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STUDIES IN THE PHENANTHRIDINE SERIES—III*

RATES OF QUATERNISATION AND NUCLEOPHILIC REPLACEMENT

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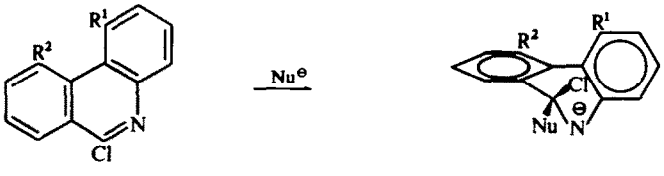
Abstract—Kinetic data are reported for the quaternisation of several alkylphenanthridines and for the reactions of some 6-chlorophenanthridines with various nucleophiles. The enhanced (and anomalous) reactivity shown by 6-chloro-1,10-dimethylphenanthridine is explained in terms of relief of steric strain. NMR data and pK_a values are reported.

IN ORDER to assess the effects of molecular overcrowding at sites remote from steric interference, we chose to apply two reactions with widely differing steric requirements to suitably substituted phenanthridine derivatives. Quaternisation at pyridine nitrogen involves attack by a lone pair in the plane of the ring and is therefore markedly retarded by proximate substituents[1] including, in the case of polycyclic systems, hydrogen atoms in *peri* positions.[2] Nucleophilic replacements at $C_{(6)}$, on the other hand, should be little affected sterically by adjacent substituents since attack takes place almost perpendicular to the ring plane.[3–4] We sought, therefore, to use the first reaction to study the immediate environment of the nitrogen atoms in planar and non-planar derivatives, and the second to examine the effect of strain produced by overcrowding: the relief of strain in passing from, for example, I ($R^1 = R^2 = Me$) to the flexible intermediate II ($R^1 = R^2 = Me$) should be favoured energetically, perhaps resulting in enhanced reactivity relative to I ($R^1 = R^2 = H$). Activation of this type had not hitherto been described, although isolated examples of enhanced reactivity toward electrophiles in, for example, fluorene[5] and acenaphthene[6] have been ascribed to ring strain.



I II

Quaternisations were carried out with MeI in nitrobenzene: the reactions were followed by titrating potentiometrically unreacted base with $HClO_4$ in AcOH. The measured rates and derived Arrhenius parameters are listed in Table 1. The values for phenanthridine itself are in good agreement with those of an earlier determination.[2] The rate-depressing effect of alkyl substituents adjacent to the ring nitrogen has been thoroughly explored in both the pyridine[7] and quinoline[8] series: the rather

TABLE 1. SECOND-ORDER RATE CONSTANTS AND ARRHENIUS PARAMETERS FOR THE REACTION OF PHENANTHRIDINE AND ITS HOMOLOGUES WITH MeI IN NITROBENZENE

Substituent	$10^4 k_2$ (60°) (1 mole^{-1} sec^{-1})	E_A[a] (kcal mole^{-1})	log PZ
None	5·22 (5·6)[2]	14·4 (14·7)[2]	6·2 (6·4)[2]
1-Methyl	5·04	14·2	6·0
1-Ethyl	4·88	14·4	6·1
3-Methyl	7·43	14·4	6·4
8-Methyl	6·75	14·7	6·5
10-Methyl	4·91	14·7	6·3
1,10-Dimethyl	7·20	14·6	6·4
3,8-Dimethyl	10·1	14·2	6·3
6-Methyl	0·16	16·3[b]	5·9
1,6-Dimethyl	0·11	16·7[c]	6·0
1-Ethyl-6-Methyl	0·11	16·8[b]	6·0

[a] From rate measurements at 60·0°, 75·0°, 81·1° and 95·0° unless otherwise indicated
[b] From rate measurements at 29·4°, 45·0° and 60·0°
[c] From rate measurements at 30·1°, 45·0° and 60·0°

larger differences in rate and activation energy between phenanthridine and 6-methylphenanthridine, compared with quinoline and 2-methylquinoline,[8] may reflect the buttressing of the *peri*-hydrogen atom at $C_{(7)}$. Within experimental error the activation energies and frequency factors for the alkylphenanthridines unsubstituted at $C_{(6)}$ are the same as for the parent base, confirming that enforced non-planarity has no major effect upon ease of quaternisation and the same situation presumably holds for similar reactions in this location.

