240. *The Dimroth Rearrangement. Part II.*[1] *Kinetic Studies.*

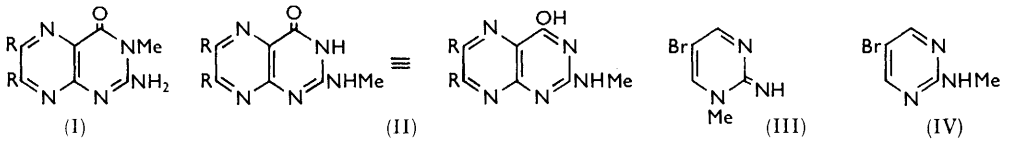
By D. D. Perrin.

The kinetics of this rearrangement (in which an alkyl group migrates from a nuclear to an extranuclear nitrogen) have been studied by using a rapid spectrophotometric method. Neutral molecules of 2-amino-3,4-dihydro-3-methyl-4-oxopteridine (I; R = H) and its 6,7-dimethyl derivative are stable but, in alkaline solutions, their anions rearrange by two well-defined consecutive reactions to yield the corresponding 4-hydroxy-2-methylaminopteridines (II). The second of these reactions, but not the first, appears to be catalysed by hydroxyl ion. Similarly, the neutral molecule of 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (III) is converted in two steps into 5-bromo-2-methylaminopyrimidine (IV); neither of these reactions is catalysed by hydroxyl ion. The instability of the anions of the aminodihydro-oxopteridines is attributed to the conversion of the 2-amino- into a 2-imino-group, followed by fission of the pyrimidine nucleus.

The migration of methyl groups from nuclear to extranuclear nitrogen atoms in the pyrimidine series has been shown, by labelling with nitrogen-15, to involve ring-fission, followed by rotation and recyclisation.[2] A similar reaction sequence, also with cleavage of a pyrimidine ring, was postulated by Taylor and Loeffler[3] for migrations of this type in

[1] Part I, Brown and Harper, preceding paper.
[2] Brown, *Nature*, 1961, **189**, 828.
[3] Taylor and Loeffler, *J. Amer. Chem. Soc.*, 1960, **82**, 3147.

the heterocyclic compounds examined by them, all of which comprised condensed pyrimidine systems. Thus, 2-amino-3,4-dihydro-3,6,7-trimethyl-4-oxopteridine (I; R = Me) rearranges in dilute alkali to form 4-hydroxy-6,7-dimethyl-2-methylaminopteridine (II; R = Me).[4]



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

A rapid-flow spectrophotometric study has now been made of the rearrangements, in alkaline solution, of the compounds (I; R = H) and (I; R = Me) to the corresponding 4-hydroxy-2-methylaminopteridines (II), and of 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (III) to 5-bromo-2-methylaminopyrimidine (IV). In the three examples studied, the reaction proceeds more or less quantitatively, and it has been used in organic synthesis, where yields of the purified rearranged material have exceeded 50%.[1,4,5] Evidence, presented below, indicates that the transformation of compound (I) into compound (II) can be represented by the reaction sequence,

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C,$$

where A is the anion of (I) and C is the anion of (II). It is possible that k_1 and k_2 may be reversible to a small extent but this was not demonstrated experimentally. The intermediate, B, has not been identified but (by analogy with the reversible ring-fission of the cation of pteridine to give 2-aminomethyleneamino-3-formylpyrazine [6]) it is possibly the anion of 2-methylguanidinopyrazine-3-carboxylic acid, which might be expected to result from hydrolytic fission of A across the 3,4-double bond.

2-Amino-3,4-dihydro-3-methyl-4-oxopteridine (I; R = H).—*The reaction* B ⟶ C. Neutral and acid solutions of the substance (I; R = H) are stable. However, when such a neutral solution is added to 2M-sodium hydroxide at 20° the ultraviolet and visible spectra change continuously, an initial rapid change during about two minutes being followed by a slower one taking upwards of half an hour. Thus, the optical density of the solution at 365 and 390 mμ passes through a minimum within two minutes of mixing and, from about three minutes after mixing (but not before that), the family of spectral curves obtained by rapid and repeated scanning have well-defined isosbestic points at 242·5, 269, 338, and 397 mμ. The spectrum taken 27 min. after mixing (Fig. 1) was close to that of the anion of an authentic specimen of the compound (II; R = H) which gave $\lambda_{max.}$ 260 and 367 mμ (log ε = 4·299 and 3·829), $\lambda_{min.}$ 300 mμ.

