664. *Reactions of Methazonic Acid. Part II.* Some 3-Aminolepidines, 3-Amino-4-arylquinolines, and Derived Compounds.*

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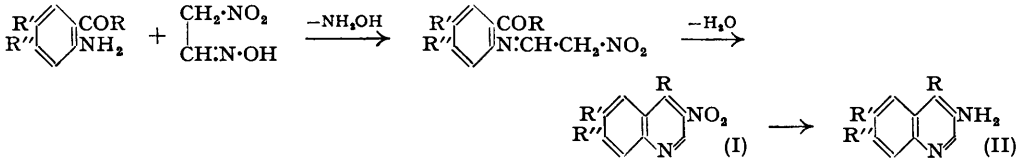
Several 3-aminolepidines and 3-amino-4-arylquinolines have been prepared by reducing the related 3-nitroquinolines described in Part I (*loc. cit.*). 3-Aminolepidine on diazotisation and treatment with pyridine gives two isomeric 3-pyridyl-lepidines. 3-Amino-4-phenyl- and 3-amino-4-*p*-methoxyphenyl-quinoline have been deaminated to 4-phenyl- and 4-*p*-methoxyphenyl-quinoline. 3-Benzamido-4-phenylquinoline is converted by phosphoric oxide into 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine, the quaternisation of which is reported.

Our aim in the present work was to utilise the 3-nitrolepidines (I; R = Me) and 4-aryl-3-nitroquinolines (I; R = Ar), prepared from methazonic acid and various ketones as described in Part I (*loc. cit.*) and illustrated below, as sources of 3-amino-compounds required for various syntheses. The inability of one of us to continue this work makes it desirable to report the results so far obtained, though they are incomplete.



As a group, 3-aminoquinolines have hitherto most frequently been prepared by methods other than the reduction of 3-nitroquinolines. Practicable methods reported in the literature have involved Hofmann or Curtius reactions with quinoline-3-carboxylic acids (Mills and Watson, *J.*, 1910, **97**, 741; Lawson, Perkin, and Robinson, *J.*, 1924, **125**, 626; Wojahn and Kramer, *Arch. Pharm.*, 1938, **276**, 291), direct replacement of the 3-hydroxyl group (G.P. 611,691, 630,769; F.P. 789,068; B.P. 448,502; U.S.PP. 2,077,903, 2,098,927) and of the 3-bromo-atom (Jansen and Wibaut, *Rec. Trav. chim.*, 1937, **56**, 709; Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320), and direct synthesis (Berlingozzi *et al.*, *Gazzetta*, 1923, **53**, 3, 369; *Atti R. Accad. Lincei*, 1923, **32**, 403; *Ann. Chim. appl.*, 1927, **17**, 250; Petrow, Stack, and Wragg, *J.*, 1943, 316). In reported preparations of 3-aminoquinolines by reduction of the nitro-compounds, the reagents used have been tin and hydrochloric acid (Bergellini and Settimj, *Gazzetta*, 1923, **53**, 601), stannous chloride (Musajo, *ibid.*, 1937, **67**, 222), iron and acetic acid (Colonna, *Boll. sci. Facoltà Chim. Ind. Bologna*, 1941, 89), sodium sulphite and hydrochloric acid, and hydrogen with Adams's catalyst (Clemo and Swan, *J.*, 1945, 867).

Several of the 3-nitrolepidines previously described (Part I, *loc. cit.*) have now been reduced on the small scale by means of stannous chloride and hydrochloric acid. In this way satisfactory yields of 3-aminolepidine (II; R = Me, R′ = R″ = H), 3-amino-6- and -7-chlorolepidine (II; R = Me, R′ = Cl or H, R″ = H or Cl), and 3-amino-4 : 6 : 7-trimethylquinoline (II; R = R′ = R″ = Me) were obtained. Likewise, 3-amino-6 : 7-*cyclo*penteno- and 3-amino-6 : 7-*cyclo*hexeno-lepidine (II; R = Me, R′R″ = $[CH_2]_3$ or $[CH_2]_4$) were prepared, but 3 : 6-dinitrolepidine (I; R = Me, R′ = NO_2, R″ = H) gave only a small yield of an unidentified amino-nitrolepidine.

