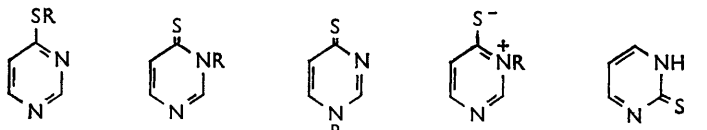
605. *Ionization Constants of Heterocyclic Substances. Part V.*[1] *Mercapto-derivatives of Diazines and Benzodiazines.*

By Adrien Albert and G. B. Barlin.

Ionization constants are reported for mercapto-diazines and -benzodiazines and for their *N*- and *S*-methyl derivatives, also the ultraviolet spectra of all the ionic species. Comparison of the ionization constants and spectra of these substances reveals that, as for the monoaza-analogues, tautomers with a hydrogen atom on nitrogen are favoured at the expense of those with hydrogen on sulphur. Where a thioamide form and a vinylogous thioamide form are possible, the former is preferred, *e.g.*, (II) rather than (III). The ratio of tautomers at equilibrium has been calculated for several examples.

The ionization constants and spectra of the corresponding hydroxy-derivatives, several of them recorded for the first time, are compared with those of the mercapto-derivatives.

In reporting the acidic and basic strengths of mercapto-derivatives of several monoaza-heteroaromatic systems (six-membered rings), we showed [2] (by comparison of their ionization constants and ultraviolet spectra with those of the *N*- and *S*-methyl derivatives) that tautomeric equilibria favoured the presence of the mobile hydrogen atom on the nitrogen rather than on the sulphur. This study has now been extended to systems with two nitrogen atoms in the same ring. Such mercapto-derivatives can be written in a number of tautomeric forms. Thus 4-mercaptopyrimidine is shown in the thiol (I), thioamide (II), vinylogous thioamide (III), and zwitterionic, *e.g.*, (IV) (R = H, throughout). In what follows, the term " mercapto-compound " is used in its traditional sense to embrace all these structures. The aim of the present work is to discover which form predominates at equilibrium. Aqueous solutions were used, so as to provide results useful for biological work.



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

Ultraviolet Spectra of Neutral Species.—Ionization constants were determined first, in order that buffers could be chosen of such a pH that only one ionic species would be present. The overall spectroscopic result may be summarized as follows. The spectra of the mercapto-compounds resemble those of their *N*-methyl derivatives very closely but are unlike those of their *S*-methyl derivatives. This generalization, however, requires qualification because three distinct types of mercapto-compound were investigated.

The first type is a symmetrical molecule in which the mercapto-group is α to both nitrogen atoms. This type offers the fewest alternative structures for decision. In our example, 2-mercaptopyrimidine (Table 1, No. 1), the spectrum is very similar to that of the *N*-methyl derivative (1,2-dihydro-1-methyl-2-thiopyrimidine) and unlike that of the *S*-methyl derivative (2-methylthiopyrimidine). So the predominant tautomer of 2-mercaptopyrimidine, in aqueous solution, has formula (V). The zwitterionic structure isomeric with (IV; R = H) is, as such, rejected because it would be expected to have merged with the structure (V) in a resonance hybrid in which the latter should predominate cf. a discussion on isomerism and resonance in 2- and 4-hydroxypyridine [3]). In what

[1] Part IV, Albert, *J.*, 1960, 1020.
[2] Albert and Barlin, *J.*, 1959, 2384.
[3] Albert and Spinner, *J.*, 1960, 1221.

TABLE 1.

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

No.	Substance	Neutral species			Proton gained (cation)			Proton lost (anion)		
		$\lambda_{max.}$ (mμ)	log ε	pH	$\lambda_{max.}$ (mμ)	log ε	pH [a]	$\lambda_{max.}$ (mμ)	log ε	pH
1	2-Mercaptopyrimidine	278, 346	4·33, 3·42 [b]	4·9	208, 285, 378	3·87, 4·51, 3·18 [b]	0·0	231, *270*	3·69, *4·23* [b]	13·0
2	*N*-Methyl	279, 344	4·26, 3·45	9·0	283, 378	4·34, 3·14 [c]	−2·95			
3	*S*-Methyl	250, *285*	4·11, *3·25*	7·0	214, 255, 313	3·48, 4·10, 3·51	−2·77			
4	3-Mercaptopyridazine	282, 355	4·11, 3·48	4·94	253, 299	3·90, 3·27	−4·20	272, 324	4·14, 3·18	12·0
5	$N_{(2)}$-Methyl	218, 281, 348	4·05, 4·10, 3·49	7·0	244, 295	3·76, 3·60	−4·20			
6	*S*-Methyl	252, 298	3·98, 3·24	6·1	222, 268, 318	3·90, 4·00, 3·11	−1·68			
7	4-Mercaptopyridazine	216, 346	3·77, 4·18	4·0	215, *260*, 300	3·78, *3·33*, 4·10	−3·03	220, 299	3·92, 3·97	9·0
8	$N_{(1)}$-Methyl	218, 352	3·88, 4·29	7·0	219, 304	3·78, 4·18	−3·03			
9	*S*-Methyl	216, 270	3·75, 3·95	7·0	218, 315	3·70, 4·19	1·0			
10	4-Mercaptocinnoline	*217*, 222, 252, 271, 305, 417	*4·46*, 4·56, 3·77, 3·63, 3·25, 4·27	4·0	211, 238, *248*, *288*, 295, 333, 369	4·10, 4·40, *4·24*, *3·36*, 3·37, 3·82, 4·02	−4·0	221, 247, 275, 380	4·52, 3·82 3·29, 4·13	9·5
11	$N_{(1)}$-Methyl	227, 265, *274*, 317, 424	4·51, 3·91, *3·79*, 3·45, 4·10	7·0	215, 244, 285, 333, *367*, 377	4·09, 4·49, 3·40, 3·68, *3·93*, 3·95	−3·0			
12	*S*-Methyl	226, *246*, *271*, 349	4·41, *4·03*, 3·28, 4·04	6·0	219, 240, *256*, *281*, 385	4·26, 4·36, *3·90*, *3·23*, 4·18	0·0			
13	1-Mercaptophthalazine	217, *281*, 289, 347	4·57, *3·83*, 3·95, 3·99	7·0	231, 273, 317, *327*	4·40, 3·76, 3·66, *3·63*	−6·05	216, *236*, 273, *282*, 334	4·74; *3·93*, 3·57, *3·55*, 3·89	12·0
14	$N_{(2)}$-Methyl	219, *280*, 289, 339	4·47, *3·71*, 3·82, 3·83	7·0	232, 274, 317, 327	4·50, 4·00, 3·65, 3·64	−6·0			
15	*S*-Methyl	216, 263, 296	4·64, 3·73, 3·81	7·0	225, 286, 321	4·45, 3·87, 3·81	1·0			
16	2-Mercaptopyrazine	227, 279, 382	3·53, 4·09, 3·82 [d]	3·48	*260*, 291, 448	*3·61*, 4·16, 3·61 [d]	−2·95	226, 270, 344	3·72, 4·05, 3·70 [d]	9·0
17	$N_{(1)}$-Methyl	222, 279, 375	3·56, 4·07, 3·81 [d]	7·0	*260*, 291, 436	*3·56*, 4·17, 3·64 [d]	−2·95			
18	*S*-Methyl	251, *300*, 322	3·89, *3·51*, 3·73 [d]	7·0	238, 267, 359	3·74, 3·98, 3·68 [d]	−2·35			
19	2-Mercaptoquinoxaline	280, *335*, 407	4·29, *3·40*, 4·07 [e]	4·3	291, 370, 488	4·39, 3·38, 3·88 [e]	−4·20	*250*, 279, 386	*4·06*, 4·22, 3·95 [e]	12·0
20	$N_{(1)}$-Methyl	278, *335*, 398	4·32, *3·47*, 4·08	7·0	289, 365, 472	4·40, 3·43, 3·91	−4·20			
21	*S*-Methyl	241, 265, 361	4·19, 4·16, 3·91 [e]	7·5	256, *275*, 397	4·32, *3·96*, 3·93 [e]	−2·01			
22	4-Mercaptopyrimidine	285, 327	4·03, 3·91 [f]	4·5	305	4·22 [f]	−2·3	292—294	4·04 [f]	13·0
23	$N_{(1)}$-Methyl	328	4·33	7·0	304	4·24	−2·01			
24	$N_{(3)}$-Methyl	287, 322	4·03, 3·91	7·15	304	4·23	−2·95			
25	*S*-Methyl	257, 279	3·85, 3·91	7·0	221, 302	3·47, 4·23	0·0			
26	2-Mercaptoquinazoline	215, 275	4·28, 4·27	5·3	218, 295	4·31, 4·55	−1·9	256, 285, 369	4·24, 4·28, 3·46	11·7
27	*S*-Methyl	257, 342	4·38, 3·43	7·0	249, 269, 321, 357	4·17, 4·25 3·32, 3·38	0·40			
28	4-Mercaptoquinazoline	215, 232, 286, 353, *366*	4·43, 4·16, 3·81, 4·15, *4·08* [g]	4·5	218, 242, 356	4·29, 4·00, 4·19	−1·0	215, *300*, 346	4·62, *3·85*, 4·11	12·0
29	$N_{(1)}$-Methyl	217, 240, 264,	4·50, 4·10, 3·58,	7·0	214, *240*, 243,	4·38, *4·09*, 4·11,	0·0			

