65. *The Reaction of 4-Chloroquinaldines and of 2-Chlorolepidines with Ammonia, and the Preparation of the Corresponding Phenyl Ethers.*

By O. G. Backeberg and J. L. C. Marais.

An investigation of the various methods for preparing 2- and 4-aminoquinoline derivatives from the corresponding chloro-compounds has shown that 4-aminoquinaldines are readily obtained in almost theoretical yield by passing ammonia into a hot phenol solution of the 4-chloro-compounds. When applied to 2-chlorolepidines, this reaction gives the amines only in small yield, the main product being the corresponding phenyl ether; these amines were best prepared by heating the chloro-compound in a sealed tube with the double compound $ZnCl_2,2NH_3$.

4-Chloroquinaldines and 2-chlorolepidines readily formed the corresponding phenyl ethers in almost theoretical yield by heating with phenol for 5 hours at 180°.

4-Aminoquinaldines and 2-aminolepidines may be prepared from the corresponding chloro-compounds by the following methods:

(1) By heating in a sealed tube with alcoholic ammonia (Ashley, Browning, Cohen, and Gulbransen, *Proc. Roy. Soc.*, **1933**, *B*, **113**, 295), or by the method of Maier-Bode for preparing 3-aminopyridine, in which 3-bromopyridine was heated in a sealed tube with concentrated aqueous ammonia in the presence of copper sulphate as a catalyst (*Ber.*, 1936, **69**, 1534). Although 4-aminoquinaldine is obtained in good yield by these methods, its 6- and 8-methoxy- and -ethoxy-derivatives are not formed from the corresponding chloro-compounds under these conditions. 2-Aminolepidine is obtained only in small yield (Klotz,

Annalen, 1888, **245**, 382), but 6-methoxy- and 6-ethoxy-2-chlorolepidine do not react with ammonia under these conditions.

(2) By reduction of the corresponding phenylhydrazino-compounds. Ephraim (*Ber.*, 1892, **25**, 2706) used this method for preparing 2-aminolepidine; when the method was applied to 6-methoxy- and 6-ethoxy-2-chlorolepidine, the corresponding amines were obtained in 30—40% yield. Backeberg (J., 1938, 1083) obtained 4-aminoquinaldine, as well as its 6- and 8-ethoxy-derivatives, in good yield by this method.

(3) By the method of Diepolder (*J. pr. Chem.*, 1923, **106**, 41), in which the chloro-compound is heated in a sealed tube with the double compound $ZnCl_2,2NH_3$, prepared according to Merz and Müller (*Ber.*, 1886, **19**, 2902). This proved to be the best method for preparing 6-methoxy- and 6-ethoxy-2-aminolepidine from the corresponding chloro-compounds, the yields of these two amines being 70% and 50% respectively.

(4) By passing ammonia into a hot phenol solution of the chloro-compound; this convenient method was used by Jensch (D.R.-P. 591,480) for the preparation of 4 : 6- and 4 : 8-diaminoquinaldine. When dry ammonia was passed into a phenol solution of the chlorolepidines at 180° for 2 hours, the corresponding 2-aminolepidines were obtained in approximately 10% yield; the main product was the corresponding phenyl ether; the chloro-compounds thus react preferentially with the phenol to a large extent. Replacement of the phenol by an inert high-boiling solvent such as *p*-dichlorobenzene yielded no amine at all. If the phenol solution was heated at 180° for 5 hours in the absence of ammonia, the phenyl ether was obtained in almost theoretical yield.

In the case of the 4-chloroquinaldines, the 4-aminoquinaldines were obtained in almost theoretical yield, and the corresponding phenyl ether did not appear to be formed; these amines are thus readily accessible compounds. If, in the absence of ammonia, the phenol solution was heated at 180° for 5 hours, the corresponding phenyl ethers were obtained in almost theoretical yield.

Experimental.

