402. *Carcinogenic Nitrogen Compounds. Part XIX.* The Aptitude of Some Aminoquinolines for Cyclisation.*

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6- and 8-Hydroxyquinoline are shown to undergo iodine-catalysed condensation reactions with primary arylamines to give the corresponding arylaminoquinolines, which afforded diaza-arsaphenanthrenes on cyclisation with arsenic trichloride but failed to give diazabenzanthracenes or diaza-arsabenzanthracenes. 3-Aminoquinoline underwent the Skraup reaction to give 1 : 9-diazaphenanthrene.

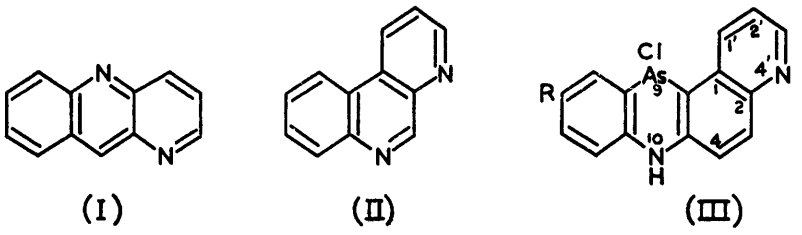
As a sequel to the study of relations between carcinogenic activity and chemical structure in the benzacridine,[1] benzocarbazole,[2] and benzophenarsazine [3] series, a similar investigation of compounds with two heterocyclic nitrogen atoms was indicated, and a simple approach seemed to be to start from readily accessible aminoquinolines and to study their aptitude to undergo various types of cyclisation.

It is known that 3-aminopyridine, unlike the 2- and the 4-isomer, undergoes the Skraup reaction with formation of 1 : 5-naphthyridine;[4] 3-aminoquinoline has now been found likewise susceptible to Skraup cyclisation, although yields were very low. The product

* Part XVIII, Buu-Hoï and Jacquignon, *J.*, 1956, 1515.

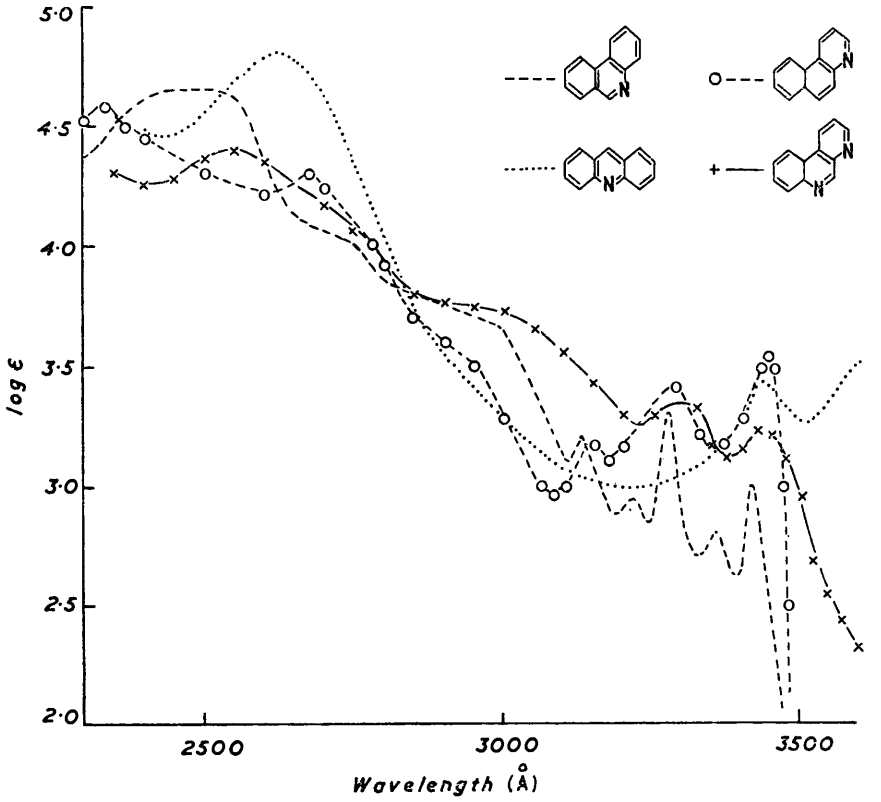
[1] See Lacassagne, Buu-Hoï, Daudel, and Zajdela, *Adv. Cancer Res.*, in the press.
[2] Lacassagne, Buu-Hoï, Royer, and Zajdela, *Compt. rend. Soc. Biol.*, 1947, **141**, 635; Lacassagne, Buu-Hoï, Zajdela, and Xuong, *Bull. Cancer*, 1955, **42**, 3.
[3] Lacassagne, Rudali, Buu-Hoï, and Royer, *Compt. rend. Soc. Biol.*, 1951, **145**, 1451.
[4] Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081; Räth, D.R.-P. 507,637; *Chem. Abs.*, 1931, **25**, 716.