The small rate differences observed, however, are consistent with some steric interaction in compounds substituted at $C_{(1)}$ and $C_{(10)}$. Thus, 3- and 8-methylphenanthridine show the slightly enhanced reactivity expected on the basis of 'normal' methyl substitution,[7-8] and the 3,8-dimethyl compound reacts approximately twice as fast as the parent base. In contrast, neither 1- nor 10-methylphenanthridine show enhanced reactivity: since inductive effects appear to be transmitted through space, identical groups at, for example, $C_{(1)}$ and $C_{(3)}$ should exert similar influences at the ring nitrogen atom (and the pK_a values of 1,10-[9] and 3,8-dimethylphenanthridine are closely similar). It seems probable, therefore, that the difference in behaviour stems from in-plane distortion of the 1- and 10-methylphenanthridine molecules: similar slight retardation is shown by 1-ethylphenanthridine.

This suggestion receives some support from NMR measurements: thus the methyl proton signals in the spectra of both 1- and 10-methylphenanthridine (6·99 and 7·01τ, respectively) are shifted downfield relative to the corresponding signals from the 3- and 8-methyl and 3,8-dimethyl derivatives (7·50τ, 7·54τ, 7·48 and 7·58τ). These downfield shifts are consistent with planar structures in which the alkyl groups are held close to the adjacent aromatic rings.[10] In contrast, the shift to higher field shown by the single methyl proton signal in 1,10-dimethylphenanthridine (7·54τ) stems from rotation of the phenyl rings about the central link, leading to decreased deshielding.

The effect is shown more clearly (7·75 and 7·77τ) in the corresponding dihydro-compound (as in the analogous dimethylphenanthrene[11] and its dihydro-derivative[12]); it must outweigh the deshielding which would be produced by direct interaction between the two sets of methyl protons. Rotation about the biphenyl link must displace the *peri* hydrogen atom at $C_{(4)}$ and the quaternisation of 1,10-dimethylphenanthridine proceeds more rapidly, in fact, than that of the parent base. Although the differences are small, the observed rates for 1-methyl-, 10-methyl- and 1,10-dimethylphenanthridine clearly do not conform to an approximate additivity relationship of the type previously observed in the pyridine series[13] and which holds for 3-methyl-, 8-methyl- and 3,8-dimethylphenanthridine. Although out-of-plane deformation of strained polycyclic aromatic systems is commonly accepted as energetically the most favourable mode of relieving steric compression.[14] on the basis of NMR evidence it has been concluded that in 4,5-dimethylphenanthrene molecular distortion occurs mainly through out-of-plane bonding of C—Me bonds.[11] Recent *a priori* calculations[15] firmly predict, however, that in addition the nucleus of 4,5-dimethylphenanthrene deviates considerably from the normal planar configuration, and the present results provide chemical evidence that the analogous dimethylphenanthridine molecule is similarly distorted.

No kinetic data for nucleophilic replacement reactions of phenanthridine derivatives have been reported hitherto[3] and the present work[16] was also aimed at allowing quantitative comparisons of the reactivity of 6-chlorophenanthridine with those of related N-heteroaromatic systems.[3–4, 17]

The reactions of 6-chlorophenanthridine and a number of its derivatives, notably the 1,10- and 3,8-dimethyl homologues, with both neutral and anionic nucleophiles were examined: in reactions other than those carried out under pseudo-unimolecular conditions, good second-order behaviour was normally observed. The autocatalysis detected in reactions involving weakly basic nucleophiles supports the assumption that normal S_N Ar 2 processes are involved and although in the case of the overcrowded system the possibility of an overall mechanistic change to a rate-determining re-aromatisation must clearly be considered, the efficiency of chlorine as a leaving group, coupled with the absence of additional centres to further stabilise the negative charge in the intermediate complex, make such a change extremely unlikely.[4]

Rate constants and derived parameters for a number of the reactions studied are shown in Table 2. Although exactly comparable data are not available, 6-chlorophenanthridine appears to show a level of activity generally similar to that of 9-chloroacridine:[18–21] thus, in the methoxydechlorination of 9-chloroacridine the energy and entropy of activation have been shown to be 17·2 kcal $mole^{-1}$ and −20·1 e.u. respectively.[20] In reactions of 6-chlorophenanthridine with both neutral and anionic nucleophiles the degree of activation relative to 1-chloroisoquinoline[19] and 2-chloroquinoline[19] is consistent with the effects of annellation at the appropriate positions in the two systems.