TABLE 1. (*Continued.*)

No.	Substance	Neutral species			Proton gained (cation)			Proton lost (anion)		
		$\lambda_{max.}$ (mμ)	log ε	pH	$\lambda_{max.}$ (mμ)	log ε	pH [a]	$\lambda_{max.}$ (mμ)	log ε	pH
		380	4·24 g		277, 358	3·75, 4·17				
30	$N_{(3)}$-Methyl	216, 233, 284, 347, 361	4·54, 4·31, 3·82, 4·13, 4·06 [g]	7·0	219, 241, 277, 349, 359	4·45, 4·19, 3·88, 4·16, 4·13	−1·20			
31	*S*-Methyl	223, 279, 322 + 331	4·42, 3·83, 4·01 + 3·96 [g]	5·5	212, 235, 342	4·10, 4·40, 4·19	0·0			
32	2,3-Dihydro-2-methyl-3-oxopyridazine	225, 287	3·38, 3·51 [h]	4·35	*210*, 265	*3·44*, 3·49	−5·0			
33	1,4-Dihydro-1-methyl-4-oxopyridazine	269	3·99 [i]	4·17	252	3·84 [j]	−2·06			
34	4-Hydroxycinnoline [k]	207, 227, 234, 253, *261*, 284, 337, 352	4·49, 4·12, 4·11, 3·98, *4·49*, 3·35, 4·09, 4·01	5·0	205, 233, 249, *294*, 305, 338	4·25, 4·47, 4·08, *3·37*, 3·54, 3·76	−3·6	211, 240, 336, *345*	4·48, 4·17, 4·02, *3·99*	11·5
35	$N_{(1)}$-Methyl [k]	212, *223*, 250, *265*, 347, 364	4·44, *4·16*, 4·02, *3·67*, 4·05, 4·06	7·0	210, 241, *257*, 299, 309, 346	4·24, 4·47, *3·93*, 3·48, 3·54, 3·74	−3·0			
36	*O*-Methyl [k]	*211*, 227, 293, 319, *328*	*4·30*, 4·59, 3·71, 3·69, *3·65*	7·0	233, 254, *296*, 307, 338	4·50, 3·97, *3·53*, 3·71, 3·79	1·0			
37	1-Hydroxyphthalazine	208, 222, *230*, *240*, 249, 271, 276, 298, 310	4·48, 4·27, *4·18*, *3·90*, 3·87, 3·77, 3·77, 3·55, 3·46	7·0	224, 256, *288*, 299, 308	4·46, 3·46, *3·64*, 3·67, 3·68	−4·65	223, 246, *295*, 301	4·15, 3·74, *3·83*, 3·84	14·0
38	$N_{(2)}$-Methyl	*223*, *241*, 250, 284, 299, 301	*4·30*, *3·83*, 3·79, 3·81, 3·70, 3·54	7·0	217, 227, *259*, *303*, 312, *318*	4·43, 4·45, *3·52*, *3·86*, 3·88, *3·85*	−6·6			
39	*O*-Methyl	212, *216*, 265, 291, 304	4·69, *4·66*, 3·74, 3·41, 3·39	7·0	224, 283, *301*, 311	4·56, 3·71, *3·62*, 3·69	1·18			
40	4-Hydroxyquinazoline [k]	226, *231*, 263, *269*, *292*, 311, 313	4·42, *4·39*, 3·75, *3·71*, *3·46*, 3·61, 3·54	7·0	*227*, 233, 275–6, 292, 303	*4·32*, 4·37, 3·69, 3·69, 3·58	0·0	*220*, 228, *274*, 280, *295*, 306, 318	*4·21*, 4·24, *3·83*, 3·85, *3·64*, 3·71, 3·59	12·0
41	$N_{(1)}$-Methyl [k]	214, 230, 271, 279, *298*, 306, 317	4·13, 4·17, 3·63, 3·67, *3·82*, 3·93 3·83	7·0	*229*, 235, 281, 293, 304	*4·31*, 4·36, 3·68, 3·71, 3·65	1·0			
42	$N_{(3)}$-Methyl [k]	225, 266, 272, *290*, 301, 313	4·42, 3·80, 3·78, *3·43*, 3·56, 3·49	7·0	*229*, 234, 279, 293, *303*	*4·34*, 4·39, 3·78, 3·74, *3·59*	1·0			

[a] pH values below 0 have been obtained in solutions of sulphuric acid to which Hammett's acidity functions have been assigned. [b] From Boarland and McOmie, *J.*, 1952, 3716. [c] Our figures differ somewhat from those of Boarland and McOmie, who measured the cation at pH 0 which is too high to exclude the neutral species. [d] Because our p*K* values differ somewhat from those of Cheeseman (*J.*, 1960, 242) we have redetermined the spectra of all species, including the methyl derivatives, but only small differences were found. [e] We have redetermined the spectra of all species of 2-mercaptoquinoxaline and its *S*-methyl derivative (Cheeseman, *J.*, 1958, 108), but the differences are small. [f] The spectrum of the neutral species is taken from Boarland and McOmie (*loc. cit.*), but we have redetermined the cationic spectrum, which they had attempted at pH 0 which is too high to exclude the neutral species. [g] For the spectra of the neutral species in alcohol see Fry, Kendall, and Morgan, *J.*, 1960, 5062. [h] The spectrum in ethanol is given by Gregory, Hills, and Wiggins (*J.*, 1949, 1248) and Mason (*J.*, 1957, 5010). [i] For the spectrum of the neutral species in ethanol see Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1956, *39*, 1755. [j] Eichenberger, Rometsch, and Druey (*loc. cit.*) give $\lambda_{max.}$ 252 mμ and ε 10,650. [k] Hearn, Morton, and Simpson (*J.*, 1951, 3318) record ultraviolet spectra but do not specify the solvent.

follows, it will be assumed that totally zwitterionic structures are stable only when the rules of valency forbid such resonance (as in 3-mercaptopyridine [2]).

