

**208.** *The Reaction between Phenylhydrazine and 4-Chloroquinoline Derivatives, and the Preparation of the Corresponding 4-Benzeneazo- and 4-Amino-compounds.*

By O. G. BACKEBERG.

Phenylhydrazine and 4-chloroquinoline derivatives react to form two isomeric products according to the conditions of the reaction, (i) the corresponding 4-*phenylhydrazino*-compound (I) if the reaction is carried out at 200° in an inert solvent. and

(ii) an isomeric substance, which is regarded as the corresponding 3-anilino-4-amino-compound (V), if the reaction is carried out in a sealed tube at 200°.

The 4-phenylhydrazino-compounds are unstable in air, and are readily oxidised by ferric chloride to the corresponding 4-benzeneazo-compounds. Reduction with zinc dust and hydrochloric acid of either the 4-phenylhydrazino- or the 4-benzeneazo-compounds gives the 4-amino-compounds; this affords a convenient method for the preparation of 4-aminoquinoline derivatives. The yields in all the above reactions are good.

Confirmation of the structure assigned to the sealed-tube reaction product is found in its conversion into the iminazole (VII) by the action of acetic anhydride.

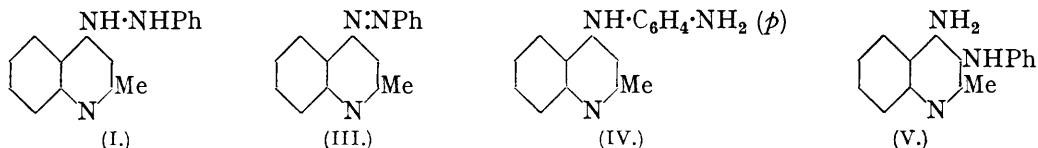
Three of the benzeneazo-compounds described appear to exist in two forms.

EPHRAIM (*Ber.*, 1893, 26, 2227) reported that, when 4-chloroquinaldine (1 mol.) and phenylhydrazine (2 mols.) were heated in an oil-bath at 115°, the product was 4-phenylhydrazinoquinaldine (I), yellowish crystals from benzene, m. p. 134°, which turned brown in air, and formed a hydrochloride, m. p. 272° (decomp.). In support of the structure assigned to the base he stated that it was reduced to 4-aminoquinaldine by zinc dust and hydrochloric acid.

An investigation of the reaction showed that, as in the reaction with hydrazine hydrate (Koenigs and von Loesch, *J. pr. Chem.*, 1935, 143, 59), two different products are obtainable according to the conditions of the reaction: (i) 4-phenylhydrazinoquinaldine (I), m. p. 188° (*hydrochloride*, m. p. 284°, decomp.); this base was formed from the reactants by heating them in equivalent amount at 200° in an inert solvent; it was oxidised in air to the red 4-benzeneazoquinaldine (III), it reduced Fehling's solution, and it was decomposed by copper sulphate in acid solution, and (ii) an isomeric substance, C<sub>16</sub>H<sub>15</sub>N<sub>3</sub> (II), m. p. 142° (*hydrochloride*, m. p. 218°, decomp.), stable in air, possessing none of the reducing properties of a hydrazine, and unchanged by reduction with zinc dust and hydrochloric acid; this compound was formed when 4-chloroquinaldine and excess of phenylhydrazine were heated in a sealed tube at 200°. Repetition of the experiment under the conditions described by Ephraim gave a tarry product, from which a small quantity of the compound (I) was isolated, but a product having m. p. 134° could not be obtained from the reaction.

The compound (I) was readily oxidised by ferric chloride in acetic acid solution to 4-benzeneazoquinaldine (III), and both the compounds (I) and (III) were so easily reduced to 4-aminoquinaldine that this affords a convenient method for the preparation of such 4-amino-compounds; furthermore, the behaviour of the compound (I) in these oxidation and reduction reactions definitely established its constitution.

It is probable that the compound (I) is the first product of the reaction, for by heating it in a sealed tube with phenylhydrazine it was transformed into the isomer (II).

