (0·5 g.) and 5N-hydrochloric acid (5 c.c.) were refluxed for an hour. The solution was evaporated almost to dryness, and on dilution with water an orange solid was obtained which was crystallised from alcohol and twice from benzene. The yellow, feathery crystals melted at 224—230°. When ammonia was added to the filtrate from the orange solid, some crude 8-nitro-4-methoxyquinaldine was recovered unchanged (m. p. 122—126°; mixed m. p. with above 124—130°).

(2) A sample of precipitate X (above) was crystallised twice from benzene. The chlorine-free, yellow needles deposited melted at 224—230°, alone or mixed with the compound obtained in (1) (Found : C, 58·3; H, 4·3. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%). 8-*Nitro*-4-*hydroxyquinaldine* is slightly soluble in water, somewhat more soluble in dilute hydrochloric acid, easily soluble in dilute sodium hydroxide. It is soluble in acetone and ether, insoluble in ligroin.

8-*Amino*-4-*methoxyquinaldine*.—The 8-nitro-compound (6 g.), dissolved in alcohol (90 c.c.), was reduced by hydrogen in the presence of Raney nickel catalyst as described above; 1·9 l. of hydrogen were absorbed. The grey crystals which separated on removal of the alcohol crystallised from alcohol as pale brown prisms (3 g.), m. p. 115—116°, insoluble in water and sodium hydroxide, slightly soluble in dilute hydrochloric acid, soluble in concentrated hydrochloric acid, benzene, acetone, and ether. For analysis the compound was converted into the *acetyl* derivative which formed white needles, m. p. 144—146° (Found : C, 67·2; H, 5·9. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1%), insoluble in cold water, slightly soluble on heating; insoluble in sodium hydroxide, soluble in dilute hydrochloric acid, alcohol, and benzene.

8-*Amino*-4-*hydroxyquinaldine*.—8-Nitro-4-hydroxyquinaldine (0·4 g.), stannous chloride (1·5 g.), and concentrated hydrochloric acid (5 c.c.) were heated at 100° for an hour. The pale yellow crystals which separated on cooling were filtered off and suspended in hot water. The tin was removed with hydrogen sulphide, and the yellow filtrate evaporated to dryness. The yellow crystalline residue was dissolved in a little water and basified with ammonia. The precipitate recrystallised from water as sheaves of colourless needles which darkened without definite melting at about 270°. This *compound* retained traces of water tenaciously even after drying in a vacuum at 78° (Found : C, 68·0; H, 6·0. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·7. $C_{10}H_{10}ON_2,\frac{1}{4}H_2O$ requires C, 67·2; H, 5·9%).

When the compound, dissolved in dilute hydrochloric acid, was treated with excess of sodium nitrite, a white precipitate immediately separated; it recrystallised from water as small, colourless needles which darkened somewhat at about 250° but did not melt below 400°. This compound, which does not couple with β-naphthol in alkaline solution, is evidently 4-*keto*-1 : 4-*dihydroquinaldine*-1 : 8-*diazoimide* (Found : N, 22·2. $C_{10}H_7ON_3$ requires N, 22·7%).

Nitration of 4-*Hydroxyquinaldine*.—The compound obtained from 4-hydroxyquinaldine and concentrated nitric acid, either by boiling (Conrad and Limpach, *loc. cit.*) or by heating at 100° for an hour, did not appear to be homogeneous, a small residue being left after extraction in hot water. Both the soluble and the insoluble fraction dissolve in ammonia, the former with a yellow and the latter with a red colour. The crude product was heated at 120° with phosphorus pentachloride and oxychloride (Conrad and Limpach, *loc. cit.*) for an hour. The product obtained on dilution with ice was washed with alkali and recrystallised from aqueous alcohol and ligroin, forming a pale yellow solid, m. p. 92—93°. Conrad and Limpach give m. p. 93—94° for 4-chloro-3-nitroquinaldine.

The nitration of 4-hydroxyquinaldine by concentrated nitric acid in cold sulphuric acid yielded a mononitro-derivative which was soluble in sodium hydroxide and ammonia to give an orange solution but appeared rather less soluble in dilute ammonia than Conrad and Limpach's product. It was readily converted into 4-chloro-6-nitroquinaldine, m. p. 140—141°, which, when mixed with the 3-nitro-derivative, melted between 75° and 105°.

We thank the Medical Research Council for a grant to one of us (B. E. H.) which enabled this work to be carried out, and also for an expenses grant which defrayed part of the cost of chemicals required.

Research Laboratory, Royal College of Physicians, Edinburgh.

[*Received, January 29th,* 1945.]