Nucleophilic Displacement Reactions in Aromatic Systems. Part III. Kinetics of the Reactions of Chloronitropyridines and Chloropyrimidines with Piperidine, Morpholine, Pyridine, and Aniline.*

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Arrhenius parameters for the reactions in ethanol of piperidine and of morpholine with 2-chloro-, 2-chloro-4-methyl-, 2-chloro-4 : 6-dimethyl-, 4-chloro-6-methyl-, and 4-chloro-2-methyl-pyrimidine are presented, and similar values for the reactions of piperidine with 2-chloro-3-nitro-, 2-chloro-5-nitro-, and 2-chloro-4-methyl-5-nitro-pyridine. The rate-diminishing influence of nuclear methyl groups *meta* to the seat of substitution is briefly discussed although the major influence is on the value of A, rather than of E. In reactions of a structurally analogous nitropyridine derivative, the methyl group also influences Arrhenius parameters by steric inhibition of NO_2–ring conjugation. Nucleophilic displacement of chlorine from the 4-position in the pyrimidine ring is associated with an energy of activation of $\sim$2000 cal. less than that for the 2-position, and E and log A for reactions of the inaccessible 4-chloropyrimidine are estimated at $\sim$10,500 cal. and 5·0 respectively. The effect of a second *ortho*-cyclic nitrogen atom on E for nucleophilic displacement is estimated as a diminution of $\sim$7500 cal. The reactivity of 2- and 4-chloropyrimidine derivatives is also compared in terms of Arrhenius parameters with that of each of a series of analogous nitro-compounds. The results are discussed in structural terms. Evidence of autocatalysis by formed acid in the reactions of chloropyrimidines with aniline, *p*-toluidine, and pyridine is provided. It is also shown that ion exchange with the solvent is unimportant in these reactions.

PARTS I and II of this series (*J.*, 1952, 437; 1953, 3392) were concerned mainly with the reactions of chloronitropyridines. The present communication records an extension of the investigation into the pyrimidine series. Neither primary aromatic amines nor pyridine showed regular kinetics in reactions with chloropyrimidines (see p. 1193). With piperidine

* Part II, *J.*, 1953, 3392.

and morpholine, however, we observed a series of second-order reactions in ethanol with various chloropyrimidines. In contrast to 2-chloropyrimidine, 4-chloropyrimidine is very difficult to prepare in quantity, and very unstable, and would almost certainly undergo solvolysis under our conditions. To study the displacement of chlorine from the 4-position in the pyrimidine nucleus we have been obliged, therefore, to utilise 4-chloro-2- and -6-methylpyrimidine. By including 2-chloro-4-methyl- and -4 : 6-dimethyl-pyrimidine we have been able to elucidate the influence of nuclear methyl groups on the reactivity of chloropyrimidines. These changes in the type of system studied made desirable a study of the kinetics of the reactions in ethanol of 2-chloro-3-nitro-, 2-chloro-5-nitro-, and 2-chloro-4-methyl-5-nitro-pyridine with piperidine, for comparison. The last chloro-compound, formerly unknown, was prepared from the available 2-amino-4-methylpyridine by a method very similar to that used for 2-chloro-5-nitropyridine (Part I, p. 438).

The mobility of halogens towards nucleophilic reagents in the 2- and 4-positions in the pyrimidine and quinazoline rings is well known in preparative work (cf. Lythgoe, *Quart. Reviews*, 1949, **3**, 181), and the instability of 4-chloropyrimidine testifies to the greater reactivity at the 4-position. However, there has been no previous kinetic work in this field, and there are very few qualitative and semiquantitative investigations on record. Andrisano and Modena (*Gazzetta*, 1951, **81**, 398) and Banks (*J. Amer. Chem. Soc.*, 1944, **66**, 1127) have studied the reactivity of more highly substituted chloropyrimidines than the simple compounds under discussion, and Banks has emphasised the influence of protons as catalysts in these reactions, a circumstance largely responsible for our choice of nucleophilic reagent. We return to this point in the discussion.

