386. *The Preparation of 4-Amino-2-styrylquinoline and Some Related Compounds.*

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Studies on the relation between chemical constitution and antibacterial action have entailed the synthesis of compounds of the type of 4-amino-2-styrylquinoline, -2-4′-*phenylbutadienylquinoline*, and -2 : 6-*distyrylpyridine*. Some improvements in the preparation of necessary intermediates are recorded. A process is described for removing an active methyl group from a pyridine-type nucleus bearing in addition an amino-group.

JENSCH (*Z. angew. Chem.*, 1937, **50**, 891) claimed that 4-amino-2-styrylquinoline displayed remarkable bactericidal properties. According to Eisleb (D.R.-P. 440,008; U.S.P. 1,967,356), this and analogous compounds may be prepared by amination of the 4-chloro-2-styrylquinolines produced by heating 4-chloroquinaldines with an aldehyde and zinc chloride. Endeavours to repeat this work led to tars from which only a poor yield of the desired product could be isolated. Accordingly, condensation of a 4-aminoquinaldine with an aldehyde in the presence of acetic anhydride and hydrolysis of the resultant 4-acetamido-2-styrylquinoline were investigated. In general, acetic anhydride was preferable to zinc chloride as condensing agent despite the fact that the additional step of hydrolysis was involved; *e.g.*, by use of zinc chloride, the yield of pure 4-amino-2-styrylquinoline was 45%, whereas the acetic anhydride method gave a yield of 77%; again, no useful product was obtained in the reaction of 4-aminoquinaldine with cinnamaldehyde in the presence of zinc chloride, whereas acetic anhydride led to a moderate yield of 4-*acetamido*-2-4′-*phenylbutadienylquinoline*. The compounds listed in Tables I and II, and 4-amino-2 : 6-distyrylpyridine, were synthesised by this general method.

4-*Amino*-2-p-*nitrostyrylquinoline* was not prepared by this method, as 4-*acetamido*-2-p-*nitrostyrylquinoline* proved unexpectedly resistant to hydrolysis. However it was obtained pure in moderate yield by heating 4-aminoquinaldine, *p*-nitrobenzaldehyde, and zinc chloride. The general method failed with 4-aminoquinaldine and *p*-dimethylaminobenzaldehyde, but the use of zinc chloride resulted in a 46% yield of 4-*amino*-2-4′-*dimethylaminostyrylquinoline*.

Schmidt (*Ber.*, 1905, **38**, 3715) prepared 6-nitro-2-styrylquinoline by heating 6-nitroquinaldine and benzaldehyde with zinc chloride, purification involving several recrystallisations from alcohol. The preparation has been improved by using acetic anhydride in place of zinc chloride, an 84% yield of pure substance being isolated directly from the reaction mixture. Reduction by stannous chloride gave 6-amino-2-styrylquinoline, m. p. 197°. This compound has recently been prepared by a similar method by Brown and Kon (*J.*, 1948, 2147) who recorded m. p. 198—199°.

4-Amino-2 : 6-dimethylpyridine was first prepared by Marckwald (*Ber.*, 1894, **27**, 1325) by pyrolysis of the corresponding 3 : 5-dicarboxylic acid, obtained by a lengthy synthesis from acetonedicarboxylic ester. Later, it was prepared by heating 2 : 6-dimethylpyridine with sodamide in toluene (Tschitschibabin, *Chem. Zentr.*, 1916, **1**, 1032). It has been found that the base is conveniently obtained by reaction of 4-chloro-2 : 6-dimethylpyridine with ammonia in boiling *p*-cresol (the use of phenol at 180° gave only 35%); 4-amino-2 : 6-dimethylpyridine melts at 192° (186°, *locc. cit.*), being very readily purified by crystallisation from benzene.

4-Amino-2 : 8-dimethylquinoline has been prepared by Hofmann degradation of 2 : 8-*dimethylcinchoninamide*, readily obtained by heating 7-methylisatin with acetone and ammonia (cf. D.R.-P. 290,703). Application of this method to 5-chloroisatin proved unsatisfactory for preparative purposes, and 6-*chloro*-4-*aminoquinaldine* was produced more readily by aminating 4 : 6-dichloroquinaldine in phenol.

