# Ionization Constants of Heterocyclic Substances. Part X.[1] Protonation of Aminopyridine-2 (and -4)-thiones

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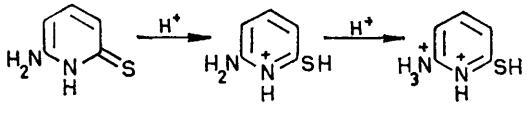
Protonation of 3- and 5-aminopyridine-2-thione and 3-aminopyridine-4-thione is shown to occur first at the primary amino-group, but 6-aminopyridine-2-thione (and probably 2-aminopyridine-4-thione) are protonated first at the sulphur atom. Ionisation constants and u.v. spectra of the mercapto-compounds and their *S*-methyl derivatives are reported and discussed.

THE protonation of aminopyridones has recently been investigated [1] by detailed study of their ionisation constants and u.v. spectra. Protonation of 3- and 5-amino-2-pyridone and 3,4-diamino-2-pyridone was shown to occur first at the 3 (or 5)-amino group, but 4- and 6-amino-2-pyridone and 2- and 3-amino-4-pyridone were found to protonate first at the oxygen atom.

In this paper, the study is extended to aminopyridine (2 and 4)-thiones.

*U.v. Spectra.*—The best evidence for the position of protonation came from an examination of the u.v. spectra (Table) of all neutral and ionic species. Monoprotonation of 6-aminopyridine-2-thione (no. 9) (1) (of



(1) (2) (3)

which the spectrum of the neutral species differs from that of 2-amino-6-methylthiopyridine) occurs on the sulphur atom (the positive charge is located on the ring nitrogen atom), with a hypsochromic shift in the long-wavelength absorption band (similar to that shown by pyridine-2-thione [2]) to give the cation (2), whose spectrum is similar to the monocation of 2-amino-6-methylthiopyridine. Further protonation of the monocation (2) gave an unstable species, but the analogous dication of 6-amino-2-methylthiopyridine (no. 10) has a spectrum similar to the monocation of 2-methylthiopyridine (because of the optical transparency of the $\overset{+}{N}H_3$ group [1,3]). The spectrum of the monocation of 6-aminopyridine-2-thione is clearly different from that of the neutral species of pyridine-2-thione indicating that the amino-group is not involved in monoprotonation. These changes are interpreted as shown in the sequence (1)—(3).

The protonation of 5-aminopyridine-2-thione (no. 11) (4) proceeds by a different route. 5-Aminopyridine-2-thione (which, like the 6-amino-isomer, has a spectrum distinct from that of the neutral species of 5-amino-2-methylthiopyridine) protonates first at the amino-group to give the monocation (5) and then at the sulphur atom

[1] Part IX, G. B. Barlin and W. Pfleiderer, *J. Chem. Soc.* (*B*), 1971, 1425.

[2] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.

[3] A. Albert, *J. Chem. Soc.*, 1960, 1020.

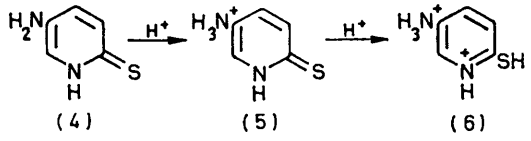
Physical properties ($pK_a$ values and spectra)

