679. *Nucleophilic Displacement Reactions in Aromatic Systems. Part II.* Kinetics of the Reactions of Chloronitropyridines and Chloro-2 : 4-dinitrobenzene with 3- and 4-Picoline.*

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Arrhenius parameters for the reactions in ethanol of chloronitropyridines and chloro-2 : 4-dinitrobenzene with 3- and 4-picoline and with *m*-toluidine are presented. The relative weakness of heterocyclic tertiary amines (cf. Part I *) as nucleophilic reagents towards aromatic chloronitro-compounds is confirmed. It is also concluded that the intervention of ethanolysis in this type of reaction (cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273) is unlikely, and that, although the various pairs of reagents may form more or less stable molecular complexes, this is of no great importance to the observed kinetics. The conclusions of Part I concerning the influence of the structure of the halogeno-compound on the Arrhenius parameters are mainly confirmed, but some anomalies have been met. It is also concluded that the influence of methyl groups on the " nucleophilic power " of pyridine bases is what would be expected. The differences between primary aromatic and tertiary heterocyclic amines in the reactions are further discussed in fundamental structural terms.

In Part I * we drew attention to the relatively low rate of displacement of chloride ions from chloronitropyridines by pyridine itself. We now present similar results for 3- and 4-picoline with the object of showing that this phenomenon is normal among heterocyclic tertiary amines, and of elucidating the influence on " nucleophilic power " of alkyl substituents in pyridine. In the discussion which follows we also examine Bunnett and Zahler's suggestion (*Chem. Reviews*, 1951, **49**, 273) that ethanolysis may intervene in reactions of the type we have studied. Also we develop the subject of " nucleophilic power " of pyridine bases. Certain reactions of *m*-toluidine have also been studied for comparison with those of 3-picoline.

Experimental

Materials.—Chloro-compounds and the aqueous ethanol for solvent were prepared as described in Part I.

Amines.—Pyridine was purified as described in Part I. 3- and 4-Picoline were purified by repeated fractionation (150 × 2·5-cm. column packed with Fenske helices) of their azeotropes with acetic acid as described by Coulson and Jones (*J. Soc. Chem. Ind.*, 1946, **65**, 169). Dr. Coulson, The Chemical Research Laboratory, Teddington, kindly determined the purity of the picolines cryoscopically, and reported 99·65 and 99·45 moles % purity for 3- and 4-picoline, respectively. In the reactions studied, these specimens showed no significant differences kinetically from specimens of 99·97 and 99·75% purity kindly supplied by Dr. Coulson. *m*-Toluidine was purified through its acetyl derivative as usual.

Products.—The following *nitro*-2-m-*toluidinopyridines* obtained are new : 3-nitro-, m. p. 95° (red needles) (Found : C, 62·9; H, 4·8; N, 18·3. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%); 5-nitro-, m. p. 128·5° (orange-yellow needles) (Found : C, 62·9; H, 4·6; N, 17·8%).

The quaternary chlorides obtained from the various chloro-compounds and 3- and 4-picoline were difficult to prepare in the pure state, those derived from 4-picoline being particularly prone to decomposition by the combined action of hydroxylic solvents and atmospheric oxygen. They are more readily prepared from solutions of the reactants in boiling anhydrous ether in an atmosphere of nitrogen. In many cases the reaction products from ethereal and from ethanolic solution have been shown to yield identical picrates or styphnates. 1-(3-*Nitro*-4-*pyridyl*)-*pyridinium picrate*, m. p. 185° (Found : C, 45·2; H, 2·3; N, 20·2. $C_{16}H_{10}O_9N_6$ requires C, 44·7; H, 2·3; N, 19·5%). 3-*Methyl*-1-(3-*nitro*-4-*pyridyl*)*pyridinium chloride*, m. p. 197·5° (prepared in dry ether) (Found : C, 52·4; H, 4·4; N, 16·0; Cl, 14·05. $C_{11}H_{10}O_2N_3Cl$ requires C, 52·5; H, 4·0; N, 16·6; Cl, 14·1%), and *picrate*, m. p. 230° (Found : C, 46·3; H, 2·7; N, 18·8. $C_{17}H_{12}O_9N_6$ requires C, 46·0; H, 2·7; N, 18·9%). 4-*Methyl*-1-(3-*nitro*-4-*pyridyl*)-

