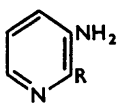
81. *Methylation of 3-Aminopyridines and Preparation of 2-Amino-3-methylaminopyridine and 2 : 3-Diaminopyridine.*

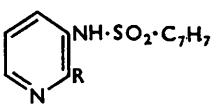
By J. W. Clark-Lewis and M. J. Thompson.

New and improved methods are described for preparation of 2-amino-3-methylaminopyridine and 2 : 3-diaminopyridine, which are more conveniently obtained from 3- than from 2-aminopyridine. Methylation of certain 3-aminopyridine derivatives yields the corresponding 3-methylaminopyridines.

Repetition on a larger scale of the only recorded preparation of 3-methylaminopyridine (60% from 3-bromopyridine and methylamine [1]) gave an inconveniently low yield (38%). Methylation of 3-aminopyridine (I; R = H) *via* the sulphonamides (II and III; R = H) however gave 3-methylaminopyridine (IV; R = H) in 70% overall yield—and 3-aminopyridine is formed almost quantitatively from 3-bromopyridine and is even more readily available from nicotinic acid or nicotinamide. Methylation of 3-aminopyridine derivatives has apparently not been attempted except for 3-nitraminopyridine which was reported by Tschitschibabin and Kirssanow [2] to give the "betaine" (V) instead of the secondary nitramine [1] (VI), but no difficulties arising from quaternisation of the heterocyclic nitrogen atom were encountered in the present work.



(I)



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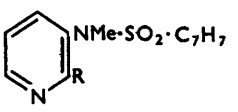

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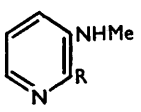

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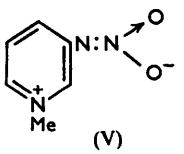

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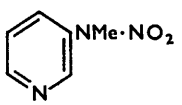

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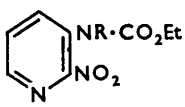
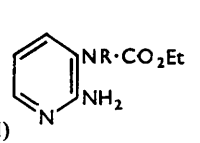


(VII)

Plazek, Marcinikow, and Stammer [1] obtained a low yield of 2-amino-3-methylaminopyridine (IV; R = NH_2) by direct amination of 3-methylaminopyridine with sodamide, and only 16% of 3-methylamino-2-nitropyridine (IV; R = NO_2) by nitration and rearrangement of the intermediate nitramine (VI). Chlorination of 3-methylaminopyridine under the conditions [3] described for 3-aminopyridine did not yield the expected 2-chloro-3-methylaminopyridine (IV; R = Cl), which was accordingly prepared by methylation of

[1] Plazek, Marcinikow, and Stammer, *Roczn. Chem.*, 1935, **15**, 365.
[2] Tschitschibabin and Kirssanow, *Ber.*, 1927, **60**, 2433.
[3] Schickh, Binz, and Schulz, *Ber.*, 1936, **69**, 2593.

3-amino-2-chloropyridine (I; R = Cl) by way of the sulphonamides (II and III; R = Cl). Reaction of 2-chloro-3-methylaminopyridine with aqueous ammonia then gave 2-amino-3-methylaminopyridine (IV; R = NH_2) (18—21% from 3-aminopyridine). The inconvenience of sealed tubes was avoided in an alternative preparation of 2-amino-3-methylaminopyridine from the nitro-compound (IV; R = NO_2) which was obtained satisfactorily by methylation of 3-ethoxycarbonylamino-2-nitropyridine (VII; R = H) and hydrolysis of the resulting urethane (VII; R = Me). Nicotinhydrazide, which may also be obtained from nicotinamide,[4] was prepared from nicotinic acid (2 mol.) *via* the acid chloride and ethyl nicotinate, and converted by the Curtius reaction on the related azide into 3-ethoxycarbonylaminopyridine (67%), which is also accessible from 3-aminopyridine and ethyl chloroformate.[5] Curry and Mason [6] have described a small-scale nitration of this urethane to 3-ethoxycarbonylamino-2-nitropyridine (VII; R = H) but numerous trials were necessary to determine conditions suitable on a larger scale (see Experimental section). Methylation of the nitrourethane (VII; R = H) proceeded smoothly and hydrolysis of the product (VII; R = Me) followed by hydrogenation gave 2-amino-3-methylaminopyridine (17% from nicotinic acid). The amino-urethanes (VIII; R = H, Me) formed by hydrogenation of the nitro-compounds (VII; R = H, Me) crystallised well, and on pyrolysis gave the glyoxalinopyridines (IX; R = H, Me). Alkaline hydrolysis of the amino-urethane (VIII; R = Me) provides a convenient alternative route to 2-amino-3-methylaminopyridine as the latter is more easily isolated than the 3-methylamino-2-nitropyridine obtained by similar hydrolysis of the nitro-urethane (VII; R = Me).