| No. | Pyridine | Ionisation (water; 20°) Charged species involved [a] | $pK_a$ | Spread (±) | Concn./M | A.w.l.[b] (nm) | Spectroscopy (water) [c] $\lambda_{max.}$ | log ε | pH [d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Unsubst. | + | 5·23 [e] | | | | | | |
| 2 | 2-$NH_2$ | 0 | | | | | 229, 287 [h] | 3·97, 3·58 | |
| | | + | 6·86 [f] | | | | 229, 300 [h] | 3·95, 3·76 | |
| | | ++ | −7·6 [g] | | | | 205, *251*, 256, *262* [i] | 3·40, *3·71*, 3·76, *3·60* | |
| 3 | 3-$NH_2$ | 0 | | | | | 231, 288 [h] | 3·91, 3·48 | |
| | | + | 5·98 [f] | | | | 250, 315 [h] | 3·88, 3·56 | |
| | | ++ | −1·5 [j] | | | | *253*, 258, *264* [i] | *3·66*, 3·69, *3·55* | |
| 4 | 4-$NH_2$ | 0 | | | | | 241, *265* [h] | 4·15, *3·38* | |
| | | + | 9·17 [f] | | | | 263 [h] | 4·22 | |
| | | ++ | −6·3 [g] | | | | 200, *250*, 256, *263* [i] | 3·46, *3·59*, 3·71, *3·54* | |
| 5 | 2=S-1-H | 0 | | | | | 273, 345 [k] | 4·03, 3·87 | |
| | | + | −1·07 [k] | | | | 238, 302 | 3·79, 3·94 | |
| | | − | 9·97 | | | | 264, 310 | 4·10, 3·67 | |
| 6 | 4=S-1-H | 0 | | | | | 231, *275*, 327 [k] | 4·02, *3·12*, 4·34 | |
| | | + | 1·43 [k] | | | | 223, 282 | 3·90, 4·23 | |
| | | − | 8·83 | | | | 222, 287 | 4·02, 4·18 | |
| 7 | 2-SMe | 0 | | | | | 247, 293 [l] | 3·94, 3·62 | |
| | | + | 3·62 [k] | | | | 250, 317 [k] | 3·86, 3·90 | |
| 8 | 4-SMe | 0 | | | | | 264 [k] | 4·10 | |
| | | + | 5·97 [k] | | | | 229, 299 | 3·94, 4·28 | |
| 9 | 6-$NH_2$-2=S-1-H | 0 | | | | | 209, 262, 356 | 4·14, 3·92, 4·14 | 5·0 |
| | | + | 0·34 | 0·05 | 0·00001 | 325 | 242, 326 | 3·86, 4·03 | −2·0 |
| | | ++ | *m* | | | | | | |
| | | − | 9·97 | 0·02 | 0·0001 | 320 | 214, 261, 319 | 4·24, 3·89, 3·95 | 12·0 |
| 10 | 2-$NH_2$-6-SMe | 0 | | | | | 210, *229*, 247, 308 | 4·19, *3·86*, 3·83, 3·90 | 7·0 |
| | | + | 4·81 | 0·03 | 0·00007 | 335 | 248, 331 | 3·85, 4·06 | 2·0 |
| | | ++ | −6·8 | 0·05 | 0·00003 | 260 | 204, 257, 332 | 3·93, 3·89, 3·86 | −9·2 |
| 11 | 5-$NH_2$-2=S-1-H | 0 | | | | | 279, 371 | 4·09, 3·83 [n,o] | 7·0 |
| | | + | 2·00 | 0·04 | 0·00003 | 340 | 280, 356 | 4·03, 3·81 [n,o] | 0·0 |
| | | ++ | −1·92 | 0·05 | 0·00001 | 280 | 244, 309 | 3·88, 3·90 [n,o] | −3·9 |
| | | − | 9·80 | 0·04 | 0·0001 | 290 | 267, 329 | 4·14, 3·56 [n,o] | 12·0 |
| 12 | 5-$NH_2$-2-SMe | 0 | | | | | 258, 317 | 4·17, 3·55 | 6·0 |
| | | + | 3·03 | 0·02 | 0·000015 | 349 | 211, 267, 348 | 3·99, 4·12, 3·42 | 1·2 |
| | | ++ | −0·58 | 0·05 | 0·000015 | 325 | 256, 328 | 3·99, 3·91 | −2·8 |
| 13 | 3-$NH_2$-2=S-1-H | 0 | | | | | 217, *248*, 272, 361 | 4·11, *3·71*, 3·83, 3·97 | 7·0 |
| | | + | 1·52 | 0·04 | 0·00002 | 275 | *220*, 273, 355 | *3·65*, 4·09, 3·81 | −0·85 |
| | | ++ | −4·64 | 0·04 | 0·00016 | 275 | 242, 302 | 3·73, 3·79 | −6·6 |
| | | − | 10·45 | 0·03 | 0·00016 | 325 | 259, 324 | 3·92, 3·88 | 13·0 |
| 14 | 3-$NH_2$-2-SMe | 0 | | | | | *243*, 308 [p] | *3·71*, 3·75 | 7·0 |
| | | + | 4·41 [p] | 0·03 | 0·0001 | 307 | 212, 257, 340 | 4·02, 3·73, 3·74 | 2·0 |
| | | ++ | −2·2 [q] | 0·04 | 0·00003 | 307 | 252, 319 | 3·70, 3·84 | −4·4 |
| 15 | 3-$NH_2$-4=S-1-H | 0 | | | | | 220, 255, 287, 340 | 4·18, 3·91, 3·39, 4·09 | 5·0 |
| | | + | 1·60 | 0·04 | 0·00003 | 353 | 233, *269*, 329 | 4·00, *3·40*, 4·13 | −0·60 |
| | | ++ | −1·67 | 0·07 | 0·00002 | 335 | 224, 283, *330* [n,o] | 3·99, 4·17, *2·69* | −4·0 |
| | | − | 9·22 | 0·05 | 0·00003 | 340 | 217, *241*, 273, 308 | 4·19, *4·03*, 3·82, 3·90 | 12·0 |
| 16 | 3-$NH_2$-4-SMe | 0 | | | | | 226, 257, 297 [p] | 4·12, 3·70, 3·62 | 9·0 |
| | | + | 6·48 [p] | 0·03 | 0·0001 | 320 | 244, 280, 319 | 4·17, 3·59, 3·88 | 4·0 |
| | | ++ | −1·88 [p] | 0·05 | 0·00008 | 305 | 231, 300 | 3·91, 4·20 | −3·9 |
| 17 | 2-$NH_2$-4=S-1-H | 0 | | | | | 223, 242, 308 | 4·27, 3·94, 4·20 | 6·0 |
| | | + | 2·93 | 0·04 | 0·0001 | 310 | 228, 266, 299 | 4·39, 4·01, 3·79 | 0·0 |
| | | ++ | −7·25 | 0·05 | 0·00002 | 295 | 227, 297 [n,o] | 3·95, 4·18 | −9·2 |
| | | − | 9·00 | 0·05 | 0·00003 | 310 | 227, 279 | 4·31, 4·11 | 11·0 |
| 18 | 2-$NH_2$-4-SMe | 0 | | | | | 227, 259, 291 | 4·40, 3·97, 3·53 | 10·0 |
| | | + | 7·00 | 0·02 | 0·00007 | 280 | 227, *232*, 280 | 4·32, *4·31*, 4·21 | 4·0 |
| | | ++ | *m* | | | | | | |
| 19 | 5-$NO_2$-2=S-1-H | 0 | | | | | *222*, *245*, 378 | *3·81*, *3·60*, 4·23 | 3·0 |
| | | + | −3·00 | 0·04 | 0·00002 | 378 | *226*, *272*, 319 | *3·76*, *3·56*, 4·18 | −5·0 |
| | | − | 6·59 | 0·03 | 0·00004 | 370 | 230, 395 | 3·93, 4·13 | 9·0 |
| 20 | 5-$NO_2$-2-SMe | 0 | | | | | 220, 339 | 3·84, 4·12 | 5·0 |
| | | + | −0·29 | 0·04 | 0·00003 | 380 | *228*, 339 | *3·73*, 4·23 | −2·5 |
| 21 | 3-$NO_2$-2=S-1-H | 0 | | | | | 260, 329, *415* | 3·79, 3·87, *3·24* | 4·0 |
| | | + | −2·49 | 0·05 | 0·0001 | 285 | 216, 284, 329 | 4·10, 3·97, 3·66 | −4·5 |
| | | − | 6·90 | 0·02 | 0·0001 | 335 | 257, 303, 408 | 4·02, 3·71, 3·09 | 10·0 |
| 22 | 3-$NO_2$-2-SMe | 0 | | | | | 232, 276, 373 | 4·13, 3·81, 3·53 | 4·0 |
| | | + | −0·64 | 0·05 | 0·00002 | 300 | 222, 298, 353 | 4·05, 4·01, 3·57 | −2·8 |
| 23 | 3-$NO_2$-4=S-1-H | 0 | | | | | 328 | 4·19 | 3·0 |
| | | + | [r] | | | | | | |
| | | − | 5·54 | 0·04 | 0·0001 | 330 | 219, 263, 288, 388 | 4·03, 3·94, 4·02, 3·20 | 9·0 |

