1303. *The Dimroth Rearrangement. Part V.*[1] *The Mechanism of the Rearrangement of 1-Alkyl-1,2-dihydro-2-iminopyrimidines in Aqueous Solution*

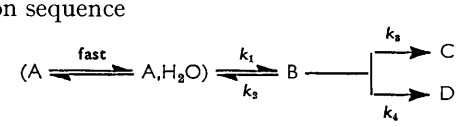
By D. D. Perrin and I. H. Pitman

In aqueous solution, 1-alkyl-1,2-dihydro-2-iminopyrimidines, *e.g.*, (I), exist in equilibrium with small amounts of the carbinolamines (IX) formed from them by covalent addition of a molecule of water. These carbinolamines undergo reversible ring fission to yield the corresponding guanidinoaldehydes, *e.g.*, (VII), which can recyclise to give either the starting materials or the corresponding 2-alkylaminopyrimidines (II). The ring-opened intermediates, which have been isolated as their oximes, decompose in strongly alkaline solution to give malondialdehyde and substituted guanidines. Malondialdehyde, which has strong ultraviolet absorption at 270 mμ, is also formed by the breakdown of 1,2-dihydro-2-oxopyrimidines in alkaline solution. Individual rate constants for the rearrangement of 1-alkyl-5-halogeno-1,2-dihydro-2-iminopyrimidines have been calculated from the measured, composite rate constants.

1,2-Dihydro-2-imino-1-methylpyrimidine (I; R = Me, R′ = H) rearranges in alkaline solutions to give 2-methylaminopyrimidine (II; R = Me, R′ = H) by a series of reactions which are not acid–base catalysed and which involve ring fission, rotation, and recyclisation.[2] The overall reaction rate is increased if the 1-methyl group is replaced by a larger alkyl group, and even more if electron-withdrawing substituents are inserted at position 5 in the pyrimidine ring.[3,4] Conversely, insertion of an electron-releasing group slows the reaction. Kinetic data for the rearrangement of 1,2-dihydro-2-imino-5-iodo-1-methylpyrimidine (I; R = Me, R′ = I) indicate that the ring fission is reversible whereas ring closure to give 5-iodo-2-methylaminopyrimidine is essentially irreversible.[5] In alkaline solutions, side-reactions can also occur. For example, at pH values below 12, the products of the rearrangement of 1,2-dihydro-2-imino-1-methylpyrimidine include not only 2-methylaminopyrimidine but also 2-hydroxypyrimidine and methylamine.[6]

[1] Part IV, D. J. Brown and J. S. Harper, *J.*, 1965, 5542.
[2] D. J. Brown, *Nature*, 1961, **189**, 828.
[3] D. J. Brown and J. S. Harper, *J.*, 1963, 1276.
[4] D. D. Perrin, *J.*, 1963, 1284.
[5] D. D. Perrin and I. H. Pitman, *Austral. J. Chem.*, 1965, **18**, 471.
[6] D. D. Perrin and I. H. Pitman, *Austral. J. Chem.*, 1965, **18**, 763.

We believe that the rearrangement of 1,2-dihydro-2-iminopyrimidines in aqueous solution involves the reaction sequence



where A is the neutral molecule of the starting material which is in equilibrium with a small amount of the adduct A,H_2O, B is the ring-opened species, C is the rearranged amine, and D is a breakdown product (which may then decompose further). Evidence in support of this scheme is presented below.

Reversible Addition of Nucleophilic Reagents to 1,2-Dihydro-2-iminopyrimidines.—The considerable covalent water addition to heterocyclic nitrogen compounds, such as the cations of quinazoline and pteridine and neutral molecules such as 2-hydroxypteridine, has been suggested to be due, in large part, to resonance stabilisation of the hydrate.[7] This factor is unlikely to be favourable in compounds such as (I) or in their cations, which have the aromatic structures (III). (The cation of 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine in water has an ultraviolet spectrum which is almost identical[3] with that of the cation of 5-bromo-2-methylaminopyrimidine.) Hence it is not surprising that spectroscopically measurable amounts of the species A,H_2O cannot be detected in aqueous solutions of the imine A. However, addition of more powerful nucleophilic reagents than water can readily be demonstrated. Table 1 summarises equilibrium constants and ultraviolet spectra for 1 : 1 addition compounds of some 1,2-dihydro-2-iminopyrimidines with bisulphite ion.

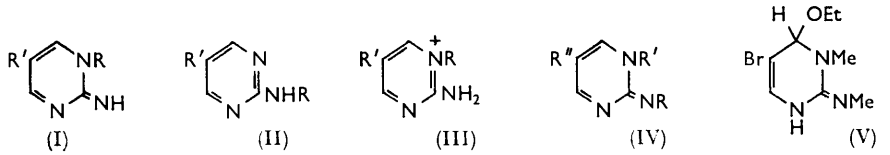
TABLE 1

Equilibrium constants and ultraviolet spectra of bisulphite adducts of substituted pyrimidines at 20°

Pyrimidine derivative	$[HSO_3^-]$ M	K (range)	Analyt. λ (mμ)	$\lambda_{max.}$ (log ε)
5-Br-1,2-H_2-2-Me-imino-1-Me	10^{-5}—10^{-1}	6000 (2000)	340	268 (3·76)
5-NO_2-1,2-H_2-4-NMe_2-2-imino-1-Me	10^{-5}	$>10^4$	313	313 (4·04)
1,2-H_2-2-imino-1-Me	10^{-4}—10^{-3}	480	302	258 (3·38)
5-Br-1,2-H_2-2-imino-1,4,6-Me_3	10^{-1}	0·6	300	—
5-Br-1,2-H_2-4-NMe_2-2-imino-1-Me	10^{-1}	<0·1	298	—
Pyrimidine	0·05—0·5	8·6 * (1)	320	—
2-NHMe	10^{-3}—10^{-2}	104 *	306	256 (3·49)
2-NH_2-4,6-Me_2	10^{-1}	<0·1 *	295	—

* Apparent equilibrium constant ([adduct]/[neutral molecule][HSO_3^-]), at pH 4·7.

