459. *Preparation of 3,4-Diamino-, 3-Amino-4-methylamino-, and 4-Amino-3-methylamino-pyridine.*

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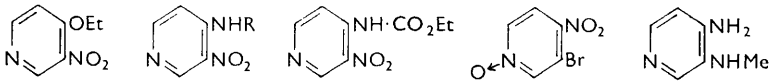
Convenient syntheses of 3,4-diamino- and 4-alkylamino-3-amino-pyridines are described. A route to 3-alkylamino-4-aminopyridines is illustrated by preparation of 4-amino-3-methylaminopyridine from 3-bromo-4-nitropyridine 1-oxide.

Nucleophilic displacement of the ethoxy-group in 4-ethoxy-3-nitropyridine (I) hydrochloride by ammonia and amines occurs readily and provides a convenient route to 4-amino- and 4-alkylamino-3-nitropyridines (II; R = H, alkyl) and the related diaminopyridines. 4-Methoxy-3-nitropyridine was used in this way be Bremer [1] before it was recognised [2] that Koenigs and Freter's "4-chloro-3-nitropyridine" [3] is 4-ethoxy-3-nitropyridine hydrochloride. Preparation of 4-ethoxy-3-nitropyridine from unstable [2] 4-chloro-3-nitropyridine was recently reported,[4] but 4-ethoxy-3-nitropyridine hydrochloride may be obtained much more simply, and almost quantitatively, from 4-hydroxy-3-nitropyridine without isolation of the chloro-intermediate. 4-Amino-3-nitropyridine (II; R = H) and 4-methylamino-3-nitropyridine (II; R = Me) were then obtained in nearly theoretical yield by heating the ethoxynitropyridine (I) hydrochloride in an autoclave with aqueous ammonia or aqueous methylamine. The primary starting material in these syntheses is 4-hydroxypyridine, but an alternative is isonicotinohydrazide: this was converted into

[1] Bremer, *Annalen*, 1935, **518**, 274.
[2] Bremer, *Annalen*, 1937, **529**, 290.
[3] Koenigs and Freter, *Ber.*, 1924, **57**, 1187.
[4] Bijlsma, den Hertog, Jouwersma, Kolder, Combé, Krol, and Buurman, *Rec. Trav. chim.*, 1956, **75**, 1187.

4-ethoxycarbonylaminopyridine, and nitration gave 4-ethoxycarbonylamino-3-nitropyridine (III) which by hydrolysis afforded 4-amino-3-nitropyridine (II; R = H), whereas hydrolysis after methylation gave 4-methylamino-3-nitropyridine (II; R = Me).



(I) (II) (III) (IV) (V)

4-Alkylamino-3-aminopyridines are therefore readily available by reduction of the 3-nitro-compounds, but synthesis of 3-alkylamino-4-aminopyridines proved more difficult. Methylation of 4-amino-3-toluene-*p*-sulphonamidopyridine, followed by hydrolysis, gave a low yield of 4-amino-3-methylaminopyridine, and it did not appear feasible to develop this into a satisfactory preparatory procedure. 3-Bromo-4-nitropyridine 1-oxide [5] (IV) and methylamine, however, gave a good yield of 3-methylamino-4-nitropyridine 1-oxide, and catalytic hydrogenation converted the *N*-oxide into the required 4-amino-3-methylaminopyridine (V). 3-Bromopyridine, obtained from 3-aminopyridine, was converted into 3-bromopyridine 1-oxide with hydrogen peroxide in preference to perphthalic acid, and the nitration step was also improved to give 3-bromo-4-nitropyridine 1-oxide (IV) in 52% overall yield from 3-aminopyridine.

The 3-amino-group in 3,4-diaminopyridine is more nucleophilic than the 4-amino-group and, as expected, reaction of the diamine with toluene-*p*-sulphonyl chloride gave 4-amino-3-toluene-*p*-sulphonamidopyridine; the isomeric 3-amino-4-toluene-*p*-sulphonamido-compound was prepared by reduction of 3-nitro-4-toluene-*p*-sulphonamidopyridine.

The pyridinediamines were converted into 1,4,6-triazanaphthalenes (to be reported later), 2-mercapto-1,3,5-triazaindene, and 1,2,3,5-tetra-azaindene for test as tumour inhibitors.

