905. *Pyrimidine Reactions. Part XII.*[1] *The Thermal Rearrangement of 2-Alkoxypyrimidines*

By D. J. Brown and R. V. Foster

The thermal rearrangement of 2-methoxypyrimidine to 1,2-dihydro-1-methyl-2-oxopyrimidine has been followed spectrometrically and shown to be a first-order reaction. It is accelerated by tertiary bases, whose efficiencies vary according to their basic strengths. Of the higher 2-alkoxypyrimidines, only the ethoxy-, isopropoxy-, and s-butoxy-homologues show any measurable rearrangement, and only in the presence of base and above 200°. A free-radical mechanism appears to be precluded by the very minor changes in rate produced by adding benzoyl peroxide or benzoquinone to the reaction mixtures. Eleven new 2-alkoxy- and 1-alkyl-1,2-dihydro-2-oxo-pyrimidines are described.

In extending earlier studies [1,2] on the alkylamination of chloropyrimidines without solvent, we have noticed that the amination of methoxypyrimidines is accompanied by more isomerisation to *N*-methylated oxopyrimidines than might be expected on the basis of existing literature.[3] To find out whether the alkylamines used were having an accelerating effect on such thermal rearrangements, we have now measured the rate of isomerisation for some simple 2-alkoxypyrimidines (I) to 1-alkyl-1,2-dihydro-2-oxopyrimidines (II), first in the absence of amine, and then in the presence of several trialkylamines. Tertiary amines were chosen to avoid competition from the amination reaction.

The required 2-alkoxypyrimidines were conveniently prepared from 2-chloropyrimidine and sodium alkoxide in the appropriate alcohol, but 2-t-butoxypyrimidine could not be so made. Authentic samples of the corresponding *N*-alkyl derivatives (II) resulted either from treatment of 2-hydroxypyrimidine with an alkyl iodide in ethanolic sodium ethoxide or from primary syntheses using an *N*-alkylurea and the diacetal of malondialdehyde. The ultraviolet spectra of these compounds showed that the isomerisation could be followed

[1] Part XI, D. J. Brown and J. M. Lyall, *Austral. J. Chem.*, 1965, **18**, in the press.
[2] D. J. Brown and J. M. Lyall, *Austral. J. Chem.*, 1964, **17**, 794; 1965, **18**, 741.
[3] T. B. Johnson and G. Hilbert, *Science*, 1929, **69**, 579; D. J. Brown, E. Hoerger, and S. F. Mason, *J.*, 1955, 211; J. L. Rabinowitz and S. Gurin, *J. Amer. Chem. Soc.*, 1953, **75**, 5758.

spectrometrically both at 265 mμ, where 2-alkoxypyrimidines absorbed strongly but their *N*-methyl isomers had little absorption, and at 310 mμ where the reverse held (Figure 1).

The rearrangement of 2-methoxypyrimidine was markedly accelerated by organic bases, which were effective in the order of their basic strengths. Thus, *N*-ethylmorpholine (pK_a 7·7) caused a four-fold incresae in rate, *N*-methylpiperidine (pK_a 10·1) a twelve-fold increase, and triethylamine (pK_a 10·6) a thirteen-fold increase at 150° (Table 1). It will

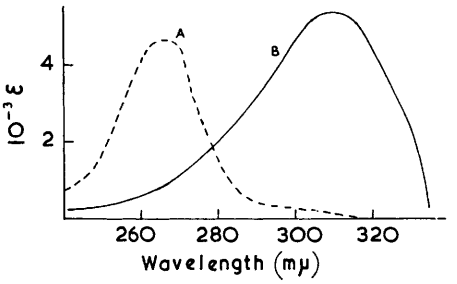


FIGURE 1. Ultraviolet absorption in ethanol of neutral molecules: (A) 2-methoxypyrimidine; (B) 1,2-dihydro-1-methyl-2-oxopyrimidine

