

721. *Tautomeric Pyridines. Part I. Pyrid-2- and -4-thione.*

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Measurement of the basicities and ultraviolet spectra of 2- and 4-mercaptopyridine and their *N*- and *S*-alkyl derivatives shows that they exist in solution predominantly in the thione form.

2- and 4-AMINOPYRIDINE exist in solution predominantly as amino-compounds<sup>1</sup> whereas 2- and 4-hydroxypyridine exist as pyridones.<sup>2</sup> Published information on the mercaptopyridines is less conclusive<sup>3-5</sup> although X-ray measurements suggest that 2-mercaptopyridine exists in the crystalline state as pyrid-2-thione.<sup>6</sup> We have now investigated the tautomeric equilibria between the thiol and thione forms of 2- and 4-mercaptopyridine by measuring the  $pK_a$  values and ultraviolet spectra of these two compounds and of their *N*- and *S*-alkyl derivatives. The results are shown in Tables 1 and 2.

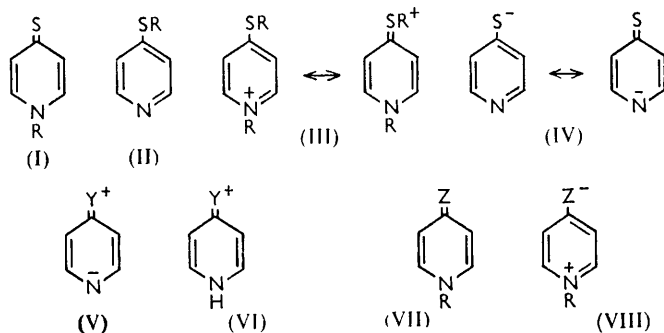
TABLE I.  $pK_a$  Values.

No.	Compound	$pK_a^a$	$\sigma^b$	Concn. (10 <sup>4</sup> M)	Wave-length <sup>c</sup> (m $\mu$ )	$pK_a$ of corresp. O-cpd.	$pK_a$ of corresp. N-cpd. <sup>d</sup>	$pK_a$ differences O-S	$pK_a$ differences N-O
1	2-Benzylthiopyridine ...	3.23 <sup>e</sup>	0.04	0.66	315	3.28 <sup>g</sup>	6.86 <sup>h</sup>	0.05	3.58
2	1-Methylpyrid-2-thione	-1.62	0.03	1.04	338	0.32	12.2	1.94	11.9
3	} Pyrid-2-thione .....	-1.38	0.01	0.79	340	0.75	—	2.13	—
4		9.81	0.03	119	—	11.62	—	1.81	—
5	4-Benzylthiopyridine ...	5.41 <sup>f</sup>	0.06	0.54	300	6.62 <sup>g</sup>	9.17 <sup>h</sup>	1.21	2.55
6	1-Methylpyrid-4-thione	1.43	0.01	0.86	329	3.33	12.5	1.90	9.2
7	} Pyrid-4-thione .....	1.48	0.03	0.51	324	3.27	—	1.79	—
8		8.65	0.03	177	—	11.09	—	2.34	—

<sup>a</sup> Arithmetical means of 6 values. Nos. 4 and 8 refer to proton loss, others to proton addition. Apparent values are given; thermodynamic  $pK_a$  may be calculated by using the concentration given (cf. ref. 2). <sup>b</sup> Standard deviation. <sup>c</sup> An entry in this column signifies that the determination was spectrometric (otherwise potentiometric). Measurements were in phosphate buffers, or sulphuric acid of known  $H_0$ , containing up to 2% ethanol. <sup>d</sup> From refs. 1 and 2. <sup>e</sup> Potentiometric titration in ethanol-water (1:1 v/v) gave  $pK_a$   $1.69 \pm 0.02$  ( $5.49 \times 10^{-2}$ M). <sup>f</sup> Potentiometric titration in ethanol-water (1:1 v/v) gave  $pK_a$   $4.63 \pm 0.03$  ( $1.80 \times 10^{-2}$ M). <sup>g</sup> These values refer to 2- and 4-methoxypyridine. <sup>h</sup> 2- and 4-Aminopyridine.

<sup>1</sup> Angyal and Angyal, *J.*, 1952, 1461.<sup>2</sup> Albert and Phillips, *J.*, 1956, 1294; Mason, *J.*, 1958, 674.<sup>3</sup> Ross, *J.*, 1951, 1374.<sup>4</sup> Renault, *Ann. Chim. (France)*, 1955, 10, 135; *Bull. Soc. chim. France*, 1953, 20, 1001.<sup>5</sup> Hannen, Lieblich, and Renfrew, *J. Amer. Chem. Soc.*, 1949, 71, 3733.<sup>6</sup> Penfold, *Acta Cryst.*, 1953, 6, 707.

