479. *Ionization Constants of Heterocyclic Substances. Part III.*[1] *Mercapto-derivatives of Pyridine, Quinoline, and* iso*Quinoline.*

By ADRIEN ALBERT and G. B. BARLIN.

Ionization constants are reported for eleven mercapto-derivatives of nitrogenous six-membered heterocyclic compounds and for their *N*- and *S*-methyl derivatives. The significance of the values is discussed. Ultraviolet spectra of all ionic species are recorded.

Spectroscopic and potentiometric evidence shows that equilibrium favours tautomers with a hydrogen atom on nitrogen at the expense of tautomers with hydrogen on sulphur. Unexpectedly, this proved to be so even for substances such as 3-mercaptopyridine which have no form with doubly bound sulphur. Ebert's equation is used to calculate the ratio of these tautomers at equilibrium in aqueous solution.

THE strengths of many heterocyclic bases (mainly 6-membered rings) and their amino-[2] and hydroxy-derivatives[1] have been discussed, but very little has been recorded about the acidic and basic strengths of their mercapto-derivatives. Likewise the ratio of tautomers at equilibrium in aqueous solution has been determined for the amino-[3] and hydroxy-derivatives,[1] but no ratios were known for mercapto-derivatives until, early

[1] Part II, Albert and Phillips, *J.*, 1956, 1294.
[2] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[3] Angyal and Angyal, *J.*, 1952, 1461.

in 1958, we published ratios for 2- and 4-mercapto-pyridine and -quinoline [4] and Jones and Katritzky published ratios for 2- and 4-mercaptopyridine.[5] The present paper describes similar determinations for several other mercapto-derivatives. Such ratios have biological interest as a first step towards investigating tautomerism in the more complex mercapto-heterocycles obtained from natural sources, *e.g.*, ergothioneine (from human blood) and the goitrogenic mercapto-oxazolines (from cabbage and other plant sources). Other mercapto-heterocycles, notably thiouracils and thioimidazoles, are much used in treating thyrotoxicosis.

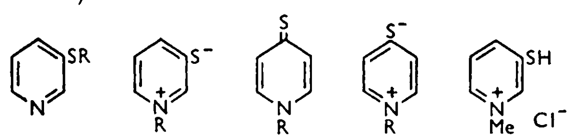
Throughout this paper, such names as " 4-mercaptopyridine " will be used in their traditional sense, without implying that the tautomer with an -SH group is necessarily present in more than a trace at equilibrium.

Spectra.—Ultraviolet spectra gave the clearest demonstration that tautomeric forms with the mobile hydrogen atom on nitrogen were favoured over those with hydrogen on sulphur. Determination of ionization constants enabled conditions to be chosen so that only one ionic species was present when each spectrum was measured. (The ratios of tautomers were more accurately ascertained from ionization constants than from spectra.)

The value of ultraviolet spectra in studies of tautomerism lies in the virtual optical transparency of a methyl group when attached to carbon, oxygen, nitrogen, or sulphur [for an example involving sulphur, compare thiophenol and thioanisole ($\lambda_{max.}$ 275 * and 280 mμ,* respectively].

Fig. 1 shows that the spectrum of 3-mercaptopyridine closely resembles that of its *N*-methyl derivative [3-mercaptopyridine methochloride (V)] adjusted in solution to pH 7 (see p*K* in Table 2) where it had lost the elements of hydrogen chloride and was entirely the zwitterion (II; R = Me). Fig. 1 also shows that the spectra of 3-mercaptopyridine and its *S*-methyl derivative (I; R = Me) are different. Hence it is evident that the neutral molecule of 3-mercaptopyridine exists, in aqueous solution, in an equilibrium that greatly favours (II; R = H) at the expense of (I; R = H). This may be contrasted with the equilibrium for 3-hydroxypyridine which favours equally the forms with hydrogen on nitrogen and on oxygen [1]

Because 2- and 4-mercaptopyridine can assume a further tautomeric form, a thioamide or vinylogous thioamide form, *e.g.*, (III; R = H), the spectrum of 4-mercaptopyridine is compared in Fig. 2 with those of its *N*- and *S*-derivatives. It is clear that here equilibrium also favours the form with the hydrogen atom on nitrogen, *i.e.*, a resonance hybrid of (III) and (IV) (R = H).



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

The spectra of the various pyridines, quinolines, and *iso*quinolines studied (Table 1) show that the spectra of all the mercapto-compounds resemble those of the *N*-methyl rather than of the *S*-methyl derivatives. Even 3-mercapto*iso*quinoline follows this rule, although the 3-position in *iso*quinoline has been considered anomalous.[7]

Table 1 and Fig. 3 reveal that the peak of longest wavelength recedes to shorter wavelengths as one passes from the neutral molecule to the anion, and still more on passing to

* Shoulders; our results refer to water solutions. Other authors found very similar results with other solvents (see ref. 6).

[4] Albert and Barlin, " Current Trends in Heterocyclic Chemistry," Butterworths, London, 1958, p. 51.
[5] Jones and Katritzky, *J.*, 1958, 3610.
[6] Robertson and Matsen, *J. Amer. Chem. Soc.*, 1950, **72**, 5248; Price and Hydock, *ibid.*, 1952, **74**, 1943.
[7] Mills and Smith, *J.*, 1922, **121**, 2724.

the cation. This is parallel to what has been found[8] for the corresponding hydroxy-analogues when " neutral molecule " refers to the oxygen analogues of (III) and (IV). But in the oxygen series, true enols are also known. These are the oxygen analogues of (I; R = H) and have $\lambda_{max.}$ still less than those of the cations, but equal to those of the *O*-methyl derivatives.[8] Table 1 reveals that no " mercapto-compound " has an absorption maximum indicative of a true thiol group, *i.e.*, none accords with that of the corresponding *S*-methyl compound. Thus forms carrying the hydrogen atom on nitrogen are preferred

FIG. 1. FIG. 2.

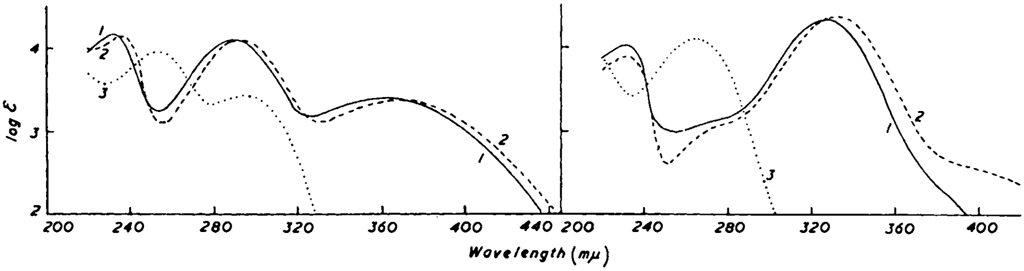
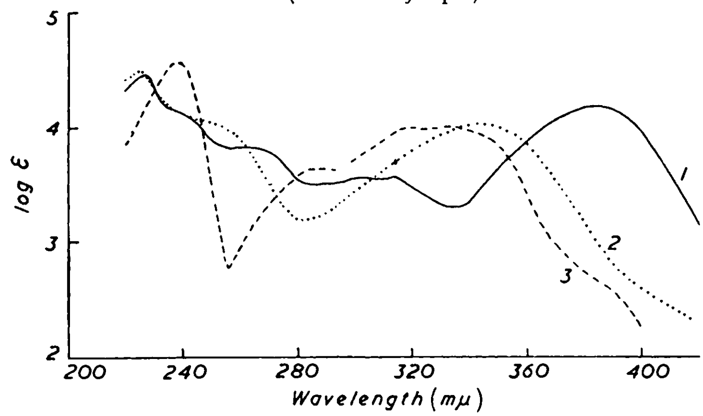


FIG. 1. *Ultraviolet spectra of* (1) 3-*mercaptopyridine and its* (2) N-*methyl and* (3) S-*methyl derivatives. All are present exclusively as neutral molecules in water at* 20°.

