972. *Analogues of 8-Hydroxyquinoline having Additional Cyclic Nitrogen Atoms. Part I. Preparative.*

By Adrien Albert and Alexander Hampton.

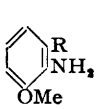
Syntheses are described of 8-hydroxycinnoline (III; R = H), 8-hydroxyquinazoline (V), 8-hydroxy-1 : 6-naphthyridine (X), and 8-hydroxy-1 : 7-naphthyridine (XII). The preparation of 8-hydroxy-1 : 7-naphthyridine by a modified Skraup reaction from 3-amino-2-hydroxypyridine affords the first example of a 3-aminopyridine undergoing ring-closure at the 4-position.

Syntheses are also reported of 6-hydroxyquinazoline and of two analogues of 8-hydroxyquinoline having two additional heterocyclic nitrogen atoms.

In continuation of a study of the antibacterial properties of 8-hydroxyquinoline and related compounds (Albert, Rubbo, Goldacre, and Balfour, *Brit. J. Exp. Path.*, 1947, **28**, 69; Rubbo, Albert, and Gibson, *ibid.*, 1950, **31**, 425) analogues of 8-hydroxyquinoline containing additional cyclic nitrogen atoms were required. These substances, it is expected, will help decide whether the site of action of 8-hydroxyquinoline is intra- or extra-cellular.

8-Hydroxycinnoline (III; R = H) was obtained from methyl 3-methoxyanthranilate (I; R = CO_2Me) by a method based on that described by Jacobs, Winstein, Henderson,

and Spaeth (*J. Amer. Chem. Soc.*, 1946, **68**, 1310) for the preparation of cinnoline. Conversion of CO_2Me into CMe_2·OH with methylmagnesium bromide was followed by dehydration in boiling toluene to the propene [I; R = CMe:CH_2] which on diazotization gave spontaneously 8-methoxy-4-methylcinnoline (II; R = OMe). This was readily converted with hydrobromic acid into 8-hydroxy-4-methylcinnoline (II; R = OH).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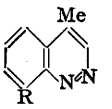
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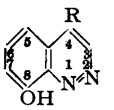
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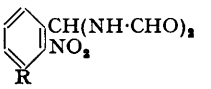
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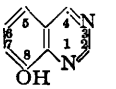

(V)

Reaction of (II; R = OMe) with benzaldehyde in the presence of zinc chloride or acetic anhydride led to profound decomposition. When (II; R = OH) was heated with benzaldehyde and acetic anhydride 8-hydroxy-4-styrylcinnoline (III; R = CH:CH·Ph) was isolated in 20% yield, the reaction again being accompanied by extensive decomposition. However, the hydrochloride of (II; R = OH) and benzaldehyde gave an almost quantitative yield of (III; R = CH:CH·Ph). Few examples have been recorded of the use of hydrogen chloride in the preparation of heterocyclic styryl compounds and it may prove useful in other difficult cases.

Treatment of (III; R = CH:CH·Ph) in pyridine at 0° with one equivalent of potassium permanganate yielded 8-hydroxycinnoline-4-carboxylic acid (III; R = CO_2H). The yield (25%) was improved by prior benzoylation of the hydroxyl group (the benzoyl group was removed during the working-up). A quantitative yield of 8-hydroxycinnoline (III; R = H) resulted when (III; R = CO_2H) was decarboxylated in ethylene glycol. Later it was learned that 8-hydroxycinnoline had recently been prepared, but by a different route (Schofield, personal communication).

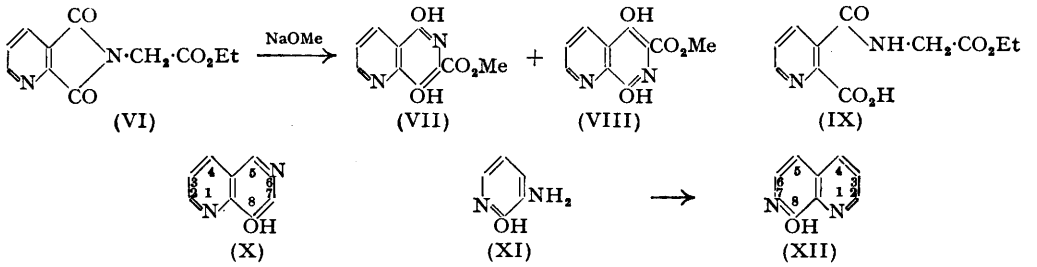
8-Hydroxyquinazoline (V) was prepared by Riedel's general method (D.R.-P. 174,941/1905) for the synthesis of quinazolines. Passing hydrogen chloride into a suspension of 3-methoxy-2-nitrobenzaldehyde in formamide gave a good yield of 3-methoxy-2-nitrobenzylidenebisformamide (IV; R = OMe), which with zinc dust and acetic acid (Bogert and McColm, *J. Amer. Chem. Soc.*, 1927, **49**, 2650) gave 8-methoxyquinazoline quantitatively. 8-Hydroxyquinazoline (V) was obtained by demethylating 8-methoxyquinazoline with aluminium chloride, and also by the action of zinc dust–acetic acid on 3-hydroxy-2-nitrobenzylidenebisformamide (IV; R = OH), but the latter route has little preparative value owing to the inaccessibility of 3-hydroxy-2-nitrobenzaldehyde. 6-Hydroxyquinazoline was obtained similarly from 3-hydroxy-6-nitrobenzylidenebisformamide (prepared in 95% yield from 3-hydroxy-6-nitrobenzaldehyde).

