559. *Quinaldine and 4-Hydroxyquinaldine Derivatives from*
m-*Chloroaniline and* m-*Toluidine.*

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Doebner–Miller and Conrad–Limpach syntheses with *m*-chloroaniline and *m*-toluidine have been investigated and optimum reaction conditions determined. The isomers obtained have been separated an orientated and the proportions of 5- to 7-substituted quinaldines and 5- to 7-substituted 4-hydroxyquinaldines have been estimated.

The modified procedure (G.P. 567,273) for the Doebner–Miller synthesis has been found to give greatly improved yields of quinaldine derivatives and to give a maximum yield at 60—70% sulphuric acid concentration. The proportion of 7-substituted isomer increases with decrease of acid concentration with both arylamines studied.

In the Conrad–Limpach synthesis the dilution of the solvent used for cyclisation appears to have practically no effect on the yield and ratio of isomers formed.

THE application of quinoline syntheses to *m*-substituted anilines, in which both positions *ortho* to the amino-group are free, may give rise to both 5- and 7-substituted derivatives. In this connexion, Bradford, Elliott, and Rowe (*J.*, 1947, 437) investigated the Skraup reaction with several *m*-substituted anilines and found that the proportion of 5- to 7-substituted quinoline was dependent on the nature of the *m*-substituent. Strongly *o-p*-directing groups, such as methyl, produced only the 7-substituted derivative, whilst weakly *o-p*-directing substituents, such as chlorine, produced a mixture in which the 7-substituted derivative predominated, and *m*-directing substituents, *e.g.*, nitro, gave a mixture in which the 5-substituted derivative predominated. The ratio of isomers was influenced by the concentration of sulphuric acid only in the case of *m*-chloroaniline. The work described in this communication was undertaken to determine the effect of the *m*-substituent in other quinoline syntheses and the effect of groups ultimately appearing in the hetero-ring on the direction of ring closure.

In the Doebner–Miller synthesis the application of the modified procedure, using *m*-nitro-benzenesulphonic acid as a water-soluble acid oxidising agent in 60—80% sulphuric acid, as described in G.P. 567,273 and by Utermohlen (*J. Org. Chem.*, 1943, **8**, 544), has been found to give a vastly improved yield (60%) of chloroquinaldines compared with the original Doebner–Miller method (*Ber.*, 1883, **16**, 2465) (21%). This procedure probably involves the smooth oxidation of the dihydroquinaldine derivative (I) to the quinaldine derivative (II) and thus
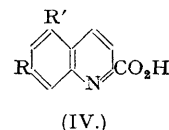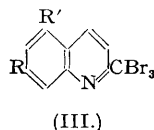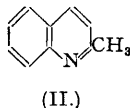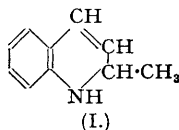
supports the mechanism suggested for this reaction by von Miller (*Ber.*, 1891, **24**, 1720; 1892, **25**, 2072). The yield of chloroquinaldines varied with the concentration of the sulphuric acid employed, and was a maximum (60%) for acid of 60% strength. When sulphuric acid of a strength outside the range 60—80% was used the yield was considerably reduced. Utermohlen (*loc. cit.*) obtained a 60% yield of 5- and 7-*chloroquinaldines* using 75% sulphuric acid but did not attempt to separate them. After unsuccessful preliminary attempts at separation of the

isomers by fractional crystallisation of the dichromates from water, the hydrochlorides from acetic acid, and the picrates and perchlorates from alcohol, we finally achieved separation by the fractional crystallisation of the picrates from 2-ethoxyethanol. It was found that a mixture of isomers resulted at all concentrations of acid investigated and that the proportion of the 7-substituted isomer increased from 67% using 80% sulphuric acid to 80% using 40% sulphuric acid. The orientation of the 5- and 7-chloroquinaldines, of which only the 7-substituted isomer had apparently been obtained previously (Bartow and McCollum, *J. Amer. Chem. Soc.*, 1904, **26**, 703), was accomplished by conversion into the corresponding 5- and 7-*chloroquinaldinic acid* (IV; R = H, R′ = Cl) and (IV; R = Cl, R′ = H), decarboxylation, and comparison with authentic specimens of the respective chloroquinolines. Conversion of the chloroquinaldines into the chloroquinaldinic acids by direct oxidation with chromic acid or by oxidation of the chloro-2-styrylquinoline with chromic acid and nitric acid was unsatisfactory. It was achieved by bromination (*cf.* Hammick, *J.*, 1926, 1302) to the 5- and 7-*chloro-ω-tribromoquinaldine* (III; R = H, R′ = Cl) and (III; R = Cl, R′ = H) and subsequent hydrolysis to the chloro-quinaldinic acids by boiling under reflux with 20% sulphuric acid for 20—30 hours.