The contrasting reaction geometries of these substitutions and the quaternisation reactions are clearly underlined by the absence of steric retardation arising from ring fusion: only very major *peri* interactions would be expected to have a significant effect on S_N Ar 2 reactions in heteroaromatic systems[4] and the small displacements of *peri* hydrogen atoms postulated in the case of, for example, 1,10-dimethylphenanthridines can have little influence on nucleophilic replacements. Any differences in

TABLE 2. RATE CONSTANTS AND ACTIVATION PARAMETERS FOR NUCLEOPHILIC REPLACEMENTS IN 6-CHLORO-PHENANTHRIDINES

Substituent(s)	Nucleophile	Solvent	Specific Rate Constants k_2 (°C) (1 mole^{-1} sec^{-1})	E_A (kcals mole^{-1})	$\Delta S^{\ddagger}$ (e.u.)
None	MeO^-	MeOH	$9{\cdot}89 \times 10^{-5}$ (30·7)		
			$3{\cdot}78 \times 10^{-4}$ (45·0)	18·8	−18·7
			$9{\cdot}56 \times 10^{-4}$ (55·2)		
3,8-Me_2	MeO^-	MeOH	$3{\cdot}22 \times 10^{-5}$ (30·7)		
			$1{\cdot}30 \times 10^{-4}$ (45·0)	19·0	−18·6
			$3{\cdot}40 \times 10^{-4}$ (55·2)		
1,10-Me_2	MeO^-	MeOH	$2{\cdot}20 \times 10^{-4}$ (13·0)		
			$1{\cdot}13 \times 10^{-3}$ (30·0)	15·9	−22·6
			$3{\cdot}48 \times 10^{-3}$ (45·0)		
None	Piperidine	MeOH	$6{\cdot}70 \times 10^{-6}$ (30·7)		
			$1{\cdot}68 \times 10^{-5}$ (45·0)	12·7	−42·6
			$3{\cdot}22 \times 10^{-5}$ (55·2)		
3,8-Me_2	Piperidine	MeOH	$3{\cdot}10 \times 10^{-6}$ (30·7)		
			$8{\cdot}70 \times 10^{-6}$ (45·0)	13·4	−41·6
			$1{\cdot}63 \times 10^{-5}$ (55·2)		
1,10-Me_2	Piperidine	MeOH	$5{\cdot}00 \times 10^{-6}$ (13·0)		
			$1{\cdot}70 \times 10^{-5}$ (30·0)	11·8	−43·6
			$4{\cdot}02 \times 10^{-5}$ (45·0)		
None	Morpholine	MeOH	$3{\cdot}73 \times 10^{-7}$ (14·2)		
			$8{\cdot}27 \times 10^{-7}$ (25·0)	12·7	−45·9
			$1{\cdot}86 \times 10^{-6}$ (36·6)		
3.8-Me_2	Morpholine	MeOH	$6{\cdot}61 \times 10^{-7}$ (30·0)	—	—
1,10-Me_2	Morpholine	MeOH	$2{\cdot}23 \times 10^{-6}$ (30·0)	—	—
None	Pyrrolidine	MeOH	$9{\cdot}86 \times 10^{-6}$ (15·0)		
			$2{\cdot}67 \times 10^{-5}$ (30·0)	11·9	−42·4
			$6{\cdot}97 \times 10^{-5}$ (45·0)		
3,8-Me_2	Pyrrolidine	MeOH	$1{\cdot}26 \times 10^{-5}$ (30·0)	—	—
None	H_2O[a]	Dioxan-20% H_2O[c] (0·005M H_2SO_4)	$4{\cdot}53 \times 10^{-7}$ (45·0)[b]	—	—
3,8-Me_2	H_2O[a]	Dioxan-20% H_2O (0·005M H_2SO_4)	$3{\cdot}93 \times 10^{-7}$ (45·0)[b]	—	—
1,10-Me_2	H_2O[a]	Dioxan-20% H_2O (0·005M H_2SO_4)	$2{\cdot}00 \times 10^{-5}$ (45·0)[b]	—	—
None	MeO^-	MeOH −40% Dioxan[c]	$1{\cdot}50 \times 10^{-4}$ (30·7)	18·3	−18·1
			$6{\cdot}02 \times 10^{-4}$ (45·0)		
			$1{\cdot}43 \times 10^{-3}$ (55·2)		
3,8-Br_2	MeO^-	MeOH −40% Dioxan	$4{\cdot}11 \times 10^{-3}$ (14·8)	15·0	−19·5
			$9{\cdot}45 \times 10^{-3}$ (25·0)		
			$2{\cdot}62 \times 10^{-2}$ (36·6)		
3,8-Cl_2	MeO^-	MeOH −40% Dioxan	$3{\cdot}70 \times 10^{-3}$ (14·8)	15·0	−19·6
			$9{\cdot}06 \times 10^{-3}$ (25·0)		
			$2{\cdot}34 \times 10^{-2}$ (36·6)		
3,8-Me_2	MeO^-	MeOH −40% Dioxan	$4{\cdot}93 \times 10^{-5}$ (30·7)	19·0	−18·2
			$1{\cdot}91 \times 10^{-4}$ (45·0)		
			$5{\cdot}15 \times 10^{-4}$ (55·2)		
1,10-Me_2	MeO^-	MeOH −40% Dioxan	$5{\cdot}65 \times 10^{-3}$ (45·0)	—	—
3.8-$(NO_2)_2$	MeO^-	MeOH −40% Dioxan	>1 (25·0)	—	—