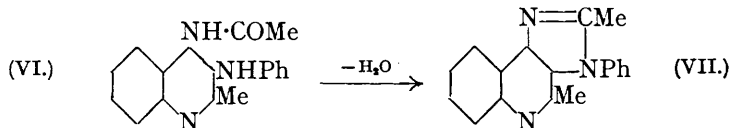


The possibility that the isomer (II) may be a benzidine or semidine transformation product of the hydrazino-compound (I) cannot be excluded, although it is rendered improbable by the fact that the compound (I) is unchanged by heating with dilute hydrochloric acid; the *p*-semidine transformation product, 4-*p*-aminoanilinoquinaldine (IV), was synthesised and found to be different from the isomer (II). By the same procedure adopted in the investigation of the structure of the isomeric product formed in the reaction with hydrazine hydrate (Backeberg and Friedmann, this vol., p. 973), in which various positions in the chloroquinoline derivative were blocked by methyl groups in order to limit the possibilities of isomerisation, it was found that the 3-position is involved in the isomeric change, and it is therefore considered that the isomer (II) is 3-anilino-4-aminoquinaldine (V); this compound was not, however, prepared by direct synthesis for com-

parison. Similarly, the sealed-tube reaction products from 6-methyl-, 5 (or 7)-methyl-, 8-methyl-, 5:7-dimethyl-, and 6:8-dimethyl-4-chloroquinoline, as well as 4-chloroquinoline, are to be regarded as the corresponding 3-*anilino*-4-*amino*-compounds.

In the case of 4-chloro-3-methylquinoline, unlike its behaviour with hydrazine hydrate (when a crystalline product was not formed), the 4-*phenylhydrazino*-compound could be obtained, but an isomeric substance was not formed in the sealed-tube reaction, confirming the fact that the 3-position is involved in the transformation of the hydrazino-compound (I) into the isomer (II).

In further support of the structure assigned to it, the isomer (II) was converted by the action of acetic anhydride into a compound  $C_{18}H_{15}N_3$ , which is regarded as 1'-*phenyl*-2:2'-*dimethylquin*(3:4:5':4')*iminazole* (VII), probably formed by the elimination of water from the unstable intermediate 3-*anilino*-4-*acetamidoquinoline* (VI), as follows:



The various methyl-substituted 4-chloroquinolines mentioned, as well as 4-chloroquinoline, were also converted into the corresponding 4-*phenylhydrazino*-compounds, being isolated in the form of their hydrochlorides; the free bases were so readily oxidised in air that they were not as a rule isolated, but the crude hydrochlorides were used for oxidation to the 4-*benzeneazo*-, and reduction to the 4-*amino*-compounds. In addition, the corresponding 4-*benzeneazo*- and 4-*amino*-compounds were prepared from 6- and 8-ethoxy-4-chloroquinoline; in this connection, 4-chloro-6-ethoxyquinoline, described by Lockhart and Turner and stated to have m. p. 65° (J., 1937, 426), was previously described by the author and found to have m. p. 78° (J., 1931, 2816; 1932, 1984).

Three of the benzeneazo-compounds described, namely, 4-*benzeneazo*-6-*methylquinoline*, 4-*benzeneazo*-6-*ethoxyquinoline*, and 4-*benzeneazoquinoline*, appear to exist in two forms. The investigation of these compounds is being continued.

#### EXPERIMENTAL.

Unless otherwise stated, the following were the experimental conditions employed:

1. *Preparation of 4-Phenylhydrazino-compounds.*—2 C.c. of phenylhydrazine (1 mol.) and the 4-chloroquinoline derivative (1 mol.) were suspended in 10 c.c. of medicinal paraffin and gradually heated to 200°, this temperature being maintained for an hour. A fairly vigorous reaction usually commenced at about 160°, and the hydrochloride of the 4-phenylhydrazino-compound separated as a bright yellow solid. After cooling, the paraffin was removed by filtration, and the solid washed with ether. The yield was almost quantitative. The hydrochlorides were sparingly soluble in hydrochloric acid, but could be crystallised from water, and, unlike the free bases, were in most cases stable in air. The bases, which were pale yellow solids, crystallised from dilute alcohol or ligroin. Kept in a desiccator, or on drying in an oven, they rapidly turned red owing to atmospheric oxidation to the 4-*benzeneazo*-compound. They reduced Fehling's solution and were decomposed by copper sulphate in acid solution; they reduced platonic chloride and did not form picrates.