The existence of isosbestic points suggested that only two light-absorbing species, one of which, B, was changing into the other, C, were present in the solutions after the first few minutes, so that the kinetics of the reaction could be studied by measuring, at suitable wavelengths, the change of optical density with time. Results in Figs. 2 and 3 show that the plot of log $(D - D_\infty)/(D_0 - D_\infty)$ against time is linear, as required for a first-order rate equation, and that the reaction is catalysed by hydroxyl ions.

The reaction A ⟶ B. The spectrophotometric study of this reaction is complicated by the further conversion of B into C so that, in general, the absorption due to pure B cannot be measured. This prevents the direct evaluation of $(D - D_\infty)$ for the reaction A ⟶ B. This difficulty can be overcome by working at a wavelength where B and C are isosbestic, so that D rapidly reaches the desired and constant value. Alternatively,

[4] Curran and Angier, *J. Amer. Chem. Soc.*, 1958, **80**, 6095.
[5] Pfleiderer, Liedek, Lohrmann, and Rukwied, *Chem. Ber.* 1960, **93**, 2015.
[6] Perrin, *J.*, 1962, 645.

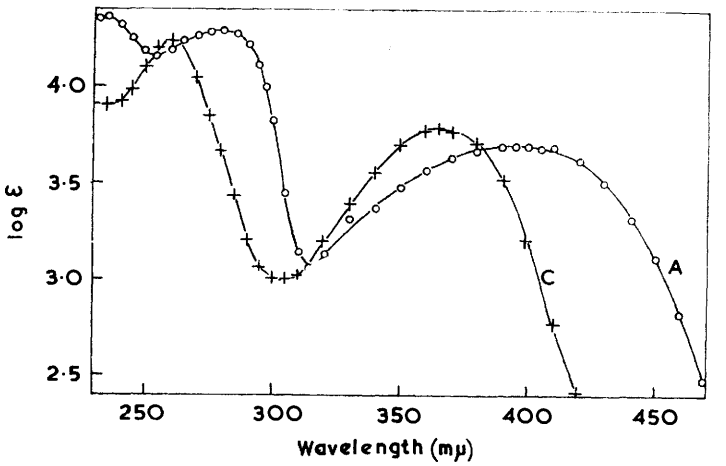


FIG. 1. A, Absorption spectrum taken within two seconds of mixing solutions 10^{-4}M in 2-amino-3,4-dihydro-3-methyl-4-oxopteridine and 2M-KOH, at 20°. Continuous-flow method. C, Absorption spectrum after the mixed solution had been left for 27 minutes.

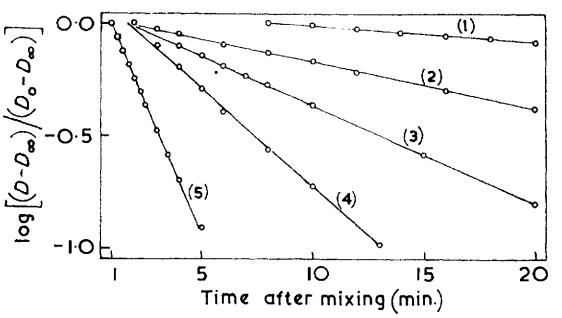


FIG. 2. Plot of log $(D - D_\infty)/(D_0 - D_\infty)$ against time, for the reaction B ⟶ C in alkaline solutions of 2-amino-3,4-dihydro-3-methyl-4-oxopteridine at 20°. Experimental details are summarised in Table 1.