The very big reduction in the equilibrium constants when methyl groups are present at positions 4 and 6 indicates that one of these is the likely site of addition of the bisulphite ion. (A comparable "blocking" effect of methyl groups is observed in the covalent



hydration of nitrogen heterocycles.[7]) The cations of the starting materials are regenerated when the bisulphite adducts are dissolved in dilute acid. Because, under these conditions, the cations of the ring-opened species are also stable, this observation confirms that ring-opening has not taken place.

Spectroscopic evidence shows that the neutral molecule of 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine also readily adds a molecule of ethanol. Ultraviolet and

[7] A. Albert and W. L. F. Armarego, *Adv. Heterocyclic Chem.*, 1965, **4**, 1.

n.m.r. spectra are listed in Tables 2 and 3. The ultraviolet spectra of the neutral species (IV; R = R′ = Me, R″ = Br) in water and in tetrahydrofuran are very similar, whereas the spectrum in dry ethanol is quite different. In alcohol–water mixtures, composite spectra are observed. For example, the spectrum of a solution in 95% ethanol suggests that 87% of the alcohol adduct and 13% of the unreacted base are present.

From the n.m.r. spectra, the alcohol adduct is believed to be 5-bromo-6-ethoxy-1,2,3,6-tetrahydro-1-methyl-2-methyliminopyrimidine (V), although the possible formation of the

TABLE 2

Ultraviolet spectra and ionisation constants of 1,2-dihydro-2-iminopyrimidines

Spectra

Derivative	Species *	Solvent	pH	$\lambda_{max.}$ (log ε)
1-Me †	n.m.	water	13·0	347 (3·45) and 237 (4·22) (ref. 3)
	cat.	water	7·6	302 (3·64) and 223 (4·09) (ref. 3)
	n.m.	THF	—	405 (infl.) (2·95), 384 (infl.) (3·24), 368 + 356 (3·35)
	n.m.	ethanol	—	351 (3·31), 310 (infl.) (3·17), 235 (4·09)
5-Br-1,2-Me_2	n.m.	water	12·8	388 (3·21), 252 (4·15)
	cat.	water	7·0	340 (3·53) and 241 (4·34) (ref. 3)
	n.m.	THF	—	398 (v. broad) (3·23), 250 (4·21)
	n.m.	ethanol	—	340 (2·78), 280 (3·89)
5-Br-1-Et	n.m.	water	13·0	369 (3·29), 246 (4·20)
	cat.	water	7·0	326 (3·55) and 237 (4·25) (ref. 1)
5-Cl-1-Me	n.m.	water	12·3	367 (3·36), 247 (4·24)
	cat.	water	7·0	323 (3·56), 233 (4·24)
5-Br-1,4,6-Me_3	n.m.	water	13·0	353 (3·49), 247 (4·20)
	cat.	water	5·0	316 (3·72) and 236 (4·15) (ref. 1)
5-I-1-Me	n.m.	water	12·3	371 (3·29), 249 (4·35)
	cat.	water	7·0	333 (3·44), 241 (4·30)

Ionisation constants

Derivative	Temp. (°c)	Ionic strength	pK_a (range)
5-Br-1,2-Me_2	10·0	0·1	11·05 ± 0·05
	20·0	0·1	10·77 ± 0·02
	30·0	0·1	10·42 ± 0·05
5-Br-1-Et	10·0	0·1	10·52 ± 0·03
	20·0	0·1	10·20 ± 0·03
	30·0	0·1	9·89 ± 0·03
5-Cl-1-Me	20·0	0·1	10·19 ± 0·05
5-Br-1,4,6-Me_3	20·0	0·1	11·01 ± 0·05
5-I-1-Me	20·0	0·1	10·24 ± 0·05
5-Br-1-Me	10·0	0·1	10·41 ± 0·02
	20·0	0·05	10·06 ± 0·03
	20·0	0·10	10·12 ± 0·03
	20·0	0·20	10·17 ± 0·02

n.m. = neutral molecule; cat. = cation. † Basic pK_a value 10·75 (ref. 15).

TABLE 3

Nuclear magnetic resonance spectra at 33·5° *

Compound	Species	Solvent	τ-Values for protons (number, position)
(IV; R = R′ = Me, R″ = Br)	n.m.	CCl_4	2·05 (1, H-4), 2·78 (1, H-6), 6·79 (3, Me on N-1), 7·05 (3, NMe on C-2)
,, ,,	cat.	D_2O	1·05 (centre of doublet, J = 3·0 c./sec.) (1, H-4), 1·33 (centre of doublet, J = 3·0 c./sec.) (1, H-6), 6·18 (3, Me on N-1), 6·85 (3, NMe on C-2)
,, (EtOH adduct)	n.m.	EtOH	3·15 (1, H-4), 4·63 (1, H-6), 6·90 (3, Me on N-1), 7·20 (3, NMe on C-2)
(IV; R = R″ = H, R′ = Me)	n.m.	EtOH	1·86 (quartet, J = 1·2, 2·3 c./sec.) (1, H-4), 2·25 (quartet, J = 1·1, 4·0 c./sec.) (1, H-6), 4·00 (quartet, J = 2·7, 3·9 c./sec.) (1, H-5) (masked by EtOH bands)
,, ,,	cat.	D_2O	1·12 (quartet, J = 2·1, 4·5 c./sec.) (1, H-4), 1·53 (quartet, J = 2·2, 6·8 c./sec.) (1, H-6), 2·86 (quartet, J = 4·8, 7·2 c./sec.) (1, H-5), 6·09 (3, Me on N-1)

* Tetramethylsilane or sodium trimethylsilylpropanesulphonate (for D_2O) as internal standard.