FIG. 2. *Ultraviolet spectra of* (1) 4-*mercaptopyridine and its* (2) N-*methyl and* (3) S-*methyl derivatives. All are present exclusively as neutral molecules in water at* 20°.

FIG. 3. *Ultraviolet spectra of* 2-*mercaptoquinoline as* (1) *molecule,* (2) *anion, and* (3) *cation, in water at* 20° (*see Table* 1 *for* pH).



in mercapto- more than in hydroxy-*N*-heterocycles (six-membered rings). The quantitative aspects of this observation will be dealt with below, under tautomeric ratios.

For completeness, it is noted that the spectrum of 5-mercaptoacridine (analogously orientated to 4-mercaptopyridine) resembles that of its *N*- and not that of its *S*-methyl derivative.[9] The considerable difference in the spectra of 2-mercapto-4-methylquinoline and its *S*-methyl derivative has also been commented on.[10a]

The spectra of the cations of the mercapto-compounds in Table 1 resemble those of the cations of the *N*- more than those of the *S*-derivatives. But the distinction is not so great as with the neutral molecules.

pK_a' *Values, representing Protons gained by the Neutral Molecule.*—The ionization

[8] Mason, *J.*, 1959, 1253.
[9] Acheson, Burstall, Jefford, and Sansom, *J.*, 1954, 3742.
[10] (*a*) Morton and Stubbs, *J.*, 1939, 1321; (*b*) Campaigne, Cline, and Kaslow, *J. Org. Chem.*, 1950, **15**, 600; Gleu and Schaarschmidt, *Ber.*, 1939, **72**, 1246.

TABLE 1. *Ultraviolet spectra of substances (in water at 20°). Values in italics refer to shoulders or inflexions.*

		Neutral molecule or zwitterion			Proton gained (cation)			Proton lost (anion)		
No.	Substance	$\lambda_{max.}$ (mμ)	log ε	pH	$\lambda_{max.}$ (mμ)	log ε	pH [a]	$\lambda_{max.}$ (mμ)	log ε	pH
	Pyridines									
2	2-Mercapto	273, 345	4·03, 3·87	4·7	238, 302	3·79, 3·94	−3·6	264, 310	4·10, 3·67	12·0
3	*N*-methyl	274, 341	4·01, 3·91	7·0	240, 301	3·76, 3·96	−3·6			
4	*S*-methyl	247, 393	3·94, 3·62	6·0	250, 317	3·86, 3·90	1·0			
5	3-Mercapto	232, 290, 362	4·15, 4·09, 3·37	5·1	221, 255, 310	4·06, 3·89, 3·50	0	219, 269, 313	3·99, 4·13, 3·41	10·0
6	*N*-methyl	236, 294, 369	4·12, 4·07, 3·34	7·0	224, 258, 314	4·07, 3·86, 3·45	0			
7	*S*-methyl	253, 294	3·94, 3·40	9·0	228, 268, 328	4·01, 3·94, 3·45	1·0			
8	4-Mercapto	231, *275*, 327	4·02, *3·12*, 4·34	4·7	223, 282	3·90, 4·23	−1·68	222, 287	4·04, 4·18	12·0
9	*N*-methyl	231, *275*, 333	3·89, *3·05*, 4·37	7·0	224, 286	3·90, 4·29	−0·90			
10	*S*-methyl	264	4·10	9·0	229, 299	3·94, 4·28	2·0			
	Quinolines									
12	2-Mercapto	275, 376	4·35, 4·14	7·0	*240*, 261, 342	*4·14*, 4·35, 4·11	−2·5	266, *288*, 354	4·37, *4·03*, 3·94	12·0
13	*N*-methyl	274, 371	4·38, 4·14	7·0	237, 260, 338 + 345	4·06, 4·39, 4·13 + 4·13	−4·0			
14	*S*-methyl	257, 338	4·36, 3·82	7·0	240, 266, 353	4·07, 4·20, 4·15	0			
15	3-Mercapto	224, 264, 289, *308*, 416	4·40, 4·33, 4·09, *3·89*, 3·54	4·21	241, *265*, 325, 357	4·56, *3·94*, 3·52, 3·62	−1·68	263, 293, 363	4·34, 4·02, 3·66	9·44
16	*N*-methyl	224, 242, 267, 292, *311*, 426	4·35, 4·20, 4·26, 4·03, *3·91*, 3·50	9·93	244, *270*, 324, 358	4·39, *3·80*, 3·61, 3·56	−0·13			
17	*S*-methyl	231, 258, *290*, 342	4·32, 4·28, *3·72*, 3·62	9·5	244 + 253, *280*, 326, 382	4·35 + 4·37, *3·94*, 3·30, 3·66	0			
18	4-Mercapto	227, *240*, 264, 303 + 314, 384	4·48, *4·13*, 3·84, 3·57 + 3·56, 4·19	6·4	239, 286, 320 + 333	4·57, 3·63, 4·00 + 4·00	−1·20	225, *250*, 344	4·49, *4·05*, 4·04	13·0
19	*N*-methyl	227, *240*, 268, 305 + 317, 392	4·44, *4·07*, 3·85, 3·36 + 3·37, 4·29	7·0	240, *289*, 320 + 334	4·36, 3·63, 4·00 + 3·99	−2·01			
20	*S*-methyl	227, 312	4·53, 4·04	9·4	238, *250*, 347	4·52, *3·96*, 4·17	1·0			
21	5-Mercapto	*254*, 278, 322, 468	*4·07*, 4·27, 3·23, 3·38	5·08	*238*, 259, *313*, 323, 373	*4·02*, 4·34, *3·44*, 3·49, 3·39	−1·68	260, 374	4·34, 3·65	13·0
22	*N*-methyl	*258*, 281, 320, 466	*4·11*, 4·23, 3·35, 3·53	7·0	*240*, 260, *312*, 323, 375	*3·97*, 4·23, *3·53*, 3·60, 3·47	1·0			
23	*S*-methyl	249, *314*, 320 + 332	4·24, *3·52*, 3·58 + 3·56	9·5	*244*, 266, 316, 401	*3·96*, 4·29, 3·03, 3·41	0			
24	6-Mercapto	<220, 245, 288, *322*, 430	>4·30, 4·18, 4·26, *3·58*, 3·32	5·22	261, 324, 356	4·50, 3·56, 3·57	−1·68	*232*, 266, 299, 368	*4·00*, 4·52, 3·85, 3·65	13·0
25	*N*-methyl	218, 293, *330*, 445	4·43, 4·55, *3·64*, 3·58	9·0	264, 327, 365	4·54, 3·61, 3·54	1·0			
26	*S*-methyl	254, *288*, 343	4·46, *3·66*, 3·57	9·4	272, 382	4·47, 3·61	0			
27	8-Mercapto	254, 280, 323, 461	4·17, 4·28, 2·99, 3·24	5·0	242, *256*, *313*, 320, *340*	4·30, *4·08*, *3·67*, 3·72, *3·33*	−2·01	263, 375	4·28, 3·55	12·0
28	*S*-methyl	251, 337	4·34, 3·62	9·5	242, *259*, *312*, 320, *350*	4·21, *4·13*, *3·61*, 3·65, *3·16*	0			
	iso*Quinolines*									
30	1-Mercapto	219, *232*, 261, *286*, 295, 371	4·59, *4·01*, 3·68, *3·85*, 3·90, 4·04	5·0	229, 272, *284*, 346, 357	4·51, 4·01, *3·81*, 3·89, 3·88	−4·20	*233*, *250*, 313, 352	*3·99*, *3·91*, 3·77, 3·89	13·0
31	*N*-methyl	222, 263, 295, 366	4·63, 3·76, 3·85, 4·02	7·0	233, 271, *288*, 347, 360	4·53, 3·94, *3·66*, 3·80, 3·82	−4·20			
32	*S*-methyl	*245*, 286 + 296, 330, *340*	*3·82*, 3·75 + 3·79, 3·79, *3·76*	9·0	225 + 230, *250*, 278 + 288; 348 + 361	4·46 + 4·44, *3·81*, 4·02 + 3·94, 3·98 + 3·98	−3·60			
33	3-Mercapto	260, 313, 415	4·44, 4·24, 3·47	4·0	245, *284*, 356	4·42, *3·58*, 3·61	−4·20	252, 303, 366	4·43, 4·27, 3·22	12·0
34	*S*-methyl	246, *269*, 280 + 290, 343	4·34, *3·89*, 3·97 + 3·91, 3·25	9·4	233, 252, 285, 373	4·19, 4·42, 3·84, 3·53	1·0			