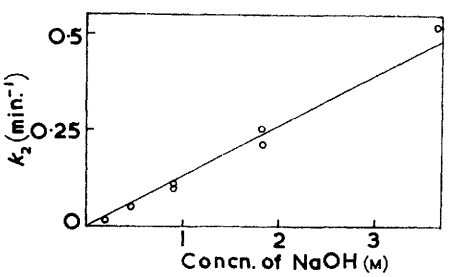


FIG. 3. Dependence of the first-order velocity constant, k_2, for the reaction B ⟶ C in alkaline solutions of 2-amino-3,4-dihydro-3-methyl-4-oxopteridine at 20°, on the concentration of sodium hydroxide.

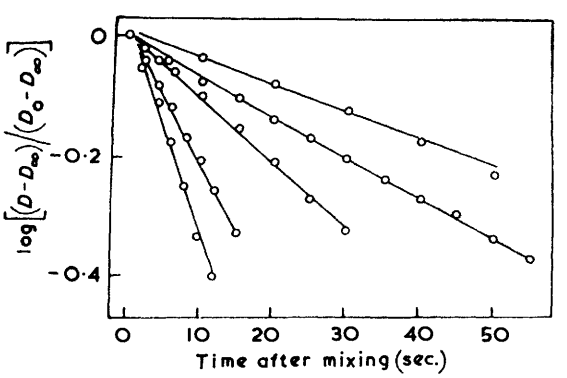


FIG. 4. Plot of log $(D - D_\infty)/(D_0 - D_\infty)$ at 430 mμ against time, for the reaction A ⟶ B in alkaline solutions of 2-amino-3,4-dihydro-3-methyl-4-oxopteridine at 20°.

Experimental details are summarised in Table 1.

Key as Fig. 2.

back-extrapolation of the plot of log $(D - D_\infty)$ *versus* time for the B ⟶ C reaction can be used to afford the optical density of pure B, which is the D_∞ value for the reaction A ⟶ B. Clearly, this back-extrapolation must not be made to the time when the solutions were mixed (and only A was present) but to some subsequent time. In the present work this time is assumed equal to $t_{\frac{1}{2}}$ for the conversion of A into B, and it is obtained by an iterative process. Although this procedure is more tedious than the isosbestic method, it has the advantage that both k_1 and k_2 are obtained under the same conditions and in the same experiment.

Results in Fig. 4 suggest that the reaction is first-order and that the rate constant increases with the concentration of sodium hydroxide present. However, because reaction proceeds through the anion of compound (I), but not through the neutral molecule (with which it is in dynamic equilibrium), observed rate constants must be multiplied by the factor, ([A] + [I])/[A], if true rate constants are to be obtained: this factor is readily calculated from the identity,

$$\mathrm{pH} = \mathrm{p}K_a + \log ([\mathrm{A}]/[\mathrm{I}]).$$

Values of k_1 at 20° (corrected by using $\mathrm{p}K_a = 13{\cdot}41$), corresponding values of k_2, and other relevant data, are summarised in Table 1.

TABLE 1.

First-order rate constants for the rearrangement of (I; R = H) and (I; R = Me) in alkali at 20°.

(I, R = H), pK = 13·41. (Analyt. λ, 290 mμ.)

	[NaOH] (M)	pH	[(I)] (M)	Analyt. λ (mμ)	Apparent k_1 (min.$^{-1}$)	True k_1 (min.$^{-1}$)	k_2 (min.$^{-1}$)
	0·183	13·30	$2{\cdot}5 \times 10^{-4}$	430	0·633	1·24	0·0161
	0·457	13·67	$2{\cdot}5 \times 10^{-4}$	430	0·935	1·48	0·0514
	0·914	13·96	$2{\cdot}5 \times 10^{-4}$	430	1·42	1·82	0·106
	1·83	14·27	$2{\cdot}5 \times 10^{-4}$	430	2·86	3·25	0·254
(5) [e]	3·66	14·66	$2{\cdot}5 \times 10^{-4}$	430	5·07	5·34	0·521
(1)	0·183	13·30	$5{\cdot}7 \times 10^{-5}$	290			0·0157
(2)	0·457	13·67	$5{\cdot}7 \times 10^{-5}$	290			0·0481
(3)	0·914	13·96	$5{\cdot}7 \times 10^{-5}$	290			0·103
(4)	1·83	14·27	$5{\cdot}7 \times 10^{-5}$	290			0·213
	0·914	13·96	$5{\cdot}7 \times 10^{-5}$	242·5 [a]	1·39	1·78	
	0·156	13·23 [b]	$1{\cdot}8 \times 10^{-4}$	397 [a]	0·514	1·29	
	0·156 [c]	13·10 [b]	$1{\cdot}8 \times 10^{-4}$	397	0·592	1·80	
	0·156 [d]	13·05 [b]	$1{\cdot}8 \times 10^{-4}$	397	0·815	2·67	
			(I, R = Me), pK = 14·20. (Analyt. λ, 290 mμ.)				
	3·66	14·66	$1{\cdot}8 \times 10^{-4}$	290	0·91	1·22	0·044