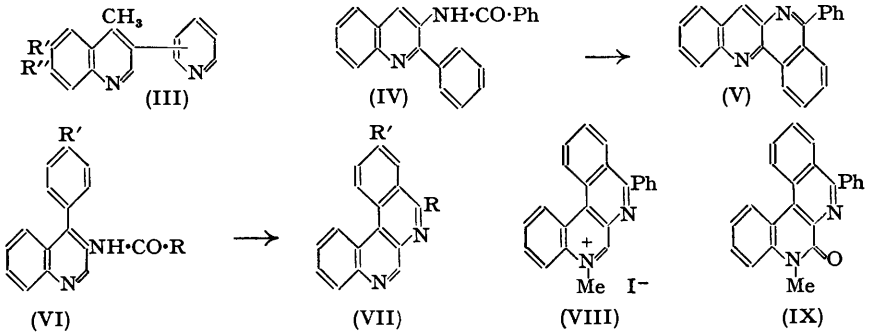
The same reagents were also found convenient for the reduction of 4-aryl-3-nitroquinolines, leading to 3-amino-4-phenyl-, -4-*p*-methoxyphenyl-, and -4-2′-pyridyl-quinoline (II; R′ = R″ = H, R = Ph, *p*-MeO·C_6H_4, or 2′-C_5H_4N, respectively).

Fluorescence in acid solution appears to be a fairly widespread property of 3-aminoquinolines, and Stark (*Ber.*, 1907, **40**, 3434) has reported the use of 3-aminoquinaldine as a fluorescence indicator in certain titrations. 3-Aminolepidine also exhibits a feeble violet fluorescence in dilute acid solution, but outstanding among the new derivatives was 3-amino-7-chlorolepidine, which showed marked blue fluorescence in both dilute acid and alcoholic solution. Equally powerful was that exhibited by 3-amino-4-phenylquinoline in alcohol, but its 4-*p*-methoxyphenyl analogue

* Part I, *J.*, 1950, 395.

was much less effective, and 3-amino-4-2′-pyridylquinoline did not fluoresce. It also seems to be a characteristic tendency of these new derivatives to retain water, even after drying *in vacuo*.

In view of the work of Coates, Cook, *et al.* (*J.*, 1943, 401), which revealed pronounced antispasmodic activity in 3-pyridylquinolines, we envisaged the preparation of the related 3-pyridyllepidines (III) from the above-described amines. Preliminary experiments showed that two isomeric 3-pyridyl-lepidines, isolated as their dipicrates, were formed from diazotised 3-amino-



lepidine and pyridine. It is of interest that these compounds form dipicrates. The complicated pattern of picrate formation shown by the experiments of Coates *et al.* (*loc. cit.*) and of Hey and Williams (*J.*, 1950, 1678) in the cases of pyridylquinolines, 4-pyridylquinaldines, and 2-pyridyl-lepidines makes it unwise, however, to draw conclusions on this basis about the compounds now described. Their orientations are being examined.

The deamination of 3-amino-4-arylquinolines appeared to offer a route, possibly superior in some cases to those already available, for the preparation of 4-arylquinolines. The action of hypophosphorous acid on diazotised 3-amino-4-phenyl- and 3-amino-4-*p*-methoxyphenyl-quinoline gave moderate yields of 4-phenyl- and 4-*p*-methoxyphenyl-quinoline, isolated as picrates. Similarly, 3-amino-4-2′-pyridylquinoline was converted into 4-2′-pyridylquinoline picrate, which completes the series of isomeric 4-pyridylquinolines (see Hey and Williams, *loc. cit.*).

Recently, Petrow, Stack, and Wragg (*loc. cit.*), by dehydration of 3-benzamido-2-phenylquinoline (IV) with phosphoric oxide, were able to synthesise the 3 : 4-6 : 7-dibenzo-1 : 5-naphthyridine derivative (V), but found 3-*p*-nitrobenzamido-2-phenylquinoline to be resinified by this treatment. From the acetamido-compound was obtained a product which despite fairly satisfactory analytical evidence was not formulated as a dibenzonaphthyridine. The application of similar cyclisations to 3-acylamino-4-arylquinolines (VI) was of interest because of the possible formation of derivatives of 3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine (VII), a ring-system hitherto unknown and related to 3 : 4-benzophenanthrene. 3-Benzamido-4-phenylquinoline (VI; R = Ph, R′ = H) was in fact converted by phosphoric oxide at 270—280° into 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine (VII; R = Ph, R′ = H). 3-Acetamido-4-phenylquinoline (VI; R = Me, R′ = H) was decomposed under these conditions, and the same reagent resinified 3-benzamido- and 3-acetamido-4-*p*-methoxyphenylquinoline (VI; R = Ph or Me, R′ = OMe) The milder reagent, phosphorus oxychloride, used so successfully in the Morgan–Walls phenanthridine synthesis (*J.*, 1931, 2447; 1938, 389), proved ineffective in these cases, causing decomposition of both acetamido-compounds and the conversion of 3-benzamido-4-*p*-methoxyphenylquinoline into a good yield of an unidentified substance, possibly $C_{16}H_{13}O_2N$, which we are examining.