This assumption decreases the number of alternative structures to be considered * for the second type, which has the mercapto-group placed β to one ring-nitrogen atom and α or γ to the other. This type is exemplified, in Table 1, by 3- and 4-mercaptopyridazine, 4-mercaptocinnoline, 1-mercaptophthalazine, 2-mercaptopyrazine, and 2-mercaptoquinoxaline. In each case, the spectrum is unlike that of the *S*-methyl derivative but almost

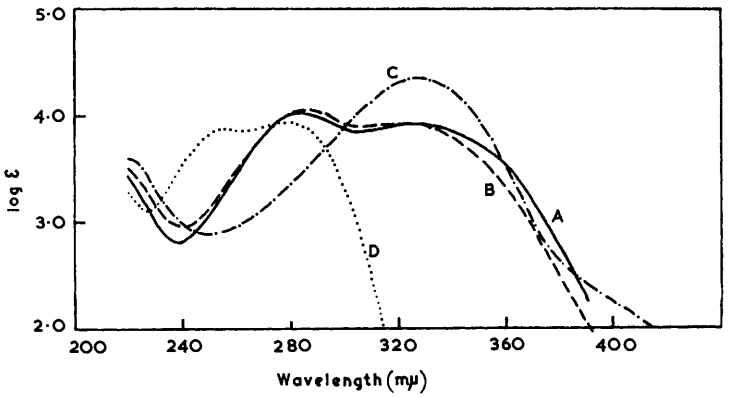


FIG. 1.

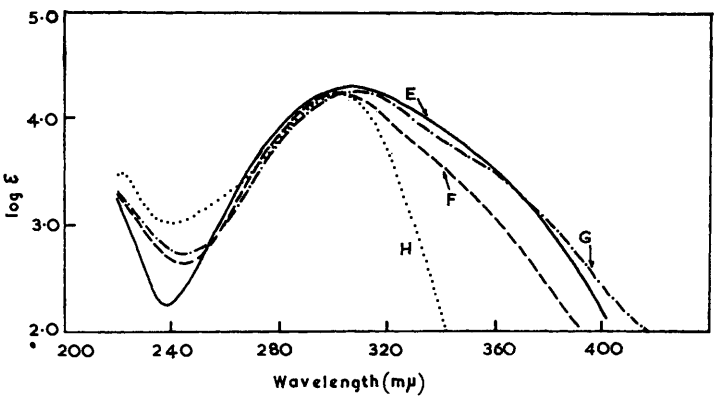


FIG. 2.

Ultraviolet spectra of (A—D) neutral molecules and (E—H) cations of: 4-mercaptopyrimidine (A) at pH 4·5, (E) at pH −2·3; 1,6-dihydro-1-methyl-6-thiopyrimidine (B) at pH 7·15, (F) at pH −2·95; 1,4-dihydro-1-methyl-4-thio-pyrimidine (C) at pH 7·0, (G) at pH −2·01; 4-methylthiopyrimidine (D) at pH 7·0, (H) at pH 0·0; all in water at 20°.

identical with that of the isomer methylated on that nitrogen atom to which the sulphur is α or γ.

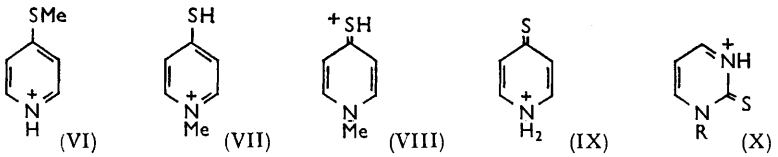
The third type is an unsymmetrical molecule in which the mercapto-group is α to one ring-nitrogen atom and α or γ to the other. This makes it necessary to discriminate carefully between two thioamide types, *e.g.*, (II) and (III) where R = H, and an additional *N*-methylated reference compound must be prepared. 4-Mercaptopyrimidine (No. 22)

* Thus, the spectrum of 4-hydroxypyridazine is almost identical with that of its 1- and unlike that of its 2-methyl derivative.[4]

[4] Mason, *J.*, 1958, 674.

is seen, from comparison of spectral data (Table 1), to have the mobile hydrogen atom mainly on a nitrogen atom, but the curves must be inspected to see which nitrogen is preferred. This is shown (Figure) to be $N_{(3)}$. In 4-mercaptoquinazoline (No. 28) $N_{(3)}$ is also favoured. The mobile hydrogen atom in 4-hydroxypyrimidine [5] also favours $N_{(3)}$ rather than $N_{(1)}$, but not to the same extent as in 4-mercaptopyrimidine. In 2-mercaptoquinazoline (No. 26), it is not yet possible to discriminate because we have not been able to obtain the requisite *N*-methyl derivatives. However, it is evident that the mobile hydrogen does not stay attached to the sulphur atom.

Ultraviolet Spectra of Anions and Cations.—In the spectra of the anions, the long-wavelength band occurs at much shorter wavelengths than in those of the neutral species. This follows the rule established [2] for the monoaza-analogues. The only exception is 2-mercaptoquinazoline (No. 26) which appears to be covalently hydrated across the 3,4-position in the neutral species and loses this water when the anion is formed, just as does 2-hydroxypteridine.[6] [Thus rapid neutralization of alkaline solutions of 2-mercaptoquinazoline gave spectra which changed rapidly. Initially maxima occurred at 284 mμ (log ε *ca.* 4·18) and >350 mμ (weak), indicating the presence of the (unstable) anhydrous neutral species. This changed at equilibrium to, mainly, the hydrated neutral species, the spectrum of which is given in the Table. This hydration cycle can be repeated many times. At pH 5·0 and pH 5·6, half-equilibrium was reached in *ca.* 1·5 and 4 seconds, respectively.]*



(VI) (VII) (VIII) (IX) (X)

The spectra of the cations have more individuality. With the monoaza-analogues, the spectra of the cations of the *S*- and *N*-methyl derivatives (of both α- and γ-mercapto-compounds) are somewhat similar, although those of the *S*-methyl derivatives are displaced to longer wavelengths by 1—17 mμ. This is compatible with both species' having analogous cations, *viz.*, (VI) for the *S*-methyl and (VII) for the *N*-methyl derivative [participation of a small proportion of canonical forms with charged sulphur, as (VIII), in a hybrid cation is not excluded]. Cations which have two hydrogen atoms on the ring nitrogen, as in (IX), are unlikely, although they have been considered to be significant for the cations of the hydroxypyridines.[7] Further, on the basis of infrared spectral evidence it has been concluded that the cations of 4-mercapto-pyridine and -quinoline are protonated at the sulphur atom.[8]

The diaza-analogues, on the other hand, present few examples of similar spectra among pairs of *N*- and *S*-methyl derivatives (see Table 1). Only 4-mercapto-pyridazine and -cinnoline resemble the monoaza-analogues in this respect (1-mercaptophthalazine is a possible additional example, but 4-mercaptopyrimidine is excluded by the curves shown in the Figure). It is concluded that " analogous cations " (as defined above) are uncommon in the diaza-series, and that most of the *N*-methyl derivatives in Table 1 form cations by protonation on nitrogen rather than on sulphur, thus resembling the monoaza-analogues. This means that the corresponding mercapto-compounds also add protons to nitrogen, because the spectrum of each cation resembles that of the *N*-methyl rather than that of the *S*-methyl derivative.

