224. *An Experimental Study of Some Potentially Tautomeric 2- and 4(6)-Substituted Pyrimidines.*

By J. R. Marshall and James Walker.

Experiments have been carried out with the object of throwing fresh light on the structure, in aqueous solutions, of pyrimidines bearing potential hydroxyl, thiol, or amino-groups in the 2- or 4(6)-positions, by the study of compounds containing not more than one such substituent. The light absorption of the potential hydroxy- and mercapto-compounds was compared with that of the corresponding (i) *O*- or *S*- and (ii) *N*-methylated derivatives at pH values carefully chosen in relation to the pK_a values of each substance to ensure the presence only of neutral molecules, cations, or, where possible, of anions. The results clearly indicate a decision in favour of the pyrimidone and thiopyrimidone structures. The situation is less clear with the potential 2- and 4(6)-aminopyrimidines. The structure of uracil is also discussed.

Anomalous chemical behaviour has long been recognised in pyrimidines bearing in the 2- or 4(6)-position a potential hydroxyl, thiol, or amino-group (cf. Lythgoe, *Quart. Reviews*, 1949, **3**, 181), and similar anomalous behaviour is observable in condensed pyrimidines, such as the purines and pteridines bearing such substituents in the pyrimidine ring. In view of the biological significance of representatives of all three ring systems, considerable interest

attaches to the structure, in particular, of potential hydroxy- and amino-pyrimidines, -purines, and -pteridines in aqueous media. In each case, the potentially prototropic system

$$(A)\quad -NH\cdot C(:X)- \rightleftharpoons -N{:}C\cdot XH \quad (B)$$

where X = O, S, or NH, is involved, and the presence of one such group in a pyrimidine in the 1 : 2(2 : 3)- or the 3 : 4(1 : 6)-position may, or may not, influence considerably the behaviour of a second in the 3 : 4(1 : 6)-, or the 1 : 2(2 : 3)-position. In the case of 4 : 6-disubstituted pyrimidines at least one substituent must be present as a formal hydroxyl, thiol, or amino-group, as in (*B*) (cf. Baddiley, Lythgoe, and Todd, *J.*, 1943, 571). An indication of differential behaviour of potential thiol substituents in the 2- and 4-positions of the pyrimidine nucleus is found in the reaction between potential 2 : 4-dimercaptopyrimidines and ammonia (or amines), whereby *only* the potential 4-thiol group is replaced by an amino (or substituted amino)-group (Hitchings *et al.*, *J. Biol. Chem.*, 1949, **177**, 357; Russell *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2279), and the replacement of the potential 4-thiol group may be interpreted in terms of nucleophilic attack by the ammonia, or amine, at a $>C{:}S$ group, as in (*A*; X = S), the potential 2-thiol group remaining unaffected as in (*B*; X = S). By way of contrast, similar reaction of 2 : 4-diethoxy- and 2 : 4-dichloro-pyrimidines with ammonia results in the replacement of both substituents at roughly equal rates with the formation of mixtures of products (Hitchings *et al.*, *loc. cit.*; present communication), yet controlled catalytic hydrogenation of 2 : 4-dichloro-6-methylpyrimidine has been made the basis of a method for the preparation of 2-chloro-4-methyl-pyrimidine (see below). That a potential 6-hydroxy-group in purines exists as in (*A*; X = O) appears to be implicit in the electrolytic reduction of uric acid, xanthine, and theobromine to the 6-deoxy-derivatives (purone, deoxyxanthine, and deoxytheobromine) (Tafel, *Ber.*, 1899, **32**, 3194, and later papers; C. F. Boehringer ü. Söhne, D.R.-P. 108,577), while 9-methyluric acid and 7 : 9-dimethyluric acid give tetrahydro-6 : 8-diketo-2-methoxy-1 : 7 : 9-trimethylpurine but no 6-methoxylated purine with diazomethane (Biltz, *J. pr. Chem.*, 1936, **145**, 94). From a systematic study of the action of diazomethane on amides and potential amides, Arndt (*Rev. Fac. Sci. Istanbul*, 1936, **1**, 1; 1944, *A*, **9**, 19; Arndt, Loewe, and Ergener, *ibid.*, 1948, *A*, **13**, 103; Ergener, *ibid.*, 1950, *A*, **15**, 91) concludes that open-chain amides never exhibit tautomerism [(*A*) ⟶ (*B*); X = O] (cf. Biltz, *Ber.*, 1939, **72**, 807), that a potential amide group incorporated into a heterocyclic ring, as in potential 2- and 4(6)-hydroxypyrimidines, rarely shows tautomeric behaviour [(*A*) ⟶ (*B*); X = O], and that the group $-CO\cdot NH\cdot CO-$, such as may be present in uracil (see below), never exhibits tautomerism. The reservation should be made, however, that it is open to doubt to what extent results obtained in ethereal solution with diazomethane are applicable to aqueous solutions since the position of equilibrium in prototropic systems, and their mobility, depend to a considerable degree on the milieu as well as on internal factors.

The usual reactions for hydroxyl groups are difficult to carry out or fail with potential 2- or 4(6)-hydroxypyrimidines, and neither potential 2- nor 4(6)-aminopyrimidines show typical amino-group behaviour towards acylating agents and sugars (Baddiley, Lythgoe, and Todd, *loc. cit.*), although 5-aminopyrimidines are acylated normally (Isay, *Ber.*, 1906, **39**, 257; Levene and Senior, *J. Biol. Chem.*, 1916, **25**, 617). The ability of potential amino-groups in the 4(6)-position of the pyrimidine ring to undergo facile hydrolytic cleavage is indicated by the fact that alkaline permanganate degradation of aminopterin gives 2-" amino "-4-" hydroxy "-pteridine-6-carboxylic acid and not the expected 2 : 4-di-" amino "-compound (Seeger *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 1753). Potential 4-amino-groups in pteridines may readily be hydrolysed by mineral acid although resistant to nitrous acid, and potential 2-amino-substituents are more stable to hydrolysis but react with nitrous acid (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2282, 2538). These observations suggest that a potential amino-group in the 4-position behaves as it might be expected to do from structure (*A*; X = NH), while a potential 2-amino-group behaves more in accordance with (*B*; X = NH), yet 2-" hydroxypyrimidine " has been prepared by alkaline hydrolysis of 2-" aminopyrimidine " (Brown, *Nature*, 1950, **165**, 1010). The above cursory, and far from complete, review of the reactions of potential hydroxy-, mercapto- and amino-pyrimidines and condensed pyrimidines conveys some impression of the difficulties in the way of attempts to assign classical structures to these substances on the basis of their reactions as the normal states of these molecules are undoubtedly profoundly disturbed by electromeric effects brought into play under the influence of reagents.

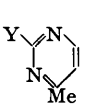
We have therefore attempted to obtain fresh light on the normal structures in aqueous solution of potential 2- or 4(6)-hydroxy- or -mercapto-pyrimidines by comparison of their ultra-violet light absorption with that of corresponding *O*-, or *S*-, and *N*-methylated derivatives;

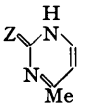
for the potential 2- or 4(6)-aminopyrimidines however, we have not had access to the necessary range of methylated reference compounds. There have been many studies of ultra-violet light absorption of substituted pyrimidines reported previously but these, for the most part, have dealt with the more accessible pyrimidines carrying two, and often more, functional groups [*e.g.*, Austin, *J. Amer. Chem. Soc.*, 1934, **56**, 2141; Cavalieri *et al.*, *ibid.*, 1948, **70**, 3875; 1950, **72**, 2587; Elion *et al.*, *ibid.*, 1946, **68**, 2137; Heyroth and Loofbourow, *ibid.*, 1931, **53**, 3441; 1934, **56**, 1728; Loofbourow *et al.*, *ibid.*, 1943, **65**, 148; *J.*, 1940, 1275; Miller *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 2206; Stimson, *ibid.*, 1942, **64**, 1604; Stimson *et al.*, *ibid.*, (i) 1941, **63**, 1827, (ii) 1943, **65**, 151, and (iii), 1945, **67**, 847, 2191; Stuckey, *Quart. J. Pharm.*, (i) 1940, **13**, 226, (ii) 1941, **14**, 217, and (iii), 1942, **15**, 370, 377; *J. Pharm. Pharmacol.*, 1949, **1**, 382], and there are few reports of any pyrimidines containing but one potentially prototropic system [(*A*) $\rightleftarrows$ (*B*)] having been examined (Smakula, *Z. physiol. Chem.*, 1934, **230**, 231; Williams *et al.*, *J. Amer. Chem. Soc.*, 1935, **57**, 1093; 1937, **59**, 528; Wintersteiner *et al.*, *ibid.*, 1935, **57**, 517). The value of some of the previous work carried out on aqueous solutions must really be regarded as slight since the hydrogen-ion concentrations at which ultra-violet light absorption has been measured have frequently been chosen without either knowledge of, or any reference to, the pK_a values of the substances being studied, with the result that absorption measurements have often been made on mixtures of ions and neutal molecules, and changes in the shapes of extinction curves with changes in pH have been attributed to " enolisation," whereas ionisation has really been the explanation of the effects observed.