Experimental

4-Ethoxy-3-nitropyridine (I) *Hydrochloride and 3-Amino-4-ethoxypyridine Hydrochloride.*—4-Hydroxy-3-nitropyridine [1,6] (60 g.) was converted with phosphorus pentachloride (100 g.) into *4-ethoxy-3-nitropyridine hydrochloride* (86 g., 98%), needles (from ethanol), m. p. 270—271°, essentially by the method of Koenigs and Freter,[3] who described the product as 4-chloro-3-nitropyridine (Found: C, 41·1; H, 4·4; Cl, 17·6. $C_7H_8N_2O_3$,HCl requires C, 41·1; H, 4·4; Cl, 17·4%). 4-Methoxy-3-nitropyridine hydrochloride has been prepared similarly.[1,2] Hydrogenation of the ethoxy-compound (5 g.) in ethanol (250 c.c.) over Raney nickel gave *3-amino-4-ethoxypyridine hydrochloride*, which crystallised from aqueous ethanol in needles (3·0 g., 70%), m. p. 216° (Found: C, 48·3; H, 6·4. $C_7H_{10}N_2O$,HCl requires C, 48·2; H, 6·4%).

4-Amino-3-nitropyridine (II; R = H).—(*a*) 4-Ethoxy-3-nitropyridine hydrochloride (18·6 g.) and aqueous ammonia (*d* 0·88; 50 c.c.) were heated under pressure at 120° for 8 hr. The crystalline 4-amino-3-nitropyridine (13·3 g., 98%) was collected, and recrystallisation from ethanol (charcoal) gave needles, m. p. 204° (lit.,[7] m. p. 200°) (Found: C, 43·6; H, 3·7; N, 29·5. Calc. for $C_5H_5N_3O_2$: C, 43·2; H, 3·6; N, 30·2%). The picrate melted at 197—198° and the hydrochloride at 260—261° (lit.,[7] 197—198° and 258—259°). *3-Nitro-4-toluene*-p-*sulphonamidopyridine* [prepared from the nitroamine (3 g.), toluene-*p*-sulphonyl chloride (5 g.), and pyridine (5 c.c.) at 100° for 2 hr.] crystallised from aqueous ethanol (charcoal) in colourless needles (6·2 g., 98%), m. p. 148—149° (Found: C, 48·7; H, 3·8; S, 11·0. $C_{12}H_{11}N_3O_4S$ requires C, 49·1; H, 3·8; S, 10·9%).

(*b*) Isonicotinohydrazide was converted into 4-ethoxycarbonylaminopyridine (70%), prisms, m. p. 129° (from benzene–hexane), as described for 3-ethoxycarbonylaminopyridine.[8] Nitration of the urethane (5 g.) as for the 3-isomer [8] gave 4-ethoxycarbonylamino-3-nitropyridine [9] (3·8 g., 60%) which crystallised from aqueous ethanol in needles, m. p. 62° (Found: C, 45·8; H, 4·4. Calc. for $C_8H_9N_3O_4$: C, 45·5; H, 4·3%). The nitrourethane (45 g.) was heated on a

[5] den Hertog, Overhoff, Beers, and de Bruyn, *Rec. Trav. chim.*, 1950, **69**, 468.
[6] Kruger and Mann, *J.*, 1955, 2755.
[7] Koenigs, Mields, and Gurlt, *Ber.*, 1924, **57**, 1179.
[8] Clark-Lewis and Thompson, *J.*, 1957, 442.
[9] Takahashi and Ueda, *Pharm. Bull.* (*Japan*), 1956, **4**, 133.

steam-bath with 2N-sodium hydroxide (400 c.c.). Filtration next day gave 4-amino-3-nitropyridine (33 g., 96%), needles, m. p. 200—201° raised by recrystallisation from ethanol to m. p. 203—204° alone and when mixed with that prepared by method (*a*).