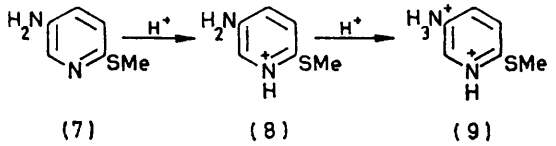
| No. | Pyridine | Ionisation (water; 20°): Charged species involved [a] | $pK_a$ | Spread (±) | Concn./M | A.w.l.[b] (nm) | Spectroscopy (water) [c]: $\lambda_{max.}$ | log ε | pH [d] |
|---|---|---|---|---|---|---|---|---|---|
| 24 | 3-$NO_2$-4-SMe | 0 | | | | | 244, *270*, 355 | 4·18, *3·81*, 3·43 | 5·0 |
| | | + | 1·98 | 0·03 | 0·00009 | 298 | 218, 251, 297, 340 | 3·77, 4·04, 3·96, 3·53 | −0·3 |
| 25 | 6-$NH_2$-2-Br | 0 | | | | | 235, 297 | 3·92, 3·74 | 5·0 |
| | | + | 2·60 | 0·02 | 0·00009 | 315 | 235, 312 | 3·83, 3·91 | 0·0 |
| 26 | 4-$NH_2$-2-Cl | 0 | | | | | (205), 245, *270* | (4·41), 4·08, *3·16* | 7·0 |
| | | + | 4·83 | 0·03 | 0·0001 | 265 | 216, *222*, 264 | 4·17, *4·07*, 4·23 | 2·0 |
| | | ++ | −7·02 | 0·06 | 0·00001 | 263 | 210, 274 | 3·72, 3·92 | −9·4 |
| 27 | 2-$NH_2$-4-Cl | 0 | | | | | 233, 292 | 3·92, 3·54 | 8·0 |
| | | + | 5·70 | 0·01 | 0·00016 | 310 | 230, *235*, *241*, 303 | 3·76, *3·74*, *3·53*, 3·76 | 3·0 |