During the course of this work the synthesis of 5-hydroxyquinoxaline was reported by several workers (King, Clark, and Davis, *J.*, 1949, 3012; Freeman and Spoerri, *J. Org. Chem.*, 1951, **16**, 438; Sorkin and Roth, *Helv. Chim. Acta*, 1951, **34**, 427). A more convenient method was demethylation of 5-methoxyquinoxaline with hydrobromic acid (yield 75%).

8-Hydroxy-1 : 6-naphthyridine (X) was prepared from methyl 5 : 8-dihydroxy-1 : 6-naphthyridine-7-carboxylate (VII) which Fels (*Ber.*, 1904, **37**, 2129) obtained from (VI) by methanolic sodium methoxide at 100° in a sealed tube. However, the latter reaction furnished also 20% of a more water-soluble substance, which by characterization as its 5-acetate was shown to be methyl 5 : 8-dihydroxy-1 : 7-naphthyridine-6-carboxylate (VIII) which had previously been obtained by Ochiai, Ishida, Nomura, Hamana, and Ishii (*Chem. Abs.*, 1951, **45**, 8018) from 3-(*N*-carbethoxymethylcarbamyl)picolinic acid (IX) and sodium methoxide. Phosphorus oxychloride converted (VII) into methyl 5-chloro-8-hydroxy-1 : 6-naphthyridine-7-carboxylate, which was dechlorinated, de-esterified, and decarboxylated by hydriodic acid (in one operation) to 8-hydroxy-1 : 6-naphthyridine (X).

2-Hydroxy-3-nitropyridine when hydrogenated in ethanol over palladium–charcoal gave 3-amino-2-hydroxypyridine (XI). This base was heated with glycerol, sulphuric acid, and arsenic pentoxide under the conditions used by Bobranski and Sucharda (*Roczn. Chem.*, 1927, **7**, 192) for the preparation of 1 : 5-naphthyridine from 3-aminopyridine, but

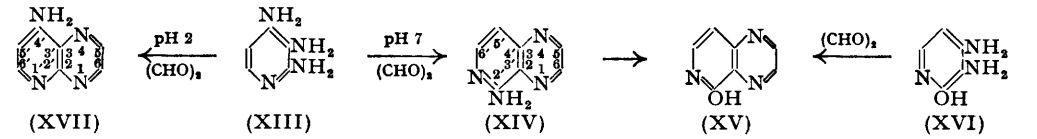
none of the desired 8-hydroxy-1 : 7-naphthyridine (XII) was formed (a compound analysing as $C_{11}H_{11}O_3N_3$ was isolated in small yield). However, when (XI) was heated with glycerol and *m*-nitrobenzenesulphonic acid in Kunz's modification of the Skraup reaction (B.P. 394,416; D.R.-P. 609,383/1930), (XII) was obtained in 20% yield. This appears



to be the first known instance of cyclisation of a 3-aminopyridine at the 4-position to give a 1 : 7-naphthyridine. Derivatives of 3-aminopyridine with no substituent in the 2-position invariably gave only 1 : 5-naphthyridine derivatives (Allen, *Chem. Reviews*, 1950, **47**, 275) and previous attempts to obtain 1 : 7-naphthyridines from 2-substituted 3-aminopyridines such as 3-amino-2 : 6-dimethylpyridine (Gulland and Robinson, *J.*, 1925, 1493) and 3-amino-2-chloropyridine (Räth, D.R.-P. 507,677/1926) were unsuccessful.

2'-Hydroxypyridino(3' : 4'-2 : 3)pyrazine (5-hydroxy-1 : 4 : 6-triazanaphthalene) (XV) was obtained when 4-amino-2-hydroxy-3-nitropyridine was hydrogenated over Raney nickel and the resulting solution of 3 : 4-diamino-2-hydroxypyridine (XVI) boiled with polyglyoxal. 2 : 3 : 4-Triaminopyridine (XIII), when heated with polyglyoxal in water at 100°, gave what seemed to be two isomeric aminopyridinopyrazines (XIV) and (XVII), the relative proportions depending on the initial pH. At pH 7 only one isomeride was produced, apparently 2'-aminopyridino(3' : 4'-2 : 3)pyrazine (XIV) because alkaline hydrolysis gave (XV) which was made unequivocally from (XVI). The other isomeride, apparently (XVII), was formed almost exclusively at pH 2 and gave on alkaline hydrolysis a second hydroxypyridinopyrazine [4'-hydroxypyridino(2' : 3'-2 : 3)pyrazine]. Both this compound and (XV) formed chelate structures with the cations of bivalent metals, confirming the presence of a hydroxy-group *peri* to a ring-nitrogen atom.

Some physical properties of these compounds will be discussed in a later paper. Biological results, a preliminary account of which has been given (Albert and Hampton, 2nd Intern. Congr. Biochem., Paris, 1952, Abs. p. 444) will be reported elsewhere.



Experimental

M. p.s are uncorrected. Microanalyses were by Mr. A. Bennett and Mr. P. R. W. Baker, Beckenham.

Confirmatory evidence of the presence of a hydroxy-group *peri* to a ring-nitrogen was always sought by this chelation test : a small crystal of pure ferrous sulphate was added to a solution of the substance in boiled-out water, producing a deep red or (more rarely) yellow-brown colour (when too much ferrous sulphate was added the colour appeared only after the addition of alkali).