corresponding 4-ethoxy-isomer cannot be excluded. The peaks at τ 6·18 and 6·09 p.p.m., respectively, for the cations of the bases (IV; R = R′ = Me, R″ = Br) and (IV; R = R″ = H, R′ = Me) are assigned to the methylamino-group, as also are the peaks at 6·79 and 6·90 p.p.m. for the base (IV; R = R′ = Me, R″ = Br) as its neutral molecule and its ethanol adduct. The higher of the two methyl peaks is due to the methylimino-group on C-2. This is consistent with the general observation (J. S. Harper, personal communication) that, in the dihydropyrimidines, methylimino-groups have higher τ-values than methyl groups on ring nitrogens. Assignments of signals to H-4 and H-6 are based on the values [8] for H-2 in pyridine (1·40 p.p.m.), H-4 in 2-aminopyrimidine (1·72 p.p.m.), and α-H in pyrrole (3·32 p.p.m.) and 3-methylindole (3·22 p.p.m.), and the displacement downfield which occurs on protonation. Similarly, the peak at 4·00 p.p.m. in the spectrum of the neutral molecule (IV; R = R″ = H, R′ = Me) is assigned to H-5 by analogy with H-3 in pyridine (approx. 3·0). For an ethanol adduct having the structure (V), the τ-value of the signal for H-6 can be predicted to occur at about 4·8 p.p.m. (observed for the ethanol adduct, 4·63 p.p.m.) if substituent effects are additive. Thus, adding the difference (0·43 p.p.m.) between the signals for H-4 in the neutral molecule and the cation of hydrated pteridine [9] to the corresponding value (3·62 p.p.m.) for the hydrated quinazoline cation [9] gives an approximate τ-value of 4·05 p.p.m. for the neutral molecule of hydrated quinazoline. The difference (0·76 p.p.m.) between the signals for H-1 in 1,2,3,4-tetrahydronaphthalene and the corresponding hydrogen in cyclohexene is a measure of the effect of removing the benzene ring, so that for (hypothetical) 1,6-dihydro-6-hydroxypyrimidine the peak for H-6 should lie at about τ 4·05 + 0·76 = 4·8 p.p.m. Finally, because there is very little difference in the effects of OH and OAlk on the position of the signal for a neighbouring CH (compare ethanol and tetrahydrofuran), the signal for the adduct (V) should also occur near this value.

No evidence was found that 1,2-dihydro-2-imino-1-methylpyrimidine adds a molecule of ethanol. This was probably due partly to the relative insensitivity of the spectroscopic methods and partly to the lower formation constant that would be expected (see Table 1).

The Equilibrium, A $\rightleftharpoons$ A,H_2O.—The (unstable) neutral molecule (IV; R = R′ = Me, R″ = Br) is obtained, initially, when solutions of its cation are mixed with aqueous alkaline solutions at pH 12. However, spectroscopic measurements show that at higher pH values another species is also formed, reaction being half complete within about 0·1 seconds. This reaction is reversible. If the cation is added to 2M-sodium hydroxide and then, after 1 second, the solution is acidified with hydrochloric acid, the cation is regenerated. A series of spectra measured between pH 12 and 14, 1 second after mixing the solutions, gave a good isosbestic point at 266 mμ, suggesting that only two absorbing species were present. From the pH dependence of the spectra, we conclude that the new substance, characterised by a single maximum [268 mμ (log ε 3·93) at pH 14] in its visible and ultraviolet spectrum, is the anion of the corresponding covalently hydrated base. Measurements at a constant wavelength (370 mμ) over the pH range 12—14, using an extrapolation method,[4] afforded an approximate equilibrium pK_a value of 13·6 $\pm$ 0·1 at 20° and I = 0·1—1·0, where $K_a = [A,OH^-](H^+)/\{[A] + [A,H_2O]\}$. Similarly, for the base (I; R = Me, R′ = Br) a value of 13·4 $\pm$ 0·1 was obtained.

By using an apparatus designed for studying faster reactions,[9] the overall hydration and ionisation process could be examined. For convenience, a wavelength (270 mμ) was chosen at which only the anion absorbed strongly. Good first-order plots were obtained for the change of optical density with time, and the rate constants calculated from them are listed in Table 4. These rates are much too rapid for them to be limiting factors in the ring-opening reactions.

Further evidence for the participation of water in these Dimroth rearrangements came

[8] Except where indicated, all n.m.r. values for reference compounds are from "N.M.R. Spectra Catalog," vols. 1 and 2, Varian Associates, California, 1962—1963.

[9] J. W. Bunting and D. D. Perrin, *J.*, 1966, to be published.

from the spectroscopic observation that solutions of free bases such as (IV; R = R″ = H, R′ = Me) and (IV; R = R′ = Me, R″ = Br) in dry solvents such as tetrahydrofuran, acetone, dioxan, and diethyl ether are stable against ring-opening and rearrangement during at least 48 hours at room temperature. On the other hand, if small concentrations of water are added, rearrangement occurs at a rate that varies in proportion to the water content. Values of the overall first-order rate constant for the first of these bases in aqueous tetrahydrofuran are given in Table 5. These constants were obtained from the plot of

TABLE 4

Rate constants for anion formation in alkaline solutions of 5-bromo-1,2-dihydro-1-methyl-2-iminopyrimidine

pH	11·07	12·06	12·94	13·06	14·0
Ionic strength	0·1	0·1	0·1	0·1	1·0
k at 20° (sec.$^{-1}$) (analyt. λ = 285 mμ)	9·5	6·7	4·1	4·1	3·2

TABLE 5

Overall first-order rate constant for the rearrangement of 1,2-dihydro-2-imino-1-methylpyrimidine

In aqueous tetrahydrofuran at 20°

% H_2O	0	1·25	2·50	3·13	5·00	12·5	25·0	50·0	100*
k (min.$^{-1}$)	—	0·0001	0·0003	0·0006	0·0008	0·0020	0·0026	0·0018	0·0031

In water at different temperatures *

Temp. (°c)	14·8	20·0	25·2	31·1
k (min.$^{-1}$)	0·0016	0·0031	0·0054	0·0109

* Adjusted to pH 13 with sodium hydroxide.

log ($D - D_\infty$) against time, using a wavelength (360 mμ) at which the product did not absorb. No alkali was added to the mixed solvents to repress ionisation of the free base, so the observed rates are less than they would be in the presence of alkali.