TABLE 2—*continued*

Substituent(s)	Nucleophile	Solvent	Specific Rate Constants k_2 (°C)(1 mole^{-1} sec^{-1})	E_A (kcals mole^{-1})	$\Delta S^{\ddagger}$ (i.u.)
None	Piperidine	MeOH	$6{\cdot}38 \times 10^{-6}$ (30·7)	12·6	−43·5
		−40% Dioxan	$1{\cdot}59 \times 10^{-5}$ (45·0)		
			$2{\cdot}98 \times 10^{-5}$ (55·2)		
3,8-Br_2	Piperidine	MeOH	$1{\cdot}22 \times 10^{-4}$ (14·2)	9·5	−44·6
		−40% Dioxan	$2{\cdot}34 \times 10^{-4}$ (25·0)		
			$4{\cdot}00 \times 10^{-4}$ (36·6)		
3,8-Cl_2	Piperidine	MeOH	$1{\cdot}07 \times 10^{-4}$ (14·2)	9·8	−44·6
		−40% Dioxan	$2{\cdot}00 \times 10^{-4}$ (25·0)		
			$3{\cdot}69 \times 10^{-4}$ (36·6)		
3,8-Me_2	Piperidine	MeOH	$3{\cdot}07 \times 10^{-6}$ (30·7)	13·3	−42·4
		−40% Dioxan	$7{\cdot}97 \times 10^{-6}$ (45·0)		
			$1{\cdot}58 \times 10^{-5}$ (55·2)		

[a] Autocatalysis observed
[b] Initial pseudo-first order rate constant (sec^{-1})
[c] Both dioxan-20% H_2O and MeOH-40% dioxan were prepared v/v

reactivity between 6-chloro-1,10-dimethylphenanthridine and its planar analogues can therefore be attributed to molecular strain.

The activation shown by 6-chlorophenanthridine itself, relative to both 1-chloroisoquinoline and 2-chloroquinoline, arises largely from a decrease in the energy of activation: thus, the entropies of activation for the piperidinodechlorination of 1-chloroisoquinoline (in EtOH)[19] and 6-chlorophenanthridine (in MeOH) are, within experimental error, the same, and that of 2-chloroquinoline (also in EtOH)[19] is only slightly less negative. With anionic nucleophiles the corresponding activation entropy differences[19,22–23] are more significant, but despite the appreciably more negative value for the tricyclic system the relative overall activation is still considerable (as shown, for example, by an approximately twenty-fold increase in the rate of methoxydechlorination relative to 2-chloroquinoline).[23]

With regard to the general influence of substitution, groups such as halogen and methyl at $C_{(3)}$ and $C_{(8)}$ show effects qualitatively predictable on the basis of non-conjugative interactions: again, the differences in reactivity can be attributed largely to changes in the energies of activation, (Table 2), presumably produced mainly by variations in the extent of repulsion between the nucleophile and the π-electron system.[4] In the MeOH-40% dioxan system chosen (for solubility reasons) the methoxydechlorination of 6-chloro-3,8-dinitrophenanthridine was too rapid to allow accurate determination by the titrimetric procedure used successfully for all the other compounds. 6-Chloro-3,8-dimethylphenanthridine was, as expected, slightly less reactive to both neutral and anionic nucleophiles than the parent compound showing, for example, two- and three-fold decreases in rate relative to 6-chlorophenanthridine for piperidino- and methoxy-dechlorination respectively. The behaviour of 6-chloro-1,10-dimethylphenanthridine was equally consistent in that activation with respect to the parent compound was observed in all the reactions

examined: because of the small amount of pure material available activation parameters were obtained for only piperidino- and methoxy-dechlorination, but from these it appears that in both cases the activation relative to the planar isomer stems from decreases in the energies of activation. The opposing changes in the corresponding entropies of activation are small but significant: a possible explanation for these lies in restricted rotation about the biphenyl link in the transition states for reactions of the overcrowded isomer.