Paper chromatograms were examined with a mercury-vapour lamp and Wood's glass filter (principaplly 365 mμ), and with a mercury resonance lamp and Chance Brothers OX7/19874 filter (principally 254 mμ), and showed blue or violet fluorescent spots. Unless otherwise stated, chromatograms were prepared in butanol (2 vol.) + 5N-acetic acid (1 vol.).

3-*Methoxy*-2-*nitrobenzaldehyde*.—This was obtained by nitration (Hodgson and Beard, *J.*, 1926, 154; 1927, 2380) of *m*-methoxybenzaldehyde, which was prepared in 95% yield by the

action of methyl sulphate and sodium hydroxide on a methanolic solution of *m*-hydroxybenzaldehyde (Livshits, Basilevskaya, Bainova, Dobrovinskaya, and Preobrazhenskii, *J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1671; cf. the method of *Org. Synth.*, 1949, **29**, 63, for which a yield of only 63—72% is claimed).

Methyl 3-Methoxyanthranilate (I; R = CO_2Me).—3-Methoxy-2-nitrobenzaldehyde (33·4 g.), potassium permanganate (30 g., 50% excess), anhydrous sodium carbonate (20 g.), and water (700 ml.) were refluxed for 30 minutes and filtered while hot, and the filtrate was acidified with hydrochloric acid. The precipitated 3-methoxy-2-nitrobenzoic acid (34·3 g., 94%), m. p. 253° (Rieche, *Ber.*, 1889, **22**, 2355, gave m. p. 251° but no details or yield), was converted into methyl 3-methoxyanthranilate in 85% yield by the method of Curd, Landquist, and Rose (*J.*, 1948, 1764).

2-(2-Amino-3-methoxyphenyl)propan-2-ol (I; R = CMe_2·OH).—Methyl 3-methoxyanthranilate (2 g.) was added in ether (20 ml.) during 30 minutes to methylmagnesium bromide (from magnesium, 1·62 g., 2 equiv.) in ether (40 ml.) at 2—5°, under nitrogen with vigorous stirring. The mixture was stirred and refluxed for 4 hours, then decomposed with ice and ammonium chloride and acidified (3N-hydrochloric acid), and the aqueous solution (pH 8) separated and extracted with ether (4 × 50 ml.). The combined ethereal extracts were dried (K_2CO_3) and the solvent removed under reduced pressure leaving crude *2-(2-amino-3-methoxyphenyl)propan-2-ol* (1·89 g., 94%) as a fawn-coloured solid, m. p. 68—72°. After two crystallizations from light petroleum (b. p. 40—60°; 50 parts) (charcoal), the compound was obtained as white plates, m. p. 77° (Found: C, 66·6; H, 8·1; N, 8·0. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3; N, 7·7%).

2-(2-Amino-3-methoxyphenyl)propene (I; R = $CMe{:}CH_2$).—The crude propan-2-ol (23·7 g.) was refluxed in dry toluene (80 ml.) containing iodine (0·01 g.) for 8 hours, during which water (2·2 ml., 95%) was collected in a separator. Toluene was removed under reduced pressure and the residue distilled at 0·1 mm. (yield, 18·9 g., 89% yield from methyl 3-methoxyanthranilate). Redistillation furnished the *propene*, b. p. 57°/0·05 mm., n_D^{25} 1·5644 (Found: C, 73·5; H, 7·7; N, 8·7. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%).

8-Methoxy-4-methylcinnoline (II; R = OMe).—Sodium nitrite (6·2 g.) in water (13 ml.) was added slowly with stirring, at −7° to −3°, to 2-(2-amino-3-methoxyphenyl)propene (14·5 g.) in water (60 ml.) and concentrated sulphuric acid (6·6 ml.). The mixture was stirred at 0° for 45 minutes and small additional amounts of sodium nitrite solution were added to maintain a slight excess. The solution was diluted with ice (350 g.) and water (350 ml.), stored in the dark at room temperature for 3 days, basified with 40% sodium hydroxide (45 ml.), and continuously extracted with benzene for 10 hours. The benzene was removed under reduced pressure. *8-Methoxy-4-methylcinnoline* was obtained as orange prisms (11·2 g., 72%), m. p. 129—130°, after crystallization from benzene (90 ml.; concentrated to 20 ml.) (charcoal). This material was used without further purification in the subsequent demethylation. Crystallization from light petroleum (b. p. 100—120°; 70 parts) (charcoal) and finally from benzene (6 parts) gave yellow prisms, m. p. 131—132° (Found: C, 69·1; H, 5·6; N, 16·5. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

8-Hydroxy-4-methylcinnoline (II; R = OH).—8-Methoxy-4-methylcinnoline (3 g.) in hydrobromic acid (48% w/v; 20 ml.) was refluxed for 10 hours. Excess of acid was removed under reduced pressure, the solid residue dissolved in water (6 ml.), and the solution adjusted to pH 4 with 6N-sodium hydroxide. Sublimation of the precipitate at 150—160°/0·1 mm., followed by crystallization from benzene (50 ml.), gave *8-hydroxy-4-methylcinnoline* as cream-coloured needles (2·3 g.), m. p. 176·5—177·5° (Found: C, 67·8; H, 4·7; N, 17·4. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