[a] 0, Neutral species; +, cation; ++, dication; − anion. [b] Analytical wavelength for spectroscopic determinations of $pK_a$. [c] Shoulders and inflexions in italics. [d] pH Values below 0 have been obtained in solutions of sulphuric acid to which Hammett acidity functions (*cf.* M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1) have been assigned. [e] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294. [f] Ref. 4. [g] M. L. Bender and Y.-L. Chow, *J. Amer. Chem. Soc.*, 1959, **81**, 3929. [h] S. F. Mason, *J. Chem. Soc.*, 1960, 219. [i] Ref. 1. [j] Ref. 3. [k] Ref. 2. [l] Ref. 2 and personal communication. [m] Instability in solutions of strong sulphuric acid prevented the determination of the second basic $pK_a$ value. [n] Density readings decrease with time. [o] Determined within 10 min of preparation of solution. [p] Determined on the picrate and the reference cell compensated with picric acid. [q] $pK_a$ *ca.* −0·6. Apparent instability of the compound did not permit the determination of this $pK_a$ value.

to give the dication (6). Both changes produce appropriate hypsochromic shifts [1,2] in the long-wavelength absorption band. The spectrum of the monocation (5)



(4) (5) (6)



(7) (8) (9)

differs from that of the monocation of 5-amino-2-methylthiopyridine (8) but is similar to that of the neutral species of 2-mercaptopyridine; and the dication (6) resembles the dication of 5-amino-2-methylthiopyridine (9) and monocation of 2-methylthiopyridine. Monoprotonation of 5-amino-2-methylthiopyridine at the ring nitrogen atom gives a bathochromic shift [2] of the long-wavelength absorption band and the resulting spectrum is different from that of the neutral species of 2-methylthiopyridine. The interpretation of these changes is shown in the sequence (4)—(9).

3-Aminopyridine-2-thione (no. 13) like its 5-amino-isomer exhibits a similar behaviour pattern and protonation is believed to proceed analogously.

Among the pyridine-4-thiones, 3-aminopyridine-4-thiones (no. 15) is also protonated first at the primary amino-group because its behaviour mirrors that described above for 5-aminopyridine-2-thione.