For ease of access, all the compounds examined by the present authors had, in addition to one potentially prototropic system, a methyl group in the 6(4)-position, and, in a few cases, two methyl groups were present—in the 4- and the 6-position. It was not expected that such *C*-methyl groups would interfere to any marked degree with the observations it was intended to make, and this assumption was justified by the results obtained. 4-Methyl-2-methylthiopyrimidine (I) was obtained in good yield by dechlorination of 4-chloro-6-methyl-2-methylthiopyrimidine, and gave, on hydrolysis with hydrochloric acid, the hydrochloride of what may be either 2-hydroxy-4-methylpyrimidine (II) or 4-methyl-2-pyrimidone (III); the latter may also be represented as the 6-methyl compound (III*a*) but, for present purposes, no distinction exists between (III) and (III*a*), and further reference to such isomerism will not be made in this communication. On treatment with phosphoryl chloride (II)/(III) gave 2-chloro-4-methylpyrimidine in poor yield, and addition of phosphorus pentachloride introduced unwanted halogen (cf. Childress and McKee, *J. Amer. Chem. Soc.*, 1950, **72**, 4271). 2-Chloro-4-methylpyrimidine, however, could be obtained conveniently by controlled catalytic hydrogenation of 2 : 4-dichloro-6-methylpyrimidine, thus giving access to 2-methoxy-4-methylpyrimidine (IV) by reaction with sodium methoxide. In contrast with the experience of McOmie and Boarland (*Chem. and Ind.*, 1950, 602) who could not isolate the intermediate thiuronium salt in the reaction between 2-chloropyrimidine and thiourea, 2-chloro-4-methylpyrimidine and thiourea gave *S*-4′-methyl-2′-pyrimidylthiuronium chloride yielding on decomposition the hydrochloride of 2-mercapto-4-methylpyrimidine (V) or 4-methyl-2-thiopyrimidone (VI). 4-Hydroxy-6-methylpyrimidine (VII), or 6-methyl-4-pyrimidone (VIII), was readily obtained by desulphurisation of 6-methyl-2-thiouracil with Raney nickel, and gave 4-chloro-6-methylpyrimidine on treatment with phosphoryl chloride. By reaction with sodium methoxide and sodium methyl sulphide 4-chloro-6-methylpyrimidine readily gave 4-methoxy-6-methylpyrimidine (IX) and 6-methyl-4-methylthiopyrimidine (X) respectively, but no intermediate thiuronium salt could be isolated in the reaction with thiourea (cf. McOmie and Boarland, *loc. cit.*) and the product isolated consisted of 4-mercapto-6-methylpyrimidine (XI) or 6-methyl-4-thiopyrimidone (XII). As *N*-methylated reference compounds, 1 : 4 : 6-trimethyl-2-pyrimidone (XIII) and 1 : 4 : 6-trimethyl-2-thiopyrimidone (XIV) were obtained by condensation of acetylacetone with methylurea and methylthiourea respectively, and the methiodide (XV) of (XIII) was also prepared for comparison with the univalent cation formed by (XIII) in acid solution. Methylation of (VII)/(VIII) with diazomethane yielded *N* : 6-dimethyl-4-pyrimidone which may have either the structure (XVI) or the structure (XVII), of which, for a reason to be given later, (XVI) is preferred. Structures analogous to (XVII) may also be considered in relation to (VII)/(VIII) and (XI)/(XII) but evidence to show whether these are of importance is not available.

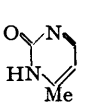
Ammonolysis of 2 : 4-dichloro-6-methylpyrimidine gave a mixture of products consisting of what may be called, for the sake of brevity, 2-amino-4-chloro-, 4-amino-2-chloro-, and 2 : 4-diamino-6-methylpyrimidine. Catalytic hydrogenation of the aminochloro-compounds afforded

(I.) Y = SMe
(II.) Y = OH
(IV.) Y = OMe
(V.) Y = SH
(XVIII.) Y = NH_2

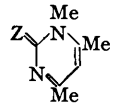




(III.) Z = O
(VI.) Z = S
(XIX.) Z = NH

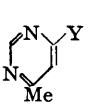


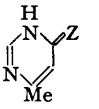
(IIIa.)



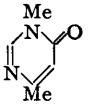
(XIII.) Z = O
(XIV.) Z = S

(VII.) Y = OH
(IX.) Y = OMe
(X.) Y = SMe
(XI.) Y = SH
(XX.) Y = NH_2

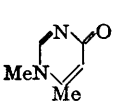




(VIII.) Z = O
(XII.) Z = S
(XXI.) Z = NH



(XVI.)



(XVII.)

	Compound.	pK_{a_1}.	pK_{a_2}.	Ultra-violet light absorption. pH of aqueous solution.	$\lambda_{max.}$.	$\log_{10} \varepsilon_{max.}$.
(III)	4-Methyl-2-pyrimidone	3·15	9·8	7·0	213, 296	4·05, 3·77
				1·0	305	3·85
				13·0	220, 290	4·06, 3·76
(XIII)	1 : 4 : 6-Trimethyl-2-pyrimidone	4·0	—	7·0	218, 297	3·82, 3·82
				0·0	307	3·96
(XV)	1 : 4 : 6-Trimethyl-2-pyrimidone methiodide	—	—	0·0	223, 311	4·18, 4·06
(IV)	2-Methoxy-4-methylpyrimidine	2·1	—	7·0, 11·0	264	3·73
				0·0	272	3·85
(VI)	4-Methyl-2-thiopyrimidone	2·2	8·0	4·7	215, 277, 338	4·01, 4·28, 3·51
				0·0	221, 285, 366	3·9, 4·4, 3·15
				11·0	269	4·24
(XIV)	1 : 4 : 6-Trimethyl-2-thiopyrimidone	3·15	—	7·0	220, 277, 332	4·03, 4·24, 3·65
				0·0	225, 283, 355	3·95, 4·37, 3·41
(I)	4-Methyl-2-methylthiopyrimidine	1·95	—	7·0, 11·0	210, 250	3·6, 4·14
				0·0	215, 253, 304	3·8, 4·15, 3·66
(VIII)	6-Methyl-4-pyrimidone	2·15	9·0	4·7	228, 263 *	3·86, 3·5 *
				0·0	229	4·02
				13·0	230, 261	4·03, 3·58
(XVI)	*N* : 6-Dimethyl-4-pyrimidone	2·1	—	7·0	224, 268	3·75, 3·56
				0·0	231, 260 †	3·94, 3·45
(IX)	4-Methoxy-6-methylpyrimidine	3·65	—	7·0, 13·0	213, 247	3·67, 3·52
				1·0	244	3·93
(XII)	6-Methyl-4-thiopyrimidone	1·8	7·3	4·7	288, 322	4·0, 4·05
				0·0	312	4·25
				11·0	292	4·2
(X)	6-Methyl-4-methylthiopyrimidine	3·25	—	7·0, 11·0	213, 277	3·84, 4·01
				1·0	223, 300	3·82, 4·3
(XVIII)/ (XIX)	2-Amino-4-methylpyrimidine	4·25 ‡	—	13·0	225, 289	4·09, 3·6
				0·0	222, 299	4·13, 3·68
(XX)/ (XXI)	4-Amino-6-methylpyrimidine	6·25	—	13·0	234, 264	3·95, 3·45
				0·0	250	4·18
(XXII)	5-Amino-4-methylpyrimidine	3·15	—	13·0	234, 293	3·91, 3·55
				0·0	253, 324	4·05, 3·6
(XXIII)	4-Methylpyrimidine	2·0 ‡	—	7·0	244	3·53
				0·0	244	3·7
(XXX; R = Me)	6-Methyluracil	~1·2	9·7	4·62	261	4·00
				13·0	277	3·83
(XXIX; R = Me)	1 : 3 : 6-Trimethyluracil	—	—	7·0	268	4·00
(XXVIII; R = R′ = Me)	2-Methoxy-6-methyl-4-pyrimidone	~1·6	8·4	4·62	253	3·91
				13·0	222, 263	3·83, 3·87

* From Williams, Ruehle, and Finkelstein (*loc. cit.*). † Inflexion.
‡ Albert, Goldacre, and Phillips (*loc. cit.*) record 4·15 and 1·98 respectively.

FIG. 1.