8-Hydroxy-4-styrylcinnoline (III; R = $CH{:}CHPh$).—Concentrated hydrochloric acid (3·3 ml.) was added to a hot solution of 8-hydroxy-4-methylcinnoline (5·3 g.) in acetone (370 ml.). The mixture was cooled at 0° and the yellow monohydrochloride (6·33 g., 98%) collected and dried at 110°. The solid was finely dispersed in benzaldehyde (25 ml.) and the mixture heated for 1·5 hours at 155—160° (bath) while a brisk stream of dry hydrogen chloride was passed through it, the colour changing to red. Benzene (150 ml.) was added and the solid collected and washed with benzene. The dried material was suspended in water (100 ml.) at 80°, the mixture brought to pH 7 with ammonia, and the yellow solid (7·81 g., 95%), m. p. 191—195°, filtered from the hot solution and dried at 110°. After crystallization from benzene (80 parts; concentrated to 10 parts) (charcoal) and from methanol (250 parts; concentrated to 75 parts) *8-hydroxy-4-styrylcinnoline* was obtained as yellow needles, m. p. 200—201° (Found: C, 77·1; H, 5·1; N, 11·4. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9; N, 11·3%).

8-*Benzoyloxy*-4-*styrylcinnoline*.—Benzoyl chloride (5·3 ml., 1·5 equiv.) was added in portions to a solution (initial temp. 40°) of crude 8-hydroxy-4-styrylcinnoline (7 g.) in dry pyridine (21 ml.), the temperature being kept below 80°. The solution was heated on the steam bath for 5 minutes and allowed to cool; the benzoate separated. Ether (300 ml.) was added and the solid washed with ether and triturated with water (140 ml.) containing concentrated aqueous ammonia (3·5 ml.). 8-*Benzoyloxy*-4-*styrylcinnoline*, crystallized three times from benzene (40 parts) formed yellow prisms, m. p. 212—213° (Found: C, 78·7; H, 4·5; N, 7·9. $C_{23}H_{16}O_2N_2$ requires C, 78·4; H, 4·6; N, 8·0%)

8-*Hydroxycinnoline*-4-*carboxylic Acid* (III; R = CO_2H).—A solution of crude 8-benzoyloxy-4-styrylcinnoline (1 g.) in pyridine (45 ml.) and water (3 ml.) was mechanically stirred and cooled (ice–salt) while potassium permanganate (1·2 g., 1 equiv.) in water (20 ml.) was added at a rate which kept the temperature at 2—5°. The mixture was stirred for 30 min. at 2—5° and for 2 hours at 20°. Manganese dioxide was filtered off and extracted twice with hot 0·1N-sodium hydroxide (60 + 40 ml.) and the combined filtrates were concentrated to *ca.* 20 ml. The solution was brought to pH 7 with concentrated hydrochloric acid and excess of acid (10 ml.) added, precipitating a mixture of benzoic acid and the hydrochloride of the desired acid. The orange solid was collected, washed with 3N-hydrochloric acid, and dried (over KOH). The filtrate and washings were continuously extracted at pH 2 with ether for 3 hours; the ether was dried (Na_2SO_4) and treated with ethereal hydrogen chloride, a further quantity of the hydrochloride being precipitated. The combined products were shaken with ethereal hydrogen chloride (20 ml.) to remove benzoic acid, and the bright red hydrochloride was collected and washed with ether. A suspension of this in water (8 ml.) was brought slowly to pH 2 (6N-sodium hydroxide), an orange-red precipitate of 8-*hydroxycinnoline*-4-*carboxylic acid* (0·44 g.; 82%), m. p. 198° (decomp.), being obtained. Crystallization from water (65 ml.) gave red needles (0·38 g.), m. p. 200° (decomp.). (Found: C, 56·8; H, 3·4; N, 14·7. $C_9H_6O_3N_2$ requires C, 56·8; H, 3·2; N, 14·7%).

8-*Hydroxycinnoline* (III; R = H).—A suspension of this acid (0·95 c.) in ethylene glycol (6 ml.) was heated under nitrogen for 12 minutes at 180°. The solid dissolved and carbon dioxide was liberated. The cooled solution was diluted with water (25 ml.) and the crystals of 8-*hydroxycinnoline* (0·53 g.), m. p. 182—183°, were collected and dried in a vacuum. Extraction of the filtrate with chloroform (6 × 15 ml.) gave a yellow crystalline solid. This was triturated with water giving a further quantity (0·17 g.), m. p. 180—182°. The compound was obtained as stout yellow needles (0·67 g., 92%), m. p. 186—187°, by sublimation at 115—120°/0·05 mm. (Found: C, 65·8; H, 4·1; N, 18·7. $C_8H_6ON_2$ requires C, 65·8; H, 4·1; N, 19·2%). The m. p. was unchanged after crystallization from benzene (40 parts).

3-*Hydroxy*-2- *and* -6-*nitrobenzaldehyde*.—*m*-Hydroxybenzaldehyde was nitrated according to Pschorr (*Annalen*, 1912, **391**, 28) and the 6- (28%) and the 2-nitro-compound (5%) were separated by the method of Heilbron, Kitchen, Parkes, and Sutton (*J.*, 1925, 2167).