In the first step of the Conrad–Limpach synthesis with ethyl acetoacetate and *m*-chloro-aniline, ethyl β-*m*-chloroanilinocrotonate (V) was obtained in good yield by use of hydrochloric acid as a catalyst in the manner suggested by Coffey, Thomson, and Wilson (*J.*, 1936, 856). Cyclisation of the crotonate in liquid paraffin oil at 240—250° (Limpach, *Ber.*, 1931, **64**, *B*, 969) gave a poor yield (20%) and a very impure product, and so, from a series of preliminary experiments using boiling diphenyl (Stephen, Tonkin, and Walker, *J.*, 1947, 1034), diphenyl ether, and diphenylamine as cyclising solvents, diphenyl was selected for use throughout. The product consisting of 5(or 7)-chloro-4-hydroxyquinaldine was separated from diphenyl by extraction with boiling benzene and purified by dissolution in aqueous sodium hydroxide. The yield obtained (35—40%) was considerably less than that recorded by Price *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1256) (72%) or Steck *et al.* (*ibid.*, 1948, **70**, 1012) (81%). These authors state that this synthesis produces only the 7-chloro-4-hydroxyquinaldine (VI) whereas the indefinite m. p. of our product, even when recrystallised from alcohol, led us to believe that both the 5- and 7-substituted isomers had been formed. Separation of the isomers by fractional crystallisation of the free bases from alcohol, the hydrochlorides from acetic acid, or the oxalates or perchlorates from alcohol was unsatisfactory. Owing to the difficulty of resolution of the reaction product the following unsuccessful attempts to synthesise both isomers unambiguously were made : (i) 4-chloroanthranilic acid or ethyl 4-chloroanthranilate was treated with acetone in the presence of sodium hydroxide solution ; (ii) ethyl 4-chloroanthranilate and ethyl sodio-acetoacetate were mixed in alcoholic acetic acid solution but did not give ethyl 7-chloro-4-hydroxyquinaldine-3-carboxylate ; (iii) the Conrad–Limpach synthesis with ethyl 4-chloro-anthranilate failed to give ethyl 5-chloro-4-hydroxyquinaldine-8-carboxylate ; and (iv) 4-chloro-2-toluene-*p*-sulphonamidobenzoic acid, heated under reflux with acetic anhydride, did not afford the mixed anhydride of 7-chloro-4-hydroxyquinaldine-3-carboxy-(5′-chloro-2′-carboxy)-anilide and toluene-*p*-sulphonic acid according to the method of Heller and Grundmann (*Ber.*, 1923, **56**, 200). Albert, Brown, and Duewell (*J.*, 1948, 1286) have since confirmed some of these failures by showing that 4-hydroxyquinoline derivatives could not be obtained from methyl anthranilate under a variety of conditions. A return to the problem of separating the isomers by fractional crystallisation of the salts revealed that, although a complete separation could not be achieved, the *picrate* of 7-chloro-4-hydroxyquinaldine could be isolated by crystallising the mixture of picrates from alcohol. The amount isolated indicated that this isomer predominated in the product. The orientation of 7-chloro-4-hydroxyquinalidine was demonstrated by reaction with phosphoryl chloride and comparison with an authentic specimen of 4 : 7-dichloro-quinaldine. Authentic specimens of 4 : 5- and 4 : 7-dichloroquinaldine were prepared from 5- and 7-chloroquinaldines respectively by oxidation to the 5- and 7-*chloroquinaldine* N-*oxide* (VII; R = H, R′ = Cl) and (VII; R = Cl, R′ = H) and treatment with phosphoryl chloride. Oxidation with perbenzoic acid was found unsatisfactory owing to the instability of the latter,

(V.)   (VI.)   (VII.)   (VIII.)
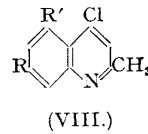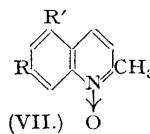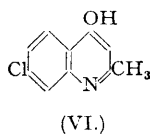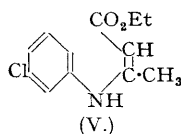
whilst the method of Newbold and Spring (*J.*, 1947, 1183) for the oxidation of pyrazine derivatives to their N-oxides with hydrogen peroxide in glacial acetic acid failed. Monoperphthalic

acid in ether, however, effected smooth oxidation to the *N*-oxides and these were obtained as hydrates which could not be dehydrated. The *N*-oxides were converted into 4 : 5-dichloro-quinaldine (VIII; R = H, R' = Cl) and 4 : 7-dichloroquinaldine (VIII; R = Cl, R' = H) according to the method of Bachman and Cooper (*J. Org. Chem.*, 1944, **9**, 302).

Using the modified procedure, the Doebner–Miller synthesis with *m*-toluidine gave a maximum yield (32%) of dimethylquinolines at a 70% sulphuric acid concentration, whilst the original Doebner–Miller method gave only a 13% yield. The orientation and characterisation of the 2 : 5- and 2 : 7-dimethylquinolines have been carried out by Manske, Marion, and Ledger (*Canad. J. Res.*, 1942, **20**, *B*, 133). From the mixture of 2 : 5- and 2 : 7-dimethylquinolines obtained, 2 : 7-dimethylquinoline was isolated by filtration through sintered glass and 2 : 5-dimethylquinoline picrate was isolated from a mixture of the picrates by fractional crystallisation from 2-ethoxyethanol. The composition of the mixture of 2 : 5- and 2 : 7-dimethylquinoline, obtained using varying concentrations but the same amount of sulphuric acid, was estimated by converting the mixture into its picrate and comparing the melting point of the latter with the melting point diagram for the system 2 : 5-/2 : 7-dimethylquinoline picrate. The results show that, as with *m*-chloroaniline, the proportion of the 7-substituted isomer increased from about 60% using 80% sulphuric acid to 82% using 60% sulphuric acid.