was not, however, the expected linear 1 : 10-diaza-anthracene (I), but the angular 1 : 9-diazaphenanthrene (II), as its ultraviolet spectrum (Figure) resembled those of phenanthridine and 5 : 6-benzoquinoline, and solutions of its salts did not show the fluorescence



(I) (II) (III)

characteristic of the acridine series. Thus, as regards Skraup cyclisation, position 2 in pyridine is more reactive than position 4, whilst with quinoline the reverse is true. The present experimental results tally with the theoretical computation of free valency indices for pyridine and quinoline effected through the molecular orbital method.[5] Hauser and



Reynolds [6] claimed to have obtained linear benzonaphthyridines from 3-aminoquinoline and ethyl acetoacetate or ethyl ethoxymethylenemalonate, but did not prove the constitution of their products.

3-Aminoquinoline does not undergo the Combes reaction [7] with acetylacetone in the

[5] Sandorfy, Vroelant, Yvan, Chalvet, and Daudel, *Bull. Soc. chim. France*, 1950, **17**, 304; Pullman and Pullman, "Les théories électroniques de la chimie organique," Masson, Paris, 1952, pp. 612, 616.
[6] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.
[7] Combes, *Compt. rend.*, 1888, **106**, 1536.

presence of phosphoric acid. The same reaction, performed with 2 : 6-diaminopyridine, resulted in 7-amino-2 : 4-dimethyl-1 : 8-naphthyridine, in confirmation of the literature,[8] but a Skraup reaction could not be effected with the latter amine.

6- and 8-Hydroxyquinoline could be condensed with primary arylamines in the presence of iodine [9] to give the corresponding 6- and 8-arylaminoquinolines, although the reaction proceeded with more difficulty than with α- and β-naphthol. These arylaminoquinolines failed to undergo Bernthsen acridine cyclisations with acetic anhydride and zinc chloride.[10] *N*-(2 : 4-Xylylamino)quinoline also failed to give a diaza-anthracene derivative when heated with lead oxide under the conditions of the Ullmann–La Torre reaction.[11] Such inertness was unexpected in view of the ease with which Senier and Compton [12] obtained diazadibenzanthracenes from 6-aminoquinoline, methylene iodide, and α- and β-naphthol. Less surprising was the failure to obtain a benzophenothiazine from 6-anilinoquinoline, sulphur, and iodide,[13] in view of Petrow and Rewald's similar observations with 4-anilino- and 4-*p*-acetamidoanilino-quinaldine.[14] 6-Anilino- and 6-*p*-toluidino-quinoline, however, reacted readily with arsenic trichloride to give hydrochlorides of substances which, in view of the known higher reactivity of position 5 in the quinoline molecule than of position 7 (cf. ref. 5), were taken to be 9-chloro-9 : 10-dihydro-10 : 4′-diaza-9-arsa-1 : 2-benzanthracene (III; R = H) and its 7-methyl homologue (III; R = Me), rather than the linear isomers. Slater recorded two similar compounds prepared by cyclisation of the appropriate quinolylaminophenylarsonic acids.[15]

Biological examination showed the 6-arylaminoquinolines to produce ready epilation when painted on mice, but no skin tumours were obtained (Dr. F. Zajdela); no tuberculostatic activity or protective effects against *X*-irradiation of mice were detected. The phenarsazine derivatives (III) had sternutatory properties.