FIG. 2

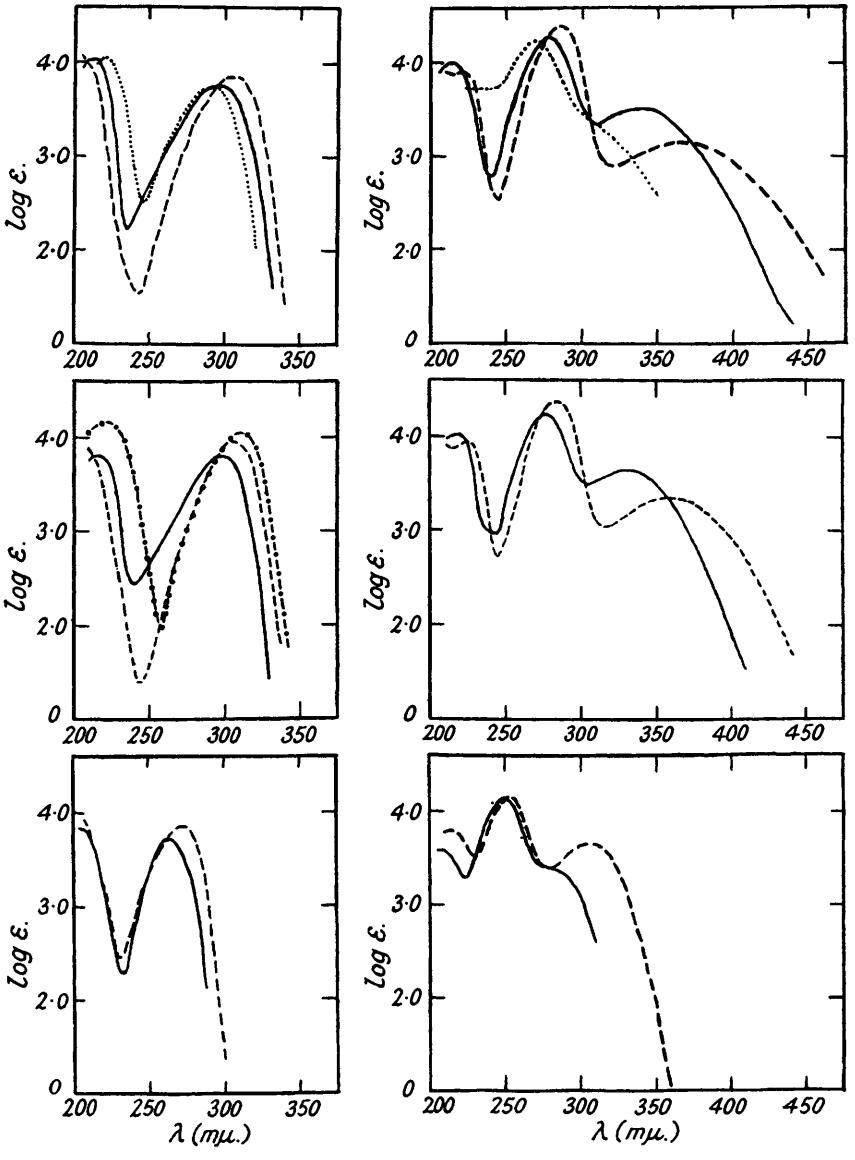


FIG. 1.

Top: 2-*Hydroxy*-4-*methylpyrimidine* (*II*) *or* 4(6)-*methyl*-2-*pyrimidone* (*III*) *in acid* (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*
Centre: 1 : 4 : 6-*Trimethyl*-2-*pyrimidone* (*XIII*) *in acid* (– – – –) *and neutral* (———) *solution.* 1 : 4 : 6-*Trimethyl*-2-*pyrimidone methiodide* (*XV*) *in acid* (· — · — · — ·) *solution.*
Bottom: 2-*Methoxy*-4-*methylpyrimidine* (*IV*) *in acid* (– – – –) *and neutral* (———) *solution.*

FIG. 2.

Top: 2-*Mercapto*-4-*methylpyrimidine* (*V*) *or* 4(6)-*methyl*-2-*thiopyrimidone* (*VI*).
Centre: 1 : 4 : 6-*Trimethyl*-2-*thiopyrimidone* (XIV).
Bottom: 4-*Methyl*-2-*methylthiopyrimidine* (*I*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

FIG. 3.

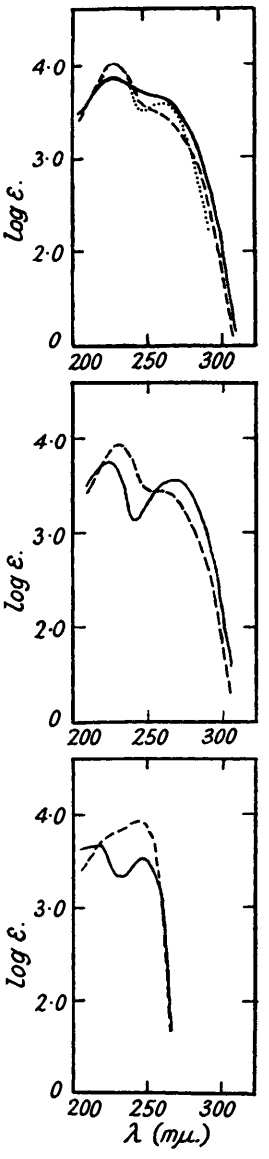


FIG. 4.

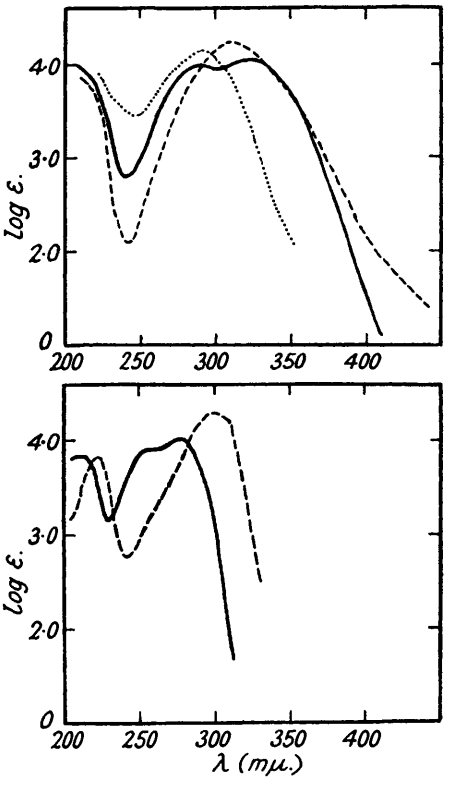


FIG. 3.

Top : 4-*Hydroxy*-6-*methylpyrimidine* (*VII*) *or* 6-*methyl*-4-*pyrimidone* (*VIII*).
Centre : *N* : 6-*Dimethyl*-4-*pyrimidone* (*XVI*)/(*XVII*).
Bottom : 4-*Methoxy*-6-*methylpyrimidine* (*IX*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

FIG. 4.

Top : 4-*Mercapto*-6-*methylpyrimidine* (*XI*) *or* 6-*methyl*-4-*thiopyrimidone* (*XII*).
Bottom : 6-*Methyl*-4-*methylthiopyrimidine* (*X*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

what may briefly be termed 2-amino-4-methyl- (XVIII)/(XIX) and 4-amino-6-methyl-pyrimidine (XX)/(XXI), without, however, implying any preference whatever for structures (XVIII) and (XX). 5-Amino-4-methylpyrimidine (XXII) was obtained by reduction, in two stages, of 2 : 4-dichloro-6-methyl-5-nitropyrimidine, obtained by applying Baddiley and Topham's technique (*J.*, 1944, 678) to 6-methyl-5-nitrouracil; a by-product in the latter reaction consisted of 2(4)-chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine analogous with the by-product obtained by King, King, and Spensley (*J.*, 1947, 1247) in applying the same

FIG. 5. FIG. 6.