The spectral evidence on the protonation of 2-aminopyridine-4-thione (no. 17) is more complex. The formation of monocation and dication is associated with hypsochromic shifts in each case and the spectrum of the dication resembles that of pyridine-4-thione monocation and suggests that a dication like (3) is formed. However the spectrum of the monocation of 2-aminopyridine-4-thione does not closely resemble that of the monocation of 2-amino-4-methylthiopyridine in which the ring nitrogen atom is protonated.[2,4,5] The strong absorption maximum at 280 nm in the spectrum of 2-amino-4-methylthiopyridine monocation probably corresponds with that at 266 nm in 2-aminopyridine-4-thione monocation (*S*-methylation of pyridine-4-thione cation is associated with a bathochromic shift of 17 nm [2]) but the latter also has a weaker absorption at 299 nm. On this evidence, 2-aminopyridine-4-thione cation appears to be composed mainly of the form analogous to (2) but this alone does not explain the weak long-wavelength absorption band.

*Discussion of Spectral Results.*—The aminopyridine-2-thiones behave as their oxygen analogues: 6-aminopyridine-2-thione is protonated at the sulphur atom to give the cation (2) which is stabilised by resonance as in the 2-aminopyridine cation; [4] and 3- and 5-aminopyridine-2-thione are protonated first at the amino-group because this is a more basic centre than the system involving the thione group and the ring nitrogen atom.

The aminopyridine-4-thiones differ from the amino-4-pyridones in their protonation. Whereas 3-amino-4-pyridone is protonated first at the oxygen atom, 3-aminopyridine-4-thione is protonated at the amino-group because the mercapto-compounds are weaker bases by *ca.* 2 pH units and this is sufficient to destabilise the form analogous to (2). 2-Amino-4-pyridone is known to monoprotonate at the oxygen atom and 2-aminopyridine-4-thione probably behaves similarly, but the presence of an additional species cannot be excluded on present evidence.

It should be emphasised that all these cationic forms are potentially tautomeric, and the above work has been directed at the determination of the predominant form.

*Ionisation Constants.*—Examination of the ionisation constants (Table) shows that the aminopyridine-2 (and

[4] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240.

[5] S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461.

-4)-thiones are much weaker bases than the aminopyridines; the lowering in basic strength ($\Delta pK_a$) varies from 6·52 units for 6-aminopyridine-2-thione to 3·93 for 2-aminopyridine-4-thione. These compounds are also from 1·26 to 2·24 units weaker than the corresponding aminopyridones.[1]

Additional evidence on the position of protonation comes from the $pK_a$ differences ($\Delta pK_a$ values) between the first and second ionisation constants. This difference is much greater for 2-aminopyridine-4-thione (10·22) than for 3-aminopyridine-4-thione (3·27) and clearly shows that in the former diprotonation involves addition of a proton to a cation like (2) whereas 3-aminopyridine-4-thione is known from spectral evidence (like its oxo-analogue) to protonate first at the amino-group to give a cation like (5).

## EXPERIMENTAL

Analyses were performed by Dr. J. E. Fildes and her staff. Solids for analyses were dried at 100° unless otherwise stated, and m.p.s were taken in Pyrex capillaries. All compounds were recrystallised to constant m.p. and were further examined for the presence of impurities by paper chromatography on Whatman No. 1 paper with (*a*) aqueous 3% ammonium chloride, or (*b*) butan-2-ol-5N-acetic acid (7 : 3) as solvent.

Ionisation constants were determined spectroscopically [6] by Mr. I. Hawkins under the supervision of Dr. D. D. Perrin. U.v. spectra were measured with a Perkin-Elmer model 450 recording spectrophotometer and $\lambda_{max.}$ and $\varepsilon$ values were checked with an Optica CF4 manual instrument (Mr. D. Light, supervised by Dr. E. Spinner).

*Bis-(6-amino-2-pyridyl) Disulphide.*—Four sealed tubes each containing 2-amino-6-bromopyridine (1·0 g),[7] ethanol (10 ml), and sodium hydrogen sulphide solution [20 ml; prepared from sodium hydroxide (16·0 g) in water (100 ml)] were heated at 175° for 16 h. The mixture was acidified with hydrochloric acid and evaporated to dryness, the residue suspended in water and adjusted to pH 7, and then hydrogen peroxide (2 ml; 30%) was added. After 10 min the suspension was evaporated to dryness. The residue was extracted with boiling ethanol and the dry product obtained was washed with water, and chromatographed in acetone over alumina. The product eluted was recrystallised from ethanol with concentration to give *bis-(6-amino-2-pyridyl) disulphide* (1·4 g), m.p. 210—212° (Found, for material dried at 109°: C, 48·4; H, 4·2; N, 22·4. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4%).