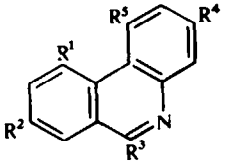
In the absence of added acid the hydrolysis of 6-chlorophenanthridine was inconveniently slow, but in 20% aqueous dioxan containing H_2SO_4 (0·005 M) the initial rates of hydrolysis (45°) of the isomeric dimethyl compounds were found to differ by approximately fifty-fold. Partial cationisation of pyridinic nitrogen by hydrogen bonding to hydroxylic solvents has a marked accelerative effect,[4,17] and it could be argued that steric inhibition of solvation by the *peri* hydrogen atoms in the planar molecules may be decreased by non-planarity in the overcrowded system. Since, however, the protonated species is clearly far more reactive than the neutral molecule it seems unlikely that such an effect would be of primary importance and the major part of the fifty-fold increase must be attributed again to relief of steric strain. Although no account was taken of any variation in the extent of protonation

TABLE 3. ULTRAVIOLET SPECTRA AND IONISATION CONSTANTS

Phenanthridine	Solvent (pH)	λ_{max} ($\log_{10}\varepsilon$)	pK_a[a]
6-Methyl	H_2O (1·0)	243 (4·59), 275sh (3·76) 312 (3·82), 350 (3·63) 362 (3·61)	5·50 ±0·02
	H_2O (13·0)	248 (4·63), 270sh (4·00), 292 (3·76) 313sh (3·26), 329 (3·32) 345 (3·33)	
1-Ethyl	EtOH (−)	247 (4·59), 272 (4·12), 294 (3·83) 334·5 (3·12), 347·5 (2·97)	
	H_2O (1·0)	242 (4·56), 272sh (4·12), 284 (4·06), 330 (3·91)	4·71 ±0·03
	H_2O (13·0)	247 (4·59), 272 (4·11), 295 (3·83) 334 (3·13), 348 (2·97)	
1.6-Dimethyl	EtOH (−)	246 (4·67), 273 (4·11), 296 (3·80) 331·5 (3·18), 347 (3·04)	
	H_2O (1·0)	243 (4·67), 280 (4·07), 325 (3·84)	5·81 ±0·03
	H_2O (13·0)	246 (4·67), 271sh (4·11), 295 (3·80) 332 (3·18), 347 (3·04)	
3.8-Dimethyl	EtOH (−)	231 (4·35), 257 (4·68), 303 (3·72) 328 (3·08), 341·5 (3·33), 357·5 (3·33)	
	H_2O (1·0)	255 (4·72), 319 (3·88), 373sh (3·59) 383 (3·61)	5·00 ±0·03
	H_2O (13·0)	231 (4·34), 257 (4·68), 3·03 (3·72) 328 (3·08), 342 (3·33), 358 (3·33)	
1-Ethyl-6-methyl	EtOH (−)	249 (4·65), 298 (3·79), 332·5 (3·14), 347 (3·00)	
	H_2O (1·0)	244 (4·64), 254sh (4·51), 283 (4·06) 325 (3·84)	5·82 ±0·02
	H_2O (13·0)	249 (4·65), 295sh (3·80), 332 (3·14) 347 (3·00)	