In the Conrad–Limpach synthesis with *m*-toluidine, ethyl β-*m*-toluidinocrotonate was readily obtained and cyclisation in refluxing diphenyl gave a mixture of the isomeric 4-hydroxy-5- and -7-*methylquinaldine* (IX; R = H, R' = CH₃) and (IX; R = CH₃, R' = H) in 53% yield. Preliminary experiments indicated that the yield and proportion of isomers were practically independent of the nature of the cyclising solvent and of the temperature in the range 250—300°. After unsuccessful attempts at separation by the fractional crystallisation of the free bases from alcohol, methanol, and acetic acid, of the hydrochlorides from acetic acid, and of the picrates and perchlorates from alcohol, and by solubility in aqueous sodium hydroxide, the mixture of isomers was finally resolved by fractional crystallisation of the oxalates from alcohol. The composition of the mixture, estimated by weighing the *oxalates* isolated, was 56% of the 5- and 44% of the 7-methyl isomer. The orientation of the 4-hydroxy-5- and -7-methylquinaldines was demon-strated by conversion into 4-*chloro*-5- and -7-*methylquinaldine* (X; R = H, R' = CH₃) and (X; R = CH₃, R' = H) and catalytic dehalogenation of the latter to 2 : 5- and 2 : 7-dimethyl-quinoline (XI; R = H, R' = CH₃) and (XI; R = CH₃, R' = H), which were compared with authentic specimens. Catalytic dehalogenation was achieved with Raney alloy and alkali according to the method of Schwenk, Papa, Whitman, and Ginsberg (*J. Org. Chem.*, 1944, **9**, 1).
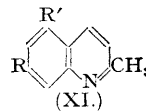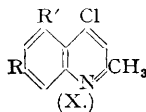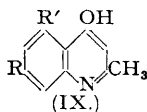
Our results for the Doebner–Miller synthesis are in contrast to those obtained for the Skraup reaction by Bradford, Elliott, and Rowe (*loc. cit.*). In that reaction the 7-substituted quinoline only was obtained with strongly *o-p*-directing, and a mixture of 5- and 7-substituted quinolines resulted from *m*-substituted anilines with weakly *o-p*-directing, substituents.

Experimental

M.p.s are corrected. Microanalyses were carried out by Drs. G. Weiler and F. B. Strauss of Oxford.

Modified Doebner–Miller Synthesis with m-*Chloroaniline.*—*m*-Chloroaniline (35·8 g., 0·28 mol.), sulphuric acid (of concentration and amount as indicated in Table I), and sodium *m*-nitrobenzene-sulphonate (70 g.) were heated, with stirring, to 120—130° and at that temperature paraldehyde (45 c.c., equiv. to 1 mol. of crotonaldehyde) was added dropwise during 20 minutes. The mixture was boiled steadily under reflux with stirring for 1½ hours and, after cooling and dilution with water (300—400 c.c.), any unchanged *m*-chloroaniline was decomposed by adding excess of sodium nitrite (20 g.) and boiling the mixture for ½ hour. The reaction mixture, while being cooled, was basified with sodium hydroxide and then distilled in steam. The steam-distillate was thrice extracted with ether and, after evaporation of the ether from the dried (CaCl₂) extract, the residual oil was distilled to give a slightly yellow oily mixture of the 5- and 7-chloroquinaldines (yields, given in Table I, are those of the distilled product). The maximum yield obtained was 60% using 60% sulphuric acid (Utermohlen, *loc. cit.*, gives 60%).

Separation of 5- *and* 7-*Chloroquinaldine.*—A solution of picric acid (36·7 g., 1·03 mols.) in 2-ethoxy-ethanol (100 c.c.) was added to a solution of the mixed isomers (27·8 g., 1 mol.) in the same solvent (245 c.c.) at 117°. After 10 minutes at that temperature, with occasional stirring, the picrate of 5-chloroquinaldine (with some 7-chloroquinaldine picrate), m.p. 238–239°, which had crystallised, was filtered. The filtrate was cooled; the almost pure picrate of 7-chloroquinaldine, m. p. 190–193°, then separated and was collected. The filtrate from the latter was used to extract the original residue at

80—85° for 10 minutes and thus gave almost pure 5-chloroquinaldine picrate, m. p. 242—243°. The proportion of 5- to 7-chloroquinaldine was estimated from the weights of pure picrate obtained, losses during separation amounting to 11—18%. The original Doebner–Miller synthesis, involving the heating, under reflux, of *m*-chloroaniline (35·8 g.), paraldehyde (45 c.c.), and concentrated hydrochloric acid (60 c.c.) for 1½ hours and working up in the manner described above for the modified procedure, gave a total yield (21%) of material which comprised 5-chloroquinaldine (11%) and 7-chloroquinaldine (89%).

5-Chloroquinaldine.—The picrate, m. p. 242—243°, was strongly basified and the base was distilled in steam and extracted with ether. After drying (CaCl₂) and evaporation of the solvent, the residual *5-chloroquinaldine* was distilled to give a slightly yellow, highly refractive oil, b. p. 276—278°/754 mm. (Found : C, 67·5 ; H, 4·6 ; N, 7·7 ; Cl, 20·5. $C_{10}H_8NCl$ requires C, 67·6 ; H, 4·5 ; N, 7·9 ; Cl, 20·0%), which, on exposure to the atmosphere, formed a *trihydrate*, colourless needles, m. p. 52—53° (Found : H₂O, 2·4. $C_{10}H_8NCl,3H_2O$ requires H₂O, 2·3%). 5-Chloroquinaldine formed a *picrate*, which crystallised from 2-ethoxyethanol in pale yellow needles, m. p. 241—243° (Found : C, 47·5 ; H, 2·6 ; N, 13·3 ; Cl, 8·5. $C_{10}H_8NCl,C_6H_3O_7N_3$ requires C, 47·0 ; H, 2·7 ; N, 13·7 ; Cl, 8·8%), a *hydrochloride*, which crystallised from alcohol–ligroin in prismatic plates, m. p. 238—240° (Found : C, 54·3 ; H, 4·3 ; Cl, 31·3. $C_{10}H_8NCl,HCl,\frac{1}{2}H_2O$ requires C, 53·8 ; H, 4·5 ; Cl, 31·8%), and a *perchlorate*, which crystallised from alcohol in colourless needles, m. p. 162—164° (Found : C, 43·6 ; H, 3·6. $C_{10}H_8NCl,HClO_4$ requires C, 43·2 ; H, 3·2%).