*6-Aminopyridine-2-thione.*—Bis-(6-amino-2-pyridyl) disulphide (0·10 g), palladium–charcoal (0·13 g; 10%), and ethanol (60 ml) were shaken with hydrogen at room temperature and pressure for 8 h. The catalyst was filtered off on Kieselguhr and washed with ethanol, and the combined filtrates evaporated to dryness under reduced pressure. The product was recrystallised from acetone to give *6-aminopyridine-2-thione* (0·047 g), m.p. 198° (Found, for material dried at 20° and 20 mmHg: C, 47·5; H, 4·7; N, 21·7. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2%).

*2-Amino-6-methylthiopyridine.*— 2-Amino-6-bromopyridine (0·5 g) [7] and aqueous sodium methylthiolate [prepared by saturating a solution of sodium hydroxide (1·9 g) in water (10 ml) with methanethiol] were heated in a sealed tube at 145° for 12 h. The product was extracted in chloroform, subjected to t.l.c. (alumina–chloroform), and recrystallised from cyclohexane to give *6-amino-2-methylthiopyridine* (0·20 g), m.p. 67—68° (Found, for material dried at 20° and 20 mmHg: C, 51·1; H, 5·9; N, 20·2. $C_6H_8N_2S$ requires C, 51·4; H, 5·75; N, 20·0%).

*2-Amino-6-methylsulphonylpyridine.*—A solution of potassium permanganate (0·8 g) in water (20 ml) was added over 3 min to a stirred solution of 2-amino-6-methylthiopyridine (0·5 g) in 8N-acetic acid (15 ml) at room temperature. The mixture was stirred for 5 min, cooled, sulphur dioxide was passed in to give a clear solution, and then adjusted to pH 7·4, and extracted with chloroform. The product obtained was recrystallised from benzene (carbon) to give *2-amino-6-methylsulphonylpyridine* (0·286 g) which after t.l.c. (alumina–chloroform) and recrystallisation from acetone had m.p. 168—170° (Found: C, 42·2; H, 4·8; N, 16·4; S, 19·0. $C_6H_8N_2O_2S$ requires C, 41·85; H, 4·7; N, 16·3; S, 18·6%).

*5-Aminopyridine-2-thione.*— 5-Nitropyridine-2-thione [8,9] [1·0 g; m.p. 189—190° (lit.,[9] 188—191°)] was reduced with stannous chloride in concentrated hydrochloric acid as described by Binz and Rath [10] except that the tin was removed by precipitation with hydrogen sulphide. The solution was adjusted to pH 5·4, and on concentration gave 5-aminopyridine-2-thione (0·209 g), m.p. 172—175° (from water) (lit.,[10] 170—171°) (Found, for material dried at 20° and 20 mmHg: C, 47·4; H, 5·0; N, 22·3. Calc. for $C_5H_6N_2S$: C, 47·6; H, 4·8; N, 22·2%).

*5-Amino-2-methylthiopyridine.*— 5-Nitro-2-methylthiopyridine was prepared in 92% yield from 5-nitropyrid-2-thione and methyl iodide in aqueous sodium hydroxide. It crystallised from cyclohexane and had m.p. 113—114° (lit.,[11] 115°) (Found: C, 41·8; H, 3·5; N, 16·4; S, 18·7. Calc. for $C_6H_6N_2O_2S$: C, 42·4; H, 3·6; N, 16·5; S, 18·8%). The 5-nitro-2-methylthiopyridine was reduced with stannous chloride in concentrated hydrochloric acid similar to the method described by Forrest and Walker [11] but at room temperature for 4 h. The 5-amino-2-methylthiopyridine was recrystallised from cyclohexane and had m.p. 72—73° (lit.,[11] 71—72°); *picrate*, m.p. 127—129° (from ethanol) (Found: C, 39·1; H, 3·0; N, 19·1. $C_{12}H_{11}N_5O_7S$ requires C, 39·0; H, 3·0; N, 19·0%).

*3-Nitropyridine-2-thione.*—2-Chloro-3-nitropyridine (5·0 g) and thiourea (2·5 g) in ethanol (50 ml) was refluxed for 3 h and the solvent evaporated. Water (50 ml) and sodium carbonate (1·5 g) were added to the thiouronium salt and the mixture was shaken for 15 min.