The product of a quinoline synthesis frequently bears a 2-methyl group whose elimination may be desirable. The facile preparation of 4-acetamido-2-styrylquinolines from 4-aminoquinaldines suggests such a method for a quinoline nucleus which bears also a 4-amino-group. *E.g.*, 4-*acetamido*-2-*styrylquinoline* was oxidised to 4-*acetamidoquinaldinic acid* which afforded 4-aminoquinoline by hydrolysis and subsequent decarboxylation (yields are good). Alternatively, 4-acetamidoquinaldinic acid could be decarboxylated to 4-acetamidoquinoline in 89% yield. Endeavours to effect simultaneous hydrolysis and decarboxylation of 4-acetamidoquinaldinic acid were unsuccessful; 65% sulphuric acid at a bath-temperature of 210° left the carboxyl group in place, and stronger acid caused sulphonation (for another example of this series of reactions, see Albert, Brown, and Duewell, *J.*, 1948, 1284).

EXPERIMENTAL.

M. p.s are not corrected.

4-*Acetamido*-2-*styryl*- and -2-4′-*phenylbutadienyl-quinoline*.—The appropriate 4-aminoquinaldine, acetic anhydride (3 mols.), and benzaldehyde, cinnamaldehyde, or anisaldehyde (3 mols.) were heated for 3 hours in a bath at 155—160°. Excess of aldehyde was removed by steam-distillation; the remaining solid was collected, ground under methanol (2 parts), and crystallised from a suitable solvent. Yields and analytical data for *compounds* prepared in this manner are given in Table I. The substances form white or pale yellow crystals.

TABLE I.

4-*Acetamidoquinolines*.

Substituents.	M. p.	Solvent.	Yield, %.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
2-Styryl	199·5°	67% ethanol	91	$C_{19}H_{16}ON_2$	78·6	5·6	9·8	79·1	5·6	9·7
8-Methyl-2-styryl	230	ethanol	83	$C_{20}H_{18}ON_2$	78·9	6·0	9·3	79·4	6·0	9·3
6-Ethoxy-2-styryl	216	ethanol	85	$C_{21}H_{20}O_2N_2$	75·2	6·0	8·45	78·85	6·1	8·4
6-Chloro-2-styryl	241·5	chlorobenzene	81	$C_{19}H_{15}ON_2Cl$			8·7			8·7
2-4′-Phenylbutadienyl	196	ethanol	53	$C_{21}H_{18}ON_2$	79·7	5·8	8·9	80·2	5·8	8·9
6-Ethoxy-2-4′-phenylbutadienyl	188	ethanol	65	$C_{23}H_{22}O_2N_2$	76·4	6·2	7·9	77·0	6·2	7·8
2-4′-Methoxystyryl	228	acetone	62	$C_{20}H_{18}O_2N_2$	74·9	5·7	8·8	75·4	5·7	8·8

4-*Amino*-2-*styryl*- and -2-4′-*phenylbutadienyl-quinoline*.—The appropriate 4-acetamido-compound was heated under reflux for 4—5 hours with 6N-hydrochloric acid (5 mols.). Ethanol (5 parts) was added to the hydrolysis mixture in the cases of 6-chloro-4-acetamido- and 4-acetamido-6-ethoxy-2-styrylquinoline and of 4-acetamido-6-ethoxy-2-4′-phenylbutadienylquinoline. After the mixture had been cooled, the hydrochloride was filtered off and warmed with dilute ammonium hydroxide to liberate the base, which was purified by crystallisation from a suitable solvent. Yields and analytical data are given in Table II. The *compounds* form yellow or buff-coloured crystals, readily soluble in N-acetic acid. The hydrochlorides are bright yellow and only sparingly soluble in cold water. The amines do not diazotise normally.

TABLE II.