[a] Isosbestic method. [b] Determined spectrophotometrically. [c] Also 1M in $NaNO_3$. [d] Also 2M in $NaNO_3$. [e] Number of experimental curve in Fig. 2.

The reaction B ⟶ C appears to be strongly base-catalysed. The relation,

$$k_2 = 0{\cdot}116[\mathrm{OH}^-] \ (\mathrm{min.}^{-1})$$

reproduces within ±0·007 all but the two highest values of k_2 given in Table 1.

The corresponding least-squares equation for k_1,

$$k_1 = 0{\cdot}88 + 1{\cdot}23[\mathrm{OH}^-] \ (\mathrm{min.}^{-1})$$

fits the results within ±0·18 but the implied, weak catalysis by hydroxyl ion is dubious and is probably only an expression for the primary salt effect when the ionic strength

increases from 0·18 to 3·66: a comparable increase is observed when sodium nitrate is added to the solution.

2-Amino-3,4-dihydro-3,6,7-trimethyl-4-oxopteridine (I; R = Me).—In alkaline solutions this compound behaves in a similar manner to its parent (I; R = H), but, owing in part to its higher pK_a (14·20) much higher concentrations of sodium hydroxide are needed if the reactions are to proceed rapidly. The spectra of the corresponding species A (max. at 289 mμ) and C (max. at 258 and 361 mμ) are very similar to those shown in Fig. 1, and B and C have isosbestic points at 275 and 307 mμ. In 3·66M-sodium hydroxide at 20°, first-order rate constants for the consecutive reactions were $k_1 = 1·22$ and $k_2 = 0·044$ min.$^{-1}$, representing times of half-reaction of 47 sec. and 16 min., respectively: for the compound (I; R = H) under the same conditions the corresponding values of $t_{\frac{1}{2}}$ are 11 sec. and 81 sec.

5-Bromo-2-imino-1-methylpyrimidine (III).—When a 5×10^{-5}M-solution of the (stable) cation of (III) is made alkaline, two consecutive reactions can readily be observed: the

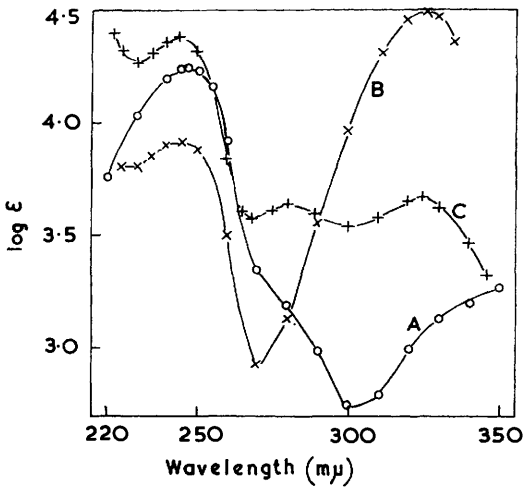
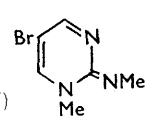


FIG. 5. Absorption spectrum taken after mixing solutions 5×10^{-5}M in 5-bromo-2-imino-1-methylpyrimidine and 0·05M-NaOH, at 20°; A, within 2 sec.; B, after 9 min.; C, after 2½ hr.