3-*Methoxy*-2-*nitrobenzylidenebisformamide* (IV; R = OMe).—A vigorous stream of dry hydrogen chloride was passed into a suspension of 3-methoxy-2-nitrobenzaldehyde (8 g.) in formamide (20 ml.). After about 15 min. the temperature reached 100°, and the aldehyde soon dissolved completely. The solution was cooled immediately to 80° and the resulting viscous suspension kept at 78—80° until it became saturated with hydrogen chloride and heat was no longer generated (about 15 minutes). The mixture was set aside overnight, rubbed with ether (3 × 20 ml.) to remove traces of unchanged aldehyde, and stirred with crushed ice (80 g.). 6N-Sodium hydroxide (about 40 ml.) was added gradually at 0° (cooling) to give pH 8. The white precipitate (9·05 g.), crystallized from water (160 ml.) containing 6N-sodium hydroxide (0·4 ml.), gave 3-*methoxy*-2-*nitrobenzylidenebisformamide* as cream-coloured needles (8·22 g., 73%), m. p. 187—188° (Found: C, 47·4; H, 4·4; N, 16·4. $C_{10}H_{11}O_5N_3$ requires C, 47·4; H, 4·4; N, 16·6%). The nitrogen analyses were obtained by the Kjeldahl method for these bisformamido-compounds; the Dumas method gave figures consistently 10—15% too high.

3-*Hydroxy*-2-*nitrobenzylidenebisformamide* (IV; R = OH).—3-Hydroxy-2-nitrobenzaldehyde (2 g.) was treated with formamide as described above and the crude product (2·42 g., 85%), m. p. 214° (decomp.), isolated at pH 3 from the diluted reaction mixture. After two crystallizations from water (8 parts) 3-*hydroxy*-2-*nitrobenzylidenebisformamide* was obtained as pale yellow needles, m. p. 239° (decomp.) (Found: C, 45·3; H, 3·8; N, 17·5. $C_9H_9O_5N_3$ requires C, 45·2; H, 3·8; N, 17·6%).

8-*Methoxyquinazoline*.—Crushed ice (340 g.) was added to a mixture of finely ground 3-methoxy-2-nitrobenzylidenebisformamide (28 g.) and zinc dust (84 g.). Acetic acid (112 ml.) was added in portions, with shaking, during 10 minutes. The mixture was then stirred at room

temperature for 3·5 hours with frequent additions of small amounts of zinc dust (total, 35 g.) during the first 1·5 hours. Excess of zinc dust was filtered off and washed with 5% acetic acid. Sodium hydroxide (270 g.) was dissolved in the combined filtrate and washings, giving a white suspension which was then extracted with ether (6 × 100 ml.). Evaporation of the dried ethereal solution gave *8-methoxyquinazoline* (17·6 g., 97%), needles, m. p. 92° [from light petroleum (b. p. 60—80°; 6 parts)] (Found: C, 67·2; H, 4·8; N, 17·7. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

8-Hydroxyquinazoline (V).—(a) *From 8-methoxyquinazoline.* 8-Methoxyquinazoline (4 g.) and anhydrous aluminium chloride (12 g.) (in a 250-ml. flask) were heated cautiously over a water bath; a vigorous reaction occurred and a red solid was formed. The mixture was then heated for 3 hours at 120—125° and the cooled solid dissolved in water (120 ml.). The solution was adjusted to pH 4 and the resulting brown suspension extracted continuously with ether for 6 hours. The dried ethereal solution was evaporated and the residual solid extracted (Soxhlet) with light petroleum (b. p. 60—80°) for 10 hours. Removal of the solvent and sublimation at 140—145°/25 mm. (3 hours) gave *8-hydroxyquinazoline* as cream-coloured needles (1·84 g., 49%), m. p. 149—150° (Found: C, 66·2; H, 4·1; N, 18·9. $C_8H_6ON_2$ requires C, 65·8; H, 4·1; N, 19·2%).

(b) *From 3-hydroxy-2-nitrobenzylidenebisformamide.* The crude bisformamide was treated with zinc dust and acetic acid as described for the preparation of 8-methoxyquinazoline. The filtered solution was made strongly alkaline with sodium hydroxide and saturated with hydrogen sulphide. The pH was adjusted to 8 and the colloidal suspension of zinc sulphide which then coagulated was filtered off. Extraction of the filtrate at pH 7 with ether (5 × 20 ml.) gave pale yellow needles (0·8 g., 66%), m. p. 148—149°, which after crystallization from water (30 ml.) melted at 149—150° and did not depress the m. p. of the above material.

3-Hydroxy-6-nitrobenzylidenebisformamide.—Reaction of 3-hydroxy-6-nitrobenzaldehyde with formamide by the method used for the 2-nitro-isomeride gave *3-hydroxy-6-nitrobenzylidenebisformamide* (95%), pale yellow needles (from water), m. p. 250° (decomp.) (Found: C, 45·5; H, 3·8%).

6-Hydroxyquinazoline.—Acetic acid (8 ml.) was added during 5 minutes to a shaken mixture of finely ground 3-hydroxy-6-nitrobenzylidenebisformamide (2 g.), zinc dust (6 g.), and crushed ice (24 g.). The mixture was stirred for 30 min. (temp. rise to 48°) and then for a further 2 hours with frequent additions of zinc dust (total 3 g.) during the first hour. The filtered solution was extracted continuously (at pH 7—8) with ether for 8 hours. The ethereal solution was evaporated and the residual mixture of solid and acetic acid adjusted to pH 5 with 3N-sodium hydroxide. The brown solid, crystallized from water (50 ml.) (charcoal), gave cream-coloured needles of *6-hydroxyquinazoline* (0·7 g., 57%), m. p. 238—239° (decomp.) (Found: C, 65·8; H, 4·1; N, 18·8%). When the temperature of the reaction mixture was kept below 15°, as recommended by Riedel (*loc. cit.*), a mixture was obtained and the yield of bisformamide was reduced.