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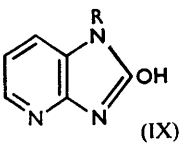

(IX)

2 : 3-Diaminopyridine (*ca.* 18%) may be obtained from 2-aminopyridine *via* chloro- (Ziegler [7]) or bromo-intermediates (Leese and Rydon [8]), but the readily available 3-aminopyridine is a better source and has been converted into the diamine (40%) by a two-stage synthesis (Schickh, Binz, and Schulz [3]). We have also prepared 2 : 3-diaminopyridine (24% from nicotinic acid) by reduction of 3-amino-2-nitropyridine [6] (I; R = NO_2) obtained by hydrolysis of the nitrourethane (VII; R = H), an intermediate in the preparation of 2-amino-3-methylaminopyridine already described. The greater length of this synthesis compared with those from 2-aminopyridine [7,8] is compensated by simplicity and higher yield. Nitration of 3-ethoxycarbonylaminopyridine to the 2-nitro-urethane (VII; R = H) (60%) is of special preparative interest because attempted rearrangement [2] of 3-nitraminopyridine with sulphuric acid gave 3-hydroxypyridine, although 3-*N*-methylnitraminopyridine behaves normally in giving 3-methylamino-2-nitropyridine [1] under these conditions. According to Zwart and Wibaut,[9] treating 3-aminopyridine nitrate with fluorosulphonic acid and with anhydrous hydrogen fluoride gives small yields of unidentified 3-amino-*x*-nitropyridines, of m. p. 186—187° and 196—197° respectively. The latter is probably 3-amino-2-nitropyridine, for which we obtain m. p. 195—196° (lit.,[6] m. p. 195—196° and [10] 203—204°).

Experimental

3-Methylaminopyridine (IV; R = H).—(*a*) 3-Bromopyridine [11] (35 g.), aqueous methylamine (45 c.c.; 25—30% w/v), and copper sulphate (2 g.) were heated for 40 hr. at 150°, diluted

[4] Fox and Field, *J. Biol. Chem.*, 1943, **147**, 651.
[5] Camps, *Arch. Pharm.*, 1902, **240**, 355; cf. ref. 11.
[6] Curry and Mason, *J. Amer. Chem. Soc.*, 1951, **73**, 5043.
[7] Ziegler, *ibid.*, 1949, **71**, 1891.
[8] Leese and Rydon, *J.*, 1954, 4039.
[9] Zwart and Wibaut, *Rec. Trav. chim.*, 1955, **74**, 1062.
[10] den Hertog and Jouwersma, *ibid.*, 1953, **72**, 125.

with water, and filtered. The filtrate (150 c.c.) was made strongly alkaline with sodium hydroxide before extraction with ether. Ether was removed from the dried ($MgSO_4$) extract and distillation of the residue under reduced pressure gave 3-bromopyridine (3·6 g.) and 3-methylaminopyridine [1] (9 g., 38%), b. p. 96°/4 mm. 3-Methylaminopyridine picrate crystallised from water in needles, m. p. 178° (lit.,[1] 178°).