optical density of the solution at 326 mμ increases from an initial value of $D_{1\text{ cm.}} = 0·07$ to a maximum of 1·44 and then, with time, falls almost to zero. Relevant spectra are shown in Fig. 5. The final solution contains 5-bromo-2-methylaminopyrimidine ($\lambda_{max.}$ 247, 328 mμ; log ε, 4·286, 3·357) as the main organic species [1] but Fig. 5 shows that an unidentified substance with $\lambda_{max.}$ at *ca.* 280 mμ is also present. This material is thought to result from a slow hydrolytic deamination of the intermediate formed during the rearrangement. Thus, a substance with an absorption maximum at 278 mμ is slowly formed in alkaline solutions of 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine (V) which readily ring-opens but cannot undergo the rearrangement. Formation of this substance from the neutral molecule (V) is unlikely because, under these conditions, the latter has a half-life of only about 6 minutes at 20°. A similar peak appears when 1-alkyl-1,2-dihydro-2-oxopyrimidines are left in alkaline solution.[1]



(V)

By representing the reaction sequence by

$$D \xrightarrow{k_1} E \xrightarrow{k_2} F$$

where D is the neutral molecule (III) and F is (mainly) 5-bromo-2-methylaminopyrimidine, first-order rate constants, k_1 and k_2, have been evaluated from the time-dependence of optical density changes. Results are summarised in Table 2.

TABLE 2.

First-order rate constants for the rearrangement of compound (III) [a] in aqueous alkali.

[NaOH] (M)	[(III)] (M)	Analyt. λ, (mμ)	Temp.	k_1 (min.$^{-1}$)	k_2 (min.$^{-1}$)
$9{\cdot}1 \times 10^{-4}$	$2{\cdot}5 \times 10^{-5}$	326	20°	0·486	0·0156
0·0183	$2{\cdot}5 \times 10^{-5}$	326	20	0·484	0·0160
0·0183	5×10^{-5}	246	20	0·468	
0·183	5×10^{-5}	246	20	0·527	
$9{\cdot}1 \times 10^{-4}$	$2{\cdot}5 \times 10^{-5}$	326	30	1·13	0·0445

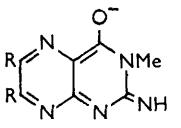
[a] 5-Bromo-1,2-dihydro-2-imino-1-methylpyrimidine, $pK_a = 9{\cdot}95$ at 20° (analyt. λ, 325 mμ).

Neither reaction is base-catalysed. A comparable value of k_1 is also obtained at lower pH values when the observed rates are corrected to allow for the presence of part of compound (III) as the (non-reacting) cation.

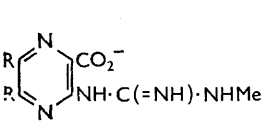
5-Bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine (V).—In its initial spectral changes, (V) parallels the iminopyrimidine (III). The absorption maximum falls steadily to less than half its initial value, there is an isosbestic point at 280 mμ, and a new peak appears at 322 mμ and increases to a value of log ε about 4·50. Rate constants for this reaction in 0·0457M-sodium hydroxide are $k_1 = 0{\cdot}110$ min.$^{-1}$ at 20° and 0·301 min.$^{-1}$ at 30° (analyt. λ, 322 mμ). Thereafter, the spectrum changes very slowly, with steady diminution of the peak at 322 mμ and the emergence of a new peak at 278 mμ: $t_{\frac{1}{2}}$ for this reaction is about 170 minutes at 30°.

DISCUSSION

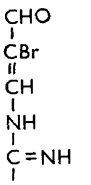
Although compounds (I; R = H) and (I; R = Me) could, conceivably, form anions by the hydration of the oxo-group to give a *gem*-diol, with subsequent loss of a proton, such a reaction is unlikely because of the absence from the molecule of strongly electron-withdrawing substituents. Instead, it is probable that anion formation arises by the loss of a proton from the 2-amino-group to form the imine (VI) which then undergoes ring-fission. The structure (VI) contains an uncharged imino-group adjacent to a saturated tertiary nitrogen atom. This sequence occurs in all compounds known to undergo the Dimroth rearrangement and it appears to confer an intrinsic instability on the molecule. Stability is restored if the imine is converted into its cation or, in the oxopteridines, into an amino-group.