5-Hydroxyquinoxaline.—A solution of 5-methoxyquinoxaline [2 g.; prepared in 67% yield from 2 : 3-dinitroanisole (Meldola and Eyre, *J.*, 1902, 988) by essentially the method of King, Clark, and Davis, *J.*, 1949, 3012] in hydrobromic acid (48% w/w; 20 ml.) was refluxed for 6 hours. The solution was adjusted to pH 4 with 5N-sodium hydroxide and the hydroxy-compound isolated with ether. Sublimation at 90°/25 mm. gave yellow needles of 5-hydroxyquinoxaline (1·35 g., 74%), m. p. 99·5° (Found: C, 66·1; H, 4·0; N, 19·1. Calc. for $C_8H_6ON_2$: C, 65·8; H, 4·1; N, 19·2%).

Methyl 5 : 8-Dihydroxy-1 : 6-naphthyridine-7-carboxylate (VII).—A warm solution of ethyl quinolyliminoacetate (39 g.) (Fels, *Ber.*, 1904, **37**, 2129; Ochiai and Arai, *J. Pharm. Soc. Japan*, 1939, **59**, 458) in methanol (350 ml.; dried over magnesium) was added to a solution of sodium methoxide [from sodium (11·7 g.) and methanol (350 ml.)]. After a few minutes a heavy red gelatinous precipitate formed. The mixture was refluxed for 6 hours, then added to aqueous oxalic acid (10% w/v; 1750 ml.) at 50°. The yellow crystalline oxalate was collected at 0°, washed with cold water (20 ml.), then dissolved in water (1600 ml.) at 80°, and the pH adjusted to 4 with 6N-sodium hydroxide. Refrigeration overnight gave cream-coloured needles (21·7 g.). Paper chromatography, with solvent water–dimethylformamide (1 : 9, by vol.), revealed that the product contained a small amount of the isomeric 1 : 7-naphthyridine derivative This was removed by two crystallizations from water (45 parts) at pH 4, giving 18·5 g. (50%) of the pure ester, m. p. 205° (decomp.) (Fels, *loc. cit.*, gave m. p. 203—205°; Ochiai and Arai, *loc. cit.*, gave 219—220°). The compound was characterized as the 8-acetate, m. p. 224° (Ochiai and Miyaki, *J. Pharm. Soc. Japan*, 1938, **58**, 764, gave m. p. 226°).

Methyl 5 : 8-Dihydroxy-1 : 7-naphthyridine-6-carboxylate (VIII).—The filtrate from the initial

crude 1 : 6-naphthyridine ester was adjusted to pH 7 and extracted with chloroform (10 × 100 ml.). Evaporation of the chloroform and crystallization from methanol (300 ml. concentrated to 50 ml.) yielded cream-coloured needles (6·8 g.), m. p. 200° (decomp.). Although paper chromatography with dimethylformamide showed that some of the dihydroxy-1 : 6-naphthyridine ester was present, the substance was shown to consist mainly of methyl 5 : 8-dihydroxy-1 : 7-naphthyridine-6-carboxylate by the preparation, in good yield, of the 5-acetate, m. p. 199° (decomp.) [Ochiai, Ishida, Nomura, Hamana, and Ishii, *loc. cit.*, give m. p. 201° (decomp.); for the unacetylated compound they give m. p. 190—205° (decomp.)]. The 1 : 6-naphthyridine ester was difficult to remove owing to its more sparing solubility in all solvents tested. However, chromatographically pure 1 : 7-naphthyridine ester, m. p. 201° (decomp.), was finally obtained after four recrystallizations of the contaminated product from methanol (30 parts).

Methyl 5-Chloro-8-hydroxy-1 : 6-naphthyridine-7-carboxylate.—Methyl 5 : 8-dihydroxy-1 : 6-naphthyridine-7-carboxylate (18 g.) and phosphorus oxychloride (90 ml.) were heated under reflux for 30 minutes. Phosphorus oxychloride was then distilled away under reduced pressure and dry chloroform distilled from the residue in order to assist removal of the reagent. The solid residue was added to a mixture of ice (200 g.) and aqueous ammonia (25 ml.; *d* 0·89), and the solution set aside for 30 minutes with occasional additions of ammonia to keep the pH at 5—6. The solution was concentrated to about 50 ml. under reduced pressure and stored at room temperature for 10 days, whereafter separation of the crude chloro-compound (13·8 g.), m. p. 219°, was complete. (Immediate extraction of the aqueous solution with chloroform, as described by Ochiai, Miyaki, and Sato, *Ber.*, 1937, **70**, 2018, gave only 40% of this quantity of crude product, m. p. 213°.) The solid was boiled with chloroform (350 ml.), and the solution filtered and evaporated to dryness. The residue was ground and suspended for 5 minutes in boiling acetone (30 ml.). The mixture was cooled to 20° and the solid collected, washed with acetone (10 ml.), and crystallized from *iso*butyl methyl ketone (680 ml.), giving straw-coloured needles of methyl 5-chloro-8-hydroxy-1 : 6-naphthyridine-7-carboxylate (10·2 g., 52%), m. p. 226° (decomp.). The pure compound melted at 228° (Ochiai, Miyaki, and Sato, *loc. cit.*, give m. p. 227°).