The product was dissolved by addition of a solution of sodium hydroxide (0·41 g) in water (3 ml), the solution was filtered, and the filtrate acidified to pH 1. The 3-nitropyridine-2-thione (4·5 g) was collected and recrystallised from ethyl acetate. It had m.p. 174—176° (decomp.) (lit.,[12] 174—175°) (Found: C, 38·3; H, 2·6; N, 17·7; S, 20·5. Calc. for $C_5H_4N_2O_2S$: C, 38·5; H, 2·6; N, 17·95; S, 20·5%). The *thiouronium salt* was recrystallised from

[6] A. Albert and E. P. Serjeant, ' The Determination of Ionization Constants,' 2nd edn., Chapman and Hall, London, 1971.
[7] H. J. den Hertog and J. P. Wibaut, *Rec. Trav. chim.*, 1936, **55**, 122.
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ethanol and had m.p. 197° (decomp.) (Found: C, 30·85; H, 3·1; N, 23·9; S, 13·65. $C_6H_7ClN_4O_2S$ requires C, 30·7; H, 3·0; N, 23·9; S, 13·6%).

3-*Aminopyridine*-2-*thione*.—3-Nitropyridine-2-thione (1·0 g) was reduced with stannous chloride (4·0 g) in 10N-hydrochloric acid (5 ml) at 100° for 1 h (*cf.* Takahashi and Maki [13]). The mixture was evaporated to dryness, water added, and the tin was removed with hydrogen sulphide. The aqueous solution was concentrated, adjusted to pH 6, and on standing gave yellow needles (0·33 g). This product after t.l.c. (alumina–ethyl acetate) and recrystallisation from water (charcoal) gave 3-aminopyridine-2-thione, m.p. 134—136° [*cf.* lit.,[13,14] 222° (decomp.); *ca.* 120°] (Found: C, 47·4; H, 4·8; N, 22·3; S, 25·5. Calc. for $C_5H_6N_2S$: C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

2-*Methylthio*-3-*nitropyridine*.— 3-Nitropyridine-2-thione (2·7 g) in N-sodium hydroxide (30 ml) was shaken with methyl iodide (2·5 ml) for 30 min. The product was extracted in chloroform and recrystallised from methanol to give 2-methylthio-3-nitropyridine (2·6 g), m.p. 104—106° (lit.,[15] 99—101°) (Found, for material dried at 20° and 20 mmHg: C, 42·3; H, 3·8; N, 16·1; S, 18·9. Calc. for $C_6H_6N_2O_2S$: C, 42·4; H, 3·6; N, 16·5; S, 18·8%).

3-*Amino*-2-*methylthiopyridine*.— 2-Methylthio-3-nitropyridine (1·0 g) was added slowly to a stirred solution of stannous chloride dihydrate (11·0 g) in 10N-hydrochloric acid (8·5 ml), the mixture stirred at 20° for 3 h, and evaporated to dryness. The residue was dissolved in water and the tin was removed by precipitation with hydrogen sulphide. The filtrate was made alkaline with ammonium hydroxide and extracted with chloroform to yield an oil which solidified. This product with ethanolic picric acid gave the *picrate* of 3-*amino*-2-*methylthiopyridine* (1·45 g), m.p. 172—173° (from ethanol) (Found: C, 39·0; H, 3·0; N, 18·9; S, 8·75. $C_{12}H_{11}N_5O_7S$ requires C, 39·0; H, 3·0; N, 19·0; S, 8·7%).

*Bis*-(2-*amino*-4-*pyridyl*) *Disulphide*.—A mixture of 2-amino-4-chloropyridine [16] (0·5 g) and sodium hydrogen sulphide (10 ml; 3N) in each of two tubes was heated at 195° for 24 h. This solution was acidified, evaporated to dryness, and the residue was diluted with water and adjusted to pH 6·4. Hydrogen peroxide (0·8 ml; 30%) was added, the mixture was allowed to stand for 10 min, and evaporated to dryness. The residue was extracted with boiling ethanol and the extract chromatographed in ethanol over a column of alumina (5″ diam.). The product eluted was recrystallised from a concentrated solution in boiling ethanol to give *bis*-(2-*amino*-4-*pyridyl*) *disulphide* (0·68 g), m.p. 206—208° (Found, for material dried at 107°: C, 48·0; H, 4·1; N, 22·2. $C_{10}H_{10}N_4S_2$ requires C, 48·0; H, 4·0; N, 22·4%).