(VI)



(VII)



(VIII)

Little is known about the mechanisms involved in the ring-opening and ring-closing steps of the rearrangement. Taylor and Loeffler [3] suggested that base-catalysis occurred, with an initial nucleophilic attack by hydroxyl ion or other base at a pyrimidine C=N bond, with subsequent cleavage of the ring. The present results do not support this hypothesis. On the contrary, the absence of hydroxyl-ion catalysis of k_1, and the structures of the rearranged products, are consistent with simple heterolytic fission of the 3,4 C–N bond in compounds (I; R = H) and (I; R = Me) and the 1,6 C–N bond in compound (III). This would probably be followed by solvent attack to give the intermediates (VII) and (VIII), derived from (I) and (III), respectively, which would also be expected on Taylor and Loeffler's reaction scheme.

Reversal of these reactions, except that water-elimination would involve the imine hydrogen, would then lead to the final products (II) and (IV) in which there is at least partial aromatic stabilisation.

The strong electron-withdrawing tendencies of the formyl group, the bromine atom, and the ethylenic double-bond might be expected to render the substituted guanidine (VIII) a much weaker base than the starting material (III), so that, under the experimental conditions, (VIII) would be present in solution almost entirely as the neutral molecule. If the limiting factor in the reaction, E ⟶ F, were the re-formation of the 1,6-bond in the pyrimidine ring the observed rate constant, k_2, would be independent of pH, as found. On the other hand, zwitterion formation would make the guanidinopyrazinecarboxylic acid (VII) a strong base so that, at pH values below its pK_a, the apparent value for k_2 would vary with the ratio of uncharged base to total concentration; this could explain the dependence of k_2 on hydroxyl-ion concentration.

From measurements at 20° and 30°, Arrhenius activation energies, E_a, for the reaction, D ⟶ E, have been estimated to be 15·1 and 18·0 kcal. for 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine (III) and 5-bromo-1,2-dihydro-1-methyl-2-methyliminopyrimidine (V), respectively. For compound (III) and the reaction E ⟶ F the corresponding activation energy was 18·2 kcal. That E_a for D ⟶ E should be greater for substance (V) than for substance (III) is as expected: the former is the stronger base (pK_a 10·67 as against 9·95), indicating greater electron-availability, and, hence, difficulty of bond-breakage, in the molecule. This is also true for the observed reaction rate, k_1, at 20°; compound (III) ring-opens 4·4 times as quickly as (V). For the same reason the absolute rates are much greater than for related pyrimidine derivatives that are stronger bases.[1]

Experimental

Materials.—The pteridine [4,7] and pyrimidine [1] derivatives used in this study were generously provided by Dr. D. J. Brown.

Methods.—Ultraviolet and visible spectra were recorded on a Shimadzu model RS 27 recording spectrophotometer, into the cell compartment of which was fitted a thermostatted 1-cm. cell attached to a modified Chance rapid-reaction apparatus.[8] The apparatus was used both for stopped-flow and for continuous-flow measurements. Sodium hydroxide concentrations at 20° were converted into pH values by taking pK_w = 14·17 and using the activity coefficients given by Åkerlof and Kegeles.[9]

Spectrophotometric pK_a values were determined by measuring the initial optical densities of freshly mixed dilute solutions of the pteridine or pyrimidine derivative and carbonate-free sodium hydroxide. For compounds (I; R = H) and (I; R = Me), where the spectrum of the fully-formed anion could not be obtained, an extrapolation method was used, K_a being given by the slope of the plot of $(D_I - D)[H^+]$ *versus* D. They are probably correct within ±0·04 logarithm unit.

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[7] Brown and Jacobsen, *J.*, 1961, 4413.
[8] Inoue and Perrin, *J. Phys. Chem.*, 1962, **66**, 1689.
[9] Åkerlof and Kegeles, *J. Amer. Chem. Soc.*, 1940, **62**, 620.