The present paper and its predecessors go some way towards achieving our original object, *viz.*, the provision of experimental results linking the kinetics of nucleophilic substitution in the benzene, pyridine, and pyrimidine series.

Experimental

Materials.—Chloro-compounds. 4-Chloro-6-methylpyrimidine was prepared by desulphurisation of 6-methyl-2-thiouracil by Williams, Ruehle, and Finkelstein's method (*J. Amer. Chem. Soc.*, 1937, **59**, 528), followed by treatment of the crude product with phosphoryl chloride (cf. Marshall and Walker, *J.*, 1951, 1004) and purification by vacuum-sublimation; it had m. p. 34·8—35·2°. 4-Chloro-2-methylpyrimidine was prepared by Gabriel's method (*Ber.*, 1904, **37**, 3638) and crystallised to a constant m. p. of 56·5—57·0° from dry (Na) light petroleum (b. p. 40—60°). 2-Chloropyrimidine and 2-chloro-4-methylpyrimidine were prepared by Howard's method (U.S.P. 2,477,409) and recrystallised to a constant m. p. of 64·5° and 47·5°, respectively, from dry light petroleum (b. p. 60—80° and 40—60°, respectively). A pure sample of 2-chloro-4 : 6-dimethylpyrimidine, given by Dr. J. F. W. McOmie, to whom gratitude is expressed, was recrystallised from light petroleum (b. p. 40—60°) and had m. p. 38·0°. 2-Chloro-3-nitro- and 2-chloro-5-nitro-pyridine were prepared as described in Part I (*loc. cit.*).

2-Chloro-4-methyl-5-nitropyridine. This was obtained by converting 2-amino-4-methylpyridine (from the Reilly Tar and Chemical Co.) into a mixture, separable by steam-distillation, of 2-amino-4-methyl-3- and -5-nitropyridine by Seide's method (*Ber.*, 1924, **57**, 791). The latter amine was converted into the corresponding 2-chloro-compound by a method very similar to that described in Part I (p. 438) for 2-chloro-5-nitropyridine (cf. Lappin and Slezak, *J. Amer. Chem. Soc.*, 1950, **72**, 2806, for the hydroxy-compound). Decolorisation of a dark methanolic solution with charcoal, followed by crystallisation from methanol between room temp. and −30°, sublimation at 50°/0·7 mm., and further recrystallisation gave *2-chloro-4-methyl-5-nitropyridine* (30%, overall yield 6·5%), m. p. 36·5° (Found: C, 41·9; H, 3·1; N, 16·3; Cl, 20·6. $C_6H_5O_2N_2Cl$ requires C, 41·8; H, 2·9; N, 16·2; Cl, 20·6%).

Amines. Piperidine ("Special Grade" free from pyridine and tetrahydropyridine, from Robinson Bros. Ltd.) was dried twice over potassium hydroxide and twice over sodium and twice fractionated (50 × 1·5 cm. column packed with Fenske helices), and a fraction of b. p. 106·4°/760·0 mm. (corr.), $n_D^{20·0}$ 1·4537, was collected (cf. Davies and McGee, *J.*, 1950, 678). Morpholine (from British Drug Houses Ltd.) was similarly purified and had b. p. 128·4°/760·0 mm. (corr.), $n_D^{20·0}$ 1·4549 (cf. Dermer and Dermer, *J. Amer. Chem. Soc.*, 1937, **59**, 1148). Pyridine, aniline, and *p*-toluidine were purified as described in Part I (*loc. cit.*).

Solvent. The 99·8% ethanol was prepared as in Part I.