On the reasonable assumption that the basicities of the individual tautomers (*e.g.*, I and II; R = H) are not greatly affected by *N*- or *S*-alkylation, the  $pK_a$  values in Table 1 indicate that 2- and 4-mercaptopyridine exist essentially as pyrid-2- and -4-thione; the thione forms are preferred by factors of *ca.*  $10^{4.5}$  and *ca.*  $10^4$  in the 2- and the 4-series



respectively. In agreement with this view, 2- and 4-mercaptopyridine as neutral species have absorption spectra similar to those of their *N*- and quite different from those of their *S*-alkyl derivatives (Table 2). In each series, all the cations show similar ultraviolet spectra since both structures (*e.g.*, I and II) give similar mesomeric cations (*e.g.*, III); *S*-alkylation causes a bathochromic shift of *ca.* 15  $m\mu$  but *N*-alkylation has little effect.

TABLE 2. Ultraviolet spectra.

No.	Ions <sup>a</sup>							
	$\lambda_{\min.}$		$\lambda_{\max.}$		$\lambda_{\min.}$		$\lambda_{\max.}$	
	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$
1	234	5.6	250	8.3	276	2.7	315	9.3
2	220	5.0	239	8.2	258	1.8	299	12.0
3	216	2.9	238	6.9	258	1.3	300	9.8
4								
5	—	—	226*	10.3	246	1.9	298	20.5
6	206	4.0	222	9.9	240	1.4	286	21.6
7	205	3.1	222	11.3	238	0.6	282	25.1
8								
Neutral molecules <sup>b</sup>								
	$\lambda_{\min.}$		$\lambda_{\max.}$		$\lambda_{\min.}$		$\lambda_{\max.}$	
	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$	$m\mu$	$10^{-3}\epsilon$
1	230	6.8	248	8.3	269	3.3	290	5.5
2	242	2.4	272	10.6	296	3.0	338	8.3
3	241	3.2	271	12.0	296	2.8	340	8.7
6								
6	—	—	231	9.6	248	1.3	329	25.4
7	—	—	230	9.9	247	1.5	324	23.6
8								

Solutions were aqueous, and phosphate buffers were used.

\* Indicates inflection.

<sup>a</sup> Nos. 1 and 5 in *N*-sulphuric acid; Nos. 2, 3, 6, 7 in 20*N*-sulphuric acid; nos. 4 and 8 in 0.1*N*-sodium hydroxide. <sup>b</sup> Nos. 1, 2, and 5 at pH 9.7; no. 3 at pH 3.1; no. 6 in *N*-sodium hydroxide; no. 7 at pH 4.8.

The anions (*e.g.*, IV) have spectra analogous to those of the corresponding cations (*e.g.*, III); presumably they have similar  $\pi$ -electron distributions. It is of interest that Hannen, Lieblich, and Renfrew<sup>5</sup> reported that the spectrum of 2-mercaptoquinoline showed a marked hypsochromic shift on passing from neutral to either acidic or basic solution; by analogy with our results this indicates that it too exists predominantly in the thione form.

Further support for our finding that 2- and 4-mercaptopyridine are properly described

as pyrid-2- and -4-thione is derived from infrared spectroscopic measurements. Of all the compounds listed in Table 2, only 2- and 4-benzylthiopyridine showed bands corresponding both to the substituent group<sup>7</sup> and to the 2- and the 4-substituted pyridine nucleus.<sup>8</sup> In their structure, therefore, the pyridine derivatives are analogous to the derivatives of pyrimidine,<sup>9</sup> purine,<sup>10</sup> and acridine<sup>11</sup> bearing a mercapto-group  $\alpha$  or  $\gamma$  with respect to a ring nitrogen, which all exist mainly in the thione form.

The position of equilibrium in pyridine derivatives bearing in positions 2 or 4 a group capable of taking part in tautomeric change is determined by the relative basicities of the two forms. For comparison, Table I also gives  $pK_a$  values for corresponding oxygen and nitrogen analogues. In compounds in the pyridine form, 2- and 4-substituents affect the basicity in two ways: (a) mesomeric electron-release stabilises the conjugate acid (as VI) more than the base (as V), and (b) inductive electron-withdrawal destabilises the conjugate acid more than the base; this is especially important in the 2-series. The observed order of basicities in the 4-series ( $Y = O^- > NR_2 > S^- > OR > H > SR$ ) and in the 2-series ( $Y = O^- > S^- > NR_2 > H > OR \sim SR$ ) is thus explained. For compounds of the pyridone type (e.g., VIII) mesomerism in the conjugate acids (as III) will be favoured in the order  $Z = NR > O > S$  as above, but mesomerism in the free bases (VII—VIII) will be favoured in the order  $Z = NR \ll O \sim S$  because oxygen is more electronegative, and sulphur less willing to form  $\pi$ -bonds, than nitrogen. This explains the observed order of basicities of compounds (VIII),  $Z = NR \gg O > S$ . It can now be understood that the position of equilibrium is similar in the hydroxy- and mercapto-pyridines, but different in the amino-compounds.

#### EXPERIMENTAL

Ultraviolet spectra were obtained by using a Cary model 14M-50 recording spectrophotometer, and infrared spectra by using a Perkin-Elmer model 21 instrument.

