382. *Long-chain Alkyl Derivatives of 2-Aminopyridine.*

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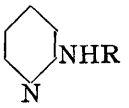
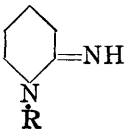
A series of alkyl derivatives of 2-aminopyridine containing 10 to 14 carbon atoms in the chain has been prepared for pharmacological trial. The position assumed by the alkyl group depends upon the experimental conditions. In the presence of sodamide, 2-alkylaminopyridines (I) are formed almost exclusively, whereas alkylation in an inert solvent without sodamide gives rise to 1-substituted derivatives of the tautomeric pyridoneimine structure (II) together with a smaller proportion of form (I). The 1-alkylpyridoneimines are strong, unstable bases, which form stable crystalline salts, but the 2-alkylaminopyridines are stable crystalline substances, which do not readily form salts with mineral acids. Proof of the structures assigned to the compounds is presented.

FEW alkyl derivatives of 2-aminopyridine have been recorded. Tschitschibabin, Konovalova, and Konovalova (*Ber.*, 1921, **54**, 814; see also Tschitschibabin and Zeide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216) showed that 2-aminopyridine reacted with methyl iodide in the presence of sodamide to give mainly 2-methylaminopyridine (I, R = Me), whereas the direct action of methyl iodide gave as main product 1-methyl-2-pyridoneimine (II, R = Me), together with a smaller amount of 2-methylaminopyridine.

They also found that the compounds differed in their reactivity towards alkali, the latter (I) being unaffected, whereas the former (II) readily evolved ammonia with the formation of 1-methyl-2-pyridone. 2-*iso*Propyl-, 2-allyl-, 2-*iso*amyl-, and 2-cetyl-aminopyridines

(I.)  (II.) 

have been prepared by the action of alkyl halides on 2-aminopyridine in the presence of sodamide (Schering-Kahlbaum, B.P. 265,167), and more recently Magidson and Menschikov (*Ber.*, 1926, **59**, 1209) have prepared 2-mono- and 2-di-*iso*amylaminopyridines by a similar process. Slotta and Francke (*Ber.*, 1930, **63**, 678), using the appropriate ester of *p*-toluenesulphonic acid and the sodium derivative of 2-aminopyridine, obtained 2-mono- and -di-propyl- and -butyl-aminopyridines.

The higher alkyl derivatives (10 to 14 carbon atoms) are conveniently prepared by the interaction of 2-aminopyridine and the alkyl halide in boiling cymene. Each alkyl halide gives rise to two isomeric monoalkylaminopyridines, which can readily be separated by taking advantage of their different basicities, as described in the experimental part. The stronger bases are formed in greater proportion and are unstable and darken on keeping or on exposure to air; they form stable salts which are very soluble in water. The weaker bases are crystalline and stable, and are very sparingly soluble in mineral acids. The work of Tschitschibabin *et al.* (*loc. cit.*) would indicate that the stronger bases are 1-alkyl derivatives of 2-pyridoneimine (II) and the weaker bases are 2-alkylaminopyridines (I). This has been confirmed in two illustrative cases : (*a*) 2-aminopyridine reacts with tetradecyl chloride in the presence of sodamide to give only the weaker base, obviously 2-*tetradecylaminopyridine*; (*b*) the weak base from the action of dodecyl bromide on 2-aminopyridine gave no trace of ammonia on long boiling with aqueous-alcoholic potassium hydroxide, whereas the strong base on similar treatment gave off ammonia and was converted into 1-dodecyl-2-pyridone.

Experimental.