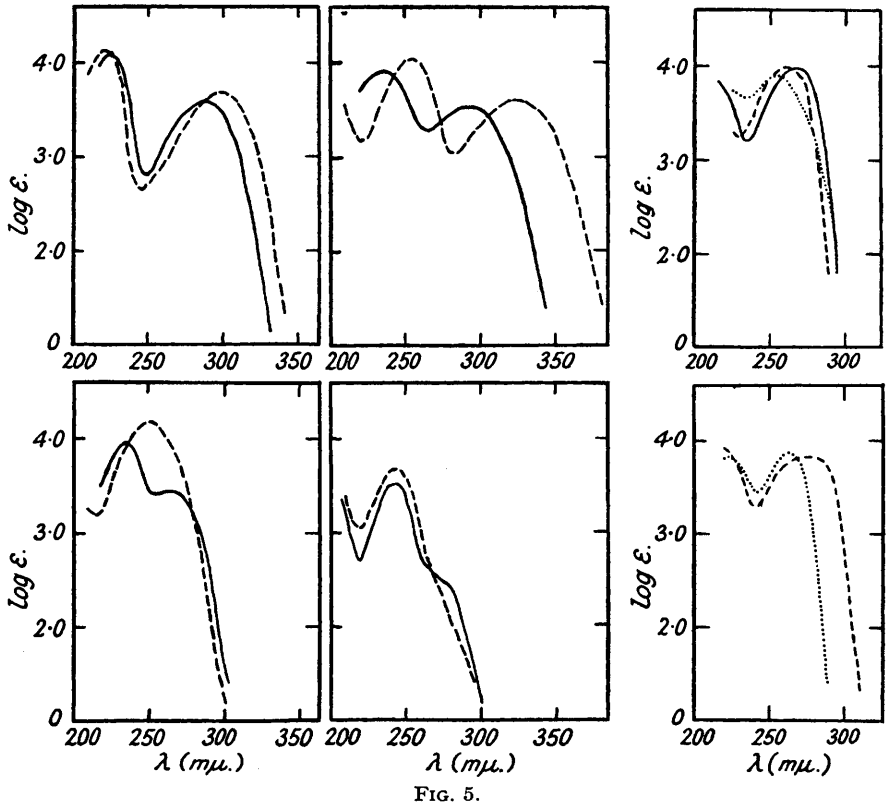


FIG. 5.

Top (left) : 2-Amino-4-methylpyrimidine (XVIII)/(XIX).
Bottom (left) : 4-Amino-6-methylpyrimidine (XX)/(XXI).
Top (right) : 5-Amino-4-methylpyrimidine (XXII).
Bottom (right) : 4-Methylpyrimidine (XXIII).
In acid (– – – –) and neutral (———) solution.

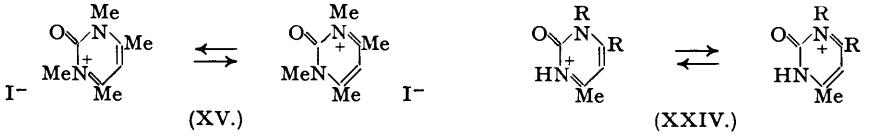
FIG. 6.

Top : 6-Methyluracil (XXX; R = Me) *at pH* 4·62 (– – – –); 1 : 3 : 6-*trimethyluracil* (*XXIX*; R = Me) *at pH* 7·0 (———); 2-*methoxy*-6-*methyl*-4-*pyrimidone* (XXVIII; R = Me) *at pH* 4·62 (· · · · · ·).
Bottom : 6-Methyluracil at pH 13 (– – – –); 2-*methoxy*-6-*methyl*-4-*pyrimidone* (· · · · · ·) *at pH* 13.

technique to barbituric acid. 4-Methylpyrimidine (XXIII) was prepared by dehalogenation of 2 : 4-dichloro-6-methylpyrimidine.

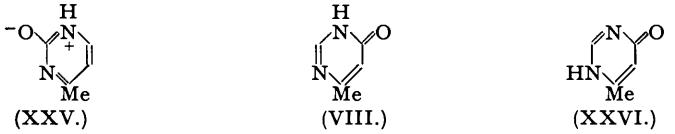
The pK_a values of all the substances being examined for ultra-violet light absorption were first determined by potentiometric titration and are recorded in the table. The light absorption was thereafter measured in aqueous solution at pH values chosen in relation to the pK_a values in such a way that essentially only neutral molecules, univalent cations, or where possible, univalent anions could have been present. Thus, measurements in acid solution, except for the limiting cases of the two most feebly basic compounds, (I) and (XI)/(XII), were carried out at pH values numerically at least 2 below the basic pK_a values, and in alkaline solution, in the case of acidic substances, at pH values numerically at least 2 above the acidic pK_a

value, ensuring at both extremes the presence of over 99% of the solute in the ionised condition. The light absorption of the un-ionised compounds was similarly measured in the middle of the pH range at pH values differing by at least 2 numerically from the relevant pK_a values, a pH value of less than 7 only being necessary in the cases of the more acidic substances. The wave-lengths of maximum extinction, and the logarithms of the molecular extinction coefficients, are recorded in the table but, as these do not convey an adequate impression of the absorption characteristics, light-extinction curves are shown in Figs. 1—6. Comparison of the light-extinction curves for (II)/(III) with those of 1 : 4 : 6-trimethyl-2-pyrimidone (XIII) and 2-methoxy-4-methylpyrimidine (IV) (Fig. 1) shows that there is close correspondence between the neutral and cationic species of the first two, but considerable difference between these and (IV), thus indicating a decision in favour of the 4-methyl-2-pyrimidone structure (III) for the potential 2-hydroxy-4-methylpyrimidine (II). The greater similarity between the light absorption of (XIII) in acid solution and that of its methiodide (XV), compared with that of (IV) in acid solution, indicates that in the formation of cations from (XIII) and (III) the proton is accepted by the second ring-nitrogen atom with the production of an extended resonating amidinium system (XXIV; R = Me or H). These observations also contraindicate the substantial contribution of the dipolar ionic form (XXV) to the structure of (III) (cf. Arndt, *loc. cit.*). Similar comparison of the light-extinction curves for (V)/(VI) with those for 1 : 4 : 6-trimethyl-2-thiopyrimidone (XIV) and 4-methyl-2-methylthiopyrimidine (I) (Fig. 2) likewise clearly indicates a decision in favour of the 4-methyl-2-thiopyrimidone structure (VI) for the potential 2-mercapto-4-methylpyrimidine (V). It is clear, moreover, that the addition of *C*-methyl groups in passing from (III) to (XIII) and from (VI) to (XIV) has had practically no effect on the absorption characteristics (cf. Williams, Ruehle, and Finkelstein, *J. Amer. Chem. Soc.*, 1935, **57**, 1093).



(XV.) (XXIV.)

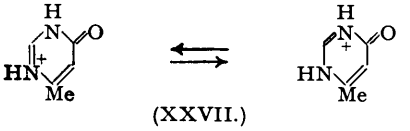
The light absorption of (VII)/(VIII) in acid solution is practically identical with that of *N* : 6-dimethyl-4-pyrimidone (XVI)/(XVII) in acid solution (Fig. 3). In neutral solution, the greater resolution achieved in the case of the latter compound makes the resemblance less striking, although it should be pointed out that Williams, Ruehle, and Finkelstein (*loc. cit.*) succeeded in obtaining rather better resolution of the longer-wave maximum of (VII)/(VIII) in neutral solution. In both acid and neutral solution, the light absorption of these two compounds, (VII)/(VIII) and (XVI)/(XVII), differs considerably from that of 4-methoxy-6-methylpyrimidine (IX), leading to the conclusion that the 6-methyl-4-pyrimidone structure (VIII) is preferred for the potential 4-hydroxy-6-methylpyrimidine (VII). The problem is rather more complex in this case than with the 2-pyrimidone since two types of structure are possible, *viz.*, (VIII) and (XXVI), in analogy with *N* : 6-dimethyl-4-pyrimidone (XVI)/(XVII). Structures (VIII) and (XVI) respectively are preferred because of the fact that no bathochromic shift is observed in passing from the one substance to the other on the analogy with the pyridones and *N*-methylpyridones, where *N*-methylation in 4-pyridone, which is analogous with (XXVI), is accompanied by a small bathochromic shift, while no such shift is



(XXV.) (VIII.) (XXVI.)

observed in passing from 2-pyridone to *N*-methyl-2-pyridone (Specker and Gawrosch, *Ber.*, 1942, **75**, 1338) or in passing from 2-quinolone to *N*-methyl-2-quinolone (Morton and Rogers, *J.*, 1925, **127**, 2698); further instances of this empirical rule will be noted later in connection with the structure of uracil. The light absorptions of 2-pyridone, *N*-methyl-2-pyridone, and 2-ethoxypyridine in acid solution resemble each other closely, as do those of 4-pyridone, *N*-methyl-4-pyridone, and 4-methoxypyridine in acid solution (Specker and Gawrosch, *loc. cit.*; cf. Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181, for analogous observations on 4-quinolone and 4-methoxyquinoline), and in these cases there can be no doubt that the proton

is accepted by the oxygen atoms of the pyridones in cation formation. On the other hand, no such behaviour is shown in the light absorptions of 6-methyl-4-pyrimidone (VII) and 4-methoxy-6-methylpyrimidine (IX) in acid solution, and, as already noted in the case of the 2-pyrimidone (III), cation formation by 6-methyl-4-pyrimidone (VIII) must take place by the acceptance of the proton by the nitrogen atom not already carrying a hydrogen atom, with the formation of an



(XXVII.)

amidinium system (XXVII). Although no comparison with the appropriate *N*-methylated reference compound has been made, the 6-methyl-4-thiopyrimidone structure (XII) is favoured for the potential 4-mercapto-6-methylpyrimidine (XI), because its absorption differs considerably from that of 6-methyl-4-methylthiopyrimidine (X) (Fig. 4).