* We are grateful to Dr. D. D. Perrin for these measurements.

[5] Brown, Hoerger, and Mason, *J.*, 1955, 211.
[6] Albert and Howell, *J.*, 1962, 1591.
[7] Spinner, *J.*, 1960, 1237.
[8] Spinner, *J.*, 1962, 3127.

Of the examples in Table 1, suspected of protonating on nitrogen, four (2-mercapto-pyrimidine, -quinazoline, -pyrazine, and -quinoxaline) show further evidence of gross abnormality by a large bathochromic shift (20—81 mμ) on passing from neutral species to cation, in place of the large hypsochromic shift (~40 mμ) found on protonation of the monoaza-analogues. 4-Mercaptoquinazoline has a similar abnormality, but less in degree.

Spectra of Oxygen Analogues.—The spectra of those hydroxy-diaza-heterocycles which have not been previously examined are placed at the end of Table 1. Sources of recorded data are listed in Table 3. It was found that the spectrum of each hydroxy-compound resembled that of its *N*-methyl derivative and was unlike that of the *O*-methyl derivative. In these properties the hydroxy- and mercapto-series resemble one another. The existence of 4-hydroxyquinazoline (Table 1, No. 40) mainly in the amide-form, type (II), rather than in the vinylogous form, type (III), is even more marked than for 4-hydroxypyrimidine.[5]

Six of the hydroxy-derivatives show a shift to longer wavelength (for the long-wavelength band) when the neutral species is converted into the anion. This shift, which is the reverse of that found in mercapto-heterocycles, occurs with 3- and 4-hydroxypyridazine, 4-hydroxypyrimidine, 2- and 4-hydroxyquinazoline, and 2-hydroxyquinoxaline. Shifts in the long-wavelength band, when the hydroxy-derivatives are converted into their cations, are usually in the same direction as for the mercapto-analogues: the sole exceptions are 4-methoxy-pyrimidine and -quinazoline, where the shift is to shorter wavelengths, and 1,2-dihydro-2-methyl-1-oxophthalazine, where the shift is to longer wavelengths. " Analogous cations," as defined above, appear to exist for the *N*- and *O*-methyl derivatives of 3- and 4-hydroxypyridazine and of 4-hydroxycinnoline (see Table 1, and the data referred to in Table 3).

Ionization Constants.—The ionization constants, determined as in Part III,[2] are listed in Table 2. The symbol pK_a' is used for the equilibrium involving capture of a proton: the larger this figure is, the stronger is the substance as a base. It is evident that the pK_a' value of each mercapto-compound lies very close to that of the *N*-methyl derivative but differs from that of the *S*-methyl derivative. This confirms what has been postulated above, namely, that equilibria in these mercapto-compounds highly favour those forms which have the hydrogen atom on nitrogen. Further, in 4-mercapto-pyrimidine (No. 22) and -quinazoline (No. 28), where tautomerism in the neutral species can be either to type (II) or to type (III), the pK_a' values show clearly that the mobile hydrogen occurs more on $N_{(3)}$ than on $N_{(1)}$ (the $N_{(1)}$- and $N_{(3)}$-derivatives form " analogous cations," as defined above). That the pK_a' values of the 1-methyl derivatives are higher than those of the corresponding 3-isomers is inevitable because (*a*) both isomers have analogous cations, so that any difference in stability is confined to the neutral species, and (*b*) $N_{(3)}$ is the preferred site for mobile hydrogen in the neutral species, as was shown above from the spectra.

The invariable rule in the monoaza-series that the pK_a' of a *N*-methyl derivative should lie several units below that of the *S*-methyl derivative is, in general, observed in the diaza-series. The important exception is 2-mercaptopyrimidine (No. 1), where the basic strength of the *N*-protonated form is apparently increased by the excellent opportunity for resonance in the symmetrical cation (X; R = H). This is, moreover, the only example of a mercapto-compound that is a stronger base than the parent substance (cf. pyrimidine, pK_a' 1·30).

The pK_a' values show the mercapto-compounds of Tables 2 and 3 to be weaker bases than the corresponding hydroxy-compounds, in most cases by 1—2 logarithmic units. Also the *N*-methyl derivatives in the sulphur series are weaker bases than those in the oxygen series. On the other hand, as was found in the monoaza-series,[2] the *S*-methyl derivatives are only slightly weaker bases than the *O*-methyl derivatives, and this is in harmony with the known similarity of the inductive effect of the methylthio- and the methoxy-group. 2-Methylthioquinazoline (pK_a' 1·60) is unusual in being a stronger base than its methoxy-analogue (pK_a' 1·31) and probably owes this strength to its being more

TABLE 2.

Ionization of substances (in water at 20°).

No.	Substance	Proton gained (cation) pK_a'	Spread (±)	Concn. (M)	Proton lost (anion) pK_a	Spread (±)	Concn. (M)	Analytical wavelength [a] (mμ)
1	2-Mercaptopyrimidine	1·35 [b]	0·03	0·0002	7·14 [b]	0·05	0·0002	294 (pK_a'); 284 (pK_a)
2	*N*-Methyl	1·66	0·02	0·00003				344
3	*S*-Methyl	0·59	0·04	0·00018				320
4	3-Mercaptopyridazine	−2·68	0·07	0·00005	8·30	0·03	0·005	280 (pK_a')
5	$N_{(2)}$-Methyl	−2·95	0·25	0·000025				281
6	*S*-Methyl	2·26	0·01	0·000025				270
7	4-Mercaptopyridazine	−0·75	0·06	0·00004	6·54	0·04	0·001	346 (pK_a')
8	$N_{(1)}$-Methyl	−0·83 [c]	0·06	0·00004				304
9	*S*-Methyl	3·26	0·03	0·005				
10	4-Mercaptocinnoline	−1·83 [c]	0·03	0·00004	7·09	0·05	0·00004	239 (pK_a'); 420 (pK_a)
11	$N_{(1)}$-Methyl	−0·80	0·05	0·00002				244
12	*S*-Methyl	3·13	0·03	0·00005				386
13	1-Mercaptophthalazine	−3·43	0·05	0·00005	9·98	0·02	0·001	240 (pK_a')
14	$N_{(2)}$-Methyl	−3·98	0·07	0·00004				240
15	*S*-Methyl	3·48	0·04	0·00002				230
16	2-Mercaptopyrazine	−0·73 [d]	0·1	0·000025	6·32 [d]	0·03	0·005	382 (pK_a')
17	$N_{(1)}$-Methyl	−0·45 [d]	0·1	0·000025				437
18	*S*-Methyl	0·48 [d]	0·06	0·000025				359
19	2-Mercaptoquinoxaline	−1·24 [e]	0·08	0·0001	7·16 [e]	0·04	0·0002	500 (pK_a'); 460 (pK_a)
20	$N_{(1)}$-Methyl	−1·01	0·04	0·0001				490
21	*S*-Methyl	0·29 [e]	0·06	0·0001				420
22	4-Mercaptopyrimidine	0·68 [f]	0·04	0·0001	6·90	0·04	0·0001	306 (pK_a'); 300 (pK_a)
23	$N_{(1)}$-Methyl	1·16	0·01	0·00003				330
24	$N_{(3)}$-Methyl	0·56	0·08	0·00003				304
25	*S*-Methyl	2·48	0·02	0·05				
26	2-Mercaptoquinazoline	0·26	0·02	0·000003	8·14	0·04	0·00003	296 (pK_a'); 252 (pK_a)
27	*S*-Methyl	1·60	0·03	0·000025				256
28	4-Mercaptoquinazoline	1·51	0·04	0·00004	8·47	0·04	0·00004	230 (pK_a'); 282 (pK_a)
29	$N_{(1)}$-Methyl	3·00	0·05	0·000025				278
30	$N_{(3)}$-Methyl	1·22	0·01	0·000025				242
31	*S*-Methyl	3·01	0·02	0·0001				350
32	2,3-Dihydro-2-methyl-3-oxopyridazine	−2·1 [g]	0·3	0·000138				300
33	1,4-Dihydro-1-methyl-4-oxopyridazine	1·02 [h]	0·02	0·000063				280
34	1,4-Dihydro-1-methyl-4-oxocinnoline	0·91	0·05	0·00025				240
35	1,2-Dihydro-2-methyl-1-oxophthalazine	−4·3	0·2	0·000125				320
36	1-Methoxyphthalazine	3·77	0·045	0·00015				313
37	1,4-Dihydro-1-methyl-4-oxoquinazoline	3·19	0·03	0·000045				317·5
38	3,4-Dihydro-3-methyl-4-oxoquinazoline	2·18	0·09	0·00027				313