2-Aminopyridine (5·9 g.; 1·25 mols.) was dissolved in warm cymene (25 c.c.), mixed with the appropriate alkyl halide (1 mol.), and heated under reflux in an oil-bath at 170—180° for 6—7 hours. With tetradecyl chloride the liquid remained clear, but in the other cases the liquid soon became cloudy and separated into two layers as the reaction proceeded. The cymene was distilled off under reduced pressure, and the viscous residual oil mixed with aqueous sodium hydroxide and extracted with ether. The ether after drying left on evaporation an oil, which was distilled, first at 30 mm. pressure to remove aminopyridine and then at 0·1—0·2 mm., a fraction boiling up to 200° being collected. This was dissolved in ether (200 c.c.) and shaken with water (100 c.c.) and sufficient dilute sulphuric acid to render the aqueous layer just acid to methyl-red. The ether on evaporation gave the 2-alkylaminopyridine in a substantially pure state, requiring only one crystallisation. The sulphate of the 1-alkyl-2-pyridoneimine can be obtained by evaporation of the aqueous layer, but, owing to the soaplike character of the salts, the solutions foam badly on concentration and it is preferable to recover the base and convert it into a salt in dry alcohol.

Decylation with decyl iodide gave a total yield 10·5 g., of which 1·43 g. consisted of 2-*decylaminopyridine*, which formed colourless prismatic rods from alcohol, m. p. 51—52° (Found : C, 76·95; H, 11·2; N, 12·0. $C_{15}H_{26}N_2$ requires C, 76·9; H, 11·2; N, 12·0%). The picrate formed soft felted needles from alcohol, m. p. 78—79°. 1-*Decyl*-2-*pyridoneimine sulphate* separated from dry alcohol in colourless, hygroscopic needles, m. p. 246° (decomp.) after sintering at 205° (Found : C, 62·9; H, 9·6; N, 9·7; S, 5·8. $C_{15}H_{26}N_2,\frac{1}{2}H_2SO_4$ requires C, 63·6; H, 9·6; N, 9·4; S, 5·7%). The picrate crystallised from alcohol in lemon-yellow rhombs, m. p. 111°.

Undecylation with undecyl bromide gave a total yield of 9·6 g., of which 2·4 g. was 2-*undecylaminopyridine*, which crystallised in colourless prismatic needles from alcohol, m. p. 60—61° (Found : C, 77·1; H, 11·3; N, 11·5. $C_{16}H_{28}N_2$ requires C, 77·1; H, 11·4; N, 11·3%).

The picrate formed soft needles from alcohol, m. p. 93—94°. 1-Undecyl-2-pyridoneimine sulphate was obtained in colourless deliquescent needles unsuitable for analysis. The *oxalate* formed colourless platelets from acetone–methyl alcohol (6 : 1), which effervesced at 205° after sintering at 165° (Found : C, 69·8; H, 10·0; N, 9·5. $C_{16}H_{28}N_2,\frac{1}{2}C_2H_2O_4$ requires C, 69·6; H, 10·0; N, 9·55%). The picrate separated in small prisms from alcohol, m. p. 116—117°.

Dodecylation with dodecyl bromide gave a total yield of 9·9 g., of which 2·6 g. was *2-dodecylaminopyridine*, which formed colourless needles from alcohol, m. p. 60° (Found : C, 78·0; H, 11·6; N, 10·6. $C_{17}H_{30}N_2$ requires C, 77·8; H, 11·5; N, 10·7%). The picrate crystallised in soft needles from alcohol, m. p. 96—97°. *1-Dodecyl-2-pyridoneimine sulphate* formed colourless needles from *iso*propyl alcohol, m. p. 255° (decomp.) after sintering at 210° (Found : C, 65·6; H, 10·1; N, 9·0; S, 5·1. $C_{17}H_{30}N_2,\frac{1}{2}H_2SO_4$ requires C, 65·5; H, 10·0; N, 9·0; S, 5·1%). The picrate formed rosettes of small stout needles from alcohol, m. p. 88—89°.

Tridecylation with tridecyl bromide (prepared by the action of bromine on silver myristate; B.P. 456,565) gave a total yield of 10·26 g., of which 2·6 g. was *2-tridecylaminopyridine*, which formed colourless needles from alcohol, m. p. 65—66° (Found : C, 78·2; H, 11·7; N, 10·1. $C_{18}H_{32}N_2$ requires C, 78·2; H, 11·7; N, 10·1%). The picrate formed needles from alcohol, m. p. 92—94°. *1-Tridecyl-2-pyridoneimine sulphate* formed colourless needles from dry alcohol, m. p. about 265° after sintering at 215° (Found : C, 66·3; H, 10·3; N, 8·8; S, 5·0. $C_{18}H_{32}N_2,\frac{1}{2}H_2SO_4$ requires C, 66·4; H, 10·2; N, 8·6; S, 4·9%). The picrate formed soft needles from alcohol, m. p. 88—93°.