(*b*) 3-Aminopyridine [12] (14·1 g.), pyridine (20 c.c.), and toluene-*p*-sulphonyl chloride (30 g.) were heated on a steam-bath for 2 hr., then poured into water. 3-Toluene-*p*-sulphonamidopyridine [13] (II; R = H) (36 g., 97%), m. p. 190°, was collected; it crystallised from ethanol in needles, m. p. 191—192° (Found: N, 11·0. Calc. for $C_{12}H_{12}O_2N_2S$: N, 11·3%). Dimethyl sulphate (19 g.) in acetone (75 c.c.) was added dropwise during 30 min. to a suspension of anhydrous potassium carbonate (40 g.) and the sulphonamide (35 g.) in boiling acetone (650 c.c.), and boiling was continued for 2 hr. The suspension was filtered when cold, and evaporation left an oily residue of 3-*N*-methyltoluene-*p*-sulphonamidopyridine (III; R = H) which was heated on a steam-bath for 3 hr. with 80% sulphuric acid (60 c.c.). The solution was diluted with water and basified with aqueous ammonia (*d* 0·88) before extraction with ether. Distillation of the residue remaining after evaporation of the ether from the dried ($MgSO_4$) solution gave 3-methylaminopyridine (11 g., 72% from 3-aminopyridine), b. p. 110°/7 mm., 76°/3 mm. (picrate, m. p. and mixed m. p. 178°).

2-Chloro-3-methylaminopyridine (IV; R = Cl).—3-Amino-2-chloropyridine (60—70%), m. p. 78—79°, was obtained by chlorination [3] of 3-aminopyridine, but 3-methylaminopyridine was recovered (77%) after attempted chlorination by the same technique. 3-Amino-2-chloropyridine (14·1 g.) was heated on a steam-bath for 4 hr. with anhydrous pyridine (25 c.c.) and toluene-*p*-sulphonyl chloride (22·5 g.). The precipitate (30·8 g., *ca.* 100%), m. p. 139—143°, formed by pouring the solution into water, consisted of *2-chloro-3-toluene*-p-*sulphonamidopyridine* (II; R = Cl) which crystallised from benzene–hexane in prisms, m. p. 144—145° (Found: Cl, 13·1; S, 11·6. $C_{12}H_{11}O_2N_2ClS$ requires Cl, 12·6; S, 11·3%). A lower yield (60%) was obtained when the reactants were heated for only 2 hr. The sulphonamide (30 g.) was methylated by the acetone–potassium carbonate technique described above for 3-toluene-*p*-sulphonamidopyridine, and evaporation of the acetone left a residue of *2-chloro*-3-N-*methyltoluene*-p-*sulphonamidopyridine* (III; R = Cl) which crystallised from benzene (100 c.c.)–hexane (60 c.c.) (charcoal) in prisms (20 g., 63%), m. p. 115—118° raised to 119° by recrystallisation (Found: C, 53·0; H, 4·5; N, 9·8. $C_{13}H_{13}O_2N_2ClS$ requires C, 52·6; H, 4·4; N, 9·4%). 2-Chloro-3-*N*-methyltoluene-*p*-sulphonamidopyridine (20 g.) was heated for 3½ hr. on a steam-bath with 80% sulphuric acid (40 c.c.), and the cooled solution was poured into ice-water and neutralised with aqueous ammonia (*d* 0·88). The solution was extracted with ether (3 × 450 c.c.) and the extract dried ($MgSO_4$) before evaporation. Distillation of the residue gave *2-chloro-3-methylaminopyridine* (8·5 g., 89%), b. p. 144°/10 mm., n_D^{25} 1·5945, which darkened on storage (Found: Cl, 25·5. $C_6H_7N_2Cl$ requires Cl, 24·9%). The picrate crystallised from water in needles, m. p. 123°. Acetylation of the amine (0·8 g.) with acetic anhydride at the b. p. for 2 hr. gave *2-chloro*-3-N-*methylacetamidopyridine* which crystallised from hexane in prisms (0·86 g., 83%), m. p. 85—86° (Found: C, 52·4; H, 4·9; N, 14·6. $C_8H_9ON_2Cl$ requires C, 52·0; H, 4·9; N, 15·2%).