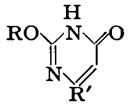
A number of significant regularities are apparent in the pK_a values of the pyrimidones, thiopyrimidones, methoxypyrimidines, and methylthiopyrimidines. Thus the sulphur-containing compounds are invariably less basic and, where possible, more acidic than their oxygen analogues. 4-Methoxy-6-methyl- (IX) and 6-methyl-4-methylthio-pyrimidine (X) are stronger bases than 2-methoxy-4-methyl- (IV) and 4-methyl-2-methylthio-pyrimidine (I), while the situation is reversed in the pyrimidones, 4-methyl-2-pyrimidone (III) and 4-methyl-2-thio-pyrimidone (VI) being stronger bases than 6-methyl-4-pyrimidone (VIII) and 6-methyl-4-thiopyrimidone (XII) respectively.

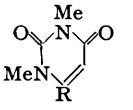
With the potential aminopyrimidines, the light-absorption measurements (Fig. 5), in the absence of comparable data for reference compounds in which prototropy has been blocked by methylation, do not allow of final conclusions being reached. On general grounds, it might be expected that a 5-aminopyrimidine would show some analogies with aromatic primary amines such as aniline and toluidine. Unlike the latter amines, however, which absorb at longer wave-lengths than their parent hydrocarbons and assume the absorption characteristics of the latter in acid solution, the absorption of 5-amino-4-methylpyrimidine (XXII) in acid solution is quite unlike that of 4-methylpyrimidine (XXIII) in neutral solution, indicating that the proton is accepted by one of the ring-nitrogen atoms of (XXII) in cation formation, as with the aminoacridines (Albert and Goldacre, *J.*, 1943 454) and the aminopyridines (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). 4-Amino-6-methylpyrimidine (XX)/(XXI) is a substantially stronger base than 2-amino-4-methylpyrimidine (XVIII)/(XIX), just as 4-amino-pyridine, -quinoline, and -quinazoline are stronger bases than 2-amino-pyridine, -quinoline, and -quinazoline (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240).

In the light of the conclusions reached above that the potential 2- and 4(6)-hydroxy- and -mercapto-pyrimidines, which we have examined, are to be represented as pyrimidones and thiopyrimidones respectively, a re-examination of the structure of uracil seemed to be warranted. Austin (*J. Amer. Chem. Soc.*, 1934, **56**, 2141) inferred that uracil had structure (XXVIII; R = R′ = H) from the fact that its light absorption in alcohol resembled that of 3-methyluracil, while differing from those of 1-methyluracil, 1 : 3-dimethyluracil (XXIX; R = H), 2 : 4-diethoxypyrimidine, and 4-ethoxy-1-methyl-2-pyrimidone, but no comparison with a reference compound of the type (XXVIII; R = alkyl, R′ = H) was attempted. Inspection of Austin's light-extinction curves shows that those of uracil and 3-methyluracil are indeed alike, while those of 1-methyluracil * and 1 : 3-dimethyluracil both show, in comparison, a small bathochromic shift, similar to that commented upon already in connection with 4-pyridone and 1-methyl-4-pyridone. Like the latter substance, 1-methyluracil and 1 : 3-dimethyluracil both have a *N*-methyl group and a >C:O group, or potential >C:O group, in the same relative 1 : 4-positions, indicating the doubtful relevance of the small bathochromic shifts observed. On these grounds we felt disinclined to agree with the rejection of structure (XXX; R = H) for uracil, and have extended Austin's study by comparing the light absorption of 2-methoxy-6-methyl-4-pyrimidone (XXVIII; R = R′ = Me), a reference compound of the type previously omitted, with those of 6-methyluracil and 1 : 3 : 6-trimethyluracil (XXIX; R = Me) in aqueous solution (Fig. 6). It is obvious that the light absorption of (XXVIII; R = R′ = Me) is unlike that of 6-methyluracil, and that those of 6-methyluracil and 1 : 3 : 6-trimethyluracil are alike apart from the small bathochromic shift in the light absorption of the latter, which we regard as

* In addition, 1-methyluracil also appears from Austin's work to show slightly stronger absorption.

irrelevant from the structural point of view in the light of our empirical generalisation and a natural consequence of *N*-methylation on the 1-nitrogen atom relative to the >C:O group in the 4-position. From these observations it is concluded that 6-methyluracil is to be represented as (XXX; R = Me) and uracil as (XXX; R = H), in agreement with the structure assigned to uracil on the basis of methylation with diazomethane (Case and Hill, *J. Amer. Chem. Soc.*, 1930, **52**, 1536). It may also be noted in passing that an analogous structure (XXXI) is preferred for 2-thiouracil on the basis of dipole-moment measurements in dioxan solution (Schneider and Halverstadt, *J. Amer. Chem. Soc.*, 1948, **70**, 2626).


(XXVIII.)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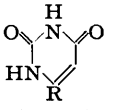
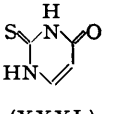

(XXX.)


(XXXI.)

Apart from the more labile chloropyrimidines the majority of the compounds described above were kindly tested by Dr. P. D'Arcy Hart for activity against the tubercle bacillus (bovine type) in Dubos medium with albumin and Tween 80. The two thiopyrimidones, (VI) and (XII), were active at 1 in 160,000; 6-methyldithiouracil was active at 1 in 40,000, and two other compounds, (I) and (XV), were active at 1 in 6,000 and at 1 in 10,000 respectively; otherwise none was active at 1 in 6000. It may be noted that 2-thiouracil has been shown to be active *in vitro* against the tubercle bacillus (Duca and Steinbach, *Amer. Rev. Tuberc.*, 1946, **53**, 594), while negligible activity has been reported by Brooks *et al.* (*J.*, 1950, 452) for a range of alkylthiopyrimidines. Dr. R. Pitt-Rivers kindly examined the effects of (VI) and (XII) on the formation of acetylthyroxine from acetyldi-iodotyrosine *in vitro* and found 0·1 molecular equivalent to produce 74% and 55% inhibition respectively in her standardised procedure (*Biochim. Biophys. Acta*, 1948, **2**, 311).

Experimental.

4-Methyl-2-methylthiopyrimidine (I).—4-Chloro-6-methyl-2-methylthiopyrimidine (100 g.) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 435) was added to a suspension of zinc powder (200 g.) in water (3 l.). The mixture was vigorously refluxed for 2 hours while aqueous ammonia (40 c.c.; *d* 0·880) was added in small portions from time to time; there was a slight evolution of methanethiol. After cooling, the unused zinc was removed and washed with ether. The aqueous solution was extracted several times with ether and, on fractionation of the dried extracts, *4-methyl-2-methylthiopyrimidine* distilled at 111°/15 mm. as a colourless liquid (71 g., 89%), n_D^{17} 1·5726 (Found: C, 51·7; H, 5·8. $C_6H_8N_2S$ requires C, 51·4; H, 5·7%). The *picrate* crystallised from about 5 parts of alcohol in yellow rhombohedral prisms, m. p. 106—108° (Found: C, 39·4; H, 2·8. $C_6H_8N_2S,C_6H_3O_7N_3$ requires C, 39·0; H, 3·0%).

An attempt (cf. Sprague *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3030) to prepare the above substance from the sodium salt of hydroxymethyleneacetone and *S*-methylthiuronium sulphate in cold aqueous solution gave less than 10% of the desired material, b. p. 114—118°/22 mm., n_D^{19} 1·5723.

4-Methyl-2-pyrimidone (III) *Hydrochloride.*—4-Methyl-2-methylthiopyrimidine (71·2 g.) was refluxed with concentrated hydrochloric acid (600 c.c.) until evolution of methanethiol ceased (*ca.* 80 minutes). The reddish-brown solution was evaporated to dryness under reduced pressure, and the residue, recrystallised from a mixture of alcohol and 3N-hydrochloric acid, gave almost colourless needles (64 g., 87%) of *4-methyl-2-pyrimidone hydrochloride*, m. p. 246° (decomp.) with discoloration above 210° (Found, on material dried over phosphoric oxide for 48 hours: C, 41·3; H, 4·9; N, 19·4. $C_5H_6ON_2,HCl$ requires C, 41·0; H, 4·8; N, 19·1%).