Reaction Products.—These were usually isolated from solutions used in kinetic experiments, and were colourless oils unless otherwise indicated. 2-Piperidinopyrimidine had b. p. 129°/14 mm., its *picrate* m. p. 121° (Found: C, 45·4; H, 4·1; N, 21·9. $C_{15}H_{16}O_7N_6$ requires C, 45·9; H, 4·1; N, 21·4%). 4-Methyl-2-piperidinopyrimidine gave a *picrate*, m. p. 135° (Found: C, 46·9; H, 4·5; N, 20·2. $C_{16}H_{18}O_7N_6$ requires C, 47·3; H, 4·5; N, 20·7%). 2-Methyl-4-piperidinopyrimidine gave a *picrate*, m. p. 169° (Found: C, 47·6; H, 4·4; N, 20·3%). [This picrate is wrongly reported in *Chem. Abs.*, 1952, **46**, 5053, for that of the 2 : 6-dimethyl compound (cf. Andrisano and Modena, *loc. cit.*).] 6-Methyl-4-piperidinopyrimidine gave a *picrate*, m. p. 172° (Found: C, 47·7; H, 4·5; N, 20·7%). 4 : 6-Dimethyl-2-piperidinopyrimidine had m. p. 62°; Brown and Kon (*J.*, 1948, 2147) gave 60—61°. 3-*Nitro*-2-*piperidinopyridine* had m. p. 52° (Found: C, 57·6; H, 6·3; N, 20·9. $C_{10}H_{13}O_2N_3$ requires C, 57·9; H, 6·3; N, 20·3%). 5-Nitro-2-piperidinopyridine had m. p. 84°; Mangini (*Ric. Sci.*, 1937, **8**, I, 427) gives 83·5—84·5°. 4-*Methyl*-5-*nitro*-2-*piperidinopyridine* had m. p. 91° (Found: C, 59·7; H, 6·8; N, 19·7. $C_{11}H_{15}O_2N_3$ requires C, 59·7; H, 6·8; N, 19·0%).

2-Morpholinopyrimidine gave a *picrate*, m. p. 153° (Found: C, 42·6; H, 3·4; N, 21·3. $C_{14}H_{14}O_8N_6$ requires C, 42·6; H, 3·6; N, 21·3%). 4-Methyl-2-morpholinopyrimidine, a low-melting solid, gave a *picrate*, m. p. 140° (Found: C, 44·2; H, 4·0; N, 20·4. $C_{15}H_{16}O_8N_6$ requires C, 44·1; H, 4·0; N, 20·6%). 2-*Methyl*-4-*morpholinopyrimidine* formed a *monohydrate*, m. p. 35° (Found: C, 55·3; H, 7·7; N, 21·2. $C_9H_{13}ON_3,H_2O$ requires C, 54·8; H, 7·7; N, 21·3%). 6-*Methyl*-4-*morpholinopyrimidine* had m. p. 93° (Found: C, 60·7; H, 7·3; N, 23·3. $C_9H_{13}ON_3$ requires C, 60·3; H, 7·3; N, 23·4%). 4 : 6-*Dimethyl*-2-*morpholinopyrimidine* had m. p. 56·5° (Found: C, 61·9; H, 7·8; N, 21·1. $C_{10}H_{15}ON_3$ requires C, 62·2; H, 7·8; N, 21·7%). 2-Morpholino-5-nitropyridine, had m. p. 142°; Cragoe and Hamilton (*J. Amer. Chem. Soc.*, 1945, **67**, 536) give m. p. 142·3—143·3°. 4-*Methyl*-2-*morpholino*-5-*nitropyridine* had m. p. 159° (Found: C, 54·0; H, 6·0; N, 18·5. $C_{10}H_{13}O_3N_3$ requires C, 53·8; H, 5·9; N, 18·8%).

Procedure.—This was as described in Parts I and II, but blank experiments showed that the chloro-compounds did not interfere with the Volhard determination of chloride ion, so it was unnecessary to extract unchanged chloro-compounds before analysing aliquot portions of the reaction solution.

Results

Detailed values for some of the reactions of secondary amines are given in Table 1, and all the results with these are summarised in Table 2. Evidence of overall order of reaction is

Table 1.

Reactions of piperidine.

2-*Chloropyrimidine at* 30·0°. (i) a = 0·4225M.