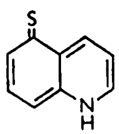
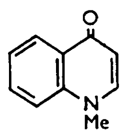
[a] pH values below 0 have been obtained in solutions of sulphuric acid to which Hammett's acidity function had been assigned.

constants, expressed as pK values, are given in Table 2. Usually, the substances in the form of neutral molecules, *e.g.*, (III; R = H or Me), were submitted to conditions of increasing acidity. Sometimes it was more convenient to submit a methochloride, *e.g.*, (V), to decreasing acidity. Potentiometric or spectrometric methods were used as was most appropriate for each case (see Part II [1] for details, also for the effects of dilution). No pK_a' of any mercapto-pyridine, -quinoline, or -*iso*quinoline had been recorded up to 1958.

Low pK_a' values in Table 2 correspond to weak bases. It is evident that the values for the mercapto-compounds are much nearer to those for the *N*-methyl than for the *S*-methyl derivatives, substantiating what has been shown above by ultraviolet spectra, *i.e.*, that equilibrium in the mercapto-compounds favours forms which have the hydrogen atom on the nitrogen.

Comparison with Part II shows that these mercapto-compounds are from 0·7 to 3·0 pK units weaker as bases than their hydroxy-analogues. The two series preserve much the same order of basic strength, the 1-*iso*quinoline derivative being the weakest base in each, followed by the 2-quinoline and 2-pyridine derivatives. The *N*-methyl derivatives of the mercapto- and the hydroxy-series also differ within similar limits. On the other hand, the *S*- and *O*-methyl derivatives differ by very little. The last observation accords with knowledge that the inductive effect of methylthio- and methoxy-groups is similar in sign and magnitude in the benzene series, *e.g.*, *m*-methylthio- and *m*-methoxy-aniline (pK 4·05 and 4·20 respectively; cf. aniline 4·62 [11]). No figures are available for comparison of the inductive effects of a mercapto- and a hydroxy-group on an aromatic base.

pK *Values, representing Protons lost by the Neutral Molecule.*—The strengths, as acids, of the mercapto-compounds are given in Table 2 (the lower the value, the stronger the acid). 6-Mercaptoquinoline (No. 24) is the example in which the mercapto-group is in a position where it is least disturbed by inductive or mesomeric effects. Only the 3-, 6-, and 8-isomers can, from considerations of valency, have no thioamide component, of the type (VI). The acidic (and basic) pK's of 5-mercaptoquinoline resemble those of the 6-isomer closely enough to suggest that the thioamide form (VI) does not stabilize the 5-isomer to any extent, although valency would permit it. This, is in keeping with all that is known of the feeble energy available for transannular tautomerism, especially when an *ortho*-quinonoid form would be involved.[12,13] In contrast, the weakness as acids (and even more so as bases) of the 2- and the 4-mercapto-derivatives of quinoline and pyridine testify to a free participation of thioamide form of the type (III; R = H) (see Part II for a discussion of the electronic basis of this weakening effect in the oxygen analogues). As with 8-aminoquinoline [2] and 8-hydroxyquinoline,[1] 8-mercaptoquinoline has abnormal pK values because of internal hydrogen-bonding.

(VI)   (VII)

Comparison with Part II shows that the mercapto-derivatives in Table 2 are, as acids, 1·5—2·4 pK units stronger than their hydroxy-analogues. The pK of thiophenol, not previously determined in water, was found to be 6·7 ± 0·1, which is to be compared with that of phenol (9·98).[11]

Ratios of Tautomers at Equilibrium.—Ebert [14] determined the ratio of tautomers in a series of zwitterionic molecules by assuming that the basic pK_a of each tautomeric form is approximately the same as that of the analogue where the mobile hydrogen is replaced by a methyl group. This principle has been usefully applied to various heterocyclic

[11] Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058.
[12] Albert, " An Introduction to Heterocyclic Chemistry," London, Athlone Press, 1959.
[13] Brown and Mason, *J.*, 1956, 3443; Mason, *J.*, 1957, 5010.
[14] Ebert, *Z. phys. Chem.*, 1926, **121**, 385.

series.[15] This assumption, that *O*-methylation would alter the inductive effect of a hydroxy-group by very little and hence would not affect the ionization of a basic group, receives support from the similar dipole moments of the hydroxy- and methoxy-groups (cf. phenol and anisole, 1·60 and 1·28 D respectively [16]). The figures are even closer for

TABLE 2. *Ionization of substances (in water at 20°).*

		Proton gained			Proton lost			
No.	Substance	pK_a'	Spread [a] (±)	Concn.[a] (M)	pK_a	Spread [a] (±)	Concn.[a] (M)	Analytical wavelength [e] (mμ)
1	Pyridine	5·23 [b]						
2	2-Mercapto	−1·07	0·06	0·0001	9·97	0·03	0·01	345 (pK_a')
3	*N*-methyl	−1·22	0·09	0·0001				341
4	*S*-methyl	3·62	0·02	0·01				
5	3-Mercapto	2·28	0·04	0·005	7·01	0·03	0·005	
6	*N*-methyl	2·27	0·06	0·005				
7	*S*-methyl	4·45	0·04	0·01				
8	4-Mercapto	1·43	0·07	0·000025	8·83	0·02	0·01	327 (pK_a')
9	*N*-methyl	1·30 [d]	0·04	0·05				
10	*S*-methyl	5·97	0·04	0·01				
11	Quinoline	4·93 [c]						
12	2-Mercapto	−1·44	0·09	0·0001	10·21	0·04	0·0001	405 (pK_a) and (pK_a')
13	*N*-methyl	−1·6	0·1	0·0000125				385
14	*S*-methyl	3·71	0·05	0·00005				360
15	3-Mercapto	2·33	0·05	0·000025	6·13	0·03	0·000025	362 (pK_a) and 241 (pK_a')
16	*N*-methyl	2·40	0·07	0·000025				426
17	*S*-methyl	3·88	0·03	0·000025				382
18	4-Mercapto	0·77	0·05	0·000025	8·83	0·02	0·000025	384 (pK_a) and (pK_a')
19	*N*-methyl	0·56	0·09	0·000025				392
20	*S*-methyl	5·81	0·03	0·000025				349
21	5-Mercapto	3·31	0·04	0·000025	6·48	0·07	0·000025	374 (pK_a) and (pK_a')
22	*N*-methyl	3·22	0·06	0·000025				466
23	*S*-methyl	4·50	0·03	0·000025				266
24	6-Mercapto	3·95	0·06	0·000025	6·5	0·1	0·000025	367 (pK_a) and 262 (pK_a')
25	*N*-methyl	4·12	0·03	0·000025				446
26	*S*-methyl	4·75	0·05	0·000025				272
27	8-Mercapto	2·05	0·04	0·000025	8·29	0·03	0·000025	280 (pK_a) and (pK_a')
28	*S*-methyl	3·50	0·01	0·000025				251
29	*iso*Quinoline	5·46 [c]						
30	1-Mercapto	−1·9	0·13	0·000025	10·82	0·04	0·000025	380 (pK_a) and (pK_a')
31	*N*-methyl	−2·13	0·08	0·000025				380
32	*S*-methyl	3·93	0·02	0·000025				362
33	3-Mercapto	0·39	0·06	0·000025	8·58	0·04	0·000025	416 (pK_a) and (pK_a')
34	*S*-methyl	3·41	0·04	0·000025				374

[a] These results are given only for new determinations. [b] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [c] Part II.[1] [d] Thermodynamic. [e] An entry in this column means that the determination was spectroscopic (otherwise potentiometric).

the mercapto- and methylthio-groups (cf. thiophenol and thioanisole 1·19 and 1·38 D respectively [16]).