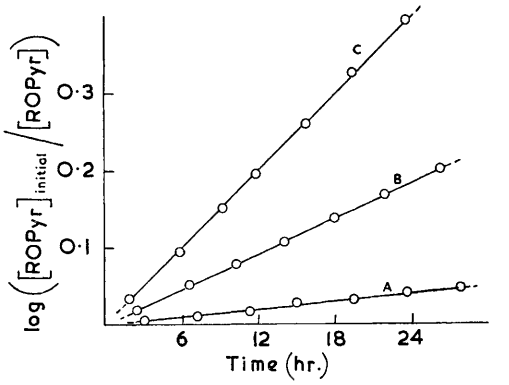


FIGURE 2. Disappearance of 2-methoxypyrimidine at 150°: (A) uncatalysed; (B) with a 5 molar proportion of *N*-ethylmorpholine; (C) with a 5 molar proportion of triethylamine

be noticed that a change in molar ratio of base from the usual 5·0 to 0·5 was accompanied by a slight increase in rate. We see this as resulting from a higher dielectric constant in the reaction mixture in the absence of a solvent rather than as a concentration effect on the kinetics. When the higher alkoxy-homologues were heated alone, no observable rearrangement occurred up to 240°, and even in the presence of triethylamine at that temperature rearrangement was very slow at best. 2-Ethoxy-, 2-isopropoxy-, and and 2-s-butoxy-pyrimidine showed a progressive decrease in absorption at 265 mμ and an increase at 315 mμ, but efforts to isolate the small percentages of *N*-alkylated products were unsuccessful. 2-Propoxy- and 2-butoxy-pyrimidine showed no such spectral changes.

Whether base-catalysed or not, the rearrangements strictly obeyed first-order kinetics (Figure 2) in their early stages, in respect of both decrease in alkoxypyrimidine (265 mμ)

TABLE 1

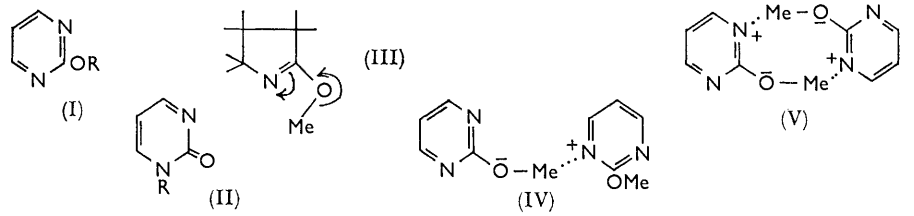
Rate constants for the thermal isomerisation of 2-alkoxypyrimidines

Alkoxy group *	Temp.	% Reaction followed	$K \times 10^7$ (sec.$^{-1}$)	$t_{0·5}$ (days)
Methoxy	150° †	5	3·5	23
	200 †	17	27	2·9
	150 ‡	12	13	6·2
	150 §	20	41	2·0
	130	10	9·7	8·3
	150	35	45	1·8
	150 ¶	18	55	1·5
	200	60	300	0·3
Ethoxy	240	10	1	80
Propoxy	240	0 **		
Butoxy	240	0 **		
Isopropoxy	220	8	0·8	100
	240	28	3	27
s-Butoxy	220	17	4	20
	240	38	9	9

* Generally with a 5 molar proportion of triethylamine. † No added amine. ‡ With *N*-ethylmorpholine. § With *N*-methylpiperidine. ¶ With an 0·5 molar proportion of triethylamine. ** Followed for 68 hr.

and increase in *N*-alkyl isomer (310—315 mμ). After 6—72 hours (according to temperature) the darkening of the mixture began to interfere seriously with spectrometric readings especially at the longer wavelength. Rate constants and the percentage of the reaction on which each is based are recorded in Table 1.

To discover whether a free-radical mechanism was involved, as suggested by Wiberg *et al.*[4] for the rearrangement of 2-methoxypyridine to 1,2-dihydro-1-methyl-2-oxopyridine, we repeated representative reactions in the presence of a free-radical inducer or remover. At 160° and without added base, 2-methoxypyrimidine rearranged at a slightly increased rate (*ca.* 1·5 times) in the presence of benzoyl peroxide, but no decrease was observed with benzoquinone; at higher temperatures, and in all base-catalysed rearrangements, neither additive had any appreciable effect. Thus, free-radicals appear to be precluded.