In view of the relation of the system (VII) to phenanthridine trypanocides (Walls, *J. Soc. Chem. Ind.*, 1947, **66**, 182), we quaternised 2-phenyl-3 : 4-5 : 6-dibenzo-1 : 7-naphthyridine with methyl sulphate, and converted the product into the methiodide. The latter substance, initially yellow, was converted by recrystallisation into lustrous black crystals of the compound (VIII). These changes may be due to polymorphism, or to variations in the degree of hydration of the product. Oxidation of this compound with alkaline potassium ferricyanide gave a product which gave an analysis in fairly satisfactory agreement with that for (IX). Such a compound could clearly not have been formed, except by the elimination of the phenyl group, had quaternisation occurred on the alternative nitrogen atom.

These various lines of work are being actively pursued.

Experimental.

(M. p.s are uncorrected.)

3-Aminolepidines and 3-Amino-4-arylquinolines.—These compounds were prepared by heating the quantities of materials stated below for 1 hour at 95°, making the mixture strongly alkaline with sodium hydroxide solution, and extracting the products with ether or chloroform. The new products are tabulated in Table I, their numbers being as in Table II.

Table I.

Product	Wt. of nitro-compound (g.)	Wt. of $SnCl_2$ (g.)	Vol. of conc. HCl (c.c.)	Product	Wt. of nitro-compound (g.)	Wt. of $SnCl_2$ (g.)	Vol. of conc. HCl (c.c.)
1	3·0	10·8	30 (*a*)	7	0·2	0·58	3 (*b*)
2	0·5	1·53	10 (*b*)	8	3·2	9·0	30, and 30 c.c. of AcOH (*a*)
3	0·6	1·83	5 ,,				
4	0·35	1·12	5 ,,	9	1·0	2·8	15, and 5 c.c. of AcOH (*b*)
5	0·25	0·75	3 ,,				
6	0·5	1·4	5 ,,	10	0·5	1·4	5 (*b*)

(*a*) Extracted with ether. (*b*) Extracted with chloroform.

Table II.

	Compound R	R′	R″	Yield, % [a]	Crystalline form [b]	M. p.	Formula	Analysis: Found C	Found H	Calc. C	Calc. H
1	Me	H	H	79	Dense pale yellow prisms	72—73°	$C_{10}H_{10}N_2,H_2O$	69·3	6·9	68·2	6·9
2	,,	Cl	,,	100	Lustreless fawn needles	189—190	$C_{10}H_9N_2Cl$	61·9	4·6	62·3	4·7
3	,,	H	Cl	80	Colourless leaflets	129—130	,,	62·7	4·7	,,	,,
4	,,	Me	Me	89	Cream needles	152—153	$C_{12}H_{14}N_2,\frac{1}{3}H_2O$	74·7	7·0	74·9	6·5
5	,,	·$[CH_2]_3$·		46	Lustreless cream plates	190—191	$C_{13}H_{14}N_2$	78·1	7·1	78·7	7·1
6	,,	·$[CH_2]_4$·		57	White needles	97—98	$C_{14}H_{16}N_2,\frac{1}{3}H_2O$	76·8	7·4	77·0	8·2
7	,,	NO_2 or H	H or NO_2	Very small	Orange crystals	241 *	$C_{10}H_9O_2N_3$	59·5	5·0	59·1	4·5
8	Ph	H	H	82	Colourless needles	127—128	$C_{15}H_{12}N_2,\frac{1}{4}H_2O$	80·4	5·75	80·2	5·6
9	*p*-MeO·C_6H_4	H	H	61	Colourless needles	199—200	$C_{16}H_{14}ON_2$	76·4	5·7	76·8	6·0
10	2′-C_5H_4N	H	H	100	Fawn prisms	143—144	$C_{14}H_{11}N_3$	75·9	5·0	75·9	5·0

[a] Of once crystallised product.
[b] Alcohol was the solvent for 9, aqueous alcohol in other cases.
* With decomposition.