2-*Aminopyridine*-4-*thione*.—(a). A mixture of bis-(2-amino-4-pyridyl) disulphide (0·10 g), palladium–charcoal (0·13 g), and ethanol (60 ml) was shaken with hydrogen at 20° for 5 h. The catalyst was filtered off on Kieselguhr and washed with ethanol, and the combined filtrates evaporated under reduced pressure. The product was recrystallised from acetone to give 2-*aminopyridine*-4-*thione* (0·048 g), m.p. 223° (decomp.) (Found, for material dried at 20° and 20 mmHg: C, 47·6; H, 5·0; N, 22·1. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2%).

(b) A mixture of 2-amino-4-methylsulphonylpyridine (0·200 g), ethanol (20 ml), and aqueous sodium hydrogen sulphide [10 ml; solution prepared from sodium hydroxide (2·8 g) in water (35 ml)] was heated in a sealed tube at 140° for 12 h. The mixture was adjusted to pH 7·2, evaporated to dryness, and the residue was extracted with acetone to give a white solid (0·176 g). This product (0·020 g) with aqueous picric acid gave a yellow precipitate (0·028 g) which crystallised from water to give the *picrate* of 2-aminopyridine-4-thione decomposing above 185° (Found: C, 37·8; H, 2·8; N, 19·8. $C_{11}H_9N_5O_7S$ requires C, 37·2; H, 2·55; N, 19·7%).

2-*Amino*-4-*methylthiopyridine*.— 2-Amino-4-chloropyridine [1] (0·2 g) and a solution of sodium methylthiolate [prepared by passing methylthiol into a solution of sodium hydroxide (1·9 g) in water (5 ml) and ethanol (20 ml) was heated in a sealed tube at 140° for 12 h. The mixture was extracted with chloroform and the product was chromatographed in benzene over alumina (6″ diam) and recrystallised from cyclohexane to give 2-*amino*-4-*methylthiopyridine* (0·147 g), m.p. 122—123° (Found: C, 51·6; H, 5·7; N, 20·05. $C_6H_8N_2S$ requires C, 51·4; H, 5·75; N, 20·0%).

2-*Amino*-4-*methylsulphonylpyridine*.—Potassium permanganate (0·16 g) in water (4 ml) was added over 5 min to a stirred solution of 2-amino-4-methylthiopyridine (0·10 g) in 8N-acetic acid (6 ml) at 20°. This mixture was cooled in ice, sulphur dioxide was passed in to clarify, adjusted to pH 7·2, and extracted with chloroform. The white solid was recrystallised from benzene to give 2-*amino*-4-*methylsulphonylpyridine* (0·080 g), m.p. 174° (Found: C, 41·75; H, 5·0; N, 16·2. $C_6H_8N_2O_2S$ requires C, 41·85; H, 4·7; N, 16·3%).

3-*Aminopyridine*-4-*thione*.— 3-Nitropyridine-4-thione [17] was reduced with stannous chloride in hydrochloric acid as described by Takahashi *et al.*[18] The 3-aminopyridine-4-thione was recrystallised from water and had m.p. 231—214·5° [lit.,[18] 213° (decomp.)].

4-*Methylthio*-3-*nitropyridine*.— 3-Nitropyridine-4-thione (1·0 g), methyl iodide (0·85 ml), and N-sodium hydroxide (9·0 ml) were shaken for 30 min at 20°, and extracted with chloroform. The product obtained was chromatographed in chloroform over alumina and recrystallised from benzene to give 4-methylthio-3-nitropyridine (0·8 g), m.p. 134—135° (lit.,[19] 133—134°).

3-*Amino*-4-*methylthiopyridine*.— 4-Methylthio-3-nitropyridine was reduced with stannous chloride and hydrochloric acid as described by Takahashi *et al.*[19] The tin was precipitated with hydrogen sulphide, the solution made alkaline, and extracted with chloroform. The product with ethanolic picric acid gave the picrate of 3-amino-4-methylthiopyridine, m.p. 173—174° (lit.,[19] 165—166°) (Found: C, 39·4; H, 3·1; N, 18·6. Calc. for $C_{12}H_{11}N_5O_7S$: C, 39·0; H, 3·0; N, 18·9%).

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