3-Ethoxycarbonylaminopyridine from Nicotinic Acid.—Finely powdered nicotinic acid (250 g.) was boiled with purified thionyl chloride (1 kg.), whereupon it dissolved and crystallisation of the acid chloride hydrochloride commenced. When reaction was complete (3½ hr.) the excess of thionyl chloride was removed under reduced pressure, ethanol (500 c.c.) was added gradually, and the solution was boiled for 15 min. The excess of ethanol was removed under reduced pressure and the residue was diluted with water and basified with sodium carbonate before extraction with ether. The ether extract was dried ($MgSO_4$) and distillation of the residue which remained after evaporation gave ethyl nicotinate [14] (275 g., 90%), b. p. 130°/40 mm., n_D^{20} 1·5020. Nicotinhydrazide (*ca.* 100%), m. p. 156° (lit.,[4] m. p. 158—159°), was prepared by stirring a warm mixture of the ester (275 g.) with 100% hydrazine hydrate (100 c.c.) until homogeneous and then evaporation of the solution to dryness. The hydrazide was dissolved

[11] Maier-Bode, *Ber.*, 1936, **69**, 1534.
[12] *Org. Synth.*, 1950, **30**, 3; den Hertog and Wibaut, *Rec. Trav. chim.*, 1936, **55**, 122; cf. ref. 9.
[13] Reitsema and Hunter, *J. Amer. Chem. Soc.*, 1949, **71**, 1680.
[14] Adkins, Kuick, Farlow, and Wojcik, *ibid.*, 1934, **56**, 2425; Hukusima, *J. Chem. Soc. Japan*, 1940, **61**, 121; *Chem. Abs.*, 1942, **36**, 7239.

in 12N-hydrochloric acid (350 c.c.) and water (200 c.c.), and the solution was cooled to 5—10° and stirred during the addition (1 hr.) of sodium nitrite (270 g.) in water (500 c.c.). Stirring was continued for 1 hr. before the addition of sodium carbonate (100 g.) in water (500 c.c.), and the azide was collected by filtration, drained, and dissolved immediately in benzene (500 c.c.). The filtrate was extracted with benzene (2 × 500 c.c.), and the combined benzene solutions (1500 c.c.) were dried ($MgSO_4$) and then boiled after the addition of ethanol (200 c.c.) until evolution of nitrogen ceased (9 hr.). The benzene solution was concentrated under reduced pressure and crystallisation of the residue from benzene–hexane (charcoal) gave 3-ethoxycarbonylaminopyridine (226 g., 67% from nicotinic acid), m. p. 86—88° (lit.,[11] m. p. 89—90°). The azide solutions are powerful skin irritants.

3-Ethoxycarbonylamino-2-nitropyridine (VII; R = H).—The above carbamate (30 g.) was treated with a mixture of 98—100% sulphuric acid (60 c.c.) and nitric acid (*d* 1·5; 60 c.c.) in a large flask, and after the initially vigorous reaction had moderated (10 min.) the mixture was heated on a steam-bath for 20 min. The solution was poured on ice (500 g.), and the precipitated nitrocarbamate (23 g., 60%), m. p. 82—83°, was collected, washed with water, and dried at 65°. 3-Ethoxycarbonylamino-2-nitropyridine [6] crystallised from aqueous ethanol in pale yellow needles, m. p. 82—83°. The above conditions were chosen after numerous trials had shown that the concentration of sulphuric acid has a marked effect upon the yield, and that reactions with larger quantities of carbamate tend to become uncontrollable. Thus when the carbamate (70 g.) was heated on a steam-bath with 92% sulphuric acid (140 c.c.) and nitric acid (*d* 1·5, 140 c.c.) the reaction became suddenly violent after proceeding normally for 1 hr. and none of the nitrocarbamate was obtained. Nitration of the carbamate (4 g.) as described by Curry and Mason [6] gave impure nitrocarbamate (60%), m. p. 77—80°, and a better product (60%), m. p. 81—82°, was obtained when the reaction time was reduced from 90 to 15 min. Heating the carbamate (4 g.) with 20% oleum (8 c.c.) and nitric acid (*d* 1·5, 8 c.c.) on a steam-bath for 30 min. gave a satisfactory yield of the nitrocarbamate (3·3 g., 65%) on the small scale, but a similar reaction with the carbamate (15 g.) was immediately violent (charring).