The Ring-opening Reaction.—The neutral molecule of 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine (IV; R = R′ = Me, R″ = Br) is a convenient substance to use in studying this reaction, and for demonstrating its reversiblility, because closure of the ring-opened intermediate (which is stable up to pH 13) leads only to the starting material. By adding the dihydropyrimidine cation to a strongly alkaline solution (0·2M-sodium hydroxide) and standing for 30 min. at 20°, an equilibrium mixture was obtained. When this solution was rapidly mixed with buffers of pH 7·4—8·2 (containing added hydrochloric acid to neutralise the sodium hydroxide in the dihydropyrimidine solution), any of the original base that remained was converted immediately into its cation which is stable against ring-opening. However, because its pK_a is only about 5—6,[5] any ring-opened material that had been formed was present under these conditions as the neutral species, so the ring-closing reaction continued. Hence, spectrophotometric measurements at a suitable wavelength (320 mμ) afforded directly the first-order rate constant, k_2, for this reaction. Values are listed in Table 6.

TABLE 6

Rate constants (at 20° and ionic strength 0·1) for ring-opening and -closing, using 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine

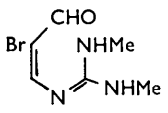
pH				7·36	7·46	8·04	8·24		
k_2				0·0241	0·0245	0·0246	0·0249		
pH	9·76	10·15	10·35	10·54	10·91	10·96	11·08	11·55	11·67
$(k_1' + k_2)$	0·0280	0·0344	0·0391	0·0452	0·0574	0·0620	0·0622	0·0740	0·0770
k_1	0·038	0·051	0·053	0·056	0·057	0·061	0·056	0·058	0·059

The sum of the apparent rate constants for the forward and back reactions was readily obtained from spectrophotometric measurements at the same wavelength by adding solutions

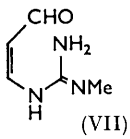
of the (stable) iminopyrimidine cation to buffers covering the pH range 9·76—11·67. These constants are given in Table 6. The pK_a value of the starting material (10·77) lies in the same region as that of the selected buffers, but only the neutral molecule of this substance undergoes ring-opening. For this reason, the apparent rate constant, k_1', for the reaction (calculated on the basis of the change in [A] + [HA$^+$]) is pH-dependent. The true constant, k_1, is obtained from k_1' by multiplying the factor, $1 + (H^+)/K_a$.

From these constants, the equilibrium composition of the solution is calculated to be, at 20°, 29% original imine and 71% ring-opened material. Using this ratio, the ultraviolet spectra of the cation and neutral molecule of the latter can readily be obtained from the spectra of equilbrium mixtures. This affords the values, $\lambda_{max.}$ 283 mμ (log ε 4·48) for the cation, and $\lambda_{max.}$ 321 mμ (log ε 4·61) for the neutral molecule of the ring-opened species which is believed to be the substituted acraldehyde (VI).

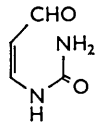
However, in substances able to undergo the Dimroth rearrangement, the ring-opened species can ring-close in two different ways, and no simple relationship exists between the individual rate constants, k_1, k_2, k_3, and the measured ones.[5] For this reason, further discussion of the kinetics of the reaction is deferred to a later section.



(VI)



(VII)



(VIII)

Evidence that the neutral molecule of 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine undergoes ring-opening comes from n.m.r. and preparative studies. The n.m.r. spectrum of the equilibrated mixture of the base in 0·05M-NaOD shows, in addition to weak bands due to residual material, only two peaks. These are at τ 1·82 p.p.m. (1 proton) and at τ 7·09 (6 protons). The latter indicates that, unlike the original base (cf. Table 3) the two methyl groups are now in similar environments. This similarity persists when the solution is acidified to pH 2, the spectrum then comprising three peaks, at τ 1·04 p.p.m. (1 proton), τ 1·76 p.p.m. (1 proton) and τ 6·92 p.p.m. (6 protons). This observation is consistent with a ring-opened species such as (VI). The peak at 1·82 p.p.m. in the neutral molecule would then be assigned to the proton on the carbon β to the formyl group. (Compare 2·05 p.p.m., from Table 3, for this proton in the initial material.)

Confirmation that the ring-opened species are aldehydes was obtained by forming their oximes. The oxime derived in this way from 1,2-dihydro-2-imino-1-methylpyrimidine was isolated as its carbonate, indicating the presence in the ring-opened species of a strongly basic group (substituted guanidine). That the substances forming the oximes were neither the starting materials nor decomposition products was demonstrated by dissolving, in dilute hydrochloric acid (to remove the hydroxylamine moiety), the oxime prepared from 1,2-dihydro-2-imino-1-methylpyrimidine and measuring the ultraviolet absorption spectrum of the solution. In such acid solutions the ring opening and closing reactions do not take place. Nevertheless, the spectrum showed that the cation of the ring-opened species was present. When the solution was added to 0·1M-sodium hydroxide, the Dimroth rearrangement continued normally.

The *Ring-closing Reaction*.—With the 5-halogenated iminopyrimidines, under the conditions of our measurements, spectroscopic studies indicate that below pH 12—13, upwards of 90% of the original material is finally converted into the corresponding alkylaminopyrimidine. Reaction is appreciably less quantitative under the same conditions for iminopyrimidines lacking electron-withdrawing substituents.[6] The final products of the reactions have also been isolated on a preparative scale and chemically characterised.[3]

Decomposition of the Ring-opened Species.—In aqueous alkaline solutions at room temperature, guanidine is hydrolysed slowly to urea.[10] Hence, because the ring-opened species

[10] J. Bell, *J.*, 1926, 1216.

in the above rearrangements are substituted guanidines they might also be expected to be converted slowly into the corresponding substituted ureas, with liberation of methylamine and ammonia. For example, the guanidine (VII) could yield the substituted urea (VIII). Such a reaction does not preclude subsequent ring-closing, which would lead, in this case, to the formation of 2-hydroxypyrimidine. This reaction has been demonstrated experimentally under conditions where 2-methylaminopyrimidine is not itself hydrolysed.[6] It has not been observed with the corresponding 5-halogenated derivatives, possibly because the ring-opened species are much weaker bases than the species derived from the parent (non-halogenated) compounds.