Experimental

1 : 9-*Diazaphenanthrene* (II).—A mixture of 3-aminoquinoline [16] (20 g.), arsenic acid (17 g.), glycerol (35 g.), and sulphuric acid (95 g.) was cautiously heated until a violent reaction set in. Once the reaction had subsided, the dark liquid was heated at 200—210° for 5 hr. and, on cooling, poured in water. After basification with sodium hydroxide, the black solid formed was repeatedly extracted with benzene, and the insoluble fraction filtered off. The residue obtained on evaporation was dissolved in ethanol, and picric acid was added. 1 : 9-*Diazaphenanthrene monopicrate* (1 g.) crystallised as yellow prisms, m. p. 231—232° (decomp. > 222°), from nitrobenzene (Found: N, 17·3. $C_{18}H_{11}O_7N_5$ requires N, 17·1%). The free *base* obtained on basification crystallised from light petroleum (b. p. 45—60°) as pale yellow needles (0·2 g.), m. p. 114° (Found: C, 79·7; H, 4·2; N, 15·2. $C_{12}H_8N_2$ requires C, 80·0; H, 4·4; N, 15·5%), giving a yellow halochromy in pure sulphuric acid; dilution with water resulted in colourless solutions with no visible fluorescence. 3-Aminoquinoline, treated with acetylacetone and phosphoric acid under the conditions of the Combes reaction,[7] was recovered unchanged.

6-*Anilinoquinoline*.—6-Hydroxyquinoline (35 g.; m. p. 194°) was readily prepared by refluxing for 4 hr. 6-methoxyquinoline (50 g.) with redistilled pyridine hydrochloride (200 g.); the solid precipitated on dilution with water and adjustment to pH 7 was collected and recrystallised from ethanol. A mixture of this compound (20 g.) and aniline (15 g.) was refluxed with iodine (0·5 g.) for 50 hr., and the product taken up in benzene; the benzene solution was washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), and the solvent evaporated. Distillation *in vacuo* of the residue afforded 6-*anilinoquinoline*, b. p. 252—253°/15 mm., which formed yellowish prisms (8 g.), m. p. 175°, from ethanol (Found: N, 12·4. $C_{15}H_{12}N_2$ requires N, 12·7%). This amine gave a *monopicrate* which crystallised as orange-yellow prisms, m. p. 224—225° (decomp. > 208°), from nitrobenzene (Found: C, 56·1; H, 3·3;

[8] Bernstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1157.
[9] Knoevenagel, *J. prakt. Chem.*, 1914, **89**, 1; Buu-Hoï, *J.*, 1952, 4346.
[10] Cf. Buu-Hoï and Lecocq, *Compt. rend.*, 1944, **218**, 792; Buu-Hoï, *J.*, 1946, 792.
[11] Ullmann and La Torre, *Ber.*, 1904, **37**, 2922; Buu-Hoï, *J.*, 1949, 670.
[12] Senier and Compton, *J.*, 1909, **95**, 1632.
[13] Cf. Buu-Hoï, *Rev. sci.*, 1945, **83**, 170.
[14] Petrow and Rewald, *J.*, 1945, 592.
[15] Slater, *J.*, 1931, 107, 1939.
[16] Mills and Watson, *J.*, 1910, **97**, 746.

N, 15·6. $C_{21}H_{15}O_7N_5$ requires C, 56·1; H, 3·2; N, 15·4%). Cobenzl [17] reported a successful Skraup reaction with 4-aminodiphenylamine, but did not describe the resulting 6-anilinoquinoline. No phenothiazine derivative was obtained on heating the last-named compound (1 mol.) at 180° with sulphur (1 mol.) and iodine, although some hydrogen sulphide was formed; the resulting melt did not give in sulphuric acid the violet-blue colour characteristic of the phenothiazine group.

9-*Chloro*-9 : 10-*dihydro*-10 : 4′-*diaza*-9-*arsa*-1 : 2-*benzanthracene* (III; R = H).—A solution of 6-anilinoquinoline (1 g.) and arsenic trichloride (0·8 g.) in *o*-dichlorobenzene (5 c.c.) was refluxed for 6 hr. The solid precipitated on cooling was collected, washed with benzene, and dried. 9-*Chloro*-9 : 10-*dihydro*-10 : 4′-*diaza*-9-*arsa*-1 : 2-*benzanthracene hydrochloride* (0·8 g.), deep yellow needles, m. p. 265—266° (decomp.), gave an orange halochromy in sulphuric acid (Found: C, 48·9; H, 3·0; N, 7·2. $C_{15}H_{11}N_2Cl_2As$ requires C, 49·3; H, 3·0; N, 7·7%). The free base could not be isolated.