2. *Preparation of 4-Benzeneazo-compounds.*—The crude 4-phenylhydrazino-hydrochloride was dissolved in acetic acid, and a slight excess of solid ferric chloride added; the solution was boiled for a short time, diluted with water, made alkaline with ammonia, and filtered. The precipitated solid was extracted with alcohol and the azo-compound obtained from the filtrate by dilution with water. The azo-compounds crystallised well from dilute alcohol, usually in brilliant red crystals, and did not form picrates or platinum salts. They dissolved readily in dilute acids. The yield was almost quantitative.

3. *Preparation of 4-Amino-compounds.*—The crude 4-phenylhydrazino-hydrochloride (1 g.) was suspended in concentrated hydrochloric acid, zinc dust added in excess, and the suspension gently boiled; addition of a little alcohol reduced frothing and increased the solubility of the hydrochloride. After a few minutes the hydrazino-hydrochloride had dissolved; the reduction was continued for a further 5 minutes, and the excess of zinc removed. The hydrochloride of the 4-amino-compound crystallised from the filtrate on cooling; it was filtered off

and washed with a little concentrated hydrochloric acid. The free bases, which were stable in air, crystallised well from water or dilute alcohol as colourless substances; the yield was almost quantitative. For the above reduction the azo-compounds could be used equally well.

4. *Preparation of the Sealed-tube Products.*—3 G. of the 4-chloroquinoline derivative and 10 c.c. of phenylhydrazine were heated in a sealed tube at 200° for 5 hours. The product was subjected to steam distillation to remove the excess of phenylhydrazine. The solid residue, together with any solid obtained from the filtrate after being made alkaline with ammonia, was dissolved in dilute hydrochloric acid, the filtered solution treated with ammonia, and the precipitate crystallised from dilute alcohol. The colourless product was stable in air, was unchanged by copper sulphate in acid solution, and did not reduce Fehling's solution. It formed a well-defined picrate and a platinum salt. The yield was usually about 4 g.

4-*Phenylhydrazinoquinaldine* (I).—The *hydrochloride* formed small yellow needles, m. p. 284° (decomp.) (Found: Cl, 12.6.  $C_{16}H_{15}N_3, HCl$  requires Cl, 12.4%). The free base, precipitated from an aqueous solution of the hydrochloride, crystallised from ligroin in small, pale yellow needles, m. p. 188° (Found: N, 16.85.  $C_{16}H_{15}N_3$  requires N, 16.9%). The compound did not undergo a benzidine transformation, being recovered unchanged, by heating in dilute hydrochloric acid solution on the water-bath for 2 hours.

4-*Benzeneazoquinaldine* (III) formed brilliant golden-red plates from dilute alcohol, m. p. 100° (Found: N, 17.2.  $C_{16}H_{13}N_3$  requires N, 17.0%). 4-Aminoquinaldine was prepared as described, m. p. 168° alone, or mixed with an authentic specimen.

The isomer (II), *i.e.*, 3-*anilino-4-aminoquinaldine* (V), formed stout colourless prisms from dilute alcohol, m. p. 142° (Found: C, 77.3; H, 6.05; N, 17.0.  $C_{16}H_{15}N_3$  requires C, 77.1; H, 6.0; N, 16.9%). The *hydrochloride* crystallised in colourless needles from dilute hydrochloric acid, m. p. 218° (decomp.) (Found: Cl, 12.6.  $C_{16}H_{15}N_3, HCl$  requires Cl, 12.4%). The platinichloride formed golden-yellow needles from alcoholic hydrogen chloride; these charred above 300° without previous melting (Found: Pt, 21.2.  $2C_{16}H_{15}N_3, H_2PtCl_6$  requires Pt, 21.4%). The picrate had m. p. 186° (decomp.). The base (V) was also formed when 4-phenylhydrazinoquinaldine (I) was heated in a sealed tube with phenylhydrazine for 5 hours at 200°, and the product isolated as described in section 4.

4-*p-Aminoanilinoquinaldine* (IV).—1 G. of 4-chloroquinaldine and 0.85 g. of *p*-aminoacetanilide were refluxed in acetic acid solution for 2 hours, and the mixture poured into water and made alkaline. The yellow gelatinous product was deacetylated by refluxing with dilute sulphuric acid for 2 hours. The base crystallised from dilute alcohol in pale yellow plates, m. p. 173° (Found: N, 16.8.  $C_{16}H_{15}N_3$  requires N, 16.9%). The picrate had m. p. 204° (decomp.).