7-Chloroquinaldine.—The picrate, m. p. 190—193°, was converted by the method used for the 5-substituted isomer into 7-chloroquinaldine, colourless needles (from ether), m. p. 77—78°, b. p. 280—282°/761 mm. (Bartow and McCollum, *loc. cit.*, give 5(or 7)-chloroquinaldine m. p. 78°) (Found : C, 67·9 ; H, 4·6 ; N, 7·7 ; Cl, 19·5. Calc. for $C_{10}H_8NCl$: C, 67·6 ; H, 4·5 ; N, 7·9 ; Cl, 20·0%). 7-Chloroquinaldine gave a *picrate*, which crystallised from 2-ethoxyethanol in large, orange-yellow needles, m. p. 191—193° (Found : C, 47·5 ; H, 2·7 ; N, 13·6 ; Cl, 8·4. $C_{10}H_8NCl,C_6H_3O_7N_3$ requires C, 47·0 ; H, 2·7 ; N, 13·7 ; Cl, 8·8%), and a *hydrochloride*, which crystallised from alcohol–ligroin in colourless needles, m. p. 248—249° (Found : C, 56·3 ; H, 4·8 ; Cl, 32·6. $C_{10}H_8NCl,HCl$ requires C, 56·1 ; H, 4·2 ; Cl, 33·2%).

TABLE I.

Yield (%) *and proportion of* 5- *and* 7-*chloroquinaldine.*

Sulphuric acid.		Yield (%) of 5- and 7-chloro-quinaldine.	Estimated composition of product.	
Concn. (%).	Quantity, c.c.		5- (%).	7- (%).
80	115	36	33	67
75	125	48	32	68
70	142	59	28	72
65	157	50	26	74
60	177	60	25	75
50	228	39	20	80
40	304	40	20	80

7-Chloro-2-styrylquinoline.—7-Chloroquinaldine (5 g.) and benzaldehyde (3 g.) were heated with anhydrous zinc chloride (2 g.) at 120° for 1 hour and then at 150° for 4 hours. After cooling, the resulting solid was ground to a fine powder and boiled with acetone (75 c.c.) ; the insoluble matter was removed by filtration and the filtrate concentrated to give 7-chloro-2-styrylquinoline (32%), which crystallised from acetone in colourless leaflets, m. p. 131° (Found : C, 76·6 ; H, 4·4 ; N, 5·2 ; Cl, 13·3. $C_{17}H_{12}NCl$ requires C, 76·8 ; H, 4·5 ; N, 5·3 ; Cl, 13·4%).

Orientation of 5- and 7-Chloroquinaldines.—*7-Chloro-ω-tribromoquinaldine.* Finely powdered fused sodium acetate (15 g.) was added with stirring to a solution of 7-chloroquinaldine (2·3 g.) in glacial acetic acid (45 c.c.) at 70—80°. When dissolution was complete, bromine (6·8 g., 3·11 mols.) in acetic acid (15 c.c.) was added with shaking during 10 minutes at the same temperature. The mixture was heated to boiling and boiled for 5 minutes until bumping became excessive, whereupon it was transferred to a steam-bath, where the reaction was completed by heating the mixture for 20 minutes. After cooling to 50°, the mixture was poured into cold water (200 c.c.) and, after being kept overnight, the precipitated *bromo*-compound was collected, washed, and dried at 90° (yield, 84%) ; m. p. 150—165°. Recrystallis-ation from alcohol to constant m. p. gave colourless needles, m. p. 175° (Found : C, 29·2 ; H, 1·4 ; N, 3·4% ; 1 mg. equiv. to 1·66 mg. of AgX. $C_{10}H_5NClBr_3$ requires C, 29·0 ; H, 1·2 ; N, 3·4% ; 1 mg. equiv. to 1·71 mg. of AgX).

7-Chloroquinaldinic acid. 7-Chloro-ω-tribromoquinaldine (8·2 g.) was heated under reflux with 20% sulphuric acid (60 c.c.) for 20 hours. After cooling, the solid, which had settled and was a mixture of unchanged bromo-compound and chloroquinaldinic acid, was filtered off, and careful addition of aqueous ammonia to the filtrate gave a white precipitate of 7-chloroquinaldinic acid, which was collected, washed, and dried (yield, 20%) ; m. p. 185—187° (decomp.) (Found : C, 57·8 ; H, 3·0 ; N, 7·0 ; Cl, 16·9. $C_{10}H_6O_2NCl$ requires C, 57·8 ; H, 2·9 ; N, 6·8 ; Cl, 17·1%).

When the acid (0·4 g.) was heated slightly above its m. p. for ½ hour and then more strongly a brown oily distillate was obtained. The latter formed an oxalate, which crystallised from alcohol in colourless needles, m. p. 164—165°, undepressed on admixture with an authentic specimen of 7-chloroquinoline oxalate, m. p. 164°.