2-Amino-3-ethoxycarbonylaminopyridine (VIII; R = H) *and 2'-Hydroxyglyoxalino(4' : 5'-2 : 3)pyridine* (IX; R = H).—3-Ethoxycarbonylamino-2-nitropyridine (3 g.) in methanol (100 c.c.) was reduced with hydrogen at room temperature and pressure over Raney nickel (W7), and the filtrate from catalyst was evaporated to dryness. The residue of *2-amino-3-ethoxycarbonylaminopyridine* crystallised from benzene (30 c.c.) in plates (1·7 g., 65%), m. p. 96·5—97·5° raised to m. p. 97·5° by recrystallisation (Found: C, 53·3; H, 6·1. $C_8H_{11}O_2N_3$ requires C, 53·0; H, 6·1%). Pyrolysis of the aminocarbamate (0·3 g.) at 160—165° caused evolution of ethanol and the melt quickly solidified. Heating was continued for a further 15 min., and crystallisation of the solid from water (25 c.c.) gave 2'-hydroxyglyoxalino(4' : 5'-2 : 3)-pyridine (0·13 g., 58%) in fine needles, m. p. 265—266° unchanged by several recrystallisations from water or by admixture with a sample of the same m. p. prepared (16%) according to Petrow and Saper [15] (who record m. p. 274°).

3-Ethoxycarbonyl-N-methylamino-2-nitropyridine (VII; R = Me).—3-Ethoxycarbonylamino-2-nitropyridine (60 g.) was boiled with acetone (300 c.c.) and anhydrous potassium carbonate (60 g.) during addition (20 min.) of dimethyl sulphate (40 g.) in acetone (200 c.c.), and thereafter for 6 hr. The filtrate from the cold suspension was evaporated and distillation of the residue gave *3-ethoxycarbonyl-N-methylamino-2-nitropyridine* (59·5 g., 93%) as a viscous yellow oil, b. p. 146°/0·05 mm., n_D^{20} 1·5238 (Found: C, 48·3; H, 5·1; N, 18·9. $C_9H_{11}O_4N_3$ requires C, 48·0; H, 4·9; N, 18·7%).

2-Amino-3-ethoxycarbonyl-N-methylaminopyridine (VIII; R = Me) *and 2'-Hydroxy-1'-methylglyoxalino(4' : 5'-2 : 3)pyridine* (IX; R = Me)—3-Ethoxycarbonyl-*N*-methylamino-2-nitropyridine (5 g.) in methanol (100 c.c.) was reduced with hydrogen at room temperature and pressure over Raney nickel (W 7; 5—10 g.), and the catalyst was removed and extracted with hot methanol (100 c.c.). Evaporation of the combined methanol solutions left a dark brown solid which crystallised from benzene in prisms (2·7 g., 82%), m. p. 127—128°. Recrystallisation from benzene (charcoal) gave *2-amino-3-ethoxycarbonyl-N-methylaminopyridine* in prisms, m. p. 129—130° (Found: C, 55·4; H, 6·6; N, 21·3. $C_9H_{13}O_2N_3$ requires C, 55·4; H, 6·7; N, 21·5%). The *N*-methylurethane sublimed at 140—150° and cyclisation, which occurred less readily than with the unmethylated urethane, was effected by heating the compound (0·5 g.) at 200° for 15 min. *2'-Hydroxy-1'-methylglyoxalino(4' : 5'-2 : 3)pyridine* (0·37 g., 96%) crystallised from benzene in needles, m. p. 199—202°, and crystallised also from water in which it is more soluble.

Material crystallised from benzene appeared from elementary analyses to retain solvent of crystallisation tenaciously, and after two crystallisations from benzene an analytical specimen, m. p. 201—202°, was prepared by recrystallisation from water followed by two sublimations at 180°/12 mm. (Found: C, 56·5; H, 4·6; N, 28·1. $C_7H_7ON_3$ requires C, 56·4; H, 4·7; N, 28·2%).

3-Methylamino-2-nitropyridine (IV; R = NO_2).—3-Ethoxycarbonyl-*N*-methylamino-2-nitropyridine (29·7 g.) was boiled for 1 hr. with potassium hydroxide (18·5 g., 2·5 mol.) in water (150 c.c.) and ethanol (100 c.c.). The cooled solution was stored at 0° and filtered from 3-methylamino-2-nitropyridine [1] (13 g., 64%), m. p. 104—106° raised to m. p. 109—110° by crystallisation (orange needles) from aqueous ethanol (Found: N, 27·1. Calc. for $C_6H_7O_2N_3$: N, 27·45%).