1 : 4 : 6-*Trimethyl-2-pyrimidone* (XIII).—This was prepared from methylurea and acetylacetone as described by Hale (*J. Amer. Chem. Soc.*, 1914, **36**, 104). Repeated extractions with chloroform were necessary to extract the product from aqueous solution; it had m. p. 62° after recrystallisation from benzene (alumina); Hale (*loc. cit.*) records m. p. 63°. Specimens exposed to the air gradually became pink, then red, especially when impure.

1 : 4 : 6-*Trimethyl-2-pyrimidone Methiodide* (XV).—1 : 4 : 6-Trimethyl-2-pyrimidone (1 g.) was treated with methyl iodide (5 c.c.). The pyrimidone soon dissolved and the methiodide crystallised. After 24 hours, the excess of methyl iodide was removed and the product separated from methanol–ethyl acetate, giving pale yellow flattened needles of the *methiodide* (1·1 g.), m. p. 194° to a red liquid, after 24 hours' desiccation (Found: C, 32·2, 32·6; H, 4·8, 5·1; N, 9·8; OMe, 0. $C_8H_{13}ON_2I,H_2O$ requires C, 32·3; H, 5·1; N, 9·4%). The mother-liquors developed a deep wine-red colour when kept.

2-Chloro-4-methylpyrimidine.—(*A*) A mixture of finely powdered 2-hydroxy-4-methylpyrimidine hydrochloride (29·3 g.) and phosphoryl chloride (150 c.c.) was kept at 120—125° (oil-bath) for 1·25 hours with intermittent shaking. The evolution of hydrogen chloride, initially brisk, became slight towards the end. The cooled red solution was filtered to remove unchanged starting material (21·3 g.). The phosphoryl chloride was removed under reduced pressure at 50°, and the residue treated with ice and neutralised with sodium hydroxide. The product (4·8 g.), recovered in ether and fractionated, afforded *2-chloro-4-methylpyrimidine* (3·9 g.), b. p. 93—93·5°/17 mm., m. p. 48—50°. Recrystallisation from

light petroleum gave elongated plates with unchanged m. p. (Found: C, 46·3; H, 4·1. $C_5H_5N_2Cl$ requires C, 46·9; H, 3·9%).

Despite numerous modifications in technique no appreciably greater conversion was achieved using phosphoryl chloride, and the addition of phosphorus pentachloride led to the formation of a polychloro-derivative. A mixture of 4-methyl-2-pyrimidone hydrochloride (15·2 g.) and phosphorus pentachloride (30 g.) in phosphoryl chloride (50 g.) was refluxed for 1·5—2 hours. The phosphoryl chloride was removed in the usual way and the residue was treated with crushed ice and aqueous sodium hydroxide to pH 9. Ether was added and the crude product (13 g.) was recovered after rejection of an insoluble brown solid (3—4 g.). On fractionation there were obtained: (i) a mixture (3·44 g.), b. p. 70—132·5°/13 mm., which did not solidify on cooling, and (ii) the main bulk (6·3 g.) of the product, b. p. 132·5—134°/13 mm., which rapidly solidified when scratched; crystallisation from light petroleum afforded brilliant long prisms of 2 : x : x : x-*tetrachloro-4-methylpyrimidine*, m. p. 43·5—45° (Found: C, 26·1; H, 0·9; N, 12·2; Cl, 60·5. $C_5H_2N_2Cl_4$ requires C, 25·9; H, 0·9; N, 12·1; Cl, 60·7%).

(*B*) By use essentially of the method of Gabriel and Colman (*Ber.*, 1899, **32**, 1533), 6-methyluracil (*Org. Synth.*, **17**, 63) was converted into 2 : 4-dichloro-6-methylpyrimidine. The reaction mixture was poured into iced water and the product was recovered in ether, the extract being washed with water and thoroughly dried before fractionation. The product, obtained in 90—95% yield as compared with the 77% yield hitherto recorded, had b. p. 108°/18·5 mm.; it gradually decomposed.

A mixture of 2 : 4-dichloro-6-methylpyrimidine (81·5 g., 0·5 mole), light magnesium oxide (25 g., 25% excess), ether (100 c.c.), and water (100 c.c.) was shaken for 16 hours at room temperature with 1·2% palladised strontium carbonate (8 g.) in hydrogen under a pressure of *ca.* 3 atms.; the theoretical volume of hydrogen (11·2 l. at N.T.P.) was absorbed. The reaction mixture was filtered, the solid being well washed with ether and water, and the crude product (52 g.) was recovered in ether after bringing the pH of the aqueous phase to 10—11. On fractionation there were obtained: (i) a small fraction, b. p. up to 90°/17·5 mm., which was not further examined; (ii) a pink-coloured main fraction (35·6 g.), b. p. 94—99°/17·5 mm., which solidified on cooling; and (iii) a mixture (7·8 g.), b. p. 99—105°/17·5 mm., which did not crystallise. The main fraction (ii) was decolorised in hot light petroleum with activated alumina and, on concentration and cooling, large prisms separated, m. p. 48—50° alone and on admixture with the product obtained as in (*A*) above.

The substance liquefied when mixed at room temperature with either 2 : 4-dichloro-6-methyl- or 4-chloro-6-methyl-pyrimidine. The use of alcoholic alkali was precluded in the above hydrogenation since 2 : 4-dichloro-6-methylpyrimidine reacted exothermally in the cold with potassium hydroxide in 80% methanol to give 2 : 4-dimethoxy-6-methylpyrimidine, m. p. 65° (lit., m. p. 69—70°). Some hydrolysis also took place in the presence of aqueous alkali.

2-*Methoxy*-4-*methylpyrimidine* (IV).—2-Chloro-4-methylpyrimidine (6·4 g.) was added to a solution of sodium methoxide (from 2·8 g. of sodium) in methanol (50 c.c.). Sodium chloride was rapidly precipitated in an exothermic reaction. After 15 minutes on the water-bath, the solution was poured into water and extracted with ether. Fractionation of the extract afforded 2-*methoxy*-4-*methylpyrimidine* (5 g.) as a colourless liquid, b. p. 89°/21 mm., n_D^{21} 1·5013 (Found: C, 58·3; H, 6·5. $C_6H_8ON_2$ requires C, 58·1; H, 6·5%).

S-4-*Methyl*-2-*pyrimidylthiuronium Chloride*.—A solution of 2-chloro-4-methylpyrimidine (1·28 g.) and thiourea (0·76 g.) in ethanol (11 c.c.) was refluxed until a test drop no longer gave a dark precipitate with ammoniacal silver nitrate (*ca.* 40 minutes). Pale orange needles (1·15 g.) separated on cooling and a further quantity (0·23 g.) was obtained on concentration of the mother-liquors. The crude product was dissolved in ethanol (10 c.c.) containing a few drops of concentrated hydrochloric acid and freed from a small residue (90 mg.) of 4-methyl-2-thiopyrimidone. On cooling, S-4′-*methyl*-2′-*pyrimidylthiuronium chloride* separated in yellow needles which became pink at 160°, reddened at 180—185°, and decomposed at 185—200° (Found: C, 35·5; H, 4·3; N, 26·8. $C_6H_9N_4SCl$ requires C, 35·2; H, 4·4; N, 27·4%).

4-*Methyl*-2-*thiopyrimidone* (VI) *Hydrochloride*.—A solution of the preceding thiuronium chloride (0·88 g.) in alcohol (25 c.c.) was heated on the water-bath with a few drops of concentrated hydrochloric acid for 8 hours, the product separating slowly during that period. Recrystallisation of the product (0·5 g.) from a large volume of alcohol (300 c.c.) containing about 1·5% of concentrated hydrochloric acid by volume and concentration to small bulk (40 c.c.) gave small yellow plates of 4-*methyl*-2-*thiopyrimidone hydrochloride*, m. p. 265° (decomp.) (Found: C, 36·6; H, 4·2; N, 17·5. $C_5H_6N_2S,HCl$ requires C, 36·9; H, 4·3; N, 17·2%).

1 : 4 : 6-*Trimethyl*-2-*thiopyrimidone* (XIV).—This compound was prepared according to Hale and Williams's method (*J. Amer. Chem. Soc.*, 1915, **37**, 598) from acetylacetone and methylthiourea.