4-*Aminoquinolines.*

Substituents.	M. p.	Solvent.	Yield, %.	Formula.	Found, %. C.	Found, %. H.	Found, %. N.	Required, %. C.	Required, %. H.	Required, %. N.
2-Styryl	173·5° [a]	60% ethanol	85	$C_{17}H_{14}N_2$	82·5	5·8	11·3	82·9	5·7	11·4
8-Methyl-2-styryl	201	ethanol	99	$C_{18}H_{16}N_2$	82·5	6·1	10·7	83·0	6·2	10·8
6-Ethoxy-2-styryl	211 [b]	60% ethanol	94	$C_{19}H_{18}ON_2$	78·0	6·2	9·7	78·6	6·25	9·65
6-Chloro-2-styryl	228	chlorobenzene	88	$C_{17}H_{13}N_2Cl$	72·4	4·6	10·1	72·7	4·7	10·0
2-4′-Phenylbutadienyl ...	170—176 [c]	67% ethanol	83	$C_{19}H_{16}N_2$	83·2	6·0	10·3	83·8	5·9	10·3
6-Ethoxy-2-4′-phenylbutadienyl	207 [d]	ethanol	83	$C_{21}H_{20}ON_2$	79·6	6·4	8·9	79·7	6·4	8·9
2-4′-Methoxystyryl	164—165	chlorobenzene	97	$C_{18}H_{16}ON_2$	77·5	5·8	10·1	78·2	5·8	10·15

[a] D.R.-P. 440,008 gives m. p. 173—175° (decomp.).
[b] D.R.-P. 440,008 gives m. p. 212°.
[c] This wide melting-range was not altered by crystallisation from chlorobenzene.
[d] U.S.P. 1,967,356 gives m. p. 185—187°.

4-*Amino*-2-4′-*dimethylaminostyrylquinoline.*—4-Aminoquinaldine (1·0 g.) and *p*-dimethylaminobenzaldehyde (2·9 g.) were heated with pulverised anhydrous zinc chloride (0·1 g.) for 2 hours in a bath at 180—185°. The mass was then heated under reflux for 10 minutes with N-hydrochloric acid (20 ml.), and the dihydrochloride of 4-*amino*-2-4′-*dimethylaminostyrylquinoline* was precipitated by the addition of concentrated hydrochloric acid (20 ml.). This salt was suspended in boiling 50% ethanol (50 ml.), and 2·5N-sodium hydroxide was added until the colour changed through red to yellow. The resulting solution was poured into water (200 ml.), and the base collected and crystallised from toluene (16 parts), giving deep-yellow crystals, m. p. 186° (46%) (Found : C, 78·5; H, 6·7; N, 14·5. $C_{19}H_{19}N_3$ requires C, 78·8; H, 6·6; N, 14·5%). The dihydrochloride is white, and the monohydrochloride scarlet, 1 part of the latter dissolving in *ca.* 800 parts of boiling water. The base is readily soluble in N-acetic acid and does not diazotise normally.

4-*Amino*-2-4′-*aminostyrylquinoline and* 4-*Amino*-2-4′-*nitrostyrylquinoline.*—(*a*) 4-Aminoquinaldine (3·2 g.), *p*-nitrobenzaldehyde (3·3 g., 1·1 mols.), and acetic anhydride (20·3 g., 10 mols.) were heated for 1 hour in a bath at 155—160°. The pale yellow crystals which separated on cooling were washed with glacial acetic acid, water, *and* a little ethanol, leaving pure 4-*acetamido*-2-4′-*nitrostyrylquinoline*, m. p. 257—258° (50%) (Found : C, 67·9; H, 4·6; N, 12·7. $C_{19}H_{15}O_3N_3$ requires C, 68·4; H, 4·5; N, 12·6%). A further amount of crude material was obtained by making the mother-liquor alkaline. Reduction by stannous chloride in concentrated hydrochloric acid gave 4-*acetamido*-2-4′-*aminostyrylquinoline* as yellow crystals (from 200 parts of ethanol), m. p. 247° (91%) (Found : N, 13·7. $C_{19}H_{17}ON_3$ requires N, 13·9%). This compound (0·35 g.) and 6N-hydrochloric acid (1·8 ml.) were heated under reflux for 3—5 hours; after the mixture had been cooled, the solid was basified by ammonium hydroxide, and the amine purified by extraction with N-acetic acid and basification of the extract. 4-*Amino*-2-4′-*aminostyrylquinoline*, thus obtained in 80% yield, formed deep-yellow crystals, m. p. 202·5°, from ethanol (15 parts) (Found : C, 77·7; H, 5·8; N, 16·1. $C_{17}H_{15}N_3$ requires C, 78·1; H, 5·8; N, 16·1%). The diazo-solution is bright yellow and couples (crimson) with alkaline β-naphthol. The dihydrochloride is flesh-coloured, and the monohydrochloride orange-red, being moderately soluble in cold water.