The relevant equation for determining R, the ratio of forms with a hydrogen atom on nitrogen to those with hydrogen on sulphur, is:[14] $R = \text{antilog}\ (pK_{SMe} - pK_{SH}) - 1$, where pK_{SMe} is the basic pK of the *S*-methyl derivative, and pK_{SH} is the basic pK of the mercapto-compound. Ideally the basic pK of the mercapto-compound should lie between those of its *N*- and *S*-methyl derivatives (in Nos. 15 and 24, Table 2, the basic pK of the mercapto-compound lies slightly below that of its *N*-methyl derivative).

Applying the above formula gives the tautomeric ratios of Table 3. In all cases, forms with a hydrogen atom on the nitrogen preponderate over those with hydrogen on sulphur (*i.e.*, for the neutral molecule in water at 20°). Comparison with the hydroxy-analogues (in Table 3) shows that this tendency is much higher for mercapto- than for hydroxy-heterocycles (six-membered rings). This is contrary to what has been believed in the past (cf., *e.g.*, ref. 10[b]) on the basis of methylation of the mercapto-compounds on sulphur

[15] Tucker and Irvin. *J. Amer. Chem. Soc.*, 1951, **73**, 1923; Green and Tong, *ibid.*, 1956, **78**, 4896; also ref. 1.
[16] Lumbroso and Marschalk, *J. Chim. phys.*, 1952, **49**, 385.

but of their hydroxy-analogues principally on nitrogen. This error illustrates the fact that chemical reactions are poor indicators of tautomeric ratios, because the most reactive tautomer is often a minor component but is regenerated as fast as it is consumed.

Although the (II) : (I) ratios (R = H in each case) are high for 3-, 6-, and 8-mercapto-quinoline and 3-mercaptopyridine, these figures are greatly exceeded by the α- and γ-mercapto-derivatives. It is evident that freedom to assume a thioamide form, *e.g.*, (III), conferred by valency on these substances, stabilizes the zwitterion form, *e.g.*, (IV), by resonance, and hence greatly increases the proportion of forms with a hydrogen atom on nitrogen. That the 5-isomer does not behave in this way by invoking the thioamide form (VI) is attributed to the well-known reluctance of transannular tautomerism to take place when an *ortho*-quinonoid form would be involved. The fairly high ratio for 3-mercapto*iso*quinoline is surprising because the failure of 3-methyl*iso*quinoline to react with benzaldehyde led to the view that between the two rings of *iso*quinoline is a fixed double bond.[7] Evidently this is a matter of degree, because the 1-mercapto-isomer has an even higher ratio.

TABLE 3. *Approximate ratios of forms having a hydrogen atom on nitrogen to those having hydrogen on sulphur (neutral molecules at equilibrium in water at* 20°).

Pyridines				*Quinolines*			
2-Mercapto	49,000	2-Hydroxy	340 [a]	2-Mercapto	140,000	2-Hydroxy	3000 [a]
3-Mercapto	150	3-Hydroxy	1 [a, b]	3-Mercapto	34	3-Hydroxy	0·06 [b]
4-Mercapto	35,000	4-Hydroxy	2200 [a]	4-Mercapto	110,000	4-Hydroxy	24,000 [a]
				5-Mercapto	15	5-Hydroxy	0·05 [b]
iso*Quinolines*				6-Mercapto	5	6-Hydroxy	0·01 [b]
1-Mercapto	680,000	1-Hydroxy	18,000 [a]	8-Mercapto	27	8-Hydroxy	0·04 [b]
3-Mercapto	1000						

[a] From Part II. [b] From ref. 17, which uses a spectroscopic method more suited to low values.

The substances with low ratios are oxidized readily in air, whereas those with high ratios are very stable.

The colours of 8-mercaptoquinoline (a violet liquid with a red, solid hydrate) have often been considered abnormal. The spectrum at long wavelengths is almost identical with that of the 5-isomer and similar to those of the 6- and the 3-isomer (Table 1). Thus the absorption above 400 mμ of these substances is apparently due to the preponderance of the zwitterionic form, *e.g.*, (II), which is present only in traces in the hydroxy-analogues (Table 3). It is considered that 2- and 4-mercaptoquinoline are less bathochromic because the zwitterion structure is modified by the thioamide component in the resonance hybrid.

Preparation of the Substances.—The mercapto-compounds, where the mercapto-group is not α or γ to a ring-nitrogen atom, were obtained (*a*) by action of potassium ethyl xanthate on the amine after diazotization, or (*b*) by reduction of the sulphonyl chloride. The α- and γ-mercapto-compounds were obtained by action of thiourea (or sodium hydrogen sulphide) on the chloro- or bromo-compounds, or of phosphorus pentasulphide on the hydroxy-compounds.

The *S*-methyl derivatives were obtained by direct methylation of the mercapto-compounds; they were examined, by paper chromatography, for freedom from the *N*-methyl isomer. Many of the *N*-methyl derivatives were obtained by quaternizing the corresponding benzoylthio-compounds, and then hydrolysing off the protective group. However the α- and γ-isomers were obtained by the action of phosphorus pentasulphide on the well-known oxygen analogues, *e.g.*, (VII). Attempts to prepare the *N*-methyl analogue of 8-mercaptoquinoline failed. For example, heating 8-benzoyl- or 8-benzyl-thioquinoline with methyl iodide gave 8-methylthioquinoline, identical with the product of a Skraup reaction on 2-methylthioaniline.

None of the substances mentioned in this paper had the unpleasant, penetrating smell reminiscent of aliphatic or aromatic mercaptans.

[17] Mason, *J.*, 1957, 5010.

EXPERIMENTAL

The potentiometric titrations were carried out, under nitrogen, as in Part II, and the values calculated from the following equations:

(*a*) for pH values below 7

$$pK_a = \mathrm{pH} - \log\{([\mathrm{B}] + [\mathrm{H}^+])/([\mathrm{BH}^+] - [\mathrm{H}^+])\}$$

(*b*) for pH values above 7

$$pK_a = \mathrm{pH} + \log\{([\mathrm{AH}] + [\mathrm{OH}^-])/([\mathrm{A}^-] - [\mathrm{OH}^-])\}$$

Spectrometric determinations of p*K* were made as in Part II. For methiodides, an equivalent of potassium iodide ($\lambda_{max.}$ 228) was placed in the blank cell.

Paper chromatography was carried out on Whatman's No. 1 paper using (*a*) 3% aqueous ammonium chloride, and (*b*) butan-1-ol-5N-acetic acid (7 : 3) as solvent.

Preparations (Analyses by Drs. J. E. Fildes, principally, and K. W. Zimmermann).—Solids were dried for analysis at 100°/0·1 mm., unless otherwise stated. M. p.s were taken in soda-glass capillaries.

2-*Mercaptopyridine*. Prepared from 2-bromopyridine and thiourea,[18] this had m. p. 130—132° (lit.,[18] 125°) (Found: C, 54·5; H, 4·45; S, 29·1. Calc. for C_5H_5NS: C, 54·0; H, 4·5; S, 28·8%). Methylation with methyl iodide and sodium hydroxide [19] gave 2-methylthiopyridine, b. p. 100—104°/33 mm. 1 : 2-Dihydro-1-methyl-2-thiopyridine, m. p. 90°, was prepared from the oxygen analogue with phosphorus pentasulphide.[20]

3-*Mercaptopyridine*. Pyridine-3-sulphonic acid,[21] m. p. 343—346°, was converted by phosphorus pentachloride into pyridine-3-sulphonyl chloride.[22] This was reduced to 3-mercaptopyridine hydrochloride stannichloride with stannous chloride [23] in 65% yield. The double salt (10 g.) was ground with sufficient 5N-sodium hydroxide almost to dissolve it at 100°. The cooled filtrate was shaken with benzoyl chloride (10 ml.). Recrystallization from light petroleum (b. p. 60—80°) gave 3-*benzoylthiopyridine* (70%), m. p. 81° (Found, for material dried at 55°/0·05 mm.: C, 66·9; H, 4·2. $C_{12}H_9ONS$ requires C, 66·95; H, 4·2%). This substance (1 g.) was refluxed with 6N-hydrochloric acid (10 ml.) under carbon dioxide for 1 hr. The benzoic acid was extracted with chloroform, and the aqueous layer adjusted to pH 4·5. Re-extraction with chloroform gave 3-mercaptopyridine (85%), crystallized from benzene–light petroleum (b. p. 60—80°) as yellow crystals, m. p. 81° (lit.,[24] 78—80°).