3,4-Diaminopyridine (6·7 g., 80%) was obtained by catalytic hydrogenation of 4-amino-3-nitropyridine (10 g.) in methanol over palladium, and it crystallised from water in needles, m. p. 220° (lit.,[10] 218—219°) (Found: C, 55·4; H, 6·4; N, 38·4. Calc. for $C_5H_7N_3$: C, 55·0; H, 6·5; N, 38·5%) [picrate, m. p. 234—236° (lit.,[11] 235—237°)]. 1,3,5-Triazaindene,[12] m. p. 168—169°, and 1,2,3,5-tetra-azaindene, m. p. 244° (lit.,[1] m. p. 240°) (Found: C, 49·6; H, 3·3; N, 46·3. Calc. for $C_5H_4N_4$: C, 50·0; H, 3·4; N, 46·7%), were prepared by known methods. 1,2,3,5-*Tetra-azaindene picrate* crystallised from benzene in needles, m. p. 194° (Found: C, 38·0; H, 2·3; N, 28·0. $C_5H_4N_4,C_6H_3N_3O_7$ requires C, 37·8; H, 2·0; N, 28·1%).

3-*Amino*-4- *and* 4-*Amino*-3-*toluene*-p-*sulphonamidopyridine.*—Hydrogenation of 3-nitro-4-toluene-*p*-sulphonamidopyridine (6 g.) in acetic acid (150 c.c.) at 5 atm. and room temperature over 5% palladised charcoal gave 3-*amino*-4-*toluene*-p-*sulphonamidopyridine* (3·8 g., 70%) which crystallised from ethanol–benzene in needles, m. p. 222—224° (Found: C, 54·7; H, 5·0; S, 12·1. $C_{12}H_{13}N_3O_2S$ requires C, 54·7; H, 5·0; N, 16·0; S, 12·2%). 3,4-Diaminopyridine (4 g.), toluene-*p*-sulphonyl chloride (9 g.), and pyridine (7 c.c.) were heated at 100° for 2 hr., giving 4-*amino*-3-*toluene*-p-*sulphonamidopyridine*, which crystallised from methanol–ethanol (charcoal) in plates (9·3 g., 96%), m. p. 245—246° (Found: C, 54·7; H, 5·1; N, 15·5; S, 12·2%).

4-*Methylamino*-3-*nitropyridine* (II; R = Me).—(*a*) 4-Ethoxycarbonylamino-3-nitropyridine (22 g.) was methylated with dimethyl sulphate (15 g.) and potassium carbonate (22 g.) in boiling acetone (200 c.c.) for 8 hr., and the suspension was then filtered. Evaporation left a residue (*ca.* 14 g.) which was hydrolysed with potassium hydroxide (9 g.) in water (75 c.c.) and ethanol (5 c.c.) at 100° for 2 hr., and the solution was then stored at 0° for 14 hr. 3-Methylamino-3-nitropyridine (6·5 g., 65%), m. p. 158—159°, was collected; it crystallised from ethanol (charcoal) in needles, m. p. 160° (lit.,[1] m. p. 162—163°) (Found: C, 47·4; H, 4·6; N, 27·4. Calc. for $C_6H_7N_3O_2$: C, 47·1; H, 4·6; N, 27·4%).

(*b*) 4-Ethoxy-3-nitropyridine hydrochloride (20 g.) and 25—30% aqueous methylamine (40 c.c.) were heated under pressure at 110° for 5 hr. Recrystallisation of the product from ethanol (charcoal) gave 4-methylamino-3-nitropyridine (14·7 g., 98%), m. p. 160° alone and when mixed with that described under (*a*).

3-*Amino*-4-*methylaminopyridine.*—4-Methylamino-3-nitropyridine (7·6 g.) in ethanol (200 c.c.) was reduced with hydrogen at 5 atm. over 1% palladised calcium carbonate for 6 hr. The filtrate from the catalyst darkened rapidly in air; it was evaporated under reduced pressure and crystallisation of the residue from benzene (charcoal) gave 3-amino-4-methylaminopyridine (5·5 g., 90%) in needles, m. p. 169—170° (lit.,[10] m. p. 169°) (Found: C, 58·0; H, 7·1; N, 33·9. Calc. for $C_6H_9N_3$: C, 58·5; H, 7·4; N, 34·1%) [picrate, m. p. 185° (lit.,[10] m. p. 184°)]. The diamine was unstable in air and light and was stored as the *dihydrochloride*, needles, m. p. 227—228° (Found: C, 37·2; H, 5·8; Cl, 36·2; N, 21·3. $C_6H_9N_3,2HCl$ requires C, 36·8; H, 5·4; Cl, 36·2; N, 21·4%).