6-*Methyl*-4-*pyrimidone* (VIII).—6-Methyl-2-thiouracil (56·8 g.) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105) was suspended in water (800 c.c.) and refluxed for 2 hours with Raney nickel (76 c.c. of sludge), which had not been exposed to temperatures exceeding 50° during its preparation. The catalyst was collected and washed with water, and the aqueous solution and washings were taken to dryness. The crude product (45 g.) was extracted with boiling ethyl acetate, leaving a sticky residue. The ethyl acetate was removed and the product was again taken up in boiling ethyl acetate with rejection of a further slight sticky residue. The extraction process was repeated twice more with the substitution of benzene for ethyl acetate, affording material (28 g., 64%) suitable for further use. Recrystallisation from ethanol (4 parts) and then from benzene (20 parts) gave pure 6-methyl-4-pyrimidone as colourless elongated prisms, m. p. 150°. Gabriel and Colman (*Ber.*, 1899, **32**, 2931) record m. p. 149—150° and Williams *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 528), m. p. 148—149°.

N : 6-*Dimethyl*-4-*pyrimidone* (XVI).—6-Methyl-4-pyrimidone (1·5 g.) in chloroform (10 c.c.) was added to ethereal diazomethane (from 10 g. of nitrosomethylurea). The precipitate which separated immediately redissolved with evolution of heat and nitrogen. After 24 hours, the solvent and excess of

diazomethane were removed, finally at 60—70°. 4-Methoxy-6-methylpyrimidine (0·23 g.) was removed from the residue at 100°/15 mm. The solid residue was recrystallised from carbon tetrachloride (alumina), giving hard colourless prisms of N : 6-*dimethyl*-4-*pyrimidone* (0·8 g.), m. p. 80—82° (Found : C, 57·9; H, 6·3; N, 22·5. $C_6H_8ON_2$ requires C, 58·1; H, 6·5; N, 22·6%).

The 4-methoxy-6-methylpyrimidine, n_D^{20} 1·4949, was converted into the *picrate* with cold aqueous picric acid. It separated from water in beautiful flattened prisms, m. p. 117°, alone and on admixture with a specimen of picrate prepared from 4-methoxy-6-methylpyrimidine obtained by the previously described route (above) (Found : N, 19·8. $C_6H_8ON_2,C_6H_3O_7N_3$ requires N, 19·8%).

4-*Chloro*-6-*methylpyrimidine*.—(*A*) 6-Methyl-4-pyrimidone (18 g.) was treated with phosphoryl chloride (150 g.) essentially as described by Gabriel and Colman (*Ber.*, 1899, **32**, 2921). The mixture was heated on the boiling water-bath for 1·25 hours, dissolution being complete in ¾—1 hour. The phosphoryl chloride was removed and the residue was treated with crushed ice, the product being isolated by basification and extraction with ether. On fractionation, the crude product (20 g.) gave pure 4-chloro-6-methylpyrimidine (14·8 g., 70%), b. p. 65·5—66·5°/12 mm., m. p. 34·5—36°. Gabriel and Colman (*loc. cit.*) record m. p. 38—39·5°.

(*B*) A slightly better yield was obtained by direct treatment with phosphoryl chloride of the crude desulphurisation product from 6-methyl-2-thiouracil, the overall yield from the latter being 53%.

The compound decomposed slowly, becoming orange. It could readily be purified by distillation preferably after being partitioned between ether and water, the orange colour passing into the aqueous phase.

4-*Methoxy*-6-*methylpyrimidine* (IX).—4-Chloro-6-methylpyrimidine (8·7 g.) was added to sodium methoxide (from 2·8 g. of sodium) in methanol (50 c.c.). Sodium chloride was immediately precipitated with evolution of heat. After 15 minutes on the water-bath the mixture was poured into water and the product recovered in ether. Fractionation of the extract afforded 4-*methoxy*-6-*methylpyrimidine* as a colourless liquid (6·65 g., 79%), b. p. 69°/21 mm., n_D^{21} 1·4950 (Found : C, 58·4; H, 6·6. $C_6H_8ON_2$ requires C, 58·1; H, 6·5%).

6-*Methyl*-4-*thiopyrimidone* (XII).—A solution of 4-chloro-6-methylpyrimidine (2·57 g.) and thiourea (1·52 g.) in ethanol (25 c.c.) was refluxed for an hour. On cooling, 6-methyl-4-thiopyrimidone (1·2 g.) separated instead of the expected *S*-6′-methyl-4′-pyrimidylthiuronium chloride. The substance crystallised from acetic acid, or from a large volume of water (charcoal), in pale yellow prisms, m. p. 255—260° (decomp.) with darkening from about 190°. Gabriel and Colman (*Ber.*, 1899, **32**, 2932) record m. p. 255° (decomp.) with sintering at 190°.

A crystalline thiuronium salt could not be isolated from the reaction mixture. In another experiment the reaction was carried out in 0·2N-hydrochloric acid and again only the thiopyrimidone was isolated though in lower yield.

6-*Methyl*-4-*methylthiopyrimidine* (X).—To a solution of sodium methyl sulphide, obtained by adding 25% aqueous sodium hydroxide (25 c.c.) to *S*-methylthiuronium sulphate (18·9 g.) and collecting the evolved methanethiol in 30% aqueous sodium hydroxide (10 c.c.), there was added 4-chloro-6-methylpyrimidine (6·43 g.). The inhomogeneous mixture was kept for 4 hours at 60—80° with intermittent shaking. Alcohol (25 c.c.) was added to effect mixing, and heating was continued under reflux on the boiling water-bath for 3 hours. After removal of the alcohol by distillation, the crude product (6·5 g.) was recovered in ether. 6-*Methyl*-4-*methylthiopyrimidine* distilled as a colourless liquid at 104°/17 mm., n_D^{20} 1·5740 (Found : C, 51·6; H, 6·1. $C_6H_8N_2S$ requires C, 51·4; H, 5·7%). The compound later solidified and recrystallisation from light petroleum gave colourless prisms, m. p. 25—28°.

Ammonolysis of 2 : 4-*Dichloro*-6-*methylpyrimidine*.—The proportions of the products formed in the ammonolysis of 2 : 4-dichloro-6-methylpyrimidine varied considerably according to the conditions of reaction (cf. Gabriel and Colman, *Ber.*, 1899, **32**, 2921; 1901, **34**, 1234). The general method used was as follows : 2 : 4-Dichloro-6-methylpyrimidine (80 g.) and alcoholic ammonia (500 c.c.), saturated at 0°, were heated in a stainless steel autoclave. The clean reaction mixture was taken to dryness and the residue was washed with chilled 2N-aqueous ammonia (300—400 c.c.). The dried mixture was boiled with benzene (30—40 c.c. per g.), and the hot solution was filtered and evaporated to give 2-" amino "-4-chloro-6-methylpyrimidine (A). The residue was continuously extracted with boiling benzene which slowly removed 4-" amino "-2-chloro-6-methylpyrimidine (B), leaving a " hydrochloride " (C) of 2 : 4-" diamino "-6-methylpyrimidine; alternatively, the last could be removed by crystallisation from water leaving 4-" amino "-2-chloro-6-methylpyrimidine. Three typical experiments are summarised in the following table.

Solvent.	Time of heating.	Temperature.	Yields (g.). (A).	(B).	(C).
Ethanol	5 hours	92°	28·1	32·9	nil
Ethanol	6 hours	95—105	15·6	16·5	30
Methanol	6 hours	95—105	0·8	4·5	50

2-Amino-4-chloro-6-methylpyrimidine separated from 12 parts of alcohol in colourless needles, m. p. 183°; Gabriel and Colman (*locc. cit.*) record m. p. 181—182°. 4-Amino-2-chloro-6-methylpyrimidine crystallised from 12 parts of alcohol in colourless prisms, m. p. 219·5°; Gabriel and Colman (*locc. cit.*) record m. p. 215—216°.

The " hydrochloride " (C) of 2 : 4-diamino-6-methylpyrimidine separated from ethanol (15 parts) in large tabular prisms, m. p. 213—215°. Consistent analytical figures were not obtained but they indicated approx. three molecules of base per molecule of hydrogen chloride (Found, on material dried over phosphoric oxide *in vacuo* : C, 43·8; H, 6·0; N, 41·2. $3C_5H_8N_4,HCl$ requires C, 44·1; H, 6·1; N, 41·1%). Free 2 : 4-diamino-6-methylpyrimidine, precipitated from the " hydrochloride " with 50%

aqueous potassium hydroxide solution, crystallised from water (1 c.c./g.), and then sublimed in a vacuum, had m. p. 185—186° (Found: C, 49·1; H, 6·5; N, 45·4. Calc. for $C_5H_8N_4$: C, 48·4; H, 6·5; N, 45·2%). Gabriel and Colman (*locc. cit.*) record m. p. 183—185°.