The chloro-compounds employed were: 4-chloroquinoline, 4-chloroquinaldine together with its 6- and 8-methoxy- and -ethoxy-derivatives, 2-chlorolepidine and its 6-methoxy- and 6-ethoxy-derivatives.

Preparation of 4-Aminoquinaldines.—3 G. of the 4-chloroquinaldine (or 4-chloroquinoline) were added to appoximately 10 g. of phenol, and the mixture heated to 180° in an oil-bath. Ammonia, dried over quicklime, was passed through the solution for 2 hours. The hydrochloride of the amine soon began to separate. The excess of phenol was removed by steam-distillation and the clear solution was concentrated to about 70 c.c. by evaporation on the water-bath, cooled, and made alkaline with sodium hydroxide. The amines were obtained in almost theoretical yield in all cases; they were readily obtained pure by crystallisation from water or dilute alcohol.

4-Amino-6-methoxyquinaldine.—Small, pale yellow needles, m. p. 209° (Found: C, 70·4; H, 6·2; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

4-Amino-8-methoxyquinaldine.—Small colourless needles, m. p. 233° (Found: C, 70·3; H, 6·2; N, 14·8%). These two amines were also prepared by the reduction of the corresponding 4-benzeneazo-compounds (J., 1938, 1083); these azo-compounds were not described in the previous communication.

4-Benzeneazo-6-methoxyquinaldine.—Fine red needles from dilute alcohol, m. p. 73° (Found: N, 15·2. $C_{17}H_{15}ON_3$ requires N, 15·2%).

4-Benzeneazo-8-methoxyquinaldine.—Orange-coloured silky needles from dilute alcohol, m. p. 130° (Found: N, 15·05%).

Preparation of 2-Aminolepidines.—(i) When the procedure described above was carried out with the chlorolepidines, an insoluble oil remained after the excess of phenol had been removed by steam-distillation. The oil readily solidified after cooling and stirring, and was then removed by filtration; this proved to be the phenyl ether (see later). The filtrate, after being concentrated on the water-bath and made alkaline with sodium hydroxide, gave the 2-aminolepidines in approximately 10% yield.

(ii) 2 G. of the chlorolepidine, 10 g. of $ZnCl_2,2NH_3$, and 2 g. of ammonium chloride were heated in a sealed tube at 210—220° for 6 hours. The product was best removed by filling the opened tube with water and keeping it overnight. The required amine, present as the hydrochloride, was extracted from the product by boiling with water, filtration from insoluble zinc salt, and precipitation with sodium hydroxide.

(iii) 2 G. of the chlorolepidine were gently heated over a bare flame with 2·5 g. (2 mols.) of phenylhydrazine. After completion of the reaction, which was accompanied by much frothing, the product was washed with water to remove phenylhydrazine hydrochloride; the crude material, which was sensitive to atmospheric oxidation, was not further purified, and was suitable for reduction to the 2-amino-compound or oxidation to the 2-benzeneazo-compound.

Reduction was effected by refluxing the above product for ½ hour with 10 c.c. of hydriodic acid (*d* 1·67) and 0·5 g. of red phosphorus. The product was diluted with water and filtered, and the filtrate made alkaline with sodium hydroxide and steam-distilled to remove aniline formed during the reduction. The residue from the steam-distillation was extracted with ether, and the amine obtained from the extract as a reddish oil which solidified on rubbing; it was then crystallised from dilute alcohol; yield 30—40%

For oxidation to the benzeneazo-compound, the above crude phenylhydrazino-compound was dissolved in glacial acetic acid and boiled for a short time with a slight excess of ferric chloride; the benzeneazo-compound was precipitated by pouring the solution into water, and was then crystallised from dilute alcohol; yield, almost quantitative.

2-*Amino*-6-*methoxylepidine*.—Small, pale yellow needles, m. p. 174° (Found: C, 70·35; H, 6·2; N, 14·8. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

2-*Amino*-6-*ethoxylepidine*.—Small colourless needles, m. p. 207° (Found: C, 71·1; H, 6·9; N, 13·9. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 6·9; N, 13·9%).