3-Amino-4-phenylquinoline, when treated with acetic anhydride at 95°, gave *3-acetamido-4-phenylquinoline*, which formed needles, m. p. 168—169°, from dilute alcohol (Found: C, 77·6; H, 5·3; N, 10·8. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%). Benzoylation was effected in pyridine with benzoyl chloride for 12 hours at room temperature. *3-Benzamido-4-phenylquinoline* gave leaflets, m. p. 164—165°, from dilute ethanol (Found: C, 81·0; H, 4·9; N, 7·9. $C_{22}H_{16}ON_2$ requires C, 81·45; H, 5·0; N, 8·6%).

3-Acetamido- [leaflets, m. p. 146—147°, from aqueous alcohol (Found: C, 74·0; H, 5·5. $C_{18}H_{16}O_2N_2$ requires C, 73·9; H, 5·5%)] and *3-benzamido-4-p-methoxyphenylquinoline* [needles, m. p. 182—183°, from the same solvent (Found: C, 77·25; H, 4·9. $C_{23}H_{18}O_2N_2$ requires C, 77·9; H, 5·1%)] were prepared similarly.

3-Pyridyl-lepidines.—The hydrochloride suspension from 3-aminolepidine (0·5 g.), concentrated hydrochloric acid (5 c.c.), and water (2 c.c.) was diazotised † at 0° with sodium nitrite (0·22 g.) in water (2 c.c.). The violet solution was diluted with iced water (20 c.c.) and added gradually to pyridine (25 c.c.) at 50°. After remaining overnight at room temperature, the pyridine was removed in steam, and the residual tar extracted with boiling benzene. The aqueous layer was also extracted with benzene, and the combined extracts were dried (Na_2CO_3) and concentrated. Treatment of the residual oil (0·35 g.) in ethanol (5 c.c.) with picric acid (1 g.) in the same solvent (10 c.c.) gave a precipitate of mixed picrates (0·62 g.; m. p. 167—176°). Crystallisation from acetone (15 c.c.) afforded a fairly pure *dipicrate* (0·27 g.), m. p. 259—260°. This, on recrystallisation, formed small yellowish-brown leaflets, m. p. 267—268° (Found: C, 48·0; H, 2·5. $C_{15}H_{12}N_2,2C_6H_3O_7N_3$ requires C, 47·8; H, 2·7%). The original acetone liquor, on addition of ethanol (10 c.c.) and concentration to 10 c.c., deposited the second

† Further experiments, to be described later, have shown this diazotisation to be complicated.

isomer [0·12 g.; m. p. 173—178° (decomp.)]. This more soluble *dipicrate* formed clusters of yellowish-brown needles, m. p. 194—195° (Found: C, 49·6; H, 3·1%), from alcohol.

4-*Phenylquinoline*.—A solution of 3-amino-4-phenylquinoline (0·5 g.) in concentrated hydrochloric acid (2 c.c.) and water (3 c.c.) was diazotised at 0° with sodium nitrite (0·15 g.) in water (1 c.c.), and treated with an ice-cold solution of hypophosphorus acid (4 c.c.; 15%). After 12 hours at 0° the solution was basified with sodium hydroxide solution and extracted with ether. The dried (Na_2CO_3) extract yielded an oil (0·36 g.) which did not crystallise. This was treated in alcohol with picric acid, and the crude precipitate (0·58 g.; m. p. 218—220°) recrystallised from alcohol; it formed fine yellow needles, m. p. 224—225° (Found: C, 57·9; H, 3·1. Calc. for $C_{15}H_{11}N,C_6H_3O_7N_3$: C, 58·1; H, 3·25%). Kenner and Statham (*J.*, 1935, 299) give m. p. 225°.

In a further experiment on the same scale, the basified reaction mixture was steam-distilled. Ether extraction of the distillate gave 4-phenylquinoline (0·19 g.), which slowly crystallised from ether–light petroleum (b. p. 40—60°) in colourless needles, m. p. 59—61°. Koenigs and Nef (*Ber.*, 1886, **19**, 2427) give m. p. 61—62°.