3-*Methylthiopyridine*. 3-Mercaptopyridine (2·5 g.) in N-sodium hydroxide (24 ml.) was shaken with methyl iodide (1·5 ml.; 1 equiv.) for 2 hr. at 20°. The solution was extracted with chloroform, giving 3-*methylthiopyridine* which distilled at b. p. 102°/17 mm. (60%) (Found: C, 57·6; H, 5·7; N, 10·9. C_6H_7NS requires C, 57·6; H, 5·6; N, 11·2%). The *hydrochloride*, prepared in alcohol and recrystallized from ethanol–benzene, had m. p. 156—158°, depressed on admixture with 3-mercaptopyridine methochloride (Found: Cl, 21·7. C_6H_8NClS requires Cl, 21·9%).

3-*Mercaptopyridine methochloride*. 3-Benzoylthiopyridine (5 g.), methanol (30 ml.), and methyl iodide (2·5 ml., 2 equiv.) were set aside at 20° for 2 days. The solvent was evaporated, and the residue recrystallized from ethanol, giving yellow 3-*benzoylthiopyridine methiodide* (60%), m. p. 163° (Found: C, 43·4; H, 3·3; N, 3·9; S, 9·0. $C_{13}H_{12}ONIS$ requires C, 43·7; H, 3·4; N, 3·9; S, 9·0%). This substance (1 g.) was refluxed with 6N-hydrochloric acid (10 ml.) under carbon dioxide for 1 hr. The benzoic acid was extracted with ether, and the aqueous layer was shaken with fresh silver chloride (0·6 g.) for 30 min. The solution was taken to dryness in a vacuum and the residue extracted with ethanol, giving 3-*mercaptopyridine methochloride* (60%), m. p. 183° (from ethanol–ethyl acetate) (Found: C, 44·5; H, 4·9; Cl, 22·2. C_6H_8NClS requires C, 44·6; H, 5·0; Cl, 21·9%). Paper chromatography revealed large differences in R_F between this and its isomer 3-methylthiopyridine hydrochloride (above).

[18] Phillips and Shapiro, *J.*, 1942, 584.
[19] Renault, *Ann. Chim. (France)*, 1955, **10**, 135.
[20] *Idem, Bull. Soc. chim. France*, 1953, **20**, 1001.
[21] McElvain and Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2233.
[22] Zienty, *J. Amer. Pharm. Assoc.*, 1948, **37**, 97.
[23] Steiger, B.P. 637,130/1950; *Chem. Abs.*, 1950, **44**, 8380.
[24] Wuest and Sakel, *J. Amer. Chem. Soc.*, 1951, **73**, 1210.

4-*Mercaptopyridine*, prepared [25] from 4-hydroxypyridine [26] and phosphorus pentasulphide, had m. p. 179—189° (decomp.) [lit., 177° (ref. 27), 186° (ref. 25)] (Found: C, 54·0; H, 4·6. Calc. for C_5H_5NS: C, 54·0; H, 4·5%). Methylation [25] gave 4-methylmercaptopyridine, m. p. 47° (lit.,[25] 45°). 1 : 4-Dihydro-1-methyl-4-oxopyridine, b. p. 153—156°/0·05 mm., was prepared [28] by methylating 4-hydroxypyridine. The product (3·7 g.) and phosphorus pentasulphide (7·4 g.) were heated to 110° under an air-condenser fitted with a drying tube. After the vigorous reaction had subsided, heating was continued at 125° for 1 hr. Water (15 ml.) was added to the cooled flask. The solution was brought to pH 7 and extracted with chloroform, giving orange 1 : 4-*dihydro*-1-*methyl*-4-*thiopyridine* (60%), m. p. 168·5—170° (from ethanol) (Found: C, 57·5; H, 5·5; N, 11·2; S, 25·7. C_6H_7NS requires C, 57·6; H, 5·6; N, 11·2; S, 25·6%).

2-*Mercaptoquinoline*. 2-Hydroxyquinoline (5 g.) and phosphorus pentasulphide (8·5 g.) in pyridine (50 ml.) were refluxed for 2 hr. The product was poured into hot water (330 ml.). The precipitate crystallized from benzene as yellow plates (45%), m. p. 178—179·5° (lit.,[29] 175°). It was characterized by oxidation with hydrogen peroxide to the disulphide, m. p. 139° (lit.,[30] 137°). The disulphide (0·21 g.) was reduced, and suspended in methanol and pyridine (4 ml. of each) with hydrazine hydrate (1 ml.). After 30 min. at 20°, dilute acetic acid was added and 2-mercaptoquinoline (0·07 g.; m. p. 178—179°) filtered off. 2-Methylthioquinoline, m. p. 58—59° [from light petroleum (b. p. 60—80°)] (lit.,[31] 55°), was prepared by methylating 2-mercaptoquinoline. 1 : 2-Dihydro-1-methyl-2-thioquinoline (m. p. 115°) was made [32] by the action of phosphorus pentasulphide on the 2-oxygen analogue.[33]

3-*Mercaptoquinoline*. 3-Aminoquinoline (30 g., 0·21 mole) was added slowly to a well-cooled and stirred mixture of 10N-hydrochloric acid (42 ml.) and ice (42 g.). Sodium nitrite (15·3 g.) in water (36 ml.) was then added during 15 min. at $<5°$. This solution was added during 30 min. to a stirred solution of potassium ethyl xanthate [34] (42 g., 0·26 mole) in water (50 ml.) at 45°. During the next hour at 45°, a red oil accumulated. The mixture was then extracted with ether, and the extract washed with 2·5N-sodium hydroxide and then water. The ether layer was dried (Na_2SO_4) and evaporated and the residue dissolved in boiling ethanol (300 ml.). Potassium hydroxide (49 g.) was added slowly and the mixture refluxed for 10 hr. under nitrogen. The ethanol was evaporated, the mixture dissolved in water, and the solution extracted with ether (discarded). The aqueous solution was shaken with benzoyl chloride (32 ml.) for a few minutes, and the 3-*benzoylthioquinoline* recrystallized from benzene–light petroleum (b. p. 60—80°) as colourless crystals (68%), m. p. 111° (Found, for material dried at 20°/1 cm.: C, 72·5; H, 4·3; N, 5·3; S, 11·9. $C_{16}H_{11}ONS$ requires C, 72·5; H, 4·2; H, 5·3; S, 12·1%).

This substance (1 g.) was refluxed with 6N-hydrochloric acid (10 ml.) under carbon dioxide for 1 hr. The benzoic acid was extracted with ether. The aqueous solution was chilled, adjusted to pH 4·5, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The oily residue, twice sublimed, gave 3-*mercaptoquinoline*, m. p. 58°, sometimes as bright red, and sometimes as pale pink, interconvertible crystals (Found: C, 66·7; H, 4·5; N, 8·7; S, 19·7. C_9H_7NS requires C, 67·05; H, 4·4; N, 8·7; S, 19·9%).