2-*Benzeneazo*-6-*methoxylepidine*.—Stout, dark red prisms, m. p. 142° (Found: C, 73·55; H, 5·35; N, 15·2. $C_{17}H_{15}ON_3$ requires C, 73·6; H, 5·4; N, 15·2%).

2-*Benzeneazo*-6-*ethoxylepidine*.—Reddish-brown plates, m. p. 162° (Found: C, 74·5; H, 5·8; N, 14·35. $C_{18}H_{17}ON_3$ requires C, 74·2; H, 5·9; N, 14·4%).

Preparation of Phenyl Ethers.—3 G. of the chloro-compound were heated with approximately 10 g. of phenol in an oil-bath at 180° for 5 hours; the excess of phenol was then removed by steam-distillation. In the case of the 4-chloroquinaldines, the residue in the steam-distillation flask was a clear solution of the hydrochloride of the 4-phenoxy-compound, from which the base was obtained in almost theoretical yield by means of sodium hydroxide.

In the case of the 2-chlorolepidines, the 2-phenoxy-compound, obtained in almost theoretical yield, was formed as the free base, and separated as an oil in the steam-distillation flask, after removal of the excess of phenol.

Both classes of ethers crystallised well from dilute alcohol. 4-Phenoxyquinoline was obtained as a thick oil which could not be made to crystallise, although it was precipitated as a solid (which may have been a hydrate) from the aqueous solution of its hydrochloride by sodium hydroxide; when the solid was collected, it changed to a pasty mass which slowly liquefied, and attempts to crystallise it gave only the thick oil referred to. It formed a *picrate*, yellow prisms from alcohol, m. p. 179° (Found: N, 12·55. $C_{15}H_{11}ON,C_6H_3O_7N_3$ requires N, 12·4%), and a *platinichloride*, orange-coloured needles from dilute hydrochloric acid, m. p. 220° (decomp.) (Found: Pt, 22·7. $2C_{15}H_{11}ON,H_2PtCl_6$ requires Pt, 22·9%).

4-*Phenoxyquinaldine* was obtained as the *monohydrate*, colourless silky needles, m. p. 78° (Found: C, 75·6; H, 5·9; N, 5·7; H_2O, 7·2. $C_{16}H_{13}ON,H_2O$ requires C, 75·9; H, 5·9; N, 5·5; H_2O, 7·1%). When dried in a vacuum over phosphoric oxide, it first liquefied and then slowly formed a colourless solid, m. p. 71·5° (Found: C, 81·65; H, 5·55; N, 5·9. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

4-*Phenoxy*-6-*methoxyquinaldine*. Small colourless needles, m. p. 112° (Found: C, 77·0; H, 5·6; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

4-*Phenoxy*-8-*methoxyquinaldine*. Shiny colourless plates, m. p. 147° (Found: C, 76·95; H, 5·5; N, 5·3%).

4-*Phenoxy*-6-*ethoxyquinaldine*. Stout colourless plates, m. p. 121° (Found: C, 77·3; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

4-*Phenoxy*-8-*ethoxyquinaldine*. Small, pale yellow needles, m. p. 100° (Found: C, 77·4; H, 6·0; N, 5·1%).

2-*Phenoxylepidine*. Colourless plates, m. p. 48° (Found: C, 81·9; H, 5·6; N, 5·8. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%).

2-*Phenoxy*-6-*methoxylepidine*. Colourless plates, m. p. 70° (Found: C, 77·2; H, 5·5; N, 5·3. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7; N, 5·3%).

2-*Phenoxy*-6-*ethoxylepidine*. Stout colourless plates, m. p. 95° (Found: C, 77·4; H, 6·1; N, 5·2. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, SOUTH AFRICA. [*Received, January 15th,* 1942.]