5-Chloro-ω-tribromoquinaldine. 5-Chloroquinaldine (6·0 g.) was brominated with bromine (18·0 g., 3·11 mols.) in glacial acetic acid (120 c.c.) containing anhydrous sodium acetate (40 g.) in the same way as 7-chloroquinaldine (yield, 91%). *5-Chloro-ω-tribromoquinaldine*, recrystallised from alcohol to constant m. p., gave colourless rhombohedra, m. p. 103° (Found : C, 29·4 ; H, 1·3 ; N, 3·1% ; 1 mg. equiv. to

1·66 mg. of AgX. $C_{10}H_5NClBr_3$ requires C, 29·0; H, 1·2; N, 3·4%; 1 mg. equiv. to 1·71 mg. of AgX).

5-Chloroquinaldinic acid. 5-Chloro-ω-tribromoquinaldine (10·0 g.) was hydrolysed in the same way as the 7-substituted isomer by boiling with 20% sulphuric acid (75 c.c.) under reflux for 26 hours (yield, 22%). Recrystallisation from aqueous alcohol to constant m. p. gave colourless needles, m. p. 176° (decomp.) (Found : C, 57·3; H, 3·1; N, 6·7; Cl, 16·8. $C_{10}H_6O_2NCl$ requires C, 57·8; H, 2·9; N, 6·8; Cl, 17·1%).

When the *acid* (0·4 g.) was distilled a light brown oil collected and formed an oxalate, m. p. 145°, undepressed on admixture with an authentic specimen of 5-chloroquinoline oxalate, m. p. 146°.

Conrad–Limpach Synthesis with m-*Chloroaniline.*—Equimolecular proportions of *m*-chloroaniline (81·4 g.) and ethyl acetoacetate (83·0 g.) were mixed at room temperature with the addition of hydrochloric acid (0·05 g.) as catalyst and set aside overnight. The lower layer of ethyl β-*m*-chloroanilinocrotonate was separated, washed twice with 25% hydrochloric acid (20 c.c.) to remove unchanged *m*-chloroaniline, and twice with water before drying (Na_2SO_4). Ethyl β-*m*-chloroanilinocrotonate (40 g.) was added dropwise during 15 minutes to diphenyl (of quantity as shown in Table II), refluxing at 254—255°, and the mixture heated under reflux for a further 10 minutes. The reaction mixture was allowed to cool, the diphenyl was extracted with boiling benzene, and the resulting 5- (and/or 7-)chloro-4-hydroxyquinaldine purified by dissolution in boiling aqueous sodium hydroxide, filtration, and precipitation with acid.

TABLE II.

Yield (%) *of* 5(*and/or* 7)-*chloro-4-hydroxyquinaldine.*

Ratio of ester : diphenyl	1 : 2	1 : 4	1 : 10	1 : 16
Diphenyl (g.)	80	160	400	640
Yield (%)	34	34	40	41

7-Chloro-4-hydroxyquinaldine.—A solution of the mixture of isomers (97·5 g.) in alcohol (225 c.c.) and 2-ethoxyethanol (50 c.c.) was mixed with a solution of picric acid (9·6 g.) in alcohol (40 c.c.) at the b. p. On cooling to 60° and maintenance at that temperature for 10 minutes almost pure 7-chloro-4-hydroxyquinaldine picrate, m. p. 234—236°, crystallised. This was collected and converted into 7-chloro-4-hydroxyquinaldine by decomposing it and extracting the picric acid twice with aqueous sodium carbonate and cooling before filtering. Recrystallisation from 80% aqueous alcohol to constant m. p. gave colourless plates, m. p. 312° (decomp.) (Price *et al., loc. cit.*, give m. p. 313·5—315°, and Steck *et al., loc. cit.*, give m. p. 315—316°) (Found : C, 61·7; H, 4·1; N, 7·1; Cl, 17·9. Calc. for $C_{10}H_8ONCl$: C, 62·0; H, 4·1; N, 7·2; Cl, 18·3%).

Orientation of 7-Chloro-4-hydroxyquinaldine.—7-Chloro-4-hydroxyquinaldine (3 g.) was boiled under reflux with phosphoryl chloride (15 c.c.) for 20 minutes. After cooling to 60°, the reaction mixture was poured on sodium hydroxide (36 g.) in water (70 c.c.) and crushed ice (300 g.) with stirring. The 4 : 7-dichloroquinaldine was precipitated, collected, washed well with water, and dried at 60—65°; m. p. 102—104° (yield, 88%). Recrystallisation from 90% aqueous alcohol gave colourless needles, m. p. 103°, undepressed on admixture with an authentic specimen of 4 : 7-dichloroquinaldine, m. p. 103°, prepared from 7-chloroquinaldine as described below.

Unambiguous Synthesis of 4 : 5- and 4 : 7-Dichloroquinaldine.—7-*Chloroquinaldine* N-*oxide.* 7-Chloroquinaldine (13·0 g.) in saturated ethereal solution was added dropwise with stirring during 10 minutes to an ethereal solution of monoperphthalic acid (22·4 g., 1·5 mols.) (*Org. Synth.*, 1940, **20**, 70; Bachman and Cooper, *loc. cit.*) at 15°. On completion of the addition, stirring was continued for 2 hours to transform the resulting oil into solid 7-chloroquinaldine *N*-oxide phthalate. The separation of the latter was completed by keeping the mixture for 2 days in the ice-chest. The phthalate (36·4 g.) was collected, dried in the air, finely ground, and stirred with excess of 5% aqueous ammonia (250 c.c.) at room temperature for ½ hour. The phthalate almost dissolved before the *N*-oxide hydrate was precipitated; the latter was collected, washed with water, and dried *in vacuo* (P_2O_5) to give 7-*chloroquinaldine* N-*oxide monohydrate* (60%), m. p. 106—111°. Recrystallisation from chloroform–ligroin to constant m. p. gave colourless needles, m. p. 119—120° (Found : C, 57·0; H, 4·6; N, 6·4; Cl, 16·9. $C_{10}H_8ONCl,H_2O$ requires C, 56·7; H, 4·7; N, 6·6; Cl, 16·8%). It formed a *picrate*, which crystallised from 2-ethoxyethanol in silky yellow needles, m. p. 133° (Found : N, 13·7, Cl, 8·0. $C_{10}H_8ONCl,C_6H_3O_7N_3$ requires N, 13·3; Cl, 8·4%).