[a] An entry in this column means that the determination was spectroscopic (otherwise potentiometric). [b] Cf. ~1·3 and 7·2 (Boarland and McOmie, *J.*, 1952, 3716). [c] The absorption due to the cation was found by extrapolation. In strong acid, constant extinction coefficients could not be obtained. [d] Our values are somewhat lower than those of Cheeseman (*J.*, 1960, 242), who measured one value in 50% ethanol. [e] Our values differ from those of Cheeseman (*J.*, 1958, 108), especially that of 2-mercaptoquinoxaline anion which was measured in 50% ethanol. [f] Cf. <1 and 6·7 (Boarland and McOmie, *loc. cit.*). [g] The compound decomposes in solutions of strong sulphuric acid. [h] Eichenberger, Rometsch, and Druey (*Helv. Chim. Acta*, 1956, **39**, 1755) give 1·1 ± 0·1.

strongly covalently hydrated in the cation, the spectrum of which is sensitive to the water content of the acid in which it is measured.

The symbol pK_a is used for the equilibrium involving loss of a proton: the smaller this figure is, the higher is the acid strength of the substance. The mercapto-derivatives of the diaza-series (Table 2) are, in general, stronger acids than those of the monoaza-series,[2] as would be expected from the strong $-I$ effect of the extra doubly-bound ring-nitrogen atom. 1-Mercaptophthalazine is outstandingly weaker than the other substances in Table 2, and this is in harmony with the outstanding weakness, as an acid, of the similarly constituted 1-mercaptoisoquinoline.[2]

Comparison of these mercapto-derivatives with their hydroxy-analogues in Tables 2 and 3 shows them to be stronger acids by 1·3—2·5 logarithmic units.

Ratio of Tautomers at Equilibrium.—In the monoaza-series,[2] application of Ebert's

equation (i) gave the ratio of NH to SH forms of the neutral species, at equilibrium, in aqueous solution:

$$R = \text{antilog } (pK'_{SMe} - pK'_{SH}) - 1. \quad \text{(i)}$$

This equation is valid only where " analogous cations " are formed (see above). In the present work its application has been limited to 4-mercapto-pyridazine (R 10,000), and -cinnoline (R 90,000), with a possible extension to 1-mercaptophthalazine (R 8 × 10^6 ?).

In two other examples, which gave both $N_{(3)}H$ and $N_{(1)}H$ forms [related as (II) and (III), respectively], the ratio of these forms was calculated from equation (ii), which is a modification of (i). This was possible because the $N_{(3)}H$ and $N_{(1)}H$ forms gave " analogous

TABLE 3.

Sources of spectra and ionization constants of hydroxy-derivatives of heterocycles with two nitrogen atoms in one ring.

Substance	Ultraviolet spectra: Unsubst.	*N*-Methyl	*O*-Methyl	pK_a
2-Hydroxypyrimidine	1, 2	3	1, 3	4
3-Hydroxypyridazine	2		2, 5	4
4-Hydroxypyridazine	2, 5	5	2, 5	4, 5
4-Hydroxycinnoline				4
1-Hydroxyphthalazine				4
2-Hydroxypyrazine	2	2, 6	2, 6	4
2-Hydroxyquinoxaline	7	7	7	4, 7
4-Hydroxypyrimidine	1, 2, 3	2, 3	2	2, 4
2-Hydroxyquinazoline	8		9	4
4-Hydroxyquinazoline			9	4

Refs.: 1, Boarland and McOmie, *J.*, 1952, 3716. 2, Mason, *J.*, 1959, 1253. 3, Brown, Hoerger, and Mason, *J.*, 1955, 211. 4, Albert and Phillips, *J.*, 1956, 1294. 5, Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1956, **39**, 1755. 6, Mason, *J.*, 1957, 5010. 7, Cheeseman, *J.*, 1958, 108. 8, Brown and Mason, *J.*, 1956, 3443. 9, Armarego, *J.*, 1962, 561.

cations " and, although this cation was not shared by the SH form, the latter was, on the evidence, relatively scarce.

$$R = \text{antilog } (pK'_{N(1)Me} - pK'_{SH}) - 1. \quad \text{(ii)}$$

This gave $R = 2$ for 4-mercaptopyrimidine, and $R = 30$ for 4-mercaptoquinazoline. These values are similar to those (R 3 and 60, respectively) obtained by applying equation (iii), which was developed by Mason for some oxygen analogues.[4]

$$R = \text{antilog } (pK'_{N(1)Me} - pK'_{N(2)Me}). \quad \text{(iii)}$$

Turning to the hydroxy-compounds in Table 2, we find R 4000 for 4-hydroxycinnoline, using equation (i). The tautomeric ratio of $N_{(3)}H$ to $N_{(1)}H$ in 4-hydroxyquinazoline is R 10, by either of the equations (ii) and (iii), in close agreement with R 7 calculated by Mason [4] from spectra.

Preparation of the Substances.—The mercapto-compounds were, in general, prepared by the action of phosphorus pentasulphide on the corresponding hydroxy-compound in pyridine, or by the action of thiourea or potassium hydrogen sulphide on the chloro-compound. 2-Mercaptopyrimidine was synthesized from malondialdehyde triethyl methyl acetal and thiourea.

All the *S*-methyl derivatives were obtained by direct methylation of the mercapto-compound.

The *N*-methyl derivatives were obtained from the oxygen analogues and phosphorus pentasulphide in benzene or pyridine, with one exception. 1,2-Dihydro-1-methyl-2-thio-pyrimidine was synthesized from malondialdehyde triethyl methyl acetal and *N*-methyl-thiourea.

Attempts to prepare 1,2-dihydro-1-methyl-2-thioquinazoline and 2,3-dihydro-3-methyl-2-thioquinazoline by a variety of methods were unsuccessful. Quaternization of 2-hydroxyquinazoline with methyl iodide gave the 3-methyl derivative, as shown by its identity on paper chromatograms with 2,3-dihydro-3-methyl-2-oxoquinazoline, prepared from *o*-aminobenzaldehyde and methyl isocyanate. Attempts failed to convert this oxo- into the thio-derivative with phosphorus pentasulphide.

Although a large number of mercapto-compounds and their *N*-methyl derivatives have been prepared by treatment of their oxygen analogues with phosphorus pentasulphide, this reaction did not occur when the carbonyl group was situated α to two ring-nitrogen atoms. For example, 1,2-dihydro-1-methyl-2-thiopyrimidine could not be prepared thus from its oxygen analogue and phosphorus pentasulphide under any conditions of solvent or temperature used.