* Part I, *J.*, 1952, 437.

pyridinium picrate, m. p. 200° (decomp.) (Found: C, 45·9; H, 2·55; N, 19·1%). 3-*Methyl*-1-(3-*nitro*-2-*pyridyl*)*pyridinium styphnate*, m. p. 136° (Found: C, 44·4; H, 2·8; N, 18·4. $C_{17}H_{12}O_{10}N_6$ requires C, 44·4; H, 2·6; N, 18·3%). 3-*Methyl*-1-(5-*nitro*-2-*pyridyl*)*pyridinium picrate*, m. p. 143·5° (Found: C, 46·3; H, 3·0; N, 18·7%). 1-(2 : 4-*Dinitrophenyl*)-4-*methylpyridinium styphnate*, m. p. 157·5° (Found: C, 42·9; H, 2·3; N, 16·7. $C_{18}H_{12}O_{12}N_6$ requires C, 42·9; H, 2·4; N, 16·7%).

TABLE 1.

Reactions of 3-*picoline.*

2-*Chloro*-5-*nitropyridine at* 60·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	1350	2450	3150	3950	5350	6950	9800	14,100
Decompn. (%)	16·9	28·6	35·1	41·6	51·8	61·3	73·5	84·7
$k \times 10^5$	5·83	5·93	5·95	6·00	6·10	6·23	6·37	6·43

Mean $k = 6·10 \pm 0·18 \times 10^{-6}$; 50% decompn. at 5097 min.

(*B*) With half the above concns.; mean $k = 5·88 \pm 0·19 \times 10^{-6}$; 50% decompn. at 10,570 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·07$.

4-*Chloro*-3-*nitropyridine at* 30·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	1400	2500	3900	5460	7170	8840	12,910
Decompn. (%)	15·9	26·4	38·0	48·5	58·2	65·7	78·8
$k \times 10^6$	5·35	5·38	5·50	5·57	5·67	5·75	5·93

Mean $k = 5·59 \pm 0·16 \times 10^{-6}$; 50% decompn. at 5610 min.

(*B*) With half the above concns.: mean $k = 5·43 \pm 0·25 \times 10^{-6}$; 50% decompn. at 11,440 min., $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·03$.

Reactions of 4-*picoline.*

Chloro-2 : 4-*dinitrobenzene at* 40·0°.

(*A*) Amine 0·400M, chloro-compound 0·100M.

Time (min.) ...	820	1150	1500	2190	2620	3750	5150	10,920
Decompn. (%)	16·8	21·8	27·3	36·3	43·1	54·6	65·1	86·7
$k \times 10^6$	9·82	9·22	9·48	9·32	9·85	9·88	9·85	9·73

Mean $k = 9·64 \pm 0·23 \times 10^{-6}$; 50% decompn. at 3297 min.

(*B*) With half the above concns.: mean $k = 9·15 \pm 0·12 \times 10^{-6}$; 50% decompn. at 6795 min. $t_{\frac{1}{2}}/t'_{\frac{1}{2}} = 2·06$.