8-Hydroxy-1 : 6-naphthyridine (X).—Methyl 5-chloro-8-hydroxy-1 : 6-naphthyridine-7-carboxylate (6·2 g.) and hydriodic acid (45 ml.; *d* 1·7; freshly distilled from red phosphorus) were heated for 1 hour in a bath at 65—75°; the temperature was raised during 30 minutes to 110° and kept there for 30 min., methyl iodide being evolved. The mixture was refluxed for 1 hour at 135—140° to effect decarboxylation, and slowly poured while still warm (about 80°) into a mechanically stirred solution of sodium sulphite heptahydrate (30 g.) in water (150 ml.). Stirring was continued until a dark oil had dissolved, then the solution was adjusted to pH 6 with sodium hydroxide and stored overnight at 20°. The solution was filtered from a brown precipitate and extracted with chloroform (10 × 40 ml.). Removal of the chloroform at reduced pressure gave a light yellow solid which when twice sublimed at 95°/0·01 mm. and finally crystallized from water (25 ml.) gave cream-coloured needles (1·32 g., 35%), m. p. 162°, of *8-hydroxy-1 : 6-naphthyridine* (Found : C, 66·2; H, 4·2; N, 19·4. $C_8H_6ON_2$ requires C, 65·8; H, 4·1; N 19·2%).

3-Amino-2-hydroxypyridine (XI).—A suspension of 2-hydroxy-3-nitropyridine (38·5 g., Binz and Maier-Bode, *Angew. Chem.*, 1936, **49**, 486) in ethanol (350 ml.) was hydrogenated over 5% palladium–charcoal (3·3 g.). After the theoretical volume of hydrogen was absorbed (6 hours), the catalyst was filtered off and washed with ethanol (50 ml.). The ethanol was evaporated at reduced pressure and the residue dried in a vacuum and crystallized from benzene (2400 ml., concentrated to 100 ml.) (charcoal) giving *3-amino-2-hydroxypyridine* as cream-coloured needles (25·2 g., 83%), m. p. 128—129° (Found : C, 55·0; H, 5·5. $C_5H_6ON_2$ requires C, 54·6; H, 5·5%).

8-Hydroxy-1 : 7-naphthyridine (XII).—Nitrobenzene (52 g.) was heated with 20% oleum (231 g.) for 1 hour at 100°. To the cooled mixture glycerol (81 g.), water (145 ml.) and 3-amino-2-hydroxypyridine (23·1 g.) were added in succession (cooling). The solution was heated under reflux for 3 hours at 140—145°, then cooled and poured on crushed ice (600 g.). Aqueous ammonia (about 350 ml.; *d* 0·89) was added to adjust the pH to 7, and the mixture filtered at 35° and then cooled to 5°, giving a precipitate of crude 8-hydroxy-1 : 7-naphthyridine. This was dissolved in water (130 ml.) and the clarified solution extracted with ether (3 × 30 ml.) at pH 5 (the ethereal solution being discarded) and then at pH 7 with chloroform for 40 hours in a continuous extractor. Evaporation of the chloroform gave light brown crystals of the naphthyridine (5·8 g.), m. p. 226—228°. An additional quantity (1·3 g.; m. p. 230—232°) was obtained by extracting the filtrate from the crude product with ether and chloroform as described

above, redissolving the chloroform-soluble portion in water, again extracting this with ether and chloroform, and finally crystallizing the product from water. Two crystallizations of the combined fractions from water (3 parts) gave *8-hydroxy-1 : 7-naphthyridine* as cream-coloured needles (6·0 g., 19·5%), m. p. 233·5° (Found : C, 65·6; H, 4·1; N, 18·8. $C_8H_6ON_2$ requires C, 65·8; H, 4·1; N, 19·2%).

Product obtained from 3-Amino-2-hydroxypyridine by a Conventional Skraup Reaction.—3-Amino-2-hydroxypyridine (0·5 g.), glycerol (0·15 g.), concentrated sulphuric acid (0·15 g.), and arsenic pentoxide (0·02 g.) were heated at 190° for 6 hours. Water (5 ml.) was added to the cooled mixture and a dark brown granular solid separated. Sublimation of this at 280°/0·4 mm. gave a yellow solid which, crystallized twice from water (400 parts), formed pale pink needles which became pale yellow on drying at 110°. The *substance* (0·15 g.) decomposed without melting at 210—215° and showed no foreign spots on paper chromatography (Found : C, 56·1; H, 4·6; N, 19·3. $C_{11}H_{11}O_3N_3$ requires C, 54·5; H, 4·6; N, 19·1%). The compound was soluble in 0·1N-sodium hydroxide and 3N-hydrochloric acid; it did not form chelate structures with bivalent metals.

4-Chloro-2-hydroxy-3-nitropyridine.—A suspension of finely ground 2 : 4-dihydroxy-3-nitropyridine (9·5 g.) (Kögl, van der Want, and Salemink, *Rec. Trav. chim.*, 1948, **67**, 29) in phosphorus oxychloride (95 ml.) was heated on the steam-bath with frequent agitation until dissolved (15 minutes), and then heated at 80° for 10 minutes. Phosphorus oxychloride was removed under reduced pressure and the residue decomposed with ice, giving a yellow mixture (9·7 g.) of 4-chloro-2-hydroxy-3-nitropyridine and 2 : 4-dichloro-3-nitropyridine. This was dried in a vacuum and triturated with chloroform (50 ml.). Crystallization of the insoluble portion (7 g.) from ethanol (100 ml., concentrated to 50 ml.) (charcoal) gave 4-chloro-2-hydroxy-3-nitropyridine as yellow plates (5·37 g., 50%), m. p. 216°. This compound was obtained in unstated yield by Kögl, van der Want, and Salemink (*loc. cit.*) as a by-product of the preparation of 2 : 4-dichloro-3-nitropyridine; no details were given for the separation of the two products.