Time (min.)	5·0	10·0	17·0	25·0	35·0	50·0	70·0	90·0
Decompn., % ...	8·5	15·6	24·4	32·5	42·1	52·6	63·5	70·8
10^4k	—	6·79	6·82	6·68	6·90	6·87	6·93	6·84

Mean $k = 6·83 \pm 0·05 \times 10^{-4}$; 50% decompn. at 47·0 min.

(ii) a = 0·2113M, b = 0·0500M; mean $k = 6·62 \pm 0·08 \times 10^{-4}$; 50% decompn. at 95·0 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·02$. Effective ratio of concentrations = 2·00. Order with respect to piperidine 0·99; with respect to 2-chloropyrimidine 1·00 (by differential method).

2-*Chloro*-4 : 6-*dimethylpyrimidine at* 40·0°. (i) a = 0·3983M.

Time (min.)	10·0	20·0	40·0	75·0	120·0	195·0	270·0	375·0
Decompn., %	3·5	8·1	16·9	28·8	41·4	55·8	66·2	75·4
10^4k	—	(1·94)	2·19	2·13	2·16	2·13	2·14	2·09

Mean $k = 2·14 \pm 0·02 \times 10^{-4}$; 50% decompn. at 161 min.

(ii) a = 0·2019M, b = 0·0500M; mean $k = 2·33 \pm 0·03 \times 10^{-4}$; 50% decompn. at 306 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1·90$. Effective ratio of concns. = 1·96.

2-*Chloro*-4-*methyl*-5-*nitropyridine at* 30·0°. (i) a = 0·3768M, b = 0·1000M.

Time (min.)	5·0	10·0	17·0	23·0	33·0	45·0	60·0	80·0
Decompn., %	10·9	20·9	33·2	42·2	54·2	64·0	73·1	81·1
10^3k	—	(1·15)	1·21	1·25	1·30	1·30	1·32	1·32

Mean $k = 1·28 \pm 0·04 \times 10^{-3}$; 50% decompn. at 28·5 min.

(ii) a = 0·1980M, b = 0·0500M; mean $k = 1·26 \pm 0·01 \times 10^{-4}$; 50% decompn. at 55·0 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 1·93$. Effective ratio of concns. = 1·83

TABLE 1. (*Continued*).

Reactions of morpholine.

2-*Chloropyrimidine at* 30·0°. (i) a = 0·4258M.

Time (min.)	15·0	30·0	50·0	75·0	105·0	150·0	198·0	300·0
Decompn., %	5·2	10·3	16·6	22·9	31·0	40·2	48·5	61·3
10^4k	—	1·51	1·51	(1·44)	1·52	1·51	1·52	1·50

Mean k = 1·51 ± 0·02 × 10^{-4}; 50% decompn. at 207 min.

(ii) a = 0·2045M, b = 0·0500M; mean k = 1·54 ± 0·03 × 10^{-4}; 50% decompn. at 420 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}}$ = 2·03. Effective ratio of concns. = 2·09. Order with respect to morpholine 1·05; with respect to chloro-compound 0·97 (by differential method).

4-*Chloro*-2-*methylpyrimidine at* 20·0°. (i) a = 0·3976M.

Time (min.)	10·0	20·0	30·0	45·0	60·0	83·0	110·0	140·0	170·0
Decompn., %	8·99	17·3	24·7	33·6	42·1	51·7	60·7	67·9	74·0
10^4k	—	4·31	4·34	4·25	4·39	4·37	4·40	4·35	4·39

Mean k = 4·35 ± 0·04 × 10^{-4}; 50% decompn. at 77·5 min.

(ii) a = 0·1988M, b = 0·0500M; mean k = 4·23 ± 0·04 × 10^{-4}; 50% decompn. at 156 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}}$ = 2·01. Ratio of concns. = 2·00.

FIG. 1.