4 : 7-Dichloroquinaldine. 7-Chloroquinaldine *N*-oxide (0·8 g.) was added slowly, in portions, to phosphoryl chloride chilled in ice, and the mixture was gently warmed and then boiled under reflux for ½ hour. The reaction mixture was cooled to 60° and poured, with vigorous stirring, on sodium hydroxide (12 g.) in water (20 c.c.) and ice (100 g.). The product was collected, washed with water, and dried at 60—70° (yield, 63%) ; m. p. 76—93°. Recrystallisation to constant m. p. from 50% aqueous alcohol gave colourless needles, m. p. 103° (Steck *et al., loc. cit.*, give m. p. 103·5—104°) (Found : C, 57·1; H, 3·3; N, 6·7; Cl, 33·3. Calc. for $C_{10}H_7NCl_2$: C, 56·6; H, 3·3; N, 6·6; Cl, 33·5%). It gave a *picrate*, which crystallised from methanol in silky yellow needles, m. p. 178° (Found : N, 13·0; Cl, 16·3. $C_{10}H_7NCl_2,C_6H_3O_7N_3$ requires N, 12·7; Cl, 16·1%).

5-Chloroquinaldine N-*oxide.* 5-Chloroquinaldine (5 g.) was slowly added dropwise to an ethereal solution of monoperphthalic acid (7·7 g., 1·5 mols.) and the mixture worked up as for the 7-substituted isomer. The phthalate (10·8 g.) gave a product, m. p. 62—65°, which, after drying *in vacuo* (P_2O_5) and recrystallisation to constant m. p., gave 5-*chloroquinaldine* N-*oxide dihydrate*, colourless needles, m. p. 67° (Found : C, 52·8; H, 5·1; N, 6·1; Cl, 15·3. $C_{10}H_8ONCl,2H_2O$ requires C, 52·4; H, 5·2; N, 6·1; Cl, 15·5%). It gave a *picrate*, which crystallised from 2-ethoxyethanol in minute silky yellow needles, m. p. 156—157° (Found : N, 13·5; Cl, 8·1. $C_{10}H_8ONCl,C_6H_3O_7N_3$ requires N, 13·3; Cl, 8·4%).

4 : 5-Dichloroquinaldine.—5-Chloroquinaldine *N*-oxide (3·1 g.) was treated with phosphoryl chloride

(15 c.c.) and worked up in the same way as 7-chloroquinaldine *N*-oxide.   The *product* had m. p. 55—65° (yield, 50%), and recrystallisation to constant m. p. from 90% aqueous alcohol gave colourless needles, m. p. 89° (Found : C, 56·8; H, 3·3; N, 6·4; Cl, 33·6. $C_{10}H_7NCl_2$ requires C, 56·6; H, 3·3; N, 6·6; Cl, 33·5%).   It formed a *picrate*, which crystallised in rosettes of lemon-yellow needles, m. p. 143° (Found : N, 13·2; Cl, 16·0. $C_{10}H_7NCl_2,C_6H_3O_7N_3$ requires N, 12·7; Cl, 16·1%).

Modified Doebner–Miller Synthesis with m-*Toluidine.*—m-Toluidine (30 g., 0·28 mol.), sulphuric acid (of concentration and amount as indicated in Table III), and sodium *m*-nitrobenzenesulphonate (70 g.) were heated to 120—130° with stirring and paraldehyde (45 c.c., equiv. to 1 mol. of crotonaldehyde) was added during 20—30 minutes at that temperature.   The mixture was heated under steady reflux during 1½ hours, during which period the b. p. increased owing to the decomposition and the volatility of the paraldehyde.   The reaction mixture was cooled, diluted with water (300—400 c.c.), treated with sodium nitrite (20 g.), and boiled for ½ hour to decompose any unchanged *m*-toluidine.   It was then cooled, basified with sodium hydroxide, and distilled in steam.   The steam-distillate was extracted with ether, and the ethereal extract dried (CaCl₂).   Evaporation of the ether and distillation of the residue gave a pale yellow oil, which at all acid concentrations investigated was a mixture of 2 : 5- and 2 : 7-dimethyl-quinoline (yields recorded in Table III are those of the distilled products).   On cooling, 2 : 7-dimethyl-quinoline crystallised from this oil.