2′-Hydroxypyridino(3′ : 4′-2 : 3)pyrazine (*5-Hydroxy-1 : 4 : 6-triazanaphthalene*) (XV).—A suspension of 4-amino-2-hydroxy-3-nitropyridine (3·46 g.; prepared from 4-chloro-2-hydroxy-3-nitropyridine according to Salemink and van der Want, *Rec. Trav. chim.*, 1949, **68**, 1013) in ethanol (90 ml.) was hydrogenated over Raney nickel. The theoretical volume of hydrogen was absorbed in 30 minutes. White granular crystals of 3 : 4-diamino-2-hydroxypyridine (XVI) which formed during the reaction were dissolved by addition of more ethanol (90 ml.) and boiling. Polyglyoxal (1·5 g.) was added to the filtered solution and the mixture refluxed for 1 hour, then concentrated to about 10 ml., giving crude *2′-hydroxypyridino(3′ : 4′-2 : 3)pyrazine hemihydrate* which after two crystallizations from alcohol (100 parts, concentrated to 20 parts) formed yellow needles (1·92 g., 57%), m. p. 270° (decomp.) (Found, for material crystallized from water and dried at 110° : C, 54·1; H, 3·8; N, 26·7. $C_7H_5ON_3,\frac{1}{2}H_2O$ requires C, 53·9; H, 3·9; N, 26·9%). The polyglyoxal used was the white hygroscopic solid which slowly separates from bottles of syrupy glyoxal.

2 : 3 : 4-Triaminopyridine Dihydrochloride.—2 : 4-Diamino-3-nitropyridine (2·8 g.) (Kögl, van der Want, and Salemink, *loc. cit.*) was suspended in ethanol (20 ml.) and hydrogenated over Raney nickel. The colourless solution was filtered into 10N-hydrochloric acid (4·5 ml.). 2 : 3 : 4-Triaminopyridine dihydrochloride (3·4 g., 95%), m. p. 246—248°, was obtained as a white crystalline precipitate. Kögl, van der Want, and Salemink (*loc. cit.*) used sodium sulphide for the reduction and gave m. p. 259°.

2′-Aminopyridino(3′ : 4′-2 : 3)pyrazine (XIV).—A solution of crude 2 : 3 : 4-triaminopyridine dihydrochloride (0·2 g.) and polyglyoxal (0·07 g.) in alcoholic N-sodium hydroxide (1 ml., 2 equiv.) was refluxed for 1 hour. The solution was filtered from sodium chloride and evaporated to dryness, and the solid residue sublimed at 140—160°/25 mm. Two crystallizations of the sublimate from 20 parts of water gave yellow needles (0·03 g., 20%), m. p. 187—188°. The compound was considered to be 2′-aminopyridino(3′ - 4′-2 : 3)pyrazine because hot 5N-sodium hydroxide converted it into the above 2′-hydroxypyridino(3′ : 4′-2 : 3)pyrazine when the procedure detailed below for the preparation of 4′-hydroxypyridino(2′ : 3′-2 : 3)pyrazine was used.

2′-Aminopyridino(3′ : 4′-2 : 3)pyrazine was also obtained in 15% yield by heating 2 : 3 : 4-triaminopyridine and polyglyoxal in water at pH 7; at pH 2 the yield was less than 1%.

4′-Aminopyridino(2′ : 3′-2 : 3)pyrazine (XVII).—Polyglyoxal (1·15 g.) was dissolved in a solution (pH 2) of 2 : 3 : 4-triaminopyridine dihydrochloride (3·4 g.) in N-sodium hydroxide (13·6 ml., 0·8 equiv.), and the mixture heated under reflux for 1 hour in a steam-bath. The cooled mixture was adjusted to pH 7 with 6N-sodium hydroxide and refrigerated overnight. A

dark orange precipitate was washed with water and then dissolved in boiling water (100 ml.). The solution was filtered and concentrated (charcoal) to about 10 ml., giving *4'-aminopyridino*-(2' : 3'-2 : 3)*pyrazine monohydrate*, which formed orange-yellow plates (1·8 g., 64%), m. p. 254—255° (decomp.), from water (charcoal); this gave no foreign spots on paper chromatography. For analysis the compound was dried for 2 hours (P_2O_5) at 110°/25 mm. (Found: C, 51·3; H, 3·7; N, 34·3. $C_7H_6N_4,H_2O$ requires C, 51·2; H, 4·9; N, 34·1%).

4'-Hydroxypyridino(2' : 3'-2 : 3)*pyrazine*.—A suspension of 4'-aminopyridino(2' : 3'-2 : 3)pyrazine monohydrate (1·7 g.) in 5N-sodium hydroxide (130 ml.) was heated for 3 hours at 140°. The yellow solution was brought to pH 6 with concentrated hydrochloric acid, filtered from precipitated silica, and evaporated to dryness. The residue was extracted (Soxhlet) with absolute ethanol for 8 hours. The alcoholic solution was evaporated to dryness and the residual solid crystallized twice from water (40 ml.), giving yellow needles (0·93 g., 61%) of chromatographically pure *4'-hydroxypyridino*(2' : 3'-2 : 3)*pyrazine*, decomp. 290—310° (Found: C, 57·2; H, 3·2; N, 28·5. $C_7H_5ON_3$ requires C, 57·2; H, 3·4; N, 28·6%).

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