Di-3-*quinolyl disulphide*. To 3-mercaptoquinoline, suspended in aqueous alcohol, 10% hydrogen peroxide was added until the red colour disappeared. The *di*-3-*quinolyl disulphide* was filtered off, giving colourless crystals (from aqueous ethanol), m. p. 150—151·5° (Found: C, 67·4; H, 3·4; N, 8·6; S, 91·8. $C_{18}H_{12}N_2S_2$ requires C, 67·5; H, 3·8; N, 8·7; S, 20·0%). The same substance was formed when a solution of 3-mercaptoquinoline in ammoniacal benzene was exposed to the air.

Methylation of 3-*mercaptoquinoline*. 3-Mercaptoquinoline (from 5 g. of 3-benzoylthioquinoline) in N-sodium hydroxide was shaken with methyl iodide (1·5 ml.). Next day an oil

[25] King and Ware, *J.*, 1939, 873.
[26] Bowden and Green, *J.*, 1954, 1795.
[27] Koenigs and Kinne, *Ber.*, 1921, **54**, 1359.
[28] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1920, **3**, 806; Tschitschibabin and Osstrowa, *Ber.*, 1925, **58**, 1708.
[29] Fischer, *Ber.*, 1899, **32**, 1297.
[30] Roos, *Ber.*, 1888, **21**, 619.
[31] Beilenson and Hamer, *J.*, 1939, 143.
[32] Gutbier, *Ber.*, 1900, **33**, 3359.
[33] Perkin and Robinson, *J.*, 1913, **103**, 1973.
[34] Cranendonk, *Rec. Trav. chim.*, 1951, **70**, 431.

and a yellow solid had separated. 3-Methylthioquinoline was obtained upon extraction with ether, and the solid, *3-methylthioquinoline methiodide* (insoluble in ether), was filtered off and recrystallized from ethanol as yellow needles (7%), m. p. 245° (Found: C, 41·6; H, 3·7; N, 4·4. $C_{11}H_{12}NIS$ requires C, 41·6; H, 3·8; N, 4·4%). Hydrogen chloride, passed into the dried ethereal solution, precipitated *3-methylthioquinoline hydrochloride*, m. p. 205—209° after recrystallization from butanol and sublimation (Found: S, 15·1. $C_{10}H_{10}NClS$ requires S, 15·15%). 2N-Ammonia gave the *free base*, which was distilled; it had b. p. 118—119°/0·2 mm. (60%) (Found: C, 68·2; H, 5·2; N, 7·9; S, 18·6. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; N, 8·0; S, 18·3%).

Methylation of 3-benzoylthioquinoline. (*a*) A mixture of 3-benzoylthioquinoline (5 g.), methyl iodide (3·5 ml., 3 equiv.), and nitrobenzene (20 ml.) was set aside at 20° for 8 days. The precipitate was crystallized from methanol, giving orange *3-benzoylthioquinoline methiodide* (70%), m. p. 199—201° (Found, for material dried at 20°/1 cm.: C, 50·0; H, 3·5; N, 3·4; S, 7·9. $C_{17}H_{14}ONIS$ requires C, 50·1; H, 3·5; N, 3·4; S, 7·9%). (*b*) 3-Benzoylthioquinoline (0·2 g.), methyl iodide (0·1 ml., 2 equiv.), and methanol (6 ml.) were heated in a sealed tube at 100° for 5 hr. The solvent was evaporated and the residue crystallized from methanol–ethanol, giving 3-methylthioquinoline methiodide (63%), m. p. 240—242° not depressed by the material obtained above from 3-methylthioquinoline (Found, for material dried at 20°/1 cm.: C, 41·5; H, 3·8; N, 4·4; S, 10·0. $C_{11}H_{12}NIS$ requires S, 10·1%).

3-Mercaptoquinoline methiodide. 3-Benzoylthioquinoline methiodide (0·5 g.) was refluxed with 6N-hydrochloric acid in an atmosphere of carbon dioxide for 1 hr. The benzoic acid was extracted with ether, the aqueous solution evaporated, and the residue crystallized from ethanol–methanol containing a little hydriodic acid, giving yellow *3-mercaptoquinoline methiodide* m. p. 229—231° (Found: N, 4·6; S, 10·5. $C_{10}H_{10}NIS$ requires N, 4·6; S, 10·6%).

4-Mercaptoquinoline. 4-Hydroxyquinoline [35] (2 g.) and phosphorus pentasulphide (4 g.) were heated at 140° for 4 hr. and at 155° for 1 hr. The product was warmed with water (8 ml.), adjusted to pH 5·5, and extracted with chloroform, giving 1·5 g. of yellow *4-mercaptoquinoline* (from much toluene). It sublimed at 125—135°/0·005 mm. to give a red form, m. p. 158—162° (decomp.) (Found: C, 67·0; H, 4·5; N, 8·5. C_9H_7NS requires C, 67·05; H, 4·4; N, 8·7%). This substance (1·16 g.) in N-sodium hydroxide (8 ml.) was shaken with methyl iodide (0·46 ml., 1 equiv.) for 30 min. The mixture was extracted with chloroform, which was dried and evaporated. The residue was extracted with light petroleum (b. p. 60—80°). The filtrate, after concentration, deposited *4-methylthioquinoline* (70%), m. p. 70—72° (Found, for material dried at 20°/1 cm.: C, 68·45; H, 5·3; N, 7·8. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; N, 8·0%). Methylation with dimethyl sulphate in N-sodium hydroxide at 20° gave also 40% of 1 : 4-dihydro-1-methyl-4-oxoquinoline, m. p. 151—152·5° not depressed by an authentic sample [36] (Found: C, 75·5; H, 5·7; N, 8·8. Calc. for $C_{10}H_9ON$: C, 75·45; H, 5·7; N, 8·8%). 1 : 4-Dihydro-1-methyl-4-thioquinoline was obtained from its oxygen analogue [36] as 4-mercaptoquinoline (above), giving yellow needles, m. p. 209—211° (lit.,[37] 209—210°).

Di-4-quinolyl sulphide. 4-Mercaptoquinoline, refluxed with charcoal in toluene for an hour, gave colourless *di-4-quinolyl sulphide*, m. p. 146—147·5° (from aqueous alcohol) (Found: C, 74·5; H, 4·1; N, 9·6; S, 11·1. $C_{18}H_{12}N_2S$ requires C, 75·0; H, 4·2; N, 9·7; S, 11·1%).

5-Mercaptoquinoline. Quinoline-5-sulphonic acid [38] (10 g.) and phosphorus pentachloride (10 g.) were heated to 130° and, when the reaction was subsiding, to 150°. Phosphoryl chloride was removed at 5 cm., and the residue added to ice, water, and sodium hydrogen carbonate. *Quinoline-5-sulphonyl chloride* (70%) was extracted with chloroform and crystallized from light petroleum (b. p. 60—80°). It softened, without melting, at 91—95° (Found: C, 47·4; H, 2·4; S, 14·0. $C_9H_6O_2NClS$ requires C, 47·5; H, 2·7; S, 14·1%). This material gave a single spot on paper chromatography in each of our two solvents (absence of isomers). When hydrolysed with alkali it gave quinoline-5-sulphonic acid which also gave a single spot in two solvents. When this regenerated acid was fused with moist sodium hydroxide at 260° it gave 65% of 5-hydroxyquinoline, m. p. 223—226° not depressed by authentic 5-hydroxyquinoline, indistinguishable from the latter on chromatograms. This chloride (14·9 g.) in 10N-hydrochloric acid (60 ml.) was added dropwise with stirring to a solution of stannous chloride dihydrate

[35] Riegel, Albisetti, Lappin, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 2685.
[36] Späth and Kalbe, *Sitzungsber. Akad. Wiss. Wien*, 1922, **131**, 421.
[37] Campaigne, Cline, and Kaslow, *J. Org. Chem.*, 1950, **15**, 600.
[38] U.S.P. 2,689,850/1954; *Chem. Abs.*, 1955, **49**, 11725.