TABLE 2.*

Amine	50·0° (i)	50·0° (ii)	60·0° (i)	60·0° (ii)	70·0° (i)	70·0° (ii)
	2-Chloro-3-nitropyridine					
3-Picoline	13·5—76·0	1·15—1·21	16·4—80·1	2·72—2·88	14·1—85·3	6·15—6·62
4-Picoline	12·8—79·5	1·90—2·10	14·8—85·1	4·53—4·87	16·1—86·2	9·83—10·72
m-Toluidine	15·2—78·5 †	15·5—16·7	15·1—83·5	31·0—32·7	—	—
	40·0°		50·0°		60·0°	
	2-Chloro-5-nitropyridine					
3-Picoline	12·5—82·9 ‡	1·04—1·12 ‡	17·2—69·7	2·52—2·72	16·9—84·7	5·83—6·43
4-Picoline	14·2—87·2 ‡	1·63—1·72 ‡	11·8—86·4	3·87—4·05	15·8—90·5	8·98—9·27
m-Toluidine	18·2—76·5	5·77—6·50	18·5—84·9	11·0—12·7	29·0—74·1	2·03—2·20
	20·0°		30·0°		40·0°	
	4-Chloro-3-nitropyridine					
3-Picoline	15·1—85·2	2·30—2·48	15·9—78·7	5·35—5·93	17·0—75·4	12·6—13·7
4-Picoline	21·7—87·9	4·05—4·28	15·5—75·4	9·27—10·2	14·7—75·9	20·8—23·3
	30·0°		40·0°		50·0°	
	Chloro-2 : 4-dinitrobenzene					
3-Picoline	14·9—80·9	2·18—2·40	12·1—73·9	5·28—5·67	16·4—78·6	12·6—13·5
4-Picoline	12·3—83·7	3·90—4·10	16·8—86·7	9·22—9·88	18·5—85·1	21·8—23·8

* Usually $a = 0·4$M, $b = 0·1$M. ‡ Temp. 39·9°.

(i) Extreme values of percentage decompn. (ii) Extreme values of $k \times 10^6$. (For mean k's at 55° see Table 3.)

† At 40°: (i) 15·4—80·5, (ii) 7·57—7·82.

Procedure.—This was the same as in Part I, the method of sealed bulbs being used, and all experiments were carried out at least in duplicate. Independently determined values of k (mean of a series in a given experiment) rarely differed by more than 1%. The position in respect of solvolysis and autocatalysis was as in Part I.

Results.—Detailed values for some of the reactions are given in Table 1 and all the results are summarised in Table 2. For primary amines

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

and for tertiary amines

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

where a is the initial concn. of base and b that of the chloro-compound. The experimentally observed times are recorded in minutes, but 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 $\pm 0{\cdot}03°$.

TABLE 3.

Reaction no.	Amine	Chloro-compound	$k^{55} \times 10^6$	E (cal.)	$\log_{10} A$
1	Pyridine	2-Chloro-3-nitropyridine	1·03	18,700	6·3
2	3-Picoline	,,	1·81	18,500	6·6
3	4-Picoline	,,	3·15	17,400	6·1
5	*m*-Toluidine	,,	22·4	14,400	5·0
6	Pyridine	2-Chloro-5-nitropyridine	1·97	18,100	6·3
7	3-Picoline	,,	4·00	17,900	6·6
8	4-Picoline	,,	6·11	17,500	6·5
9	*m*-Toluidine	,,	15·8	12,900	3·8
10	Pyridine	4-Chloro-3-nitropyridine	32·1	16,900	6·8
11	3-Picoline	,,	39·8	15,600	6·0
12	4-Picoline	,,	66·4	15,100	5·9
13	Pyridine	1-Chloro-2 : 4-dinitrobenzene	11·1	16,700	6·2
14	3-Picoline	,,	19·9	17,100	6·7
15	4-Picoline	,,	30·9	16,900	6·7

Values of k are usually accurate to $\pm 3\%$, of E to ± 300 to ± 500 cal., of log A to $\pm 0{\cdot}3$—$0{\cdot}5$ unit.