Alternatively, the ring-opened species can undergo hydrolytic fission to yield an alkyl(or dialkyl)guanidine and (substituted or unsubstituted) malondialdehyde. Thus, formation of *NN'*-dimethylguanidine and bromomalondialdehyde from 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine was established by the isolation and characterisation of their derivatives. Subsequently, spectroscopic studies showed that the previously unidentified material, absorbing strongly at 270 mμ, which is formed as a by-product of the rearrangement of 1,2-dihydro-2-imino-1-methylpyrimidine above pH 13, is malondialdehyde. Freshly distilled malondialdehyde (prepared by Hüttel's method [11]) had $\lambda_{max.}$ 267 mμ (log ε 3·93) for the anion in 0·1M-sodium hydroxide, and at 245 (log ε 3·54) for the neutral molecule in 0·1M-hydrochloric acid. Spectroscopic studies and the isolation of derivatives indicate that malondialdehyde is also the light-absorbing product formed by the irreversible breakdown in strong alkali of 1,2-dihydro-2-oxo-1-methylpyrimidine. For example, after a solution of this base in 0·1M-sodium hydroxide had stood at room temperature for 3 days, the solution had only one absorption maximum, at 267 mμ (log ε 3·99). On acidification, this changed to 245 mμ (log ε 3·64).

Reaction Kinetics for the Rearrangement.—Experimental evidence is consistent with the proposed reaction sequence for the rearrangement of 1-alkyl-1,2-dihydro-2-iminopyrimidines in aqueous alkaline solutions. In such a scheme, the individual rate constants, k_1, k_2, and k_3 (neglecting for the moment k_4), must be obtained from composite rate constants, y_1 and y_2, to which they are related by the expressions [5]

$$y_1 = \tfrac{1}{2}\{k_1 + k_2 + k_3 + [(k_1 + k_2 + k_3)^2 - 4k_1k_3]^{\frac{1}{2}}\}$$
$$y_2 = \tfrac{1}{2}\{k_1 + k_2 + k_3 - [(k_1 + k_2 + k_3)^2 - 4k_1k_3]^{\frac{1}{2}}\}$$

In the case ($k_3 < k_1$) where pseudo-equilibrium between starting material and ring-opened species is reached, *i.e.*, the concentration of the latter passes through an observable maximum, at a time $t_{max.}$ (which varies with the ratio of the extinction coefficients of the initial and final materials [5]), the individual constants can be evaluated. Once this maximum has been passed, the plot of 2·303 log $(D - D_\infty)$ against time affords y_2 directly. Further, y_1 and y_2 are related to $t_{max.}$ by the expression [5]

$$t_{max.} = [2{\cdot}303/(y_1 - y_2)]\log(y_1/y_2)$$

if a wavelength is chosen such that the initial and final materials have the same extinction coefficient.

In the same way that addition of the equilibrium mixture to solutions of suitable pH values was used to obtain k_2 for the ring-closing reaction to give 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine (see above), the sum of k_2 and k_3 can be found from measurements on solutions of 1-alkyl-1,2-dihydro-2-iminopyrimidines that have been allowed to reach pseudo-equilibrium. Hence the individual rate constants can be calculated.[5]

Results for 1,2-dihydro-2-imino-5-iodo-1-methylpyrimidine at 20° are set out in Table 7, while Table 8 summarises results at other temperatures and for other halogenated compounds.

[11] R. Hüttel, *Ber.*, 1941, **74**, 1825.

TABLE 7

First-order rate constants (min.$^{-1}$) for the rearrangement of 5-iodo-1,2-dihydro-2-imino-1-methylpyrimidine in water at 20° and $I = 0{\cdot}1$

pH	5·68	6·37	6·80	6·86	7·06	7·30	7·49	8·20	8·65	8·73
$k_2 + k_3$ ...	0·055	0·093	0·102	0·107	0·110	0·112	0·111	0·112	0·115	0·117

pH	y_2	$t_{max.}$ (min.)	y_1	k_1'	k_1 *	k_2	k_3 †
9·34	0·0063	24·6	0·125	0·020	0·179	0·072	0·039
9·56	0·0087	21·2	0·138	0·036	0·208	0·078	0·033
9·74	0·0114	18·6	0·151	0·051	0·212	0·077	0·034
9·98	0·0141	16·4	0·164	0·067	0·189	0·076	0·035
10·34	0·0178	12·0	0·202	0·090	0·195	0·078	0·033
10·82	0·0216	10·9	0·243	0·154	0·194	0·077	0·034
10·86	0·0220	10·6	0·253	0·165	0·205	0·077	0·034
11·20	0·0223	10·2	0·266	0·177	9·196	0·077	0·034
11·68	0·0234	9·5	0·289	0·201	0·209	0·077	0·034
11·98	0·0251	9·2	0·291	0·205	0·209	0·075	0·036
12·44	0·0255	8·1	0·342	—	—	—	—
12·68	0·0271	7·4	0·417	—	—	—	—
12·94	0·0285	6·4	0·460	—	—	—	—
13·31 ($I = 0{\cdot}5$)	0·0365	5·1	0·572	—	—	—	—
14·00 ($I = 1{\cdot}0$)	0·0420	5·7	0·465	—	—	—	—

* From k_1' by multiplying by the factor $1 + (H^+)/K_a$. † Taking $(k_2 + k_3) = 0{\cdot}111$.