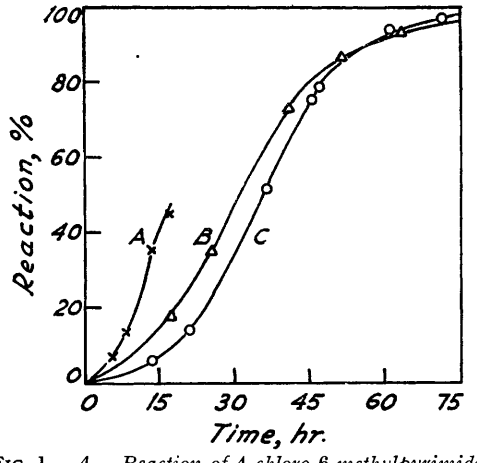


FIG. 2.

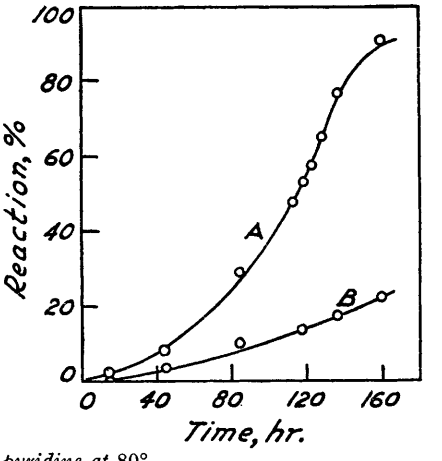


FIG. 1. *A. Reaction of* 4-*chloro*-6-*methylpyrimidine with pyridine at* 80°.
B and C. Reactions of 2-*chloropyrimidine with* p-*toluidine and aniline respectively at* 80°.

FIG. 2. *A and B. Reactions of* 2-*chloro*-4 : 6-*dimethylpyrimidine with pyridine at* 90° *and* 80° *respectively.*

TABLE 2.

	Piperidine			Morpholine		
Chloro-compound	20·0° (i)	30·0° (i)	40·0° (i)	20·0° (i)	30·0° (i)	40·0° (i)
2-Chloropyrimidine	32·2—34·3	67·9—69·3	125—132	7·48—7·94	15·0—15·2	27·6—29·3
2-Chloro-4-methylpyrimidine	13·4—14·0	28·0—29·2	52·7—55·5	3·26—3·32	6·59—6·86	13·7—14·2
2-Chloro-4 : 6-dimethylpyrimidine	5·55—5·80	11·0—11·5	20·9—21·9	1·35—1·38	2·69—2·88	5·31—5·59
4-Chloro-2-methylpyrimidine	162—167	292—308	512—532	42·5—44·0	75·8—78·7	132—138
4-Chloro-6-methylpyrimidine *	113—116	213—217	356—382	28·1—29·5	55·4—55·7	97·5—98·9
2-Chloro-3-nitropyridine †	217—221	413—426	764—792	—	—	—
2-Chloro-5-nitropyridine †	345—354	663—678	1180—1230	—	—	—
2-Chloro-4-methyl-5-nitropyridine †	63·9—65·9	121—132	237—247	—	—	—

(i) Extreme values of 10^5k in l. $mole^{-1}$ $sec.^{-1}$ for a given experiment. Not less than 70% of the reaction was usually studied. (For mean k's at 30·0°, see Table 3.) Values of x at "infinite" time always corresponded to 99·8—100·0% reaction.

* For this compound, k = 2·82 × 10^{-5} at 0° and 5·28 × 10^{-5} at 8·6°.

† a = 0·2M, b = 0·0500M.

given for selected examples, and of the order with respect to each reactant, determined by the differential method (Laidler, "Chemical Kinetics," New York, 1950, p. 14), for reactions of 2-chloropyrimidine. The experimentally observed times are recorded in min., but the velocity

coefficients are given in the usual units, viz., l. mole^{-1} sec.$^{-1}$. Errors in k given after the $\pm$ sign are mean deviations from the mean. Temperatures are accurate to $\pm 0{\cdot}03°$. As usual, the second-order velocity coefficient, k, is given by

$$k = \frac{1}{2t(0{\cdot}5a - b)} 2{\cdot}303 \log_{10} \frac{b}{0{\cdot}5a} \cdot \frac{0{\cdot}5a - x}{b - x}$$

where a is the initial amine concentration (nearly either 0·4 or 0·2M) and b is the initial chloro-compound concentration (either 0·1000 or 0·0500M). Because of the relative rapidity of the reactions, velocity coefficients were calculated by using the time of the first observation as the effective zero, so no values of k are given corresponding to the first time observation.