2-*Amino*-4-*methylpyrimidine* (XVIII)/(XIX).—A mixture of 2-amino-4-chloro-6-methylpyrimidine (7·2 g.) in acetone (200 c.c.) and potassium hydroxide (2·8 g.) in water (100 c.c.) was shaken with 1·2% palladised strontium carbonate (2 g.) in hydrogen at atmospheric pressure, the calculated volume of hydrogen being absorbed in 3 hours. The filtered solution was taken to dryness and the residue was extracted with boiling ethanol (70 c.c.). Evaporation of the alcohol and crystallisation of the residue from water afforded colourless plates (3·7 g.) of 2-amino-4-methylpyrimidine, m. p. 158—160°. Backer and Grevenstuk (*Rec. Trav. chim.*, 1942, **61**, 291) record m. p. 154·5—156·5°, and Gabriel and Colman (*locc. cit.*), m. p. 159—160°. The compound gradually evolved ammonia when boiled with 20% sodium hydroxide solution.

4-*Amino*-6-*methylpyrimidine* (XX)/(XXI).—A solution of 4-amino-2-chloro-6-methylpyrimidine (2·9 g.) in methanol (200 c.c.) was shaken with 5% palladised charcoal (0·4 g.) in hydrogen at atmospheric pressure. Hydrogen (470—500 c.c.) was absorbed during 16 hours and there was no subsequent absorption. The filtered solution was evaporated and the residue, in water (10 c.c.), was basified with potassium hydroxide (4 g.), which precipitated the free base (2·3 g.), m. p. 196—198°. Recrystallisation from water (6 c.c.) and vacuum-sublimation gave pure 4-amino-6-methylpyrimidine (1·42 g., 65%), m. p. 197°. Backer and Grevenstuk (*loc. cit.*) record m. p. 197—197·5°, and Gabriel and Colman (*locc. cit.*) m. p. 194—195°. The solubility in cold water was about 10%. When the compound was heated with 25% aqueous sulphuric acid to 180° for 2 hours, no darkening occurred and some 6-methyl-4-pyrimidone was isolated from the reaction mixture besides unchanged amine.

2 : 6-*Dichloro*-6-*methyl*-5-*nitropyrimidine*.—Dimethylaniline (10 g.) was added carefully to a suspension of 6-methyl-5-nitrouracil (8 g.) (Gabriel and Colman, *Ber.*, 1901, **34**, 1242) in phosphoryl chloride (40 c.c.), and the mixture was refluxed for 45 minutes. The dark green mixture was cooled, then poured on ice, and the product (8 g.) was recovered in ether. On fractional distillation there were obtained: (i) 2 : 4-dichloro-6-methyl-5-nitropyrimidine (6·4 g.), b. p. 137°/23 mm., m. p. 53—54·5° after crystallisation from light petroleum (lit., m. p., 53—54·5°), and (ii) a fraction, b. p. 188°/2 mm., which solidified on cooling. The latter substance separated from alcohol (10 c.c.) in yellow columnar prisms (0·75 g.), m. p. 111—113°, resolidifying to melt at 127°. It was dried *in vacuo* at 100° over phosphoric oxide for 6 hours after which treatment there was no sintering on immersion in a bath at 120° and the pure 2(4)-*chloro*-6-*methyl*-4(2)-*methylanilino*-5-*nitropyrimidine* had m. p. 128°; the substance slowly sublimed during the drying (Found: C, 52·2; H, 4·2; N, 19·7; Cl, 13·1. $C_{12}H_{11}O_2N_4Cl$ requires C, 51·7; H, 4·0; N, 20·1; Cl, 12·7%).

5-*Amino*-4-*methylpyrimidine* (XXII).—2 : 4-Dichloro-6-methyl-5-nitropyrimidine was reduced with zinc powder and boiling water to 5-amino-2-chloro-4-methylpyrimidine in the manner described by Gabriel and Colman (*Ber.*, 1901, **34**, 1250), and the crude product, m. p. 87°, was used directly. A solution of 5-amino-2-chloro-4-methylpyrimidine (2·7 g.) in water (30 c.c.) was shaken at 55° with 1·2% palladised strontium carbonate (0·5 g.) in hydrogen at atmospheric pressure until no further absorption took place (*ca.* 7 hours). The filtered solution was treated with sodium hydrogen carbonate and evaporated to dryness. The residue was extracted with boiling ethanol and the extract was evaporated to dryness. The halogen-free product was then purified by extraction with benzene, sublimation in a vacuum and crystallisation from benzene giving pure 5-amino-4-methylpyrimidine (1 g.) m. p. 150—151·5°; Gabriel and Colman (*locc. cit.*) record m. p. 152—153°.

2 : 4-*Bisamidinothio*-6-*methylpyrimidine Dihydrochloride and* 2 : 4-*Dithio*-6-*methyluracil*.—A solution of 2 : 4-dichloro-6-methylpyrimidine (3·26 g.) and thiourea (3·04 g.) in ethanol (50 c.c.) was refluxed for 1·5 hours, after which the reaction for thiourea with ammoniacal silver nitrate solution had become minimal. After cooling, the product (4·93 g.) was removed and treated with cold dilute hydrochloric acid (25 c.c.). The yellow insoluble portion (2·7 g.) was dissolved in aqueous potassium hydroxide and reprecipitated by the addition of acetic acid (cf. Gabriel and Colman, *Ber.*, 1899, **32**, 2922), giving 2 : 4-dithio-6-methyluracil (1·5 g.), m. p. above 380°, with discoloration from 250° to 260° (Found: C, 38·5; H, 3·9. Calc. for $C_5H_6N_2S_2$: C, 38·0; H, 3·8%). Gabriel and Colman (*locc. cit.*) record m. p. >280°.

The above dilute hydrochloric acid washings were evaporated to dryness in a vacuum at 40—50°, leaving a colourless crystalline residue (1·91 g.). It was dissolved in boiling methanol (25 c.c.) and treated with hot ethyl acetate (25 c.c.). When cold, the colourless crystals of pure 2 : 4-bisamidinothio-6-methylpyrimidine dihydrochloride (1·67 g.) were collected, m. p. 260° (decomp.) with pink coloration at 185—190° (Found, on material dried *in vacuo* over silica gel for 48 hours: C, 25·3; H, 4·3; N, 25·3. Calc. for $C_7H_{10}N_6S_2,2HCl,H_2O$: C, 25·2; H, 4·2; N, 25·2%). Polonovski and Schmitt (*Compt. rend.*, 1950, **230**, 754) record m. p. *ca.* 285° (decomp.) for this dihydrochloride and m. p. *ca.* 240° for the derived 2 : 4-dithio-6-methyluracil..

The dihydrochloride was very soluble in water and, on boiling, an aqueous solution readily decomposed to give the dithiouracil.

4-*Methylpyrimidine* (XXIII).—This was prepared (Gabriel and Colman, *Ber.*, 1899, **32**, 1534) by the action of zinc powder and boiling water on 2 : 4-dichloro-6-methylpyrimidine. Some 2-chloro-4-methylpyrimidine was obtained as a by-product. 4-Methylpyrimidine was finally purified by fractionation and had b. p. 86°/114 mm., n_D^{29} 1·4916.

1 : 3 : 6-*Trimethyluracil* (XXIX; R = Me).—This substance was obtained in excellent yield by methylation of 6-methyluracil with methyl sulphate, following the conditions adopted by Davidson and Baudisch (*J. Amer. Chem. Soc.*, 1926, **48**, 2379), in the case of uracil; it had m. p. 113° (lit., 111—112°).

2-*Methoxy*-6-*methyl*-4-*pyrimidone* (XXVIII; R = R′ = Me).—This compound was prepared by Bruce's method (*J. Amer. Chem. Soc.*, 1904, **26**, 454) with slight modifications. The product, which

separated from alcohol in colourless flattened prisms, had m. p. 207°, as recorded by Bruce, only on rapid heating, otherwise molecular rearrangement took place with fusion at 195°, followed by resolidification (Found: C, 52·1; H, 5·7; OMe, 21·5. Calc. for $C_6H_8O_2N_2$: C, 51·4; H, 5·7; OMe, 22·1%).

Physical Measurements.—(a) pK_a *values.* The compound (1 millimol.) was dissolved in N/20-hydrochloric acid (20 c.c.). The pH of the solution was measured (Cambridge pH-meter), and measured after every addition of 0·1 c.c. during titration with N-sodium hydroxide. The pK_a was calculated from each pH reading, taking into account the strength of the solution. In the case of compounds isolated as the hydrochlorides, these were dissolved in water before titration. Owing to its sparing solubility five times the above dilution was used for (XII), and the solution in alkali was titrated with acid.

(b) *Light absorption.* Light-absorption measurements were made with the Beckman D.U. quartz spectrophotometer at the pH values recorded in the Table. The buffer solutions used were: acetate (pH 4·7), phosphate (pH 7·0), glycine–sodium hydroxide (pH 11·0), together with N- (pH 0) and N/10-hydrochloric acid (pH 1·0) and N/10-sodium hydroxide (pH 13).

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