DISCUSSION

Intervention of Ethanolysis.—Bunnett and Zahler (*loc. cit.*) have suggested that there may be a concurrent ethanolysis in reactions such as those under discussion because of equilibria of the type $R_3N + EtOH \rightleftharpoons R_3HN^+ + EtO^-$ (i). Reaction (ii) may then compete with (iii) or (iv) according to the nature of the amine:

$$R'X + EtO^- \longrightarrow R'OEt + X^- \quad \text{(ii)}$$

$$R'X + R_3N \longrightarrow R'R_3N^+ + X^- \quad \text{(iii)}$$

$$R'X + 2R_2NH \longrightarrow R_2NR' + R_2H_2N^+ + X^- \quad \text{(iv)}$$

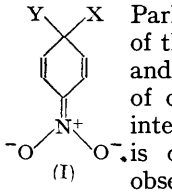
On consideration of reactions (ii) and (iii) it is easily seen that $dx/dy = k_3/k_2\{[R_3N]/[EtO^-]\}$, where y and x are the values of $[X^-]$ at time t due to (ii) and (iii) respectively, and k_2 and k_3 are corresponding rate coefficients. Remembering that $K_b/[R_3HN^+] = [EtO^-]/[R_3N]$ from (i), we have $dx/dy = k_3/k_2\{[R_3HN^+]/K_b\}$. To a close approximation $[R_3HN^+] = y$, whence $dx/dy = k_3y/k_2K_b$, and $y = (2K_bk_2x/k_3)^{\frac{1}{2}}$. For the reaction of chloro-2 : 4-dinitrobenzene with pyridine in ethanol at 25°, K_b is $5{\cdot}6 \times 10^{-15}$ (Goldschmidt and Mathiesen, *Z. phys. Chem.*, 1926, **119**, 447; Danner, *J. Amer. Chem. Soc.*, 1922, **44**, 2832), k_3 is $8{\cdot}4 \times 10^{-7}$ l. mol.$^{-1}$ sec.$^{-1}$ (Part I), and k_2 is $12{\cdot}5 \times 10^{-2}$ l. mol.$^{-1}$ sec.$^{-1}$ (Baudet, *Rec. Trav. chim.*, 1924, **43**, 707), whence $y = 4 \times 10^{-5}x^{\frac{1}{2}}$. Thus in this case ethanolysis is negligible. Data are not available for calculating K_b at other temperatures, but from corresponding values for aqueous solutions and the appropriate energies of activation, it seems unlikely that the above conclusion would be substantially different at any of the temperatures used in this work. Although appropriate values of k_2 are not available for the reactions of chloronitropyridines, Mangini and Frenguelli's results (*Gazzetta*, 1939, **69**, 86) make similar conclusions almost certain for these reactions.

We now consider reactions of type (iv), in which the use of strongly basic secondary amines may cause ethanolysis. Now $dx/dy = k_4/k_2\{[R_2H_2N^+]/K_b\}$, and to a close approximation $[R_2H_2N^+] = (x + y)$, whence $dx/dy = k_4/k_2K_b\{(x + y)\}$, which gives on integration $x = e^{cy}/c - (y + c^{-1})$ where $c = k_4/k_2K_b$, whence $y = c^{-1} \ln\{c(x + y + c^{-1})\}$.

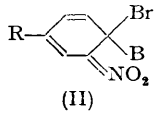
Consider, as an example, piperidine in reaction with chloro-2 : 4-dinitrobenzene. K_b for piperidine in ethanol at 25° is $\sim 10^{-7}$ (Ogston, *J.*, 1936, 1023), and is unlikely to exceed 10^{-6} even at 100°, while the ratio k_2/k_4 is ~5 for 25° (Bunnett *et al.*, *loc. cit.*, p. 340) and increases to ~25 at 100°. We take 10^5 as a representative value of c, and when $(x + y)$ is 10^{-2}, *i.e.*, at 10% "apparent reaction," an approximate calculation shows that x/y is ~140. Moreover, at n% "apparent reaction," $\alpha_n = (v_2/v_4)_n = k_2[EtO^-]_n/k_4[R_2NH]_n = \{c[R_2H_2N^+]\}^{-1}$. To a close approximation $[R_2H_2N^+] = 0{\cdot}01nm$, where m is the initial molarity of R'X, in our work usually 0·1. Hence, putting $c = 10^5$, we have $\alpha_n = 10^{-2}n^{-1}$. Hence, even with strongly basic amines at up to 100°, the rate of ethanolysis becomes negligible compared with that of the main reaction as soon as n exceeds a few units. Therefore by taking an appropriate zero of time the effect of ethanolysis can be eliminated entirely.