3-*Methylamino*-4-*nitropyridine* 1-*Oxide.*—3-Aminopyridine [13] (28·6 g.) was converted into 3-bromopyridine (30 g., 66%), b. p. 61—63°/15 mm., by the Sandmeyer reaction (cuprous bromide and hydrobromic acid). 3-Bromopyridine (8·95 g.) in glacial acetic acid (35 c.c.) and 30% hydrogen peroxide (10 c.c.) was converted during 14 hr. at 70—80° into 3-*bromopyridine* 1-*oxide* (9·6 g., 95%), b. p. 118°/0·2—0·3 mm., b. p. 129—130°/1·5 mm., m. p. 42°, deliquescent (Found: Br, 46·2. C_5H_4BrNO requires Br, 45·9%). This *N*-oxide (2·25 g.) in 92% sulphuric acid (4 c.c.) was added to a cooled mixture of nitric acid (*d* 1·5; 6 c.c.) and 92% sulphuric acid (5 c.c.) and then warmed at 90° for 1½ hr., to give 3-bromo-4-nitropyridine 1-oxide (2·15 g., 84%) in pale yellow needles, m. p. 154—155° (lit.,[5] m. p. 152—153°). This (3 g.) was heated on a steam-bath with 15% methanolic methylamine (10 c.c.) for 30 min. before removal of the solvent under reduced pressure; the residue of 3-*methylamino*-4-*nitropyridine* 1-*oxide* crystallised from ethanol (charcoal) in needles (3·55 g., 90%), m. p. 227° (Found: C, 42·6; H, 4·2; N, 24·8. $C_6H_7N_3O_3$ requires C, 42·6; H, 4·2; N, 24·9%).

4-*Amino*-3-*methylaminopyridine.*—(*a*) 3-Methylamino-4-nitropyridine 1-oxide (1·2 g.) in

[10] Weidenhagen, Train, Wegner, and Nordström, *Ber.*, 1942, **75**, 1936.
[11] Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690.
[12] Weidenhagen and Weeden, *Ber.*, 1938, **71**, 2347; Albert and Pedersen, *J.*, 1956, 4683.
[13] Allen and Wolff, *Org. Synth.*, 1950, **30**, 3.

methanol (50 c.c.) and acetic acid (2 c.c.) was hydrogenated over Raney nickel at room temperature and pressure during 1½ hr., the suspension was filtered, and the residue washed with boiling methanol. The filtrate was made strongly alkaline with aqueous sodium hydroxide before continuous extraction with ether for 36 hr. Evaporation of the ether and crystallisation of the residue from light petroleum (b. p. 40—60°) gave 4-*amino*-3-*methylaminopyridine* (0·7 g., 87%) in needles, m. p. 114° (Found: C, 58·4; H, 7·6; N, 34·3. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·2%). The *picrate* melted at 233° (Found: C, 41·1; H, 3·6; N, 24·1. $C_6H_9N_3,C_6H_3N_3O_7$ requires C, 40·9; H, 3·4; N, 23·9%).

(*b*) 4-Amino-3-toluene-*p*-sulphonamidopyridine (10 g.) was treated for 8 hr. in boiling acetone (400 c.c.) with methyl sulphate (5 g.) and anhydrous potassium carbonate (10·5 g.). Evaporation of the filtrate left a semi-solid residue which was hydrolysed with 80% sulphuric acid (10 c.c.) on a steam-bath for 3 hr. The diluted solution was basified with sodium hydroxide before extraction with ether (36 hr.) to separate the diamine, which crystallised from light petroleum (b. p. 40—60°) (charcoal) in needles (1·3 g., 30%), m. p. 114° alone and when mixed with that obtained by method (*a*).

2-*Mercapto*-1,3,5-*triazaindene*.—Carbon disulphide (1·6 g.) in ethanol (5 c.c.) was added to a solution of 3,4-diaminopyridine (2 g.) in ethanol (25 c.c.), and the mixture was boiled for 6 hr. 2-*Mercapto*-1,3,5-*triazaindene* crystallised from the cold solution and recrystallisation from aqueous ethanol (charcoal) gave prisms (1·7 g., 62%), m. p. 370° (Found: C, 47·8; H, 3·4; S, 20·8. $C_6H_5N_3S$ requires C, 47·7; H, 3·3; S, 21·2%), $\lambda_{max.}$ in N-sodium hydroxide 232 (ε 23,500) and 298—299 mμ (ε 14,000), $\lambda_{min.}$ 261 mμ (ε 2900).

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