The courses of the reactions of aniline, *p*-toluidine, and pyridine with certain chloropyrimidines are displayed in Figs. 1 and 2.

Discussion

Mechanism of the Substitution Process.—Although the stereochemical difficulties discussed by Chapman and Parker (*J.*, 1951, 3301) do not apply to the formation of "intermediates of some stability" (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 299) in the reactions under consideration, yet it seems unnecessary to postulate this. Whereas in electrophilic aromatic substitution there is crucial evidence, in the case of aromatic nitration, favouring the formation of a complex between the nitronium ion and the aromatic system, there is no such evidence relating to the reactions which are the subject of this communication. The reaction solutions do not develop colour—this is also observed in the reactions of pyridine bases with halogenonitropyridines during most of the reaction—nor has a search of the literature revealed examples of complex formation, either of the "Meisenheimer" type (Bunnett et al., *loc. cit.*, p. 304) or of the "molecular" type (cf. Landauer and McConnell, *J. Amer. Chem. Soc.*, 1952, **74**, 1221), between pyrimidine derivatives and piperidine or morpholine. Although conceding some of the advantages of the "stable intermediate" theory (cf. Berliner, Quinn, and Edgerton, *ibid.*, 1950, **72**, 5305), we prefer, for the present, to treat the reactions under discussion as simple bimolecular nucleophilic aromatic substitutions.

The results displayed in Figs. 1 and 2 provide evidence in favour of the acid catalysis of nucleophilic displacements from basic heterocyclic systems investigated by Banks (*loc. cit.*), by Maggiolo and Phillips (*J. Org. Chem.*, 1951, **16**, 376) and by Morley and Simpson (*J.*, 1949, 1014). The strongly acidic anilinium or *p*-toluidinium ions, formed by the reactions which are the subject of Fig. 1, protonate the 2-chloropyrimidine in increasing proportion as the reaction proceeds, resulting in a typical autocatalytic process. It was surprising to find the same phenomenon with pyridine as reagent, for its reactions apparently generate no acid. However, the autocatalytic effect is very marked (Figs. 1 and 2). For the reaction of 2-chloropyrimidine with pyridine in ethanol at 90°, the "apparent" second-order rate coefficient increases linearly with percentage reaction (x) according to the law $10^6k = 0{\cdot}063x + 4{\cdot}3$. We tentatively ascribe this to solvolysis, with the liberation of protons, of the 2′-pyrimidylpyridinium chloride presumably produced first. Moreover, the absence of autocatalysis with amines of sufficiently great basic strength is readily understood, and in contrast with other chloro-heterocyclic compounds, the uncatalysed reactions of the chloropyrimidines occur at measurable speeds at ordinary temperatures (cf. Morley and Simpson, *loc. cit.*).

One of us has shown that in these reactions the ratio, α_n, of the rate of ethanolysis to that of the main reaction at n% "apparent reaction" is given by $\alpha_n = \{c[R_2H_2N^+]\}^{-1}$, where $c = k_4/k_2K_b$ (cf. Part II, p. 3394, and Bunnett and Zahler, *loc. cit.*, p. 344). Taking k_2 as $1{\cdot}0 \times 10^{-3}$ (Russell-Hill, unpublished) and k_4 as $3{\cdot}3 \times 10^{-4}$ for the reactions of 2-chloropyrimidine at 20°, and K_b as not greater than 10^{-6} (cf. Hägglund, *J. Chem. Phys.*, 1942, **10**, 215; Cavell and Chapman, *Chem. and Ind.*, 1953, 1266), we find $\alpha_n \not> 1/300n$, so that in this case ethanolysis may be neglected. The same conclusions almost certainly hold for the remaining reactions, especially those of morpholine, a much weaker base than piperidine. Moreover, this disposes of the possibility that the steady rate coefficients

observed may be due to a fortuitous combination of falling values caused by ethanolysis and rising values caused by acid-catalysis.