Reversibility.—We have found no evidence of a "readily reversible attack" by pyridine or its homologues on chloro-2 : 4-dinitrobenzene mentioned by Leahy and Miller (*Chem. and Ind.*, 1953, 40). The corresponding pyridinium salt loses not more than 0·5% of its chloride ion after one month in ethanol at 40°, and in all the reactions we have studied, after about 30 times the half-life, chloride-ion titrations correspond to 99·0—100·0% reaction.

Aromatic Nucleophilic Substitution.—Bunnett and Zahler (*loc. cit.*) make the fundamental assumption that *all* nitro-activated substitutions "proceed through intermediates of some stability" which are formulated as in (I). One of us (Chapman and Parker, *J.*, 1951, 3301) has argued against this assumption, and recent studies of the molecular complexes formed by aniline and *m*-dinitrobenzene (Landauer and McConnell, *J. Amer. Chem. Soc.*, 1952, **74**, 1221) suggest that the formation of complexes is not due to covalent-bond formation but to "an acid–base interaction" (cf. Mulliken, *ibid.*, p. 811) and that the geometry of the complex is quite different from that required by (I). Preliminary spectroscopic observations in these laboratories (B. Capon, unpublished) indicate that, for α-naphthylamine and for aniline, equilibrium in complex formation with chloro-2 : 4-dinitrobenzene is rapidly attained, and that if the substitution process involves a complex of type (I), the anionisation of the halogen is probably rate-determining. Despite Berliner and Monack's arguments (*ibid.*, p. 1578), it is very difficult to understand the facilitating effect of additional *o*- and *p*-nitro-groups on nucleophilic substitution, in terms of a rate-determining anionisation of halogen. Also, Francel's spectroscopic observations (*ibid.*, p. 1268) confirm the suggestion that a nitro-group *ortho* to halogen is not coplanar with the ring, so its influence on electron density at the seat of substitution is mainly inductive, a point overlooked by Berliner *et al.* (*loc. cit.*). Complexes of type (II) (*idem*, *ibid.*) are also rendered improbable. However, we await the results of *X*-ray crystallographic studies on *o*- and *p*-chloronitrobenzene before coming to a conclusion on this point, and assume a one-stage bimolecular process for these reactions.



(I)



(II)

Influence of the Structure of the Halogeno-compound on the Parameters of the Arrhenius Equation.—The results assembled in Table 3 mainly confirm in broad outline the conclusions reached in Part I (*loc. cit.*, p. 445). Replacement of a nitro-group *ortho* to the seat of substitution by a cyclic nitrogen atom always increases E by 400—800 cal., log A remaining almost constant. Moving the nitro-group from the 5- to the 3-position in 2-chloropyridine usually increases E by ~600 cal., but reactions of 4-picoline are anomalous in this respect. Consideration of the reactions of pyridine only, leads to an over-simplification of the facilitating influence of a "*para*" cyclic nitrogen atom on nucleophilic displacement, for comparison of reactons 11 and 13, and 12 and 14, suggests that the cyclic nitrogen atom is more effective than a nitro-group in diminishing the value of E, although, as this is associated with a diminution of log A in the same sense, specific rates

are not so strongly affected and structural interpretations are largely precluded. The reactions of 4-chloro-3-nitropyridine with 3- and 4-picoline appear from the values of E and log A to be characterised by a degree of solvation in the transition state unusually high among this group of reactions.

Nucleophilic Power of Pyridine Bases.—The weakness of these bases as nucleophilic reagents relative to corresponding primary aromatic amines with considerably smaller basic dissociation constants in aqueous solution at 25°, is amply confirmed by the results of Tables 3 and 4, and those given in Part I. Moreover, we are now able to elucidate the influence of methyl substituents on the nucleophilic power of pyridine bases. Relevant experimental results are assembled in Table 4, in which reactions of 2-chloro-5-nitropyridine are considered, as these are least complicated.