(48 g.) in 10N-hydrochloric acid (105 ml.). Water (84 ml.) was added and the mixture was refrigerated overnight, giving 5-mercaptoquinoline as its stannichloride complex. This was benzoylated as was 3-mercaptopyridine. The crude *5-benzoylthioquinoline* was chromatographed in chloroform on alumina and crystallized (m. p. 88°) from light petroleum (b. p. 80—100°) (Found, for material dried at 60°/1 mm.: C, 71·8; H, 4·45; N, 5·25; S, 12·05. $C_{16}H_{11}ONS$ requires C, 72·5; H, 4·2; N, 5·3; S, 12·1%). This substance (4 g.) was refluxed with 6N-hydrochloric acid (40 ml.) for an hour under carbon dioxide. Benzoic acid was extracted with ether, and the aqueous layer adjusted to pH 3. *5-Mercaptoquinoline monohydrate* was filtered off and gave red crystals, m. p. 87·5—89°, from aqueous ethanol (Found, for material dried at 20°/1 cm.: C, 60·7; H, 5·0; N, 7·8; S, 17·7. C_9H_7NS,H_2O requires C, 60·3; H, 5·1; N, 7·8; S, 17·9. Found, for material dried as before, but in the presence of phosphoric oxide: C, 66·6; H, 4·4; S, 19·8. C_9H_7NS requires C, 67·05; H, 4·4; S, 19·9%). The anhydrous substance is pale pink.

Di-5-quinolyl disulphide. 5-Mercaptoquinoline, oxidized with hydrogen peroxide as was the 3-isomer (above), gave *di-5-quinolyl disulphide*, m. p. 109° [from benzene–light petroleum (b. p. 60—80°)] (Found, for material dried at 70°/1 mm.: C, 67·6; H, 3·8; N, 8·6; S, 19·65. $C_{18}H_{12}N_2S_2$ requires C, 67·5; H, 3·8; N, 8·7; S, 20·0%). Aerial oxidation gave the same product.

5-Methylthioquinoline. An aqueous solution of 5-mercaptoquinoline hydrochloride [from hydrolysis as above of 5-benzoylthioquinoline (2 g.)] was made alkaline with 10N-sodium hydroxide and shaken with methyl iodide (0·5 ml., 1 equiv.) for 15 min. The oil was extracted with ether; dry hydrogen chloride precipitated 80% of yellow 5-methylthioquinoline hydrochloride, m. p. 241—243·5° (from butanol and after sublimation). 2N-Ammonia gave *5-methylthioquinoline*, b. p. 104°/0·1 mm. (Found: C, 68·6; H, 5·2. $C_{10}H_9NS$ requires C, 68·5; H, 5·2%).

5-Mercaptoquinoline methiodide. 5-Benzoylthioquinoline (0·2 g.), methyl iodide (0·1 ml., 2 equiv.), and nitromethane (1 ml.) were set aside at 20°. The yellow *5-benzoylthioquinoline methiodide* (50%), collected after 7 days and crystallized from ethanol, had m. p. 207° (Found: C, 50·3; H, 3·5; N, 3·4; S, 8·0. $C_{17}H_{14}ONIS$ requires C, 50·1; H, 3·5; N 3·4; S 7·9%). This substance (0·4 g.) and 6N-hydrochloric acid (5 ml.) were refluxed for an hour under carbon dioxide, and the benzoic acid was extracted with ether. The aqueous layer was taken to dryness at 5 cm. The residue (65%), crystallized from ethanol containing a little hydriodic acid, gave yellow *5-mercaptoquinoline methiodide*, m. p. 189° (Found: C, 39·5; H, 3·4; N, 4·5; S, 10·55. $C_{10}H_{10}NIS$ requires C, 39·6; H, 3·3; N, 4·6; S, 10·6%). *5-Benzoylthio-1-methylquinolinium hydrogen sulphate* was similarly produced from 5-benzoylthioquinoline, dimethyl sulphate, and nitrobenzene. The nitrobenzene was distilled off with water at 5 cm., and the residue, recrystallized from ethanol–ethyl acetate, had m. p. 170—172° (Found: C, 53·8; H, 4·1; N, 3·65. $C_{18}H_{17}O_5NS_2$ requires C, 54·1; H, 4·0; N, 3·7%).

6-Mercaptoquinoline was obtained [39] by condensing sulphanilic acid with glycerol and treating the quinoline-6-sulphonic acid, in turn, with phosphorus pentachloride, stannous chloride, benzoyl chloride, and hydrochloric acid. It was a red oil, b. p. 114°/0·1 mm. (Found: N, 8·55; S, 19·65. Calc. for C_9H_7NS: N, 8·7; S, 19·9%). This substance (2·15 g.), methyl iodide (0·83 ml., 1 equiv.), and N-sodium hydroxide (13 ml.) were shaken for 15 min. and extracted with chloroform. *6-Methylthioquinoline methiodide* (20%) remained undissolved and gave yellow crystals (from alcohol), m. p. 237—238·5° (Found: C, 41·9; H, 4·0; N, 4·3; S, 10·0. $C_{11}H_{12}NIS$ requires C, 41·6; H, 3·8; N, 4·4; S, 10·1%). The chloroform extract yielded *6-methylthioquinoline* (55%), m. p. 44—46° [from light petroleum (b. p. 60—80°)] (Found, for material dried at 20°/1 cm.: C, 68·9; H, 5·3; N, 7·8. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; N, 8·0%).

6-Mercaptoquinoline methiodide. 6-Benzoylmercaptoquinoline [39] (1·5 g.; m. p. 147—149°), methyl iodide (0·75 ml., 2 equiv.), and methanol (6 ml.) were heated in a tube at 100° for 5 hr., giving yellow *6-benzoylthioquinoline methiodide* (90%), m. p. 205—207·5° (Found: C, 50·2; H, 3·5; N, 3·4; S, 7·8. $C_{17}H_{14}ONIS$ requires C, 50·1; H, 3·5; N, 3·4; S, 7·9%). This substance (1 g.) was shaken with fresh silver chloride in water at 20° for 25 min. The filtrate gave yellow 6-benzoylthioquinoline methochloride quantitatively; this had m. p. 180—182·5° (from ethanol–ethyl acetate). On acid hydrolysis as for the 5-isomer, it gave 80% of cream-coloured *6-mercaptoquinoline methochloride*, m. p. 219—221·5° (from ethanol) (Found: C, 56·4;

[39] Ponci and Gialdi, *Il Farmaco, Ed. sci.*, 1954, **9**, 459; *Chem. Abs.*, 1955, **49**, 11657.

H, 4·9; N, 6·75; S, 15·0. $C_{10}H_{10}NClS$ requires C, 56·7; H, 4·8; N, 6·6; S, 15·5%). 6-Benzoylthioquinoline methiodide, hydrolysed as was the 3-isomer (above), gave 6-*mercaptoquinoline methiodide*, m. p. 225—227° (Found: N, 4·5; S, 10·4. $C_{10}H_{10}NIS$ requires N, 4·6; S, 10·6%).

8-*Mercaptoquinoline*. Quinoline-8-sulphonic acid was made by sulphonating quinoline with fuming sulphuric acid (30% SO_3) [40] and converted into the sulphonyl chloride, m. p. 131° [from light petroleum (b. p. 80—100°)] (lit.,[41] 129°), which was reduced with stannous chloride to the stannichloride complex of 8-mercaptoquinoline.[42] This was oxidized to di-8-quinolyl disulphide (m. p. 206—208°) by the method of Badger and Buttery [41] but with ten times the proportion of iodine. Other batches were converted [42] into 8-benzoyl- and 8-benzyl-thioquinoline, m. p. 109—112° and 114° respectively. Of the methods described for 8-mercaptoquinoline dihydrate (m. p. 58—59°), acid hydrolysis [42] of the benzoyl derivative was found best.