Tetradecylation with tetradecyl chloride gave a total yield of 12·48 g., of which about half was *2-tetradecylaminopyridine*; this formed colourless soft needles from alcohol, m. p. 69° (Found : C, 78·4; H, 11·6; N, 9·2. $C_{19}H_{34}N_2$ requires C, 78·5; H, 11·8; N, 9·6%). The picrate formed needles from alcohol, m. p. 83°. *1-Tetradecyl-2-pyridoneimine sulphate* crystallised in colourless needles from dry alcohol, m. p. about 260° after sintering at 190° (Found : C, 67·3; H, 10·2; N, 8·4; S, 4·7. $C_{19}H_{34}N_2,\frac{1}{2}H_2SO_4$ requires C, 67·2; H, 10·4; N, 8·25; S, 4·7%). The picrate formed rosettes of stout needles from alcohol, m. p. 88°.

Tetradecylation in the presence of sodamide. Powdered sodamide (0·95 g.), dry toluene (20 c.c.), and 2-aminopyridine (2·35 g.) were heated under reflux for 1½ hours. Tetradecyl chloride (5·8 g.) was slowly added, and the mixture boiled for 4½ hours. After cooling, water was added, and the toluene separated, dried, and evaporated. The residue, which solidified on cooling, was distilled at 30 mm. pressure to remove aminopyridine, and then at 0·1 mm. The fraction, b. p. up to 190°, was dissolved in ether and shaken with water and a few drops of N-sulphuric acid. The base recovered from the aqueous part amounted to 0·12 g. and perhaps contained some 1-tetradecyl-2-pyridoneimine, but the picrate prepared from the fraction was not pure. The ether on evaporation gave a mixture of unchanged tetradecyl chloride and 2-tetradecylaminopyridine (2·37 g.), m. p. 69—70°, which were separated by fractional distillation.

Benzylation with benzyl bromide gave a yield of 6·83 g., of which 1·42 g. was 2-benzylaminopyridine, which formed thin quadrangular plates from alcohol, m. p. 98°. Tschitschibabin *et al.* record m. p. 93—94° (Found : C, 78·1; H, 6·45; N, 15·1. Calc. for $C_{12}H_{12}N_2$: C, 78·2; H, 6·6; N, 15·2%). The *sulphate* of 1-benzyl-2-pyridoneimine formed colourless needles from dry alcohol, m. p. 261° (decomp.) (Found : C, 61·7; H, 5·7; N, 11·9; S, 6·8. $C_{12}H_{12}N_2,\frac{1}{2}H_2SO_4$ requires C, 61·75; H, 5·6; N, 12·0; S, 6·9%). The hydrochloride melted at 198—199° (Tschitschibabin *et al.* record m. p. 202—203°).

1-Dodecyl-2-pyridone.—1-Dodecyl-2-pyridoneimine sulphate (1·0 g.) was heated under reflux with potassium hydroxide (2 g.) in 50% aqueous alcohol (20 c.c.). After 5 minutes ammonia was detected in the gas swept out by a current of nitrogen. After 56 hours no more ammonia could be detected. The alcohol was evaporated, and the residue extracted with ether; the oil thus obtained (0·7 g.) was not crystalline. It gave a *picrate*, which formed yellow needles from alcohol, m. p. 96—97° (Found : C, 56·2; H, 6·5; N, 11·5. $C_{17}H_{27}ON,C_6H_3O_7N_3$ requires C, 56·3; H, 6·2; N, 11·4%).

2-Dodecylaminopyridine gave no trace of ammonia when heated for a day with aqueous alcoholic potassium hydroxide.

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