Experimental

Ionization constants were determined as previously described.[2] Paper chromatography (ascending) was carried out on Whatman No. 1 paper with (*a*) 3% aqueous ammonium chloride, and (*b*) butan-1-ol–5N-acetic acid (7 : 3) as solvent.

Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 110° unless otherwise stated. M. p.s were taken in soda-glass capillaries.

3-Mercaptopyridazine and its Derivatives.—3-Mercaptopyridazine, prepared from 3-hydroxypyridazine [9] and phosphorus pentasulphide in pyridine,[10] had m. p. 169—170°. Methylation with methyl iodide and sodium hydroxide [10] gave 3-methylthiopyridazine, b. p. 73°/0·1 mm., m. p. 39—40° (lit.,[10] b. p. 138°/15 mm., m. p. 37—38°). 1,6-Dihydro-1-methyl-6-thiopyridazine, m. p. 108—109°, was prepared from the oxygen analogue,[10] b. p. 56°/0·5 mm., m. p. 46° (lit.,[10] b. p. 110°/15 mm., m. p. 35°), and phosphorus pentasulphide in xylene.

4-Mercaptopyridazine.—4-Hydroxypyridazine [11] was prepared from dichlorosuccinic acid [12] through chloromaleic anhydride,[13] b. p. 190°/710 mm. (lit., b. p. 193—194°), 4-chloro-3,6-dihydroxy-,[14] 3,4,6-trichloro-,[14] and 3,6-dichloro-4-hydroxy-pyridazine.[11] Phosphorus pentasulphide (3 g.) was added to a boiling solution of 4-hydroxypyridazine in pyridine (50 ml.). Then the mixture was refluxed for 4 min., cooled, diluted with water, and evaporated under reduced pressure. After further evaporations with water, the residue was extracted with ethanol and chromatographed over alumina, giving *4-mercaptopyridazine* (95%) which, after sublimation (150°/0·005 mm.) and recrystallization from ethanol as yellow needles, had m. p. 206—210° (decomp.) (Found, for material dried in a vacuum over sodium hydroxide: C, 42·65; H, 3·55; S, 28·75. $C_4H_4N_2S$ requires C, 42·85; H, 3·6; S, 28·6%).

4-Methylthiopyridazine.—4-Mercaptopyridazine (0·6 g.) in N-sodium hydroxide (6 ml.) was shaken with methyl iodide (0·4 ml., 1·2 equiv.) for 15 min. The solution was extracted with chloroform, giving 4-methylthiopyridazine (0·57 g., 84%). The *picrate*, prepared in, and recrystallized from, ethanol, had m. p. 149—150·5° (Found, for material dried at 90°: C, 37·3; H, 2·65; N, 19·6; S, 8·9. $C_{11}H_9N_5O_7S$ requires C, 37·2; H, 2·55; N, 19·7; S, 9·0%). The *hydrochloride*, prepared in benzene and recrystallized from ethanol–ethyl acetate, had m. p. 190—191° (Found: C, 36·9; H, 4·3; N, 17·3; S, 19·6; Cl, 21·7. $C_5H_7ClN_2S$ requires C, 36·9; H, 4·35; N, 17·25; S, 19·7; Cl, 21·8%).

1,4-Dihydro-1-methyl-4-thiopyridazine.—1,4-Dihydro-1-methyl-4-oxopyridazine [11] (0·81 g.; m. p. 96·5—97·5°) and phosphorus pentasulphide (1·6 g.) were refluxed in benzene (60 ml.) for 1·5 hr. The benzene was evaporated, the excess of phosphorus pentasulphide decomposed by warm water, and the solution evaporated to dryness. Extraction of the residue with ethanol gave *1,4-dihydro-1-methyl-4-thiopyridazine* (0·66 g., 71%) as yellow needles, m. p. 164—165·5° (Found, for material dried at 110°/0·5 hr.: C, 47·35; H, 4·7; N, 21·9; S, 25·35. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

[9] Homer, Gregory, Overend, and Wiggins, *J.*, 1948, 2195.
[10] Duffin and Kendall, *J.*, 1959, 3789.
[11] Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1956, **39**, 1755.
[12] Terry and Eichelberger, *J. Amer. Chem. Soc.*, 1925, **47**, 1067.
[13] Michael and Tissot, *J. prakt. Chem.*, 1895, **52**, 331.
[14] Mizzoni and Spoerri, *J. Amer. Chem. Soc.*, 1954, **76**, 2201.

2-*Mercaptopyrimidine*, prepared from malondialdehyde triethyl methyl acetal and thiourea,[15] had m. p. 229—230° (decomp.). Methylation [16] gave 2-methylthiopyrimidine b. p. 100—101°/49 mm. (lit., 109°/28 mm.), n_D^{14} 1·5880 (lit., 1·5880).

1,2-*Dihydro*-1-*methyl*-2-*thiopyrimidine*.—10N-Hydrochloric acid (1 ml.) was added to a mixture of malondialdehyde triethyl methyl acetal (2 g.; from Kay-Fries Chemicals Inc., N.Y.) and *N*-methylthiourea [17] (1 g., 1·1 equiv.) in ethanol (20 ml.), which was then set aside at 20° overnight and later evaporated to dryness. The residue was dissolved in water (20 ml.), and the solution was made alkaline with potassium carbonate, extracted with chloroform, and chromatographed over alumina, giving 1,2-*dihydro*-1-*methyl*-2-*thiopyrimidine* (0·67 g., 55%), m. p. 189—191·5° (from ethanol) (Found: C, 47·7; H, 4·9; N, 22·1; S, 25·6. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

4-*Mercaptopyrimidine* was prepared from 4-hydroxypyrimidine by reaction of 4-chloropyrimidine hydrochloride [18] and thiourea. It had m. p. 187° (lit.,[18] 187°). Its hydrochloride (1·22 g.) in N-sodium hydroxide (16·4 ml.) was shaken with methyl iodide (0·5 ml.) for 15 min. The mixture was extracted with chloroform, giving 4-*methylthiopyrimidine* (0·67 g., 65%), b. p. 86—87°/12 mm. (Found: C, 47·5; H, 4·9; N, 21·9; S, 25·2. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

1,6-*Dihydro*-1-*methyl*-6-*thiopyrimidine*.—1,6-Dihydro-1-methyl-6-oxopyrimidine was prepared from 4-hydroxypyrimidine and ethereal diazomethane.[5] The product, once crystallized from light petroleum (b. p. 60—80°), had m. p. 120—123° (lit., 125—126°). This substance (0·2 g.) and phosphorus pentasulphide (0·6 g., 1·5 mol.) were refluxed in pyridine (6 ml.) for 1·5 hr. The solvent was removed under reduced pressure, the excess of phosphorus pentasulphide decomposed by warm water, the solution adjusted to pH 4, and the product extracted with chloroform. The 1,6-*dihydro*-1-*methyl*-6-*thiopyrimidine*, crystallized from light petroleum (b. p. 60—80°), had m. p. 97—98·5° (0·15 g., 71%) (Found, for material dried at 20°/10 mm.: C, 47·4; H, 4·8; N, 22·2; S, 25·5. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

1,4-*Dihydro*-1-*methyl*-4-*thiopyrimidine*.—1,4-Dihydro-1-methyl-4-oxopyrimidine, was prepared by desulphurization (Raney nickel) of 1,4-dihydro-1-methyl-2-methylthio-4-oxopyrimidine,[5] had m. p. 159° (lit., 155—156°). It (0·5 g.) and phosphorus pentasulphide (1 g.) were refluxed in pyridine (10 ml.) for 1 hr., the pyridine evaporated under reduced pressure, and the residue extracted with boiling ethanol, giving 53% of 1,4-*dihydro*-1-*methyl*-4-*thiopyrimidine* as yellow needles, m. p. 246° (Found, for material dried at 20°/10 mm.: C, 47·4; H, 4·8; N, 22·0; S, 25·3%).