8-*Methylthioquinoline*. (*a*) *o*-Methylthioaniline [43] (2·8 g.), arsenic pentoxide (2·9 g.), glycerol (6·2 g.), and 36N-sulphuric acid (5·6 g.) were refluxed for 1·5 hr. Water (50 ml.) was added, and the mixture made alkaline and extracted with chloroform, giving 8-methylthioquinoline (44%) which, when recrystallized from light petroleum (b. p. 60—80°), then aqueous alcohol, had m. p. 85° (lit.,[44] 78—80°) (Found, for material dried at 20°/1 cm.: C, 68·5; H, 5·3; N, 7·8. Calc. for $C_{10}H_9NS$: C, 68·5; H, 5·2; N, 8·0%).

(*b*) 8-Mercaptoquinoline dihydrate (2·1 g.), N-sodium hydroxide (12 ml.), and methyl iodide (0·7 ml., 1 equiv.) were shaken for 30 min. The 8-methylthioquinoline (75%) had m. p. 84—85·5° (Found: C, 68·6; H, 5·1; N, 8·1%).

(*c*) Ethereal diazomethane (from nitrosomethylurea, 1 g.), added to 8-mercaptoquinoline (0·3 g.) in methanol (30 ml.) at 0°, gave 8-methylthioquinoline (77%), m. p. 82·5—84°.

(*d*) 8-Benzoylthioquinoline (0·2 g.), methanol (5 ml.), and methyl iodide (0·1 ml.), set aside at 20° for 2 days, gave yellow 8-*methylthioquinoline hydriodide*, m. p. 196—197·5° (from ethanol) (Found: C, 39·4; H, 3·3; N, 4·6. $C_{10}H_{10}NIS$ requires C, 39·6; H, 3·3; N, 4·6%).

(*e*) 8-Benzylthioquinoline (1 g.), methyl iodide (0·6 ml., 2·5 equiv.), and methanol (13 ml.), at 100° for 6 hr., gave 8-methylthioquinoline hydriodide (40%), m. p. 189—193° (Found: C, 39·7; H, 3·3; N, 4·6%).

The m. p.s of the bases from methods (*b*)—(*e*) were not depressed when mixed with material (*a*) from the Skraup reaction.

*Methylation of di-*8-*quinolyl disulphide*. This substance (0·1 g.), methyl iodide (0·08 ml.), and methanol (3 ml.), heated at 100° for 8 hr., gave dark brown crystals (0·1 g.) believed to be *di-*8-*quinolyl disulphide methiodide periodide*, m. p. 198° (from methanol) (Found: C, 31·5; H, 2·0; N, 3·9. $C_{19}H_{15}N_2I_3S_2$ requires C, 31·8; H, 2·1; N, 3·9%). The colour was discharged by sulphur dioxide solution. Di-8-quinolyl disulphide (0·2 g.) and methyl iodide (4 ml.), at 100° for 3 hr., gave 8-methylthioquinoline (75%), m. p. and mixed m. p. 82·5—84°, and a purple-brown benzene-insoluble product, believed to be 8-*methylthioquinoline methiodide periodide* (15%), m. p. 129—130° (from ethanol) (Found: C, 23·4; H, 2·0; N, 2·3; S, 5·5. $C_{11}H_{12}NI_3S$ requires C, 23·1; H, 2·1; N, 2·45; S, 5·6%). Di-8-quinolyl disulphide (0·38 g.), dimethyl sulphate (0·9 ml.), and nitrobenzene (4 ml.) were heated at 150° for 1·3 hr. The crystals formed on cooling were recrystallized from ethanol–methanol, giving a yellow substance of unknown constitution (0·22 g.), m. p. 218—220° (Found: C, 41·9; H, 4·3; N, 4·7, 4·9; S, 21·9%).

8-Chloroquinoline methochloride [45] could not be transformed into 8-mercaptoquinoline methiodide by heating it in alcohol with thiourea at 150° or with sodium hydrogen sulphide at 175°; nor was this substance obtained by heating "diazoxine," the anhydride of 8-hydroxyquinoline methohydroxide,[46] with phosphorus pentasulphide.

1-*Mercapto*iso*quinoline*. 1-Hydroxy*iso*quinoline [1] (1 g.) and phosphorus pentasulphide (1 g.) were heated at 155° for 3·5 hr. Water (8 ml.) was added and the solution neutralized and extracted with chloroform, giving orange-brown 1-*mercapto*iso*quinoline* (90%), m. p. 171° (from ethanol) (Found: C, 66·6; H, 4·4; S, 19·8. C_9H_7NS requires C, 67·05; H, 4·4; S, 19·9%).

[40] McCasland, *J. Org. Chem.*, 1946, **11**, 277.
[41] Badger and Buttery, *J.*, 1956, 3236.
[42] Edinger, *Ber.*, 1908, **41**, 937.
[43] Foster and Reid, *J. Amer. Chem. Soc.*, 1924, **46**, 1936; Brand and Stallman, *Ber.*, 1921, **54**, 1578.
[44] Taylor, *J.*, 1951, 1150.
[45] Claus and Schöller, *J. prakt. Chem.*, 1893, **48**, 140.
[46] Phillips and Keown, *J. Amer. Chem. Soc.*, 1951, **73**, 5483.

This substance (2·8 g.) in N-sodium hydroxide (55 ml.) was shaken with methyl iodide (1·2 ml.) for 5 min. The mixture, extracted with chloroform, gave 80% of 1-*methylthio*iso*quinoline*, b. p. 100°/0·08 mm. (Found: C, 68·7; H, 5·3; S, 18·3. $C_{10}H_9NS$ requires C, 68·5; H, 5·2; S, 18·3%). 1 : 2-Dihydro-2-methyl-1-oxo*iso*quinoline [1] (1 g.) and phosphorus pentasulphide (1 g.), at 135° for 4 hr., gave yellow 1 : 2-dihydro-2-methyl-1-thio*iso*quinoline (95%), m. p. 112° (from dilute alcohol) (lit.,[47] 110°).

3-*Mercapto*iso*quinoline*. 3-Hydroxy*iso*quinoline was prepared from 3-methyl- (through 3-formyl- and 3-amino-) *iso*quinoline.[48] The hydroxy-compound (1 g.), phosphorus pentasulphide (3 g.), and tetralin (20 ml.) were refluxed with stirring at 180° for 4 hr., then cooled. Next day, the precipitate was extracted with benzene (charcoal), giving orange-red 3-*mercapto*iso*quinoline* (20%), m. p. 217° (from benzene) (Found: C, 66·9; H, 4·4; N, 8·5%). This substance was also obtained in small yield (m. p. 204—207°) by heating 3-chloro*iso*quinoline [49] and aqueous sodium hydrogen sulphide at 205° for 70 hr. (Found: S, 19·7%). However, 3-*benzoylthio*iso*quinoline*, m. p. 139° [from light petroleum (b. p. 60—80%)], was obtained in 40% yield by benzoylating the alkaline filtrate (Found: C, 72·2; H, 4·0; S, 12·2. $C_{16}H_{11}ONS$ requires C, 72·5; H, 4·2; S, 12·1%). 3-Mercapto*iso*quinoline (0·09 g.), methyl iodide (0·05 ml.), and N-sodium hydroxide (1 ml.) were shaken for a few minutes and extracted with ether. Hydrogen chloride, passed into the dried extract, gave 3-*methylthio*iso*quinoline hydrochloride*, pale yellow crystals after sublimation, m. p. 197—199° (Found: C, 56·7; H, 4·9; N, 6·6; S, 15·0. $C_{10}H_{16}NClS$ requires C, 56·7; H, 4·8; N, 6·6; S, 15·1%).

Department of Medical Chemistry, Australian National University,
Canberra, Australia. [*Received, February 9th*, 1959.]

[47] Peak and Stansfield, *J.*, 1952, 4067.
[48] Case, *J. Org. Chem.*, 1952, **17**, 471; Boyer and Wolford, *ibid.*, 1956, **21**, 1297; Baumgarten and Dirks, *ibid.*, 1958, **23**, 900; Teague and Rowe, *J. Amer. Chem. Soc.*, 1951, **73**, 688.
[49] Haworth and Robinson, *J.*, 1948, 777; Baer and Kates, *J. Amer. Chem. Soc.*, 1945, **67**, 1482.