(*b*) 4-Aminoquinaldine (3·3 g.), *p*-nitrobenzaldehyde (6·9 g.), and pulverised anhydrous zinc chloride (0·5 g.) were heated in a bath at 170° for 10 minutes and then boiled under reflux for 30 minutes with N-hydrochloric acid (50 ml.). After the excess of *p*-nitrobenzaldehyde had been removed by steam-distillation, the residual solid was boiled with dilute ammonium hydroxide solution, and the 4-*amino*-2-4′-*nitrostyrylquinoline* purified by crystallisation from acetone; deep yellow crystals, m. p. 249°; yield, 49% (Found : N, 14·3. $C_{17}H_{13}O_2N_3$ requires N, 14·4%). The base formed gels with dilute acetic and lactic acid. Reduction by stannous chloride in concentrated hydrochloric acid gave 4-amino-2-4′-aminostyrylquinoline (91%), identical with the compound produced by method (*a*).

6-*Amino*-2-*styrylquinoline.*—6-Nitroquinaldine (3·8 g.), benzaldehyde (6·4 g., 3 mols.), and acetic anhydride (12·2 g., 6 mols.) were heated under reflux for 4 hours in a bath at 165—170°. After the mixture had been cooled, the solution deposited yellow crystals which were washed with a little glacial acetic acid and then with water, and dried at 120°, affording pure 6-nitro-2-styrylquinoline, m. p. 192° (84%). Reduction by stannous chloride in concentrated hydrochloric acid gave 6-amino-2-styrylquinoline (94%) as buff-coloured crystals, m. p. 197°, from ethanol (50 parts) or chlorobenzene (6 parts) (Found : C, 82·4; H, 5·7; N, 11·4. Calc. for $C_{17}H_{14}N_2$: C, 82·9; H, 5·7; N, 11·4%). The compound forms a yellow diazo-solution which couples (crimson) with alkaline β-naphthol.

4-*Amino*-2 : 6-*distyrylpyridine.* 4-Amino-2 : 6-dimethylpyridine (1·4 g.), acetic anhydride (7·2 g., 6 mols.), and benzaldehyde (7·6 g., 6 mols.) were heated in a bath at 175—180° for 10 hours; excess of benzaldehyde was removed by steam-distillation leaving a semi-solid mass which was washed with water and dried in a desiccator. The solid so obtained was heated under reflux for 2·5 hours with 6N-hydrochloric acid (9 ml.) and ethanol (5 ml.), and the resulting mixture poured into excess of ammonium hydroxide, boiled for 30 minutes, and cooled. The liquid was decanted and the tarry residue triturated with cold ethanol (5 ml.), giving a solid, m. p. 220—221° (32%). Crystallisation from ethanol (70 parts) gave 4-*amino*-2 : 6-*distyrylpyridine* as light brown crystals, m. p. 223·5° (Found : C, 84·1; H, 6·0; N, 9·3. $C_{21}H_{18}N_2$ requires C, 84·5; H, 6·1; N, 9·4%).

4-*Amino*-2 : 8-*dimethylquinoline*.—7-Methylisatin (12 g.), ammonium hydroxide (10%; 74 ml.), and acetone (6 ml.) were heated under reflux for 1 hour and then cooled; crystalline 2 : 8-*dimethylcinchoninamide* (82%) was collected; m. p. 218—220°. Repeated recrystallisation from ethanol gave cream-coloured crystals, m. p. 224° (Found : N, 13·9. $C_{12}H_{12}ON_2$ requires N, 14·0%). This amide (9 g.) was added to a solution of bromine (7·3 g.) in 10% potassium hydroxide (125 ml.) at 5°; the resulting solution was stirred for 45 minutes at 5°, treated with more 10% potassium hydroxide (72 ml.), and after 5 minutes heated to 60° for 20 minutes. After the mixture had cooled, the crude 4-amino-2 : 8-dimethylquinoline was collected and purified by crystallising the hydrochloride from the minimum quantity of water and regenerating the base with 5N-sodium hydroxide; yield, 3·4 g.; m. p. 134—135°. Crystallisation from benzene raised the m. p. to 137°, not altered by crystallisation from water (Backeberg, *J.*, 1938, 1083, recorded m. p. 141°) (Found : C, 76·2; H, 7·0; N, 16·15. Calc. for $C_{11}H_{12}N_2$: C, 76·7; H, 7·0; N, 16·3%).