6-p-*Toluidinoquinoline*.—This *amine* (10 g.), prepared by heating for 48 hr. a mixture of 6-hydroxyquinoline (10 g.) and *p*-toluidine (8 g.) with iodine (0·2 g.), formed yellowish prisms, m. p. 143°, b. p. 258—260°/15 mm., from ethanol (Found: N, 11·7. $C_{16}H_{14}N_2$ requires N, 12·0%); its picrate formed orange needles, m. p. 222—223° (decomp. > 206°), from nitrobenzene. 9-*Chloro*-9 : 10-*dihydro*-7-*methyl*-10 : 4′-*diaza*-9-*arsa*-1 : 2-*benzanthracene hydrochloride* (III; R = Me) was obtained from this amine (1 g.) with arsenic trichloride (0·8 g.) in *o*-dichlorobenzene, as deep yellow prisms, m. p. 290—291° (decomp.) (Found: C, 50·8; H, 3·1; N, 7·3. $C_{16}H_{13}N_2Cl_2As$ requires C, 50·7; H, 3·4; N, 7·4%).

6-(2 : 4-*Xylidino*)*quinoline* (10 g.), obtained from 6-hydroxyquinoline (10 g.), 2 : 4-dimethylaniline (9 g.), and iodine (0·2 g.), formed yellow needles, m. p. 110°, b. p. 257—260°/14 mm., from ethanol (Found: N, 11·0. $C_{17}H_{16}N_2$ requires N, 11·3%); its picrate crystallised as orange-yellow needles, m. p. 214°, from nitrobenzene. No diazabenzanthracene derivative was obtained on heating this amine with lead oxide at 320—350°.

Condensations of 8-*Hydroxyquinoline*.—A mixture of 8-hydroxyquinoline (20 g.), aniline (15 g.), and iodine (0·5 g.) was refluxed for 8 days, and the product then worked up in the usual way; 8-*anilinoquinoline* (5 g.) was a pale yellow oil, b. p. 222—223°/12 mm. (Found: N, 12·8%), and its *monopicrate* formed orange-red needles, m. p. 132°, from ethanol (Found: C, 56·1; H, 3·3; N, 15·6%). 8-p-*Toluidinoquinoline* (16 g.), similarly prepared from 8-hydroxyquinoline (20 g.) and *p*-toluidine (16 g.), was a pale yellow oil, b. p. 233—234°/12 mm. (Found: N, 12·2%), and also gave a *monopicrate* which formed orange-red needles, m. p. 133°, from ethanol (Found: C, 56·7; H, 3·7; N, 15·3. $C_{22}H_{17}O_7N_5$ requires C, 57·0; H, 3·7; N, 15·1%). 8-p-*Toluidinoquinoline* (17 g.) was a pale yellow oil, b. p. 231—232°/12 mm. (Found: N, 12·0%), giving a *monopicrate* which formed orange-red prisms, m. p. 95—96°, from ethanol (Found: N, 15·0%). 8-(2 : 4-*Xylidino*)*quinoline* was a viscous yellow oil (15 g.), b. p. 240°/15 mm. (Found: N, 11·1%).

7-*Acetamido*-2 : 4-*dimethyl*-1 : 8-*naphthyridine*.—A suspension of the amine (5 g.; prepared according to Bernstein *et al.*[8]) in benzene was refluxed with acetic anhydride (2·5 g.) for 30 min. The benzene was evaporated, and the residue washed with ethanol, dried, and recrystallised from pyridine, to give needles (4 g.), m. p. 297°, sublimable above 250° (Found: C, 67·3; H, 5·9; N, 19·2. $C_{12}H_{13}ON_3$ requires C, 67·0; H, 6·0; N, 19·5%). Heating 7-amino-2 : 4-dimethyl-1 : 8-naphthyridine with arsenic acid, glycerol, and sulphuric acid as for the synthesis of 1 9-diazaphenanthrene resulted only in recovered material.

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[17] Cobenzl, *Chem. Z.*, 1915, **39**, 859.