1'-*Phenyl-2 : 2'-dimethylquin(3 : 4 : 5' : 4')iminazole* (VII).—An acetic acid solution of the isomer (II) was boiled for a few minutes with acetic anhydride. On cooling, a white solid separated, which crystallised from alcohol in fine colourless needles, m. p. 124° (Found: N, 15.35.  $C_{18}H_{15}N_3$  requires N, 15.4%). It formed a *platinichloride*, orange-coloured needles, which decomposed above 300° without previous melting (Found: Pt, 20.5; *i.e.*, *M*, 270.3.  $2C_{18}H_{15}N_3, H_2PtCl_6$  requires Pt, 20.4%; *i.e.*, *M*, 273). The filtrate from the iminazole (VII) was diluted with water and made alkaline; 3-*anilino-4-acetamidoquinaldine* (VI), thus precipitated, crystallised from dilute alcohol in colourless needles, m. p. 117° (Found: N, 14.25.  $C_{18}H_{17}ON_3$  requires N, 14.4%). The conditions for obtaining this acetyl derivative could not be accurately determined, and it was not always obtained in the filtrate from the iminazole. A specimen, kept in a corked tube, was found some months later to have changed into the iminazole (VII). The iminazole was also formed by refluxing the isomer (II) with acetic acid for 1 hour.

4-*Phenylhydrazino-6-methylquinaldine* formed small, pale yellow needles from ligroin, m. p. 205° (Found: N, 15.9.  $C_{17}H_{17}N_3$  requires N, 16.0%).

4-*Benzeneazo-6-methylquinaldine* appeared to exist in two forms. When first prepared, it was obtained from dilute alcohol in fine, red, silky needles, m. p. 104° (Found: N, 16.1.  $C_{17}H_{15}N_3$  requires N, 16.1%). From the mother-liquor, large, ruby-coloured, diamond-shaped plates separated on standing, m. p. 128° (Found: N, 16.2%). Later attempts to prepare the product, m. p. 104°, were unsuccessful and always resulted in formation of the compound, m. p. 128°. A re-examination of the needles after some months showed that they now had m. p. 128°.

4-*Amino-6-methylquinaldine*.—The same product was obtained from the reduction of either of the above benzeneazo-compounds, m. p. 104° and 128°. It formed fine colourless needles from dilute alcohol, m. p. 205° (Found: N, 16.1, 16.4.  $C_{11}H_{12}N_2$  requires N, 16.3%).

3-*Anilino-4-amino-6-methylquinaldine* crystallised in small colourless plates from dilute alcohol, m. p. 100° (Found: N, 16.4.  $C_{17}H_{17}N_3$  requires N, 16.0%). The picrate had m. p. 215° (decomp.).

4-Benzeneazo-5 (or 7)-methylquinaldine formed fine red needles from dilute alcohol, m. p. 76° (Found: N, 16.0.  $C_{17}H_{15}N_3$  requires N, 16.1%).

4-Amino-5 (or 7)-methylquinaldine crystallised in small colourless needles from dilute alcohol, m. p. 161° (Found: N, 16.0.  $C_{11}H_{12}N_2$  requires N, 16.3%).

3-Anilino-4-amino-5 (or 7)-methylquinaldine formed colourless needles from dilute alcohol, m. p. 137° (Found: N, 16.1.  $C_{17}H_{17}N_3$  requires N, 16.0%). The picrate had m. p. 195° (decomp.).

4-Benzeneazo-8-methylquinaldine formed orange-coloured plates from dilute methyl alcohol, m. p. 104° (Found: N, 16.1.  $C_{17}H_{15}N_3$  requires N, 16.1%), and 4-amino-8-methylquinaldine, large, colourless, hexagonal prisms from water, m. p. 141° (Found: N, 16.15.  $C_{11}H_{12}N_2$  requires N, 16.3%).

3-Anilino-4-amino-8-methylquinaldine. Small colourless plates from dilute alcohol, m. p. 101° (Found: N, 16.2.  $C_{17}H_{17}N_3$  requires N, 16.0%). The picrate had m. p. 197° (decomp.).

4-Benzeneazo-5:7-dimethylquinaldine. Fine red needles from dilute alcohol, m. p. 126° (Found: N, 15.4.  $C_{18}H_{17}N_3$  requires N, 15.3%).