6-*Chloro*-4-*aminoquinaldine*.—Crude 4 : 6-dichloroquinaldine was prepared from 6-chloro-4-hydroxyquinaldine by phosphorus oxychloride according to the general method of Albert and Gledhill (*J. Soc. Chem. Ind.*, 1945, **64**, 169T). This substance (5 g.) and dried phenol (40 g.) were heated in a bath at 175—180° while a steady stream of ammonia was passed through the solution for 3 hours. After removal of phenol by steam-distillation, the solution was poured into excess of 5N-sodium hydroxide yielding 6-*chloro*-4-*aminoquinaldine*, m. p. 186° (77% based on 6-chloro-4-hydroxyquinaldine). Crystallisation from benzene (20 parts) gave white crystals, m. p. 186° (Found : C, 61·85; H, 4·7; N, 14·4. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7; N, 14·5%).

4-*Amino*-2 : 6-*dimethylpyridine*. 4-Chloro-2 : 6-dimethylpyridine (3·65 g.) and dry *p*-cresol (18 g.) were heated in a bath at 205—210° while a steady stream of dry ammonia was passed through the solution for 5 hours. Working up as above and crystallisation from benzene gave pure 4-amino-2 : 6-dimethylpyridine, m. p. 192° (72%) (Found : C, 68·5; H, 8·2; N, 22·7. Calc. for $C_7H_{10}N_2$: C, 68·8; H, 8·3; N, 22·9%).

4-*Acetamidoquinaldinic Acid*.—4-Acetamido-2-styrylquinoline (4·6 g.) in pyridine (32 ml.) and water (6·5 ml.) was stirred vigorously while powdered potassium permanganate (6·7 g.) was added during 1 hour, the internal temperature being kept at 18—20°. Water (total of 20 ml.) was added from time to time to permit stirring, as the mixture became thick with inorganic matter. Stirring was continued for 30 minutes, then the mixture was made acid to Congo-paper with dilute sulphuric acid and decolorised by the addition of sodium hydrogen sulphite. The precipitated acid was collected, washed with ether, and extracted with 2N-sodium carbonate; concentrated hydrochloric acid was added to the extract, precipitating the required acid, m. p. 237° (decomp.) (82%). Crystallisation from water (600 parts) gave 4-*acetamidoquinaldinic acid* as cream-coloured crystals, m. p. 238° (decomp.) (Found : C, 59·9; H, 4·6; N, 11·8. $C_{12}H_{10}O_3N_2,\frac{1}{2}H_2O$ requires C, 60·2; H, 4·6; N, 11·7%).

4-*Aminoquinaldinic Acid*.—4-Acetamidoquinaldinic acid (0·67 g.) was added to water (1 ml.) and sulphuric acid (*d* 1·84; 1 ml.) and heated under reflux in a bath at 208—210° for 2·5 hours. The solution was poured into water (2 ml.), and ammonium hydroxide solution added. 4-Aminoquinaldinic acid separated as light-brown crystals, m. p. 281—282° (decomp.) (68%) [cf. Bergstrom, *J. Org. Chem.*, 1938, **3**, 233, who recorded m. p. *ca.* 280·5—281° (decomp.)].

4-*Aminoquinoline*.—4-Aminoquinaldinic acid (0·37 g.) was heated in liquid paraffin (2·5 ml.) at 280—290° for 5 minutes. After cooling, the mixture was diluted with light petroleum (5 ml.), giving 4-aminoquinoline, 0·23 g., m. p. 152—153° after crystallisation from benzene. The m. p. was not depressed on admixture with an authentic specimen of anhydrous 4-aminoquinoline (m. p. 154°).

4-*Acetamidoquinoline*.—Liquid paraffin (10 ml.) was heated to 290° and stirred while 4-acetamidoquinaldinic acid (2 g.) was added during 5 minutes; after a further 5 minutes the mixture was cooled and diluted with light petroleum (5 ml.), giving 4-acetamidoquinoline (1·44 g.), m. p. 174—175° after crystallisation from water (cf. 176° recorded by Claus, *J. pr. Chem.*, 1897, **56**, 190).

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