TABLE 8

First-order rate constants (min.$^{-1}$) for the rearrangement of some 1-alkyl-1,2-dihydro-2-iminopyrimidines in water ($I = 0{\cdot}1$)

Derivative	Temp. (°c)	y_1	y_2	k_1	k_2	k_3
5-Cl-1-Me	10·8	0·120	0·004	0·103	0·021	0·005
	20·0	0·346	0·015	0·290	0·067	0·019
	29·6	0·992	0·051	0·802	0·200	0·064
	38·0	2·432	0·144	1·924	0·520	0·188
5-Br-1-Me	9·9	0·114	0·005	0·094	0·023	0·007
	20·0	0·361	0·019	0·287	0·077	0·024
	29·6	1·027	0·060	0·812	0·221	0·078
	37·9	2·310	0·183	1·787	0·500	0·241
5-Br-1-Et	10·0	0·101	0·005	0·094	0·011	0·006
	20·0	0·293	0·020	0·262	0·038	0·023
	29·6	0·807	0·068	0·702	0·113	0·080
	37·8	1·929	0·202	1·662	0·276	0·241
5-Br-1,2-Me_2 ...	10·0	—	—	0·018	0·007	—
	20·0	—	—	0·059	0·025	—
	29·6	—	—	0·175	0·083	—
	37·8	—	—	0·399	0·217	—
5-I-1-Me	10·0	0·094	0·006	0·073	0·023	0·009
	20·0	0·289	0·023	0·209	0·077	0·034
	29·6	0·813	0·076	0·560	0·231	0·114
	37·9	1·967	0·220	1·355	0·542	0·329

However, in cases where k_3 is greater than k_1, these conditions are not met, and appreciable quantities of the ring-opened species may not be present, so the starting material seems to go directly to final product. This occurs, for example, with 1,2-dihydro-2-imino-1-methylpyrimidine, in which, nevertheless, the same mechanism is believed to operate. Thus, the formation of the intermediate ring-opened species can be demonstrated by its isolation, in good yield, as its stable oxime. Such systems give good first-order rate constants, which are approximately equal to the values of y_2, by plotting the time-dependent changes in optical density. The same constants are obtained from measurements of the rate of disappearance of starting material or of the formation of end-product. Results for 5-bromo-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine are shown in Table 9. Because the neutral molecule of starting material, but not its cation, is the reactive species, the observed rate constant has to be multiplied by $[1 + (H^+)/K_a]$ to obtain the true overall rate constant. In this way, approximate values of $y_2 = 0{\cdot}00303$ and $0{\cdot}00431$ min.$^{-1}$ at 20° were found for 1-methyl- and 1-ethyl-1,2-dihydro-2-iminopyrimidine, respectively.

TABLE 9

Overall rate constant (min.$^{-1}$) for the rearrangement of 5-bromo-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine in water (I = 0·1)

At 20°

pH	10·56	10·74	10·94	11·65	11·64	12·06	12·70
$k_{obs.}$	0·008 †	0·010 †‡	0·0125 †	0·0220 ‡	0·0222 †	0·0246 †	0·0301 †
$k_{corr.}$ *	0·031	0·030	0·0271	0·0271	0·0271	0·0271	0·0307

At different temperatures

Temp. (°c)	14·8	20·0	25·2	31·1
$k_{corr.}$	0·0149	0·0271	0·0455	0·0796

* Corrected using the pK_a value interpolated from Table 2. † Measured at 315 mμ, for appearance of product. ‡ Measured at 354 mμ, for disappearance of starting material.

Independent of the relative values of k_1 and k_3, the time $t_{\frac{1}{2}}$ taken to form half of the final concentration of rearranged product from starting material is related to y_1 and y_2 by the equation

$$e^{-y_2 t_{\frac{1}{2}}} = (y_1 - y_2)/2y_1$$

Where y_1 and y_2 can be measured, $t_{\frac{1}{2}}$ can be calculated. In some cases, $t_{\frac{1}{2}}$ must be obtained by direct experiment. Where no appreciable amount of intermediate is present but significant decomposition to give side-products occurs, $t_{\frac{1}{2}}$ is taken as the time for half reaction of the starting material. Values of $t_{\frac{1}{2}}$ are collected in Table 10. Conversely, if y_2 and $t_{\frac{1}{2}}$ are known, y_1 can be calculated from this expression, and hence the sum of $k_1 + k_2 + k_3$ ($=y_1 + y_2$). For 1-methyl- and 1-ethyl-1,2-dihydro-2-iminopyrimidine, this method gives y_1 = 0·03 and 0·024 min.$^{-1}$, respectively, at 20°.

Using solutions of 5-chloro-1,2-dihydro-2-imino-1-methylpyrimidine that had stood for some time, the same overall rate constant was obtained from spectroscopic measurements of the disappearance of ring-opened material or of the formation of either the side-product or the rearranged material. This confirmed that the ring-closing reaction and side-product formation occurred concurrently, so the rate constants that are calculated from

TABLE 10

Times for half-formation of rearranged products from 1-alkyl-1,2-dihydro-2-iminopyrimidines

Derivative ...	5-Cl-1-Me	5-Br-1-Me	5-I-1-Me	5-Br-1-Et	5-Br-1,4,6-Me$_3$	1-Me	1-Et
$t_{\frac{1}{2}}$ (min.)	49	39	31	38	26 *	253 *	192 *
pH	12·2	12·2	12·2	12·2	13·0	13·0	13·0

* Time for half-conversion of starting material.

the experimental values of y_1 and y_2 are k_1, k_2, and ($k_3 + k_4$). To obtain the individual values of k_3 and k_4 it would be necessary to determine the relative concentrations, at any specified time, of the decomposition product and the rearranged amine. Unlike the other reactions, the breakdown of the ring-opened species is base-catalysed, so at high pH values the overall rate constants show an upward trend with increasing hydroxyl concentration. This is illustrated by the results for pH values greater than 12 in Table 7. Conversely, in obtaining the estimates of k_1, k_2, and k_3 given in this Paper, we have been able to select pH ranges for our measurements so that the decomposition reactions have been negligible.

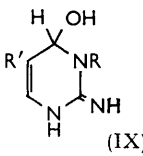
Variation between 0·05 and 1·0 in the ionic strengths of solutions used for kinetic studies produced no significant changes in the rate constants for the rearrangement of 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine. This absence of salt effects supports the conclusion that the rate-determining steps in these reactions involve uncharged species.