Pyrid-4-thione prepared<sup>12</sup> from pyrid-4-one had m. p. 184—186° (lit.,<sup>12</sup> m. p. 186°).

*1-Methylpyrid-4-thione*.—Pyrid-4-one<sup>12</sup> (1.8 g.), potassium hydroxide (0.6 g.), and methyl iodide (3.6 g.), when refluxed for 3 hr. and then evaporated, gave 1-methylpyrid-4-one (1.0 g., 50%) on chloroform-extraction of the residue. The crude product (1.0 g.) [m. p. 89—90° (lit.,<sup>13</sup> m. p. 92—94°)] was heated with pulverised phosphorus pentasulphide (2.0 g.) for 5 hr. at 130°. The product was dissolved in hot aqueous 3N-sodium hydroxide (ca. 20 c.c.) and extracted with chloroform. Evaporation of the extracts gave the *thione* (0.3 g., 26%), yellow plates (from ethanol), m. p. 161—163° (Found: C, 57.7; H, 5.7.  $C_6H_7NS$  requires C, 57.6; H, 5.6%).

*4-Benzylthiopyridine*.—4-Pyridylpyridinium chloride hydrochloride<sup>14</sup> (10 g.) under pyridine (10 c.c.) was saturated with hydrogen sulphide, benzyl chloride (6.6 g.) was added, and the whole heated for 4 hr. at 125°. Volatile material was removed at 100°/20 mm. and the residue basified with aqueous sodium carbonate and extracted with ether. From the extracts, the *pyridine* (4 g., 45%) was obtained in plates (from ether), m. p. 61—62° (Found: C, 71.4; H, 5.5.  $C_{12}H_{11}NS$  requires C, 71.6; H, 5.5%). Infrared bands due to the 2-pyridine nucleus<sup>8</sup> were: 3000 (50), 1584 (195), 1560 (75), (—), 1418 (200), 1280 (25), 1147 (40), {1123 (220) and 1088 (15)}, 1043 (30), 986 (30) [figures in parentheses denote  $\epsilon_A$  values (cf. ref. 8)].

*Pyrid-2-thione*.—2-Chloropyridine (11.3 g.), thiourea (7.6 g.), and ethanol (30 c.c.) were refluxed for 1 hr., then mixed with aqueous ammonia ( $d$  0.88; 15 c.c.) and kept for 5 days at 20°. Volatile material was removed at 100°/15 mm; the *thione* (8.0 g., 72%) (from benzene) had m. p. 124—126° (lit.,<sup>15</sup> m. p. 125°).

<sup>7</sup> Katritzky and Lagowski, *J.*, in the press.

<sup>8</sup> Katritzky and Gardner, *J.*, 1958, 2198; Katritzky and Hands, *J.*, 1958, 2202.

<sup>9</sup> Marshall and Walker, *J.*, 1951, 1004; Boarland and McOmie, *J.*, 1952, 3716.

<sup>10</sup> Brown and Mason, *J.*, 1957, 682.

<sup>11</sup> Acheson, Burstall, Jefford, and Sanson, *J.*, 1954, 3742.

<sup>12</sup> King and Ware, *J.*, 1939, 873.

<sup>13</sup> Tschitschibabin and Ossetrowa, *Ber.*, 1925, 58, 1708.

<sup>14</sup> Bowden and Green, *J.*, 1954, 1795.

<sup>15</sup> Phillips and Shapiro, *J.*, 1942, 584.

1-Methylpyrid-2-thione, prepared <sup>16</sup> from 1-methylpyrid-2-one,<sup>17</sup> had m. p. 88—90° (lit.,<sup>16</sup> m. p. 89—90°).

2-Benzylthiopyridine.—Pyrid-2-thione (0.55 g.), benzyl chloride (0.63 g.), and acetone (5 c.c.) were kept for 15 hr. at room temperature. Precipitated material was taken up in 30% aqueous sodium hydroxide (5 c.c.) and extracted with chloroform. From the extracts, the pyridine (0.78 g., 75%), b. p. 92—94°/0.1 mm., was obtained; it solidified to needles, m. p. 28.5—29.5° (Found: N, 7.1. C<sub>12</sub>H<sub>11</sub>NS requires N, 7.0%) (lit.,<sup>4</sup> oil, b. p. 153—154°/4 mm.). Infrared bands due to the 4-pyridine nucleus <sup>8</sup> were: 2950 (75), 1580 (300), 1540 (20), 1484 (90), 1411 (90), 1066 (35), 984 (20).

We thank Sir Alexander Todd, F.R.S., for his interest in this work. Part of this work was carried out during the tenure (by A. R. K.) of an I.C.I. Fellowship.

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[Received, March 24th, 1958.]

<sup>16</sup> Gutbier, *Ber.*, 1900, **33**, 3359.

<sup>17</sup> Prill and McElvain, *Org. Synth.*, 1946, Coll. Vol. 2, p. 419.

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