Estimation of Mixtures of 2 : 5- *and* 2 : 7-*Dimethylquinoline.*—It was found impossible to separate these two isomers, but by filtration of the partly solidified mixture through sintered glass pure 2 : 7-di-methylquinoline was isolated.   The oily filtrate, containing both isomers, was converted into a mixture of the picrates, extraction of which with 2-ethoxyethanol at 95—100° gave a residue of pure 2 : 5-di-methylquinoline picrate, m. p. 222°.   The previously isolated 2 : 7-dimethylquinoline was converted into its picrate and a m. p. diagram for the system 2 : 5/2 : 7-dimethylquinoline picrates drawn.   From this diagram the compositions of the mixtures of 2 : 5- and 2 : 7-dimethylquinolines, obtained using different concentrations of acid, were estimated (see Table III).   The original Doebner–Miller synthesis, involving the boiling of *m*-toluidine (30 g.), paraldehyde (45 c.c.), and concentrated hydrochloric acid (60 c.c.) for 1½ hours, followed by working up in the manner described for the modified procedure, gave a total yield (13%) of a mixture of 2 : 5-dimethylquinoline (18%) and 2 : 7-dimethylquinoline (82%).

TABLE III.

Yield (%) *and proportion of* 2 : 5- *and* 2 : 7-*dimethylquinoline.*

Sulphuric acid.		Yield (%) of 2 : 5- and 2 : 7-dimethyl-quinoline.	M. p. of picrate.	Estimated composition of product.	
Concn. (%).	Quantity. (c.c.).			5- (%).	7- (%).
80	115	12	183°	45 *	55 *
75	125	29	183·5°	28	72
70	142	32	187°	22	78
65	157	26	—	—	—
60	177	20	188·5°	18	82

* Not much reliance can be placed on these figures since they occur on the flat part of the m. p. curve.

Recrystallisation, from ligroin, of the 2 : 7-dimethylquinoline isolated from the mixture gave colour-less needles, m. p. 61—62°, b. p. 265°/745 mm. (Manske, Marion, and Ledger, *loc. cit.*, give m. p. 61°). This formed a picrate, golden-yellow plates (from 2-ethoxyethanol), m. p. 196°, a styphnate, yellow plates (from 2-ethoxyethanol), m. p. 220—221°, and a trinitro-*m*-cresol complex, m. p. 250° (Manske, Marion, and Ledger, *loc. cit.*, give m. p. 196°, 222°, and 250°, respectively).   2 : 5-Dimethylquinoline, which was isolated as its picrate, which crystallised from 2-ethoxyethanol in lemon-yellow needles, m. p. 222°, formed a styphnate, yellow needles (from 2-ethoxyethanol), m. p. 206° (Manske, Marion, and Ledger, *loc. cit.*, give m. p. 223° and 207°, respectively).

Conrad–Limpach Synthesis with m-*Toluidine.*—Equimolecular proportions of *m*-toluidine (64·3 g.) and ethyl acetoacetate (78 g.) were mixed at room temperature with the addition of hydrochloric acid (0·05 g.) as catalyst and set aside overnight.   The resulting emulsion of the ester was disrupted by the addition of a concentrated sodium chloride solution, and the ester separated.   It was washed by such a solution containing hydrochloric acid and dried (Na₂SO₄) (yield, 74%).   Ethyl β-*m*-toluidinocrotonate (80 g.) was added dropwise to diphenyl (320 g.) refluxing at 254—255° during 25 minutes, and the mixture boiled under reflux for a further 10 minutes.   The diphenyl was extracted 4 times with boiling benzene, and the resulting 4-hydroxymethylquinaldines were purified by dissolving them in boiling aqueous sodium hydroxide (decolorising charcoal), filtering, and reprecipitating them with acid.   The product, after cooling, was collected, washed with water, and dried (yield, 53%).   Experiments in which small amounts of ester (5 g.) were cyclised in refluxing diphenyl using ratios of ester : solvent from 1 : 2 to 1 : 20 indicated that the yield (50—60%) and the proportion of the isomers were independent of the concentrations at which cyclisation was carried out.

Separation of 4-*Hydroxy*-5- *and* -7-*methylquinaldines.*—The resulting mixture of isomers was separated by fractional crystallisation of the oxalates from alcohol.   A boiling solution of oxalic acid (7·6 g.) in alcohol (60 c.c.) was added to a solution of the mixture of isomers (20·8 g.) in alcohol (125 c.c.).   The solution was allowed to cool to 60° and maintained at that temperature for 10 minutes, during which period the oxalate of 4-hydroxy-5-methylquinaldine separated.   This was collected and dried (yield, 8·4 g.); m. p. 200—204°.   On cooling the filtrate to room temperature, the oxalate of 4-hydroxy-7-methylquinaldine separated, was collected, and dried (yield, 6·8 g.); m. p. 171—174°.   The losses during separation amounted to 40% and from the weights of oxalates the proportion of 4-hydroxy-5- to

4-hydroxy-7-methylquinaldine was estimated as 56 : 44. In experiments in which the cyclisation of the ethyl β-*m*-toluidinocrotonate was carried out in diphenylamine at 250—260° and in refluxing diphenylamine (302°), with an ester : solvent ratio of 1 : 4 in both cases, the yields were 44% and 50%, and the proportions of 4-hydroxy-5- to 4-hydroxy-7-methylquinaldine was 47 : 53 and 44 : 56 respectively, thus indicating only slight variations in the yield and the porportion of the isomers with variation of temperature and the nature of the solvent.

4-Hydroxy-5-methylquinaldine.—From its oxalate 4-hydroxy-5-methylquinaldine was obtained by hydrolysis with sodium hydroxide at the b. p. and neutralisation with acid. After cooling to complete the separation, the product was collected, washed, and dried, m. p. 267—271°. Recrystallisation (from methanol) to constant m. p. gave colourless prismatic needles, m. p. 278° [Backeberg and Friedmann, *J.*, 1938, 975, give 4-hydroxy-5(or 7)-methylquinaldine, m. p. 273°] (Found : C, 76·2 ; H, 6·4 ; N, 8·5. Calc. for $C_{11}H_{11}ON$: C, 76·3 ; H, 6·4 ; N, 8·0%). It formed an *oxalate*, which crystallised from alcohol in colourless prismatic plates, m. p. 213° (Found : C, 66·3 ; H, 5·5 ; N, 6·6. $C_{11}H_{11}ON,H_2C_2O_4$ requires C, 66·0 ; H, 5·5 ; N, 6·4%).