DISCUSSION

The present results indicate that the Dimroth rearrangement of a 1-alkyl-1,2-dihydro-2-iminopyrimidine is initiated by the ring-opening of its covalently hydrated neutral molecule to give a guanidino-aldehyde. This reaction could occur by the transfer of a proton

from the oxygen of the hydrate to the nearby nitrogen atom through a (solvent) water molecule as bridge, the transfer being accompanied by the appropriate bond rearrangements. By closure of the ring, the guanidino-aldehyde can form either the starting material or the rearranged product. The reversibility of the ring-opening reaction has also been demonstrated using 1-alkyl-2-alkylimino-1,2-dihydropyrimidines in which the two alkyl groups are different; equilibration of their aqueous solutions yields predominantly the isomer which has the smaller alkyl group on the ring nitrogen.[1]

The water adduct, A,H_2O, is a carbinolamine (IX) which is analogous to the heterocyclic " pseudo-bases " [12] formed from quaternary ammonium salts and to the carbinolamines which have been postulated as intermediates in the hydrolysis and formation of Schiff bases.[13] These adducts form anions which have ultraviolet absorption spectra similar to those of the corresponding ethanol and bisulphite addition compounds. Thus, the anion of the adduct (IX; R = Me, R′ = Br) has $\lambda_{max.}$ 268 mμ (log ε 3·93), and the ethanol and bisulphite adducts of the base (IV; R = R′ = Me, R″ = Br) have $\lambda_{max.}$ 280 mμ (log ε 3·89) and 268 mμ (log ε 3·76), respectively.



(IX)

Similarly, the ring-opening and -closing reactions parallel the reactions postulated for the pseudo-bases and the reversible hydrolysis of Schiff bases. Hence,[12,13] electron-withdrawing substances in the iminopyrimidine ring would be expected, first, to favour adduct formation and facilitate the subsequent prototropic ring-fission reaction, and, secondly, to slow the ring-closing reaction. The wide range of equilibrium constant values for the bisulphite adducts of the iminopyrimidines studied in the present work suggests that there is a similar wide variation in the extent to which neutral molecules of starting material add water covalently. Direct comparison of values of k_1 for halogenated and unsubstituted 1-alkyl-2-iminopyrimidines is not possible, because this constant cannot be obtained for the latter. Nevertheless, an upper limit of k_1 for unsubstituted iminopyrimidines is set by $(y_1 + y_2)$ which, as expected, is less than the measured k_1 for the 5-halogenated compounds. In general, substituents which lower the pK_a value of the iminopyrimidine should increase the rate of the ring-opening reaction. However, it must be remembered that k_1 is still a composite constant because its value also depends on the degree of hydration of the initial iminopyrimidine.

The absence of base catalysis in either the ring-opening or the ring-closing reactions is consistent with the observation that strongly basic amines will reversibly attack a carbonyl group without acid–base catalysis.[13] On the other hand, preliminary studies of the Dimroth rearrangement of the weaker bases comprising nitro-derivatives of pyrimidine and pyridine suggest that in these cases the reactions are acid–base catalysed. This is also consistent with observations on the effect of the strengths of bases on the kinetics of Schiff base formation.[13]

Ring-closure of guanidino-aldehydes would be expected to proceed through a covalently hydrated form (C,H_2O) of the end product, by analogy with A,H_2O. In cases where the substance C has appreciable aromatic character, rapid conversion of C,H_2O into C should occur, so the former is not detected spectroscopically. However, the observation that 2-aminopyrimidine and, to a lesser extent, pyrimidine itself readily form bisulphite adducts suggests that even in such cases the solutions might contain traces of the corresponding covalent hydrates. This would provide a mechanism for the reported [14] interconversion of [$^{15}N_3$]cytosine and [*amino*-^{15}N]cytosine.

At high pH values, the observed rate of formation of ring-opened intermediates from iminopyrimidines falls off because the hydrated species A,H_2O is present as its anion which is stable against further reaction.

Results of an earlier study of the Dimroth rearrangement [4] were interpreted in terms of

[12] D. Beke, *Adv. Heterocyclic Chem.*, 1963, **1**, 167.
[13] E. H. Cordes and W. P. Jencks, *J. Amer. Chem. Soc.*, 1963, **85**, 2847.
[14] I. Wempen, G. B. Brown, T. Ueda, and J. J. Fox, *Biochemistry*, 1965, **4**, 54.

two consecutive irreversible reactions. The rate constants reported at that time are now seen to be composite and to approximate to values of y_1 and y_2, but are somewhat higher because of simultaneous decomposition of the ring-opened intermediate.

Approximate energies and entropies of activation have been calculated from the values of k_1, k_2, and k_3 listed in Table 8, using Arrhenius plots. Although the estimated errors in the rate constants, namely $\pm 5\%$ for k_1, $\pm 9\%$ for k_2, and $\pm 10\%$ for k_3 (assuming an uncertainty of $\pm 3\%$ in the measured quantities y_2 and $k_2 + k_3$), are rather large, the activation energies for the reactions A ⟶ B, B ⟶ A, and B ⟶ C all lie within the ranges $18{\cdot}5 \pm 0{\cdot}5$, $20{\cdot}5 \pm 1{\cdot}5$, and $22{\cdot}5 \pm 0{\cdot}5$ kcal., respectively, for the four iminopyrimidines studied. Similarly, for 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine the values for A ⟶ B and B ⟶ A are 19 and 22 kcal. The entropy changes for the reversible ring-opening reactions appear, in all cases, to be small (less than 10 cal.deg.$^{-1}$), suggesting that the ring-opened intermediates are probably intramolecularly hydrogen-bonded.

Experimental

Microanalyses were carried out by Dr. J. E. Fildes and her staff.

Materials.—1,2-Dihydro-2-imino-1-methylpyrimidine and 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine were prepared through their hydriodides.[15] Except for 5-chloro- and 5-iodo-1,2-dihydro-2-imino-1-methylpyrimidine hydrochloride, which were the gift of Mr. M. N. Paddon-Row, the iminopyrimidines were provided by Dr. D. J. Brown.

Sodium pyrosulphite (B.D.H. Laboratory Grade) was purified by precipitation from aqueous solution with ethanol, and dried under a vacuum. Immediately before use, solutions were prepared in freshly boiled and cooled distilled water through which nitrogen had been bubbled for several hours. Concentrations of sulphite ion were checked iodometrically.