2-*Mercaptopyrazine*.—2-Hydroxypyrazine [19] (1 g.) and phosphorus pentasulphide (1·5 g.) in pyridine (8·5 ml.) were refluxed for 45 min., and the pyridine was evaporated. The residue, dissolved in N-sodium hydroxide (15 ml.), was filtered and adjusted to pH 2 with 10N-hydrochloric acid. After chilling, the precipitate was filtered off and recrystallized from water, giving 2-mercaptopyrazine (46%) as yellow plates, m. p. 229° (lit.,[20] 215—218°) (Found, for material dried at 20°/10 mm.: S, 28·7. Calc. for $C_4H_4N_2S$: S, 28·6%). This product (0·47 g.) in N-sodium hydroxide (15 ml.) was shaken with methyl iodide (0·3 ml.) for 20 min. and extracted with ether. The extract gave 2-methylthiopyrazine (68%) which sublimed at 30°/0·1 mm. as a pale cream solid, m. p. 44—47° (lit.,[21] 45—47·5°) (Found: C, 48·2; H, 4·6; N, 22·2; S, 25·0. Calc. for $C_5H_6N_2S$: C, 47·6; H, 4·8; N, 22·2; S, 25·4%). 1,2-Dihydro-1-methyl-2-oxopyrazine was prepared from 2-hydroxypyrazine and diazomethane [22] and sublimed.[23] This substance (0·1 g.) and phosphorus pentasulphide (0·3 g.) were refluxed in pyridine (3 ml.) for 2 hr., the excess of pyridine evaporated, and the residue warmed with water, adjusted to pH 7 with sodium carbonate, and extracted with chloroform. The product, crystallized from light petroleum (b. p. 60—80°), gave 1,2-dihydro-1-methyl-2-thiopyrazine (0·06 g., 53%) as yellow needles, m. p. 132° (lit.,[21] 134—135°) (Found: C, 47·4; H, 5·0; N, 22·1; S, 25·7. Calc. for

[15] Hunt, McOmie, and Sayer, *J.*, 1959, 525.
[16] Boarland and McOmie, *J.*, 1952, 3716.
[17] Moore and Crossley, *Org. Synth.*, 1941, **21**, 83.
[18] Boarland and McOmie, *J.*, 1951, 1218.
[19] Erickson and Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400.
[20] Roblin and Clapp, *J. Amer. Chem. Soc.*, 1950, **72**, 4890.
[21] Cheeseman, *J.*, 1960, 242.
[22] Dutcher, *J. Biol. Chem.*, 1947, **171**, 321.
[23] Albert and Phillips, *J.*, 1956, 1294.

$C_5H_6N_2S$: C, 47·6; H, 4·8; N, 22·2; S, 25·4%). 2-Methylthiopyrazine and 1,2-dihydro-1-methyl-2-thiopyrazine had been prepared independently before the publication by Cheeseman.[21]

4-Mercaptocinnoline.—4-Hydroxycinnoline,[24] m. p. 227° prepared by diazotization of 2-aminoacetophenone,[24] with phosphorus pentasulphide in boiling pyridine gave 4-mercaptocinnoline,[25] m. p. 205—207° (lit., 202—205°). Methylation of this with methyl iodide in sodium hydroxide gave 4-methylthiocinnoline,[25] m. p. 96·5—97° (lit., 98°). 1,4-Dihydro-1-methyl-4-oxocinnoline, prepared from 4-hydroxycinnoline and dimethyl sulphate in potassium hydroxide,[26] had m. p. 157·5—159° (lit., for hemihydrate, m. p. 165—166·5°) (Found, for sublimed material: C, 63·5; H, 5·3; N, 16·8. Calc. for $C_9H_8N_2O,\frac{1}{2}H_2O$: C, 63·9; H, 5·35; N, 16·6%). This compound (1·07 g.) and phosphorus pentasulphide (2·2 g.) in benzene (50 ml.) were refluxed for 30 min. The benzene was evaporated, water added to decompose the excess of phosphorus pentasulphide, and the solution extracted with chloroform. The extract was chromatographed over alumina, giving a red crystalline residue (0·98 g., 83%) which crystallized from benzene–light petroleum (b. p. 60—80°) as red leaflets of *1,4-dihydro-1-methyl-4-thiocinnoline*, m. p. 182—184·5° (Found: C, 61·5; H, 4·5; N, 15·85; S, 18·15. $C_9H_8N_2S$ requires C, 61·35; H, 4·6; N, 15·9; S, 18·2%).

4-Chlorocinnoline was prepared from 4-hydroxycinnoline with phosphorus pentachloride and phosphorus oxychloride.[27] With sodium methoxide in methanol it gave 4-methoxycinnoline,[26] m. p. 127—128°.

1-Mercaptophthalazine.—1-Hydroxyphthalazine [28] (1 g.) and phosphorus pentasulphide (2 g.) in pyridine (50 ml.) was refluxed for 1·5 hr., cooled, diluted with water (30 ml.), and evaporated to dryness under reduced pressure. The residue was extracted with chloroform and chromatographed over alumina. 1-Mercaptophthalazine formed yellow crystals, m. p. 169—170° (lit.,[29] 170—175°), from ethanol (Found: C, 59·2; H, 3·75; N, 17·15; S, 19·6. Calc. for $C_8H_6N_2S$: C, 59·25; H, 3·75; N, 17·3; S, 19·75%). This material (1 g.) in N-sodium hydroxide (6 ml.) was shaken with methyl iodide (0·91 g.) for 30 min. and the solution extracted with chloroform. The light yellow residual liquid, extracted with light petroleum (b. p. 60—80°), gave light yellow crystals of 1-methylmercaptophthalazine, m. p. 75—77° (lit.,[29] 74—75°).

Dimethyl sulphate (2 ml.) was added dropwise to a solution of 1-hydroxyphthalazine (2 g.) in 4N-potassium hydroxide (54 ml.) at 50°, the temperature raised to 70° for 10 min., and the mixture allowed to cool. Extraction with chloroform gave 1,2-dihydro-2-methyl-1-oxophthalazine (1·04 g.) which, crystallized from light petroleum (b. p. 60—80°), had m. p. 112—114° (lit.,[30] 114°). This compound (1 g.) and phosphorus pentasulphide (2 g.) in pyridine (50 ml.) was refluxed for 1 hr., water (30 ml.) added, and the solution taken to dryness. Extraction of the residue with ethanol gave yellow crystals of 1,2-dihydro-2-methyl-1-thiophthalazine (0·9 g.), m. p. 128—129° (lit.,[29] 126—127°) (Found: C, 61·45; H, 4·6; N, 15·95; S, 18·2. Calc. for $C_9H_8N_2S$: C, 61·35; H, 4·6; N, 15·9; S, 18·2%).