TABLE 4.

Base	$-$ og K_b (25° in H_2O)	ΔH° (cal./mole)	$-\Delta S^\circ$ (cal./° K)	$-$ log k (25°)	E (cal./mole)	log A
Aniline	9·42 [1]	6100	22·8	5·80	13,100 [3]	3·8 [3]
m-Toluidine ...	9·31 [1]	5900	22·8	5·66	12,900	3·8
p-Toluidine	8·93 [1]	5300	23·2	5·34	12,700 [3]	3·9 [3]
Pyridine	8·84 [2]	8700	11·0	6·89	18,100	6·3
3-Picoline	8·34 [2]	8100	—	6·61	17,900	6·6
4-Picoline	7·97 [2]	7500	—	6·39	17,500	6·5

[1] Calculated from values given by Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3468. [2] Herington, *Discuss. Faraday Soc.*, 1950, No. 9, 26. [3] Part I, p. 443.

Values of K_b for ethanolic solution are not available for pyridine bases, but the values for aqueous solution are usually greater by a constant factor of $\sim 10^4$ (Goodhue and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1329). There is an empirical correlation between the heat of ionisation of the bases in aqueous solution and the energy of activation of their reactions with 2-chloro-5-nitropyridine in ethanol: a similar trend is also noticeable for the reactions of 2-chloro-3-nitropyridine, but those of 4-chloro-3-nitropyridine and those of chloro-2 : 4-dinitrobenzene are anomalous (cf. p. 3392). It is concluded that methyl groups in the 3- or the 4-position exert the same kind of influence in primary aromatic and tertiary heterocyclic amines, *viz.*, electron accession to the nitrogen atom by induction from the 3-position, and induction and hyperconjugation from the 4-position.

In our previous discussion of the differences between primary aromatic and tertiary heterocyclic amines as nucleophilic reagents one feature has been neglected. The nitrogen atom in pyridine is in the sp^2 hybridised state and remains so on protonation (cf. Coulson, "Valence," Oxford, 1952, p. 240), and probably remains so in any process of "quaternisation." In aniline, however, the conjugation of the amino-group with the ring demands that the nitrogen atom be more or less sp^2 hybridised (cf. ammonia) but on protonation or "quaternisation" a change to sp^3 hybridisation occurs, and an electron pair, formerly occupying a delocalised orbital formed by overlap of a p orbital of nitrogen with a π orbital of the ring, enters a localised molecular orbital formed by overlap of a sp^3 hybridised orbital of nitrogen and a suitable orbital of hydrogen or carbon.

One important feature of attaining the transition state in the "quaternisation" of pyridine or aniline is energy liberated by partial formation of the new bond. This will differ for the two systems because of the differences outlined above, and from the graph given by Coulson (*Proc. Roy. Soc.*, 1951, *A*, **207**, 67), admittedly applying to two carbon atoms rather than a carbon and a nitrogen atom, it seems that this energy would not be less for reactions of pyridine. For aniline, however, attainment of the transition state also involves partial loss of the "additional resonance energy" (cf. Coulson, *op. cit.*, p. 247), variously estimated at 3—6 kcal. per mole. It is probable that neither of these factors will facilitate the reactions of aniline and similar primary amines relatively to those of pyridine. However, consideration of the entropies of activation suggests that solvation of the transition state is stronger for primary than for tertiary amines, and this, together with the "net *ortho*-effect" discussed in Part I, is probably the cause of the observed differences in Arrhenius parameters.

Finally, it is noteworthy that the scanty evidence in the literature on kinetics of

analogous reactions of pyridine and aniline (cf. Baker, *J.*, 1932, 1148, 2631; 1933, 1128) suggests that, on the whole, very marked differences between primary aromatic and tertiary heterocyclic amines as nucleophilic reagents are not observed in reactions with phenacyl halides, thus reinforcing our view of the importance of an *ortho*-nitro-group in the halogeno-compound in accounting for the differences we have observed.

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