Influence of Nuclear Methyl Groups on the Reactivity of Chloropyrimidines and Related Nitro-compounds.—Nuclear *meta*-methyl groups influence these nucleophilic displacements in two ways: by inductive electron release to the seat of substitution, and, when *ortho* to an activating nitro-group, by steric inhibition of the conjugation of the nitro-group with the aromatic system, so that the configuration of the system depends on a compromise between steric compression energy and loss of stabilisation by conjugation. The purely polar effect of a *para*-methyl group has been measured by Berliner and Monack (*J. Amer. Chem. Soc.*, 1952, **74**, 1574): E is raised by 1100 cal. (cf. also Bevan, Hughes, and Ingold, *Nature*, 1953, **171**, 301). *meta*-Methyl groups inserted in chloro-2 : 4-dinitrobenzene have been studied by Miller and his associates (*J.*, 1952, 3550; 1953, 1475), who observed a diminution of rate by a factor of 5·4 at 0° and 2·6 at 100·8°. Our own results (Table 2) show that a *meta*-methyl group substituted into 2-chloropyrimidine reduces the reaction rate by a factor of ~2·4 and a second group has a very similar effect, for reactions of both piperidine and morpholine in the temperature range 20—40°. The same uniformity is not, however, observed in the Arrhenius parameters (Table 3). For reactions of piperidine, the

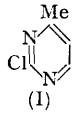
TABLE 3.

Chloro-compound	Amine	30·0°, 10^4k	E (cal./mole)	$\log_{10} A$
2-Chloropyrimidine	Piperidine	6·70	12,400	5·7
	Morpholine	1·52	12,300	5·0
2-Chloro-4-methylpyrimidine	Piperidine	2·80	12,500	5·4
	Morpholine	0·691	13,000	5·2
2-Chloro-4 : 6-dimethylpyrimidine	Piperidine	1·13	12,100	4·8
	Morpholine	0·281	12,600	4·5
4-Chloro-2-methylpyrimidine	Piperidine	30·0	10,600	5·1
	Morpholine	7·71	10,700	4·6
4-Chloro-6-methylpyrimidine	Piperidine	21·4	11,000	5·2
	Morpholine	5·55	11,100	4·7
2-Chloro-3-nitropyridine	Piperidine	41·9	12,000	6·2
2-Chloro-5-nitropyridine	Piperidine	67·1	11,500	6·1
2-Chloro-4-methyl-5-nitropyridine	Piperidine	12·6	12,400	6·0

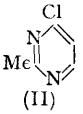
Units of A and k are l. mole^{-1} sec.$^{-1}$. Energies of activation are accurate to ±300 cal., values of $\log_{10} A$ to ±0·3 unit. The values of k are mean values from independent determinations and are accurate to ±2%.

variations in E are barely significant, but there is a steady downward trend in log A. Any explanation of these observations must at present be rather speculative, so we defer discussion of this point until further investigations are complete. The reactions of morpholine fall roughly within the same pattern, though there are some anomalies.

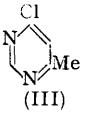
Insertion of a methyl group *ortho* to the nitro-group in 2-chloro-5-nitropyridine raises E by ~1000 cal., A remaining constant, in reactions with piperidine: a similar phenomenon is observed with chloro-2 : 4-dinitrobenzene where E is raised by 1400 cal. (B. Capon, unpublished work). It is clear that steric inhibition of the conjugation of the nitro-group has more effect than the purely polar effect in methylpyrimidine derivatives, though not than that measured by Berliner and Monack (*loc. cit.*).