2-Amino-3-methylaminopyridine (IV; R = NH_2).—(*a*) 3-Methylamino-2-nitropyridine (7 g.) in methanol (100 c.c.) was reduced with hydrogen at room temperature and pressure over Raney nickel catalyst (W7), and the product (4·1 g., 73%), m. p. 122—123°, b. p. 138°/1 mm., was distilled in nitrogen. Recrystallisation from benzene (80 c.c.) gave 2-amino-3-methylaminopyridine in needles, m. p. 124—125° (lit.,[1] m. p. 124°) (Found: N, 34·5. Calc. for $C_6H_9N_3$: N, 34·1%). The picrate crystallised from water in needles, m. p. 234—235° (lit.,[1] m. p. 234°).

(*b*) The diamine was more conveniently obtained from the 2-nitrourethane by alkaline hydrolysis of the intermediate 2-amino-3-ethoxycarbonyl-*N*-methylaminopyridine. 3-Ethoxycarbonyl-*N*-methylamino-2-nitropyridine (11·5 g.) in methanol (100 c.c.) was reduced catalytically as already described, and the filtrate from catalyst was diluted with water. Methanol was removed by distillation under reduced pressure and the amino-urethane (5·7 g.) crystallised from the aqueous solution (50 c.c.). The filtrate was boiled for 2 hr. after the addition of sodium hydroxide (7 g.), and 2-amino-3-methylaminopyridine (0·6 g.) was extracted with ether. The amino-urethane (5·7 g.) was boiled for 2 hr. with aqueous 10% sodium hydroxide (100 c.c.) and then extracted continuously with ether. 2-Amino-3-methylaminopyridine, obtained by evaporation of the ether, crystallised from benzene in needles (1·37 g.) (total 1·97 g., 31% from the nitro-urethane), m. p. 122—124°.

(*c*) 2-Chloro-3-methylaminopyridine (8·0 g.) was heated with aqueous ammonia (*d* 0·88; 40 c.c.), water (20 c.c.), and copper sulphate (1 g.) in a sealed tube at 130° for 30 hr., and the cooled solution was extracted six times with ether. The ethereal solution was evaporated, and distillation of the residue gave the amine (3·75 g., 54%), b. p. 134°/*ca.* 1 mm., which crystallised from benzene in needles (3·25 g.), m. p. 124—125° alone and when mixed with a specimen prepared by method (*a*) (Found: C, 58·9; H, 7·1. Calc. for $C_6H_9N_3$: C, 58·5; H, 7·3%) (picrate, m. p. 234—235°).

3-Amino-2-nitropyridine (I; R = NO_2).—A solution of 3-ethoxycarbonylamino-2-nitropyridine (22·5 g.) in 2·5N-sodium hydroxide (200 c.c.) was stored at 25° and filtered after 48 hr. from 3-amino-2-nitropyridine (12·7 g., 86%), bright yellow needles, m. p. 194—196° raised by recrystallisation from aqueous ethanol to m. p. 195—196° (lit.,[6] m. p. 195—196° and [10] 203—204°). Hydrolysis is accelerated by heating, but the product is inferior.

2 : 3-Diaminopyridine (I; R = NH_2).—3-Amino-2-nitropyridine (3·0 g.) in methanol (100 c.c.) was reduced within a few minutes by hydrogen at room temperature and pressure over the relatively large quantity of Raney nickel (3—4 g., W7) necessary for smooth reduction, and the suspension was then filtered and the catalyst was washed with boiling methanol (100 c.c.). The filtrate, which became intensely blue on exposure to air, was evaporated to dryness, and crystallisation of the residue from benzene (charcoal) gave 2 : 3-diaminopyridine (1·66 g., 71%) in colourless needles, m. p. 113—114° (lit.,[6,7] m. p. 113—114°; m. p.[8] 112°; Leese and Rydon [8] record m. p. 116°, and Petrow and Saper [15] m. p. 118·5—119·5°).

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[15] Petrow and Saper, *J.*, 1948, 1389.