4-Amino-5:7-dimethylquinaldine. Small, matted, silky, colourless needles from water, m. p. 166° (Found: N, 14.95.  $C_{12}H_{14}N_2$  requires N, 15.05%).

3-Anilino-4-amino-5:7-dimethylquinaldine. Colourless tablets from dilute alcohol, m. p. 127° (Found: N, 15.0.  $C_{18}H_{19}N_3$  requires N, 15.15%). The picrate had m. p. 215° (decomp.).

4-Benzeneazo-6:8-dimethylquinaldine. Red needles from dilute alcohol, m. p. 117° (Found: N, 15.0.  $C_{18}H_{17}N_3$  requires N, 15.3%).

4-Amino-6:8-dimethylquinaldine. Long cream-coloured needles from dilute alcohol, m. p. 165° (Found: N, 15.0.  $C_{12}H_{14}N_2$  requires N, 15.05%).

3-Anilino-4-amino-6:8-dimethylquinaldine. Plates from dilute alcohol, m. p. 105° (Found: N, 15.3.  $C_{18}H_{19}N_3$  requires N, 15.15%). The picrate had m. p. 216° (decomp.).

4-Benzeneazo-6-ethoxyquinaldine. Small red needles from ligroin, m. p. 105°; after cooling, the m. p. of the solidified melt rose to 109° (Found: N, 14.2.  $C_{18}H_{17}ON_3$  requires N, 14.4%).

4-Amino-6-ethoxyquinaldine. Colourless plates from dilute alcohol, m. p. 197° (Found: N, 13.85. Calc. for  $C_{12}H_{14}ON_2$ : N, 13.9%). Schwabe, Eisleb, and Jensch (D.R.-P. 440,008) give m. p. 195°.

4-Benzeneazo-8-ethoxyquinaldine. Orange-red, fine, silky needles from ligroin, m. p. 117° (Found: N, 14.6.  $C_{18}H_{17}ON_3$  requires N, 14.4%).

4-Amino-8-ethoxyquinaldine. Small colourless needles from dilute alcohol, m. p. 222° (Found: N, 13.8.  $C_{12}H_{14}ON_2$  requires N, 13.9%).

4-Benzeneazoquinoline. Small brick-red needles from dilute methyl alcohol, m. p. 70°; after a few days the m. p. was found to be 89° (Found: N, 17.8.  $C_{15}H_{11}N_3$  requires N, 18.0%).

4-Aminoquinoline, isolated as the picrate, formed yellow needles from alcohol, m. p. 277° (Koenigs, *Ber.*, 1907, 40, 651, gives 274°) (Found: N, 18.6. Calc. for  $C_9H_8N_2, C_6H_5O_7N_3$  requires N, 18.8%).

3-Anilino-4-aminoquinoline. Shining plates from dilute alcohol, m. p. 134° (Found: N, 17.85.  $C_{15}H_{13}N_3$  requires N, 17.85%). The picrate had m. p. 218° (decomp.).

*Reactions of 4-Chloro-3-methylquinaldine.*—When this chloro-compound was heated with an equivalent of phenylhydrazine as described in section 1, the hydrochloride of 4-phenylhydrazino-3-methylquinaldine, which turned gummy if left exposed to the air owing to oxidation, was obtained; from it the corresponding 4-benzeneazo- and 4-amino-compounds were obtained. When, however, the reactants were heated together in a sealed tube as described in section 4, an explosion resulted, and repeated attempts to obtain a product were unsuccessful. Accordingly, 2 g. of the phenylhydrazino-hydrochloride mentioned above were heated with 6 c.c. of phenylhydrazine in a sealed tube at 200° for 5 hours; when the tube was opened, considerable pressure was noticed and a strong odour of ammonia was detected. The product was subjected to steam distillation to remove the excess of phenylhydrazine, but nothing crystalline was obtained from the gummy residue.

4-Benzeneazo-3-methylquinaldine formed dark red needles from dilute alcohol, m. p. 133° (Found: N, 16.25.  $C_{17}H_{15}N_3$  requires N, 16.1%), and 4-amino-3-methylquinaldine, colourless needles from water, m. p. 189° (Found: N, 16.1.  $C_{11}H_{12}N_2$  requires N, 16.3%).

The author thanks Prof. H. Stephen for his interest in the investigation, and Mr. C. A. Friedmann, M.Sc., for assistance with some of the experimental work.