(I)



(II)



(III)

(IV)

(V)

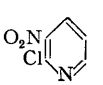
	(I)	(II)	(III)	(IV)	(V)
E (cal.)	12,500	10,600	11,000	12,400	19,900
log A	5·4	5·1	5·2	5·7	5·5

* D. Q. Russell-Hill, unpublished.

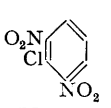
Reactivity of 2- and 4-Chloropyrimidine Derivatives.—The instability of 4-chloropyrimidine precludes direct comparison of the mobility of chlorine in the 2- and the 4-position of the pyrimidine nucleus. However, direct comparison can be made in methylated derivatives as shown above (reactions of piperidine). The isomeric change on going from (I) to (II) results in a fall in E of ~2000 cal., and a slight fall in log A, a phenomenon very similar

to that reported in Part II (p. 3394) for reactions of chloronitropyridines with pyridine bases. This is attributable to the difference between an *ortho*- and a *para*-quinonoid transition state. Unfortunately, quantum-mechanical analysis of this type of problem (cf. Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 283) does not seem to be sufficiently discriminating to yield useful results. An estimate of the Arrhenius parameters for the reactions of 4-chloropyrimidine itself may be obtained by comparing the observed values for compounds (I)—(IV), giving a log A value of ~5·0 and an upper limit to E of ~10,500 cal. Comparison of the results for (IV) and (V) indicates that variation of structure within the pyrimidine field is of small importance relative to the insertion of the second hetero-atom, which reduces E by ~7500 cal. The comparable magnitude involved on passing from the benzene to the pyridine series is at least 7000 cal. (Part I, p. 446).

(VI)

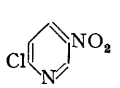


(VII)

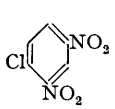


(VIII)

(IX)



(X)



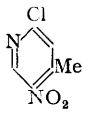
(XI)

	(VI)	(VII)	(VIII)	(IX)	(X)	(XI)
E (cal.)	12,400	12,000	12,200 *	~10,500	11,500 †	10,200 ‡
log A	5·7	6·2	5·9	~5·0	6·1	5·6

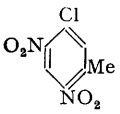
* P. W. Soanes, unpublished. † Part I. ‡ Brady and Cropper, *J.*, 1950, 507.

Above are shown the effects of various cyclic nitrogen–exocyclic nitro-group transformations. In our view the similarity of the parameters for (VI) and (VIII) is largely fortuitous. The reaction parameters of (VI) are determined by absence of steric hindrance, *ortho*-quinonoid transition state, and weak inductive effect of cyclic nitrogen; those of (VIII) by a degree of steric inhibition of nitro-group–ring conjugation, powerful inductive effects of nitro-groups, and a " net *ortho*-effect " in which classical steric hindrance predominates. Compound (VII) occupies a roughly intermediate position. The results for (IX)—(XI) largely confirm those obtained in Part II.

(XII)



(XIII)



(XIV)

	(XII)	(XIII)	(XIV)
E (cal.)	11,000	12,400	11,600 *
log A	5·2	6·0	6·3

* B. Capon, unpublished.

Considering the figures for (XII)—(XIV) and for (X) and (XI), we estimate that the " correction " for the steric effect of a methyl group *ortho* to a nitro-group *para* to the seat of substitution is an increase in E of 900—1400 cal., so that the net effect of replacing cyclic nitrogen by $>C-NO_2$ in (XII) is largely in the log A term. This analysis is, however, only tentative since the reactions of compounds (X)—(XIV) do not constitute an isoentropic series.

Throughout the foregoing, it has been assumed that formation of the transition state involves a change from trigonal towards tetrahedral hybridisation at the attacked carbon, with imposition of negative charge on ring nitrogen (cf. Ingold, " Structure and Mechanism in Organic Chemistry," London, 1953, p. 808, for a formulation of the transition state).

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