Whilst there is no direct evidence as to whether the thermal isomerisation proceeds by an intra- or inter-molecular path, it may be significant that in all known pyrimidine cases [5] the methyl group has migrated only to an α- and never to a γ-nitrogen atom, although such γ-migration has been observed in other series, *e.g.*, in the formation of 1,4-dihydro-1-methyl-4-oxopyridine from 4-methoxypyridine.[6] In addition, Tieckelmann and his colleagues [7] have recently discovered a formally similar α-migration in alkenyloxypyrimidines, *e.g.*, (I; R = CH_2·CH:CH_2), and related pyridines, which appears to proceed as an *ortho*-Claisen reaction. These facts could suggest a mechanism of the four-centre intramolecular type as proposed [8] for the transformation [9] of the methoxypyrroline (III) into its *N*-methyl isomer; the electron-rich nitrogen atom would act as a nucleophile, and it would account for the slower isomerisation of the higher homologues. A similar conclusion has been reached for the rearrangement [10] of 2-methoxypyridine *N*-oxide into 1,2-dihydro-1-methoxy-2-oxopyridine. On the other hand, an intermolecular route has been experimentally proven [4] in the analogous case of 2-methoxypyridine. In addition, the well known acid [11] and alkyl halide [5] catalysis of the isomerisation as well as the base-catalysis observed in the present work can best be explained by an intermolecular ion-pair type of intermediate, *e.g.*, (IV) * or (V),* as postulated [12] for the thermal rearrangement of 4-methoxypyridine.

Experimental

Analyses were done by Dr. J. E. Fildes and her staff. Spectra were measured with a Shimadzu RS27 spectrophotometer.

Measurement of Isomerisation Rate.—Samples of the alkoxypyrimidine (*ca.* 0·001 mol.) were weighed into a short length of Pyrex glass tubing sealed at one end, and the amine (*ca.*

* The charges indicated represent those being developed during the formation of the activated complex.

[4] K. B. Wiberg, T. M. Shryne, and R. R. Kintner, *J. Amer. Chem. Soc.*, 1957, **79**, 3160.
[5] D. J. Brown, " The Pyrimidines," Interscience, New York, 1962, p. 371.
[6] L. Haitinger and A. Lieben, *Monatsh.*, 1885, **6**, 279; *Ber.*, 1885, **18**, 381 (Referate), 929.
[7] H. J. Minnemeyer, J. A. Egger, J. F. Holland, and H. Tieckelmann, *J. Org. Chem.*, 1961, **26**, 4425; F. J. Dinan, H. J. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, 1963, **28**, 1015; F. J. Dinan and H. Tieckelmann, *ibid.*, 1964, **29**, 892.
[8] L. A. Cohen and B. Witkop, in " Molecular Rearrangements," ed. P. de Mayo, Interscience, New York, 1964, vol. 2, p. 981.
[9] S. Petersen and E. Tietze, *Chem. Ber.*, 1957, **90**, 909.
[10] F. J. Dinan and H. Tieckelmann, *J. Org. Chem.*, 1964, **29**, 1650.
[11] *E.g.*, K. Eichenberger, A. Staehlin, and J. Druey, *Helv. Chim. Acta*, 1954, **37**, 837.
[12] E. Spinner and J. C. B. White, unpublished work.

0·005 mol.) added to each. The tubes were sealed, and heated in an oil thermostat for the required times. The contents of each tube were carefully washed out with absolute ethanol into a volumetric flask, from which suitable dilutions were made for the spectroscopic measurement against a standard solution of untreated alkoxypyrimidine. The quantity of alkoxypyrimidine remaining was indicated by the relative peak heights at 265 mμ, with an appropriate minor correction for the absorption of the *N*-alkyl isomer. The first-order rate constants were calculated from the plots of log (initial concn. of alkoxypyrimidine/observed concn. of alkoxypyrimidine) against time (as in Figure 2).

Alkoxypyrimidines (Table 2).—A solution of 2-chloropyrimidine [13] (5·0 g.) in the appropriate alcohol (50 ml.) was added with stirring to the same alcohol (50 ml.) with which sodium (1·0 g.) had reacted. The mixture was warmed under reflux on a steam-bath for 1 hr. and then cooled. A little solid carbon dioxide was added, and salts were filtered off. Distillation of the filtrate gave the alkoxypyrimidine.