2-Mercaptoquinazoline.—2-Hydroxyquinazoline [31] (1 g.) and phosphorus pentachloride (1·5 g., 1·05 equiv.) in phosphorus oxychloride (15 ml.) were refluxed for 30 min. and the excess of phosphorus oxychloride removed under reduced pressure. The cooled residue was dissolved in chloroform and shaken with cold aqueous sodium carbonate until the washings remained alkaline. The chloroform layer was dried (Na_2SO_4) and the solvent recovered, giving 2-chloroquinazoline (0·43 g., 38%) which, crystallized from light petroleum (b. p. 60—80°), had m. p. 107—108° (lit.,[32] 108°) (Found: C, 58·2; H, 3·15; Cl, 21·85; N, 16·75. Calc. for $C_8H_5ClN_2$: C, 58·4; H, 3·05; Cl, 21·55; N, 17·0%). This compound and alcoholic potassium hydrogen sulphide gave 2-mercaptoquinazoline [33] which, when sublimed (150°/0·005 mm.), had m. p. 230—231° (lit., 229—231°). 2-Mercaptoquinazoline was also produced when 2-chloroquinazoline (0·1 g.) and thiourea (0·1 g.) in methanol (1 ml.) were refluxed for 1 hr., the solvent evaporated, and the residue warmed with 2·5N-sodium hydroxide on a steam-bath for 1 hr.

[24] Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 419.
[25] Castle, Ward, White, and Adachi, *J. Org. Chem.*, 1960, **25**, 570.
[26] Schofield and Simpson, *J.*, 1945, 512.
[27] Busch and Klett, *Ber.*, 1892, **25**, 2847.
[28] Gabriel and Neumann, *Ber.*, 1893, **26**, 521.
[29] Fujii and Sato, Ann. Report G. Tanabe Co., Ltd., 1956, **1**, 1, 3 (*Chem. Abs.*, 1957, **51**, 6650).
[30] von Rothenberg, *J. prakt. Chem.*, 1895, **51**, 140.
[31] Gabriel and Posner, *Ber.*, 1895, **28**, 1029.
[32] Gabriel and Stelzner, *Ber.*, 1896, **29**, 1300.
[33] Gabriel, *Ber.*, 1903, **36**, 800.

Neutralization of the solution with acetic acid precipitated 2-mercaptoquinazoline. This compound (0·65 g.), dissolved in N-sodium hydroxide (6·5 ml.), was shaken with methyl iodide (0·5 ml.) for 30 min. The solution was extracted with chloroform, giving *2-methylthioquinazoline* which gave white crystals (0·41 g., 58%) from light petroleum (b. p. 60—80°). It had m. p. 59—60° (Found, for material dried in a vacuum at 20°: C, 61·1; H, 4·55; N, 15·8; S, 18·1. $C_9H_8N_2S$ requires C, 61·3; H, 4·6; N, 15·9; S, 18·2%).

2-Hydroxyquinazoline (1 g.), methyl iodide (2·5 ml.), and methanol (5 ml.) were heated in a sealed tube at 100°/3 hr. After chilling, the crystals (0·58 g.) were collected, and recrystallized from methanol, giving *2-hydroxyquinazoline methiodide*, m. p. 238—239·5° (Found, for material dried at 110°/20 mm.: C, 37·55; H, 3·1; N, 9·5. $C_9H_9IN_2O$ requires C, 37·5; H, 3·15; N, 9·7%).

o-Aminobenzaldehyde [34] (5·5 g.) and methyl isocyanate (8 ml.) in benzene (25 ml.) were refluxed for 2·5 hr. and then evaporated. The residue was warmed with 5N-hydrochloric acid for 1 hr., and the solution was then cooled, diluted with water, neutralized to pH 7, filtered, and evaporated to dryness. The residue was extracted with boiling ethanol. The extract, concentrated and allowed to crystallize, gave *4-ethoxy-1,2,3,4-tetrahydro-3-methyl-2-oxoquinazoline* (1·94 g.), m. p. 146—148° (Found: C, 64·5; H, 6·8; N, 13·7. $C_{11}H_{14}N_2O_2$ requires C, 64·1; H, 6·85; N, 13·6%). This white product sublimed, giving yellow crystals of *2,3-dihydro-3-methyl-2-oxoquinazoline*, m. p. 204—208° (Found: C, 67·9; H, 5·1. $C_9H_8N_2O$ requires C, 67·5; H, 5·0%). Chromatography of the latter compound and 2-hydroxyquinazoline methiodide in (*a*) aqueous ammonium chloride, (*b*) butanol–acetic acid, and (*c*) Kwietny and Bergmann's [35] solvent No. 5, gave identical spots for the two compounds, indicating that quaternization of 2-hydroxyquinazoline takes place on $N_{(3)}$.

4-Mercaptoquinazoline.—This was prepared from 4-hydroxyquinazoline [36] and phosphorus pentasulphide in pyridine.[37] When sublimed at *ca.* 200°/0·05 mm., it had m. p. 318—323° (decomp.) (lit.,[37] 320—322°). It is much more readily decomposed by air, and by cold acid and alkali, than is 4-mercaptoquinoline. Methylation with methyl iodide in sodium hydroxide gave 4-methylthioquinazoline, m. p. 65—66° (lit.,[38] 68°). 1,4-Dihydro-1-methyl-4-oxoquinazoline was prepared from 4-hydroxyquinazoline (through 4-chloro- [39] and 4-phenoxy-quinazoline).[40] When sublimed it had m. p. 137—140° (lit., anhydrous, 141—142°). This compound with phosphorus pentasulphide in pyridine gave 1,4-dihydro-1-methyl-4-thioquinazoline,[37] m. p. 198—199° (lit., 192—194°) (Found, for material dried at 100°/20 mm.: C, 61·35; H, 4·6; N, 15·7; S, 18·2. Calc. for $C_9H_8N_2S$: C, 61·3; H, 4·6; N, 15·9; S, 18·2%). 3,4-Dihydro-3-methyl-4-oxoquinazoline was prepared from 4-hydroxyquinazoline with methyl iodide in methanolic sodium methoxide.[41] When sublimed it had m. p. 103·5—105° (lit., anhydrous, 105°); with phosphorus pentasulphide in pyridine it gave 3,4-dihydro-3-methyl-4-thioquinazoline,[37] m. p. 141—142·5° (lit., 144—147°) (Found, for material dried at 110°/20 mm.: C, 61·2; H, 4·6; N, 15·8; S, 18·1%).

2-Mercaptoquinoxaline.—This was prepared [42] from 2-hydroxyquinoxaline [43] through 2-chloroquinoxaline.[43] It had m. p. 209° (lit., 204—205°) (Found, for material dried at 100°/0·1 mm.: N, 17·1. Calc. for $C_8H_6N_2S$: N, 17·3%). With methyl iodide in sodium hydroxide [44] it gave 2-methylthioquinoxaline, m. p. 46° (lit., 46—47°). 1,2-Dihydro-1-methyl-2-oxoquinoxaline was prepared from 2-hydroxyquinoxaline with dimethyl sulphate and sodium hydroxide.[45] It had m. p. 119° (lit., 120—121°). This compound (0·5 g.), phosphorus pentasulphide (1 g.), and benzene (10 ml.) were refluxed on a steam-bath for 20 min. (severer conditions caused much decomposition). The solvent was removed and the residue warmed with 5N-ammonia (10 ml.) and extracted with chloroform. The extract gave *1,2-dihydro-1-methyl-2-thioquinoxaline* (0·40 g., 73%) which crystallized from aqueous ethanol as yellow

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needles, m. p. 123—125° (Found, for material dried at 20°/10 mm.: C, 61·4; H, 4·5; N, 16·2. $C_9H_8N_2S$ requires C, 61·3; H, 4·6; N, 15·9%).

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