4-p-*Methoxyphenylquinoline*.—3-Amino-4-*p*-methoxyphenylquinoline (1 g.) in concentrated hydrochloric acid (2 c.c.) and water (3 c.c.) was diazotised at 0° with sodium nitrite (0·28 g.) in water (2 c.c.). The precipitated diazonium salt was redissolved by addition of iced water (20 c.c.) and hypophosphorous acid (3·5 c.c.; 30%), and after 24 hours at 0° the mixture was basified and extracted with ether. The oily residue (0·86 g.) from concentration of the dried (Na_2CO_3) extract was converted into crude 4-*p*-methoxyphenylquinoline picrate (1·02 g.), which crystallised from alcohol in reddish-brown crystals, m. p. 234—235° (Found: C, 57·9; H, 3·6. Calc. for $C_{16}H_{13}ON,C_6H_3O_7N_3$: C, 56·9; H, 3·5%). Kenner and Statham (*loc. cit.*), give m. p. 232—234° (decomp.). The free base, which was not analysed, was obtained by decomposition of the picrate with sodium hydroxide solution. It formed leaflets, m. p. 82—83°, from light petroleum (b. p. 40—60°).

4-2′-*Pyridylquinoline Picrate*.—3-Amino-4-2′-pyridylquinoline (0·1 g.) in concentrated hydrochloric acid (1 c.c.) and water (2 c.c.) was diazotised at 0° with sodium nitrite (0·04 g.) in water (1 c.c.), and the solution was treated with hypophosphorous acid (2 c.c.; 30%). After 12 hours at 0° the solution was made alkaline with sodium hydroxide solution and extracted with ether, giving on concentration an oil (0·11 g.) which did not crystallise. The *picrate* (0·06 g.; m. p. 197—200°), formed in alcoholic solution, separated from ethanol as a pale yellow solid, m. p. 199—200° (Found: C, 56·2; H, 3·5. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 3·0%).

2-*Phenyl*-3 : 4-5 : 6-*dibenzo*-1 : 7-*naphthyridine and its Quaternisation*.—An intimate mixture of 3-benzamido-4-phenylquinoline (0·1 g.) and phosphoric oxide (2 g.) was kept at 270—280° for 2 hours and then treated with ice, and the grey solid was collected and extracted with acetone–concentrated ammonia solution (3 : 1 by vol.). Concentration of the extract afforded silky needles (0·05 g., m. p. 154—155°). The pure *naphthyridine*, after crystallisation from dilute aqueous alcohol, melted at 157—158° (Found: C, 85·9; H, 4·5; N, 9·5. $C_{22}H_{14}N_2$ requires C, 86·3; H, 4·6; N, 9·15%).

The above compound (0·2 g.) and methyl sulphate (0·08 g.) were heated under reflux in benzene (10 c.c.) for 2 hours, the solvent was evaporated, and the residual gum dissolved in hot water (25 c.c.). Addition of potassium iodide solution precipitated the methiodide [0·25 g.; m. p. 232—235° (decomp.)] as a flocculent yellow solid which crystallised from ethanol (20 c.c.) in orange-yellow needles (0·19 g.), m. p. 234—235° (decomp.). In subsequent crystallisations from ethanol the compound separated as orange-yellow needles, golden leaflets, and finally as black needles with a golden reflex. When heated the last turned yellow at 143° and melted at 231—232° (decomp.) (Found: C, 56·4; H, 3·9. $C_{23}H_{17}N_2I,2H_2O$ requires C, 56·9; H, 4·4%).

Oxidation of the quaternary salt (0·1 g.) with potassium ferricyanide (0·3 g.), water (25 c.c.), and 2N-sodium hydroxide solution (10 c.c.) at 95° for 1 hour with stirring, followed by extraction with benzene, provided a solid (0·03 g.), m. p. 123—128°. The *substance* separated from benzene–ligroin (b. p. 60—80°) as small fawn needles, m. p. 135—137° (decomp.) (Found: C, 83·5; H, 5·5. $C_{23}H_{16}ON_2$ requires C, 82·1; H, 4·8%).

Attempted Cyclisation of 3-*Benzamido*-4-p-*methoxyphenylquinoline*.—The benzamido-compound (2 g.) and phosphorus oxychloride (20 c.c.) were heated under reflux for 30 hours, and the mixture was decomposed with ice and basified with ammonia solution. Crystallisation of the solid (1·3 g.) from dilute alcohol gave fine needles of a *substance*, m. p. 118—119° (Found: C, 75·8, 76·2; H, 5·25, 5·2; N, 4·1, 6·3. $C_{16}H_{13}O_2N$ requires C, 76·5; H, 5·2; N, 5·6%).

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