Tetrahydrofuran (May and Baker Laboratory Chemical) was shaken for several hours with ferrous sulphate, filtered, and refluxed for several hours over sodium–lead amalgam. The fraction distilling between 66° and 67° was collected and stored in the dark under nitrogen for not more than 48 hr. before use. All other chemicals used in kinetic and equilibrium studies were of AnalaR grade.

Bisulphite Adducts.—Equilibrium constants were calculated from absorption spectral measurements at a constant wavelength, using a solution of the imine hydrochloride (10^{-4}M) in an acetic acid–sodium acetate buffer (pH 4·7) which was mixed with an equal volume of an aqueous sodium hydrogen sulphite solution. In all cases, equilibrium was reached within several minutes of mixing. The approximate spectra of the adducts were obtained in this way by using buffered 1% sodium hydrogen sulphite solution. The occurrence of well defined isosbestic points in the spectra of imine–bisulphite mixtures indicated that not more than one adduct was formed in each case.

1,2-Dihydro-2-imino-1-methylpyrimidine (0·5 g.), dissolved in water (10 ml.), was added to a sodium hydrogen sulphite solution (10%; 10 ml.). After 20 min. in a closed flask at room temperature, the precipitated *adduct* was washed with aqueous ethanol and dried over phosphorus pentoxide at room temperature (Found: C, 31·85; H, 4·85; N, 22·3; S, 16·75. $C_5H_9N_3O_3S$ requires C, 31·4; H, 4·75; N, 22·0; S, 16·75%). The *adduct* similarly prepared from 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine retained a molecule of water even after drying at 50° under reduced pressure (Found: C, 23·7; H, 3·85; N, 13·9. $C_6H_{10}BrN_3O_3S,H_2O$ requires C, 23·85; H, 3·95; N, 13·9%). Unlike the iminopyrimidine cations, which have only one intense infrared band (around 1630 cm.$^{-1}$) between 1600 and 1700 cm.$^{-1}$, the bisulphite adducts have several additional intense bands in this region. These bands are absent from the bisulphite ion itself. Also, the strong bands which are found in the spectrum of sodium hydrogen sulphite in the region 970—1170 cm.$^{-1}$ are displaced in the adducts by 30—60 cm.$^{-1}$ to higher values.

Oximes.—1,2-Dihydro-2-imino-1-methylpyrimidine hydrochloride (0·15 g.), dissolved in aqueous sodium hydroxide (0·05M; 5 ml.), was mixed with an aqueous solution of hydroxylamine hydrochloride (140 mg., 10 ml.) saturated with sodium carbonate. After standing for 2 hr. at room temperature, the solution was brought to pH 8·5 by adding powdered solid carbon dioxide.

[15] D. J. Brown, E. Hoerger, and S. F. Mason, *J.*, 1955, 4035.

The *precipitate*, washed with distilled water (25 ml.) and dried under a vacuum over phosphorus pentoxide, had m. p. 95·0° (decomp.) (Found: C, 35·4; H, 5·85; N, 27·75. $C_5H_9N_4O,H_2CO_3$ requires C, 35·3; H, 5·95; N, 27·45%). When a drop of concentrated hydrochloric acid was added to the solid oxime carbon dioxide was evolved (lime–water test). Similar compounds were obtained as derivatives of the 5-halogenated iminopyrimidines but, because of their weaker basic character, difficulty was experienced in purifying them.

In all cases, the infrared spectra of the oximes were similar to one another, but differed from those of the starting materials and the products of the rearrangement. They showed a characteristic band near 1670 $cm.^{-1}$.

Bromomalondialdehyde Dianil.—5-Bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydrochloride (0·25 g.), dissolved in aqueous sodium hydroxide (M; 15 ml.), was set aside for 8 hr. at 20°. It was acidified to pH 3 by adding dilute hydrochloric acid, and added to a solution of aniline hydrochloride (0·25 g.) in dilute hydrochloric acid (15 ml.). After refluxing on a water-bath and cooling, the precipitate was washed with a little water and dissolved in the minimum volume of aqueous ethanol. The pale yellow *dianil*, precipitated by addition of strong ammonia solution, had m. p. 144° (from aqueous ethanol) (lit.,[16] 145°) (Found: C, 59·9; H, 4·25; N, 9·25. $C_{15}H_{13}BrN_2$ requires C, 59·8; H, 4·35; N, 9·3%).

Similarly, malondialdehyde *dianil* was obtained from 1,2-dihydro-2-imino-1-methylpyrimidine and 1,2-dihydro-1-methyl-2-oxopyrimidine. The products had m. p. and mixed m. p. 113·5° (lit.,[17] 115°) (Found, for the material from 1,2-dihydro-2-imino-1-methylpyrimidine: C, 81·15; H, 6·55; N, 12·8. $C_{15}H_{14}N_2$ requires C, 81·05; H, 6·35; N, 12·6%).

NN′-*Dimethylguanidine Picrate.*—5-Bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine hydrochloride (0·25 g.), dissolved in aqueous sodium hydroxide (M; 15 ml.), was set aside for 8 hr. at 20°. After acidifying the solution to pH 5 with dilute hydrochloric acid, a saturated aqueous solution of picric acid (25 ml.) was added and the mixture was placed in the refrigerator. The *product* that separated was recrystallised from water and, after drying, had m. p. 176° (lit.,[18] 178°) (Found: C, 34·55; H, 3·8; N, 26·5. $C_9H_{12}N_6O_7$ requires C, 34·2; H, 3·85; N, 26·6%).

Physical Measurements.—Ultraviolet and visible spectra were obtained on a Shimadzu RS 27 recording spectrophotometer. Where species were relatively stable, their extinction coefficients and maxima were checked on an Optica CF 4 spectrophotometer. The spectra of unstable species were measured using a rapid-reaction apparatus.[19] Spectrophotometric pK-values were determined as described previously,[4] except that the following buffer systems, adjusted to ionic strengths of 0·05, 0·1, and 0·2 with sodium chloride, were used: pH 7—9, Na_2HPO_4–borax; pH 9—11, Na_2CO_3–borax; pH 11—12, NaOH–Na_2HPO_4. N.m.r. spectra were determined at 33·5° by Mr. S. E. Brown, using a Perkin-Elmer R10 60 Mc. instrument.

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