4-Hydroxy-7-methylquinaldine.—From its oxalate *4-hydroxy-7-methylquinaldine* was obtained in a similar manner ; recrystallisation to constant m. p. (from alcohol) gave minute colourless needles, m. p. 261° (Found : C, 76·6 ; H, 6·8 ; N, 8·4. $C_{11}H_{11}ON$ requires C, 76·3 ; H, 6·4 ; N, 8·1%). It formed an *oxalate*, which crystallised from alcohol in pale brown prisms, m. p. 173—175° (Found : C, 66·3 ; H, 5·6 ; N, 6·9. $C_{11}H_{11}ON,H_2C_2O_4$ requires C, 66·0 ; H, 5·5 ; N, 6·4%).

Orientation of 4-Hydroxy-5- and -7-methylquinaldine.—*4-Chloro-5-methylquinaldine.* 4-Hydroxy-5-methylquinaldine (2 g.) was heated under reflux with phosphoryl chloride (6 c.c.) for 20 minutes. After cooling to 60° the reaction mixture was poured on a mixture of sodium hydroxide (12 g.) in water (20 c.c.) and crushed ice (150 g.) with stirring, and the *product* which was precipitated was collected, washed, and dried (yield, 82%) ; m. p. 66—71°. It was recrystallised to constant m. p. from 50% aqueous alcohol to give colourless needles, m. p. 74° (Found : C, 68·7 ; H, 5·4 ; N, 7·0 ; Cl, 18·7. $C_{11}H_{10}NCl$ requires C, 69·0 ; H, 5·3 ; N, 7·3 ; Cl, 18·5%). It formed a *picrate*, which crystallised from 2-ethoxyethanol in golden-yellow plates, m. p. 188—189° (Found : N, 13·1 ; Cl, 8·5. $C_{11}H_{10}NCl,C_6H_3O_7N_3$ requires N, 13·3 ; Cl, 8·4%).

When the chloro-compound (1 g.), dissolved in a solution of sodium hydroxide (3 g.) in water (20 c.c.) at 90° by the addition of sufficient alcohol (14 c.c.), was catalytically dehalogenated by the gradual addition of finely powdered Raney alloy (3 g.) during ½ hour and maintenance at 90° for 1 hour, the mixture divided itself into an upper alcoholic layer and a lower aqueous layer containing insoluble Raney nickel and an alkaline solution of sodium aluminate. The former layer was acidified with hydrochloric acid and evaporated to dryness. The hydrochloride was dissolved in water, basified, and extracted with ether. The ethereal extract was dried (Na_2SO_4) and the ether evaporated to leave a reddish-brown oil. This oil gave a picrate, which crystallised from 2-ethoxyethanol in yellow needles, m. p. 217—218° undepressed on admixture with an authentic specimen of 2 : 5-dimethylquinoline picrate, and a trinitro-*m*-cresol complex, which crystallised from 2-ethoxyethanol in yellow plates, m. p. 198—199° (Manske, Marion, and Ledger, *loc. cit.*, give m. p. 201°) (Found : C, 53·7 ; H, 4·0. Calc. for $C_{11}H_{11}N,C_7H_5O_7N_3$: C, 54·0 ; H, 4·0%).

4-Chloro-7-methylquinaldine.—4-Hydroxy-7-methylquinaldine (2 g.) was similarly heated under reflux with phosphoryl chloride (6 c.c.) for 25 minutes (yield, 59%). The *product* was purified by recrystallisation from aqueous alcohol, followed by sublimation to give colourless needles, m. p. 56—57° (Found : C, 68·6 ; H, 5·3 ; N, 7·0 ; Cl, 18·5. $C_{11}H_{10}NCl$ requires C, 69·0 ; H, 5·3 ; N, 7·3 ; Cl, 18·5%). It formed a *picrate*, which crystallised from 2-ethoxyethanol in minute lemon-yellow needles, m. p. 209—210° (Found : N, 13·0 ; Cl, 8·8. $C_{11}H_{10}NCl,C_6H_3O_7N_3$ requires N, 13·3 ; Cl, 8·4%).

When the chloro-compound (0·85 g.) was catalytically dehalogenated as above with Raney alloy (3 g.), a light brown oil, which solidified on cooling, was obtained. Recrystallisation of this solid from ligroin gave colourless needles, m. p. 57° (2 : 7-dimethylquinoline, m. p. 61°). It gave a picrate, which crystallised from 2-ethoxyethanol in golden-yellow needles, m. p. 197° (Manske, Marion, and Ledger, *loc. cit.*, give 2 : 7-dimethylquinoline picrate, m. p. 196°), and a trinitro-*m*-cresol complex, which crystallised from 2-ethoxyethanol in golden-yellow needles, m. p. 250° (decomp.) (Found : C, 53·8 ; H, 3·8. Calc. for $C_{11}H_{11}N,C_7H_5O_7N_3$: C, 54·0 ; H, 4·0%), undepressed on admixture with an authentic specimen of 2 : 7-dimethylquinoline trinitro-*m*-cresol complex, m. p. 250° (decomp.).

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