TABLE 2

2-Alkoxypyrimidines

Alkoxyl group	B. p./mm.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Methoxy *	69—70°/22	78	54·2	5·8	25·0	$C_5H_6N_2O$	54·5	5·5	25·4
Ethoxy	77—78/20	73	57·6	6·4	22·95	$C_6H_8N_2O$	58·05	6·5	22·6
Propoxy	92—93/22	72	60·5	7·0	20·2	$C_7H_{10}N_2O$	60·85	7·3	20·3
Isopropoxy	90—91/18	75	60·85	7·1	20·1	,,	,,	,,	,,
Butoxy	96—98/18	72	63·6	7·7	18·7	$C_8H_{12}N_2O$	63·1	7·95	18·4
s-Butoxy	89—90/18	63	63·1	8·0	18·8	,,	,,	,,	,,

* Cf. M. P. V. Boarland and J. F. W. McOmie, *J.*, 1952, 3716; D. J. Brown and L. N. Short, *J.*, 1953, 331.

1-*Alkyl*-1,2-*dihydro*-2-*oxopyrimidines* (Table 3).—(*a*) 2-Hydroxypyrimidine [14] (4·8 g.) alkyl iodide (0·06 mol.), and sodium ethoxide (from sodium, 1·15 g.) were heated under reflux until the solution was no longer alkaline. The ethanol was distilled off, and the gummy residue shaken with chloroform. The extract was filtered and passed through a short column of activated alumina. The residue from evaporation was crystallised from acetone–light petroleum.

(*b*) Hydrochloric acid (20 ml.) was added to a mixture of 1-ethoxy-1,3,3-trimethoxypropane (20·2 g.) and *N*-alkylurea (0·12 mol.) in ethanol (50 ml.). The mixture was set aside at 25° for *ca.* 85 hr., after which the ethanol was removed under reduced pressure. The residue, dissolved in water, was neutralised with dilute sodium carbonate solution, and the pyrimidine was extracted into chloroform. Removal of the solvent gave the product which was recrystallised as above. Its picrate recrystallised from water or ethanol.

TABLE 3

1-Alkyl-1,2-dihydro-2-oxopyrimidines

Alkyl group	Method	M. p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
Methyl.....	*b*	131—132° *	26	54·8	5·8	25·3	$C_5H_6N_2O$	54·5	5·5	25·4
Ethyl	*a*, *b*	64—65	38, 28	57·8	6·5	22·5	$C_6H_8N_2O$	58·05	6·5	22·6
Picrate.....	—	131	—	40·8	3·0	—	$C_{12}H_{11}N_5O_8$	40·8	3·1	—
Propyl	*a*, *b*	36	20, 24	60·5	7·2	20·0	$C_7H_{10}N_2O$	60·85	7·3	20·3
Isopropyl.....	*b*	90	46	60·5	7·4	20·2	,,	,,	,,	,,
Picrate.....	—	166—167	—	42·6	3·5	—	$C_{13}H_{13}N_5O_8$	42·5	3·6	—
Butyl	*b*	40—41	36	63·45	7·8	18·2	$C_8H_{12}N_2O$	63·1	7·95	18·4
s-Butyl.....	*b*	48—50	26	63·2	8·0	18·3	,,	,,	,,	,,
t-Butyl.....	*b*	131—132	18	63·3	8·0	18·6	,,	,,	,,	,,
Picrate.....	—	150 (decomp.)	—	44·0	4·1	—	$C_{14}H_{15}N_5O_8$	44·1	4·0	—

* Cf. m. p. 125—126° and 127—128° recorded by J. J. Fox and D. Van Pragg, *J. Amer. Chem. Soc.*, 1960, **82**, 486, and by D. J. Brown *et al.*,[3] respectively.

1,2-*Dihydro*-1-*methyl*-2-*oxopyrimidine by Isomerisation*.—2-Methoxypyrimidine (1·0 g.) and triethylamine (4·6 g.) were heated in a sealed tube at 160° for 4 hr. After refrigeration, the solid was digested with acetone and the resulting solution passed through a short column of

[13] I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Synth.*, 1955, **35**, 34.
[14] D. J. Brown, *Nature*, 1950, **165**, 1010.

alumina. Concentration and addition of light petroleum gave the oxopyrimidine (0·1 g.; cf. *ca.* 50% isomerisation shown by spectrum), m. p. 130—131° (from acetone), undepressed on admixture with the material described above.

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