[a] In aqueous solution at 25°

TABLE 4. ANALYTICAL DATA



Substituents					M.p. solvent	Formula	Calculated		Found	
R^1	R^2	R^3	R^4	R^5			C	H	C	H
H	H	OMe	H	H	51–52,[a] aq. MeOH					
H	Me	OMe	Me	H	74–75, MeOH	$C_{16}H_{15}NO$[b]	80·9	6·4	80·8	6·3
Me	H	OMe	H	Me	oil[c,d]	$C_{16}H_{15}NO$	80·9	6·4	81·2	6·4
H	H	NC_5H_{10}	H	H	82–83, MeOH	$C_{18}H_{18}N_2$	82·4	6·9	82·6	7·1
H	Me	NC_5H_{10}	Me	H	109–110, MeOH	$C_{20}H_{22}N_2$	82·7	7·6	82·7	7·4
Me	H	NC_5H_{10}	H	Me	46–47[e,d]	$C_{20}H_{22}N_2$	82·7	7·6	82·2	7·6
H	H	NC_4H_8	H	H	136–137, EtOH	$C_{17}H_{16}N_2$	82·2	6·5	81·7	6·5
H	Me	NC_4H_8	Me	H	162–163, MeOH	$C_{19}H_{20}N_2$	82·6	7·3	82·6	7·5
H	H	NC_4H_8O	H	H	97–98,[f] EtOH					
H	Me	NC_4H_8O	Me	H	149–150, EtOH	$C_{19}H_{20}N_2O$	78·0	6·9	77·8	6·9
Me	H	NC_4H_8O	H	Me	57–58[d,g] MeOH	$C_{19}H_{20}N_2O$	78·0	6·9	77·2	6·8
H	Br	OMe	Br	H	168–169, EtOH	$C_{14}H_9NOBr_2$	45·8	2·5	46·3	2·3
H	Cl	OMe	Cl	H	184–185, EtOH	$C_{14}H_9NOCl_2$	60·4	3·3	60·2	3·1
H	Br	NC_5H_{10}	Br	H	139–140, EtOH	$C_{18}H_{16}N_2Br_2$	51·5	3·8	51·6	3·7
H	Cl	NC_5H_{10}	Cl	H	115–116,[h] MeOH	$C_{18}H_{16}N_2Cl_2$	65·3	4·9	64·9	4·4
H	NO_2	OMe	NO_2	H	250–251,[i] dioxan–EtOH	$C_{14}H_9N_3O_5$	56·2	3·0	56·7	3·6
H	NO_2	NC_5H_{10}	NO_2	H	243–244,[i] aq. dioxan	$C_{18}H_{16}N_4O_4$	61·4	4·6	61·9	4·3

[a] Reese[34] reports m.p. 52°
[b] Nitrogen: calculated 5·9. Found 6·1%
[c] B.p. 144°/0·1 mm
[d] Shown to be homogeneous by TLC
[e] B.p. 206°/0·3 mm
[f] Reese[34] reports m.p. 94–96°
[g] B.p. 210°/0·09 mm
[h] Chlorine: found, 21·0: calculated, 21·4%
[i] Preparative runs only

of the two bases (which is unknown), the pK_a values of 1,10- and 3,8-dimethylphenanthridine are closely similar and it seems unlikely, therefore, that a difference of basic strengths contributes greatly to the observed variation in reactivity.

The acid-catalysed hydrolyses of 6-chlorophenanthridine and both the dimethyl homologues showed autocatalysis.

Pyrrolidine has not often been used in quantitative reactivity studies: although pyrrolidine and piperidine have closely similar pK_a values in H_2O (11·27 and 11·22, respectively)[24] the former proved somewhat more effective as a nucleophile reacting, for example, more than four times faster with 6-chlorophenanthridine than did piperidine. The reactions of the weaker base morpoline (pK_a 8·70)[25] were autocatalytic: a similar effect was observed earlier in the morpholino-dechlorination of 2-chloroquinoline.[19]

The ionization constants of the new alkyl-phenanthridines were measured spectrophotometrically in aqueous solution: spectral details and pK_a values are given in Table 3. The small steric requirement of the hydrated proton is demonstrated by the increase in basic strength brought about by methyl substitution at $C_{(6)}$, contrasting sharply with the 50-fold decrease in the rate of methiodide formation.

EXPERIMENTAL

M.ps are uncorrected. Phenanthridine was obtained from Aldrich Chemical Co. Inc. and the alkylphenanthridines were either prepared as described previously[26] or by the application of known methods. Only brief details are given below. NMR spectra were measured at 60 MHz in CCl_4 solution with TMS as internal standard.

2-*Amino-6-ethylbiphenyl* was obtained from the corresponding 2-carboxylic acid[27] by the Curtius procedure as a colourless oil, b.p. 137°/2·5 mm (43%). The 2-*formamido* derivative formed white prisms, m.p. 93–94°, from light petroleum. (Found: C, 79·8; H, 6·6. $C_{15}H_{15}NO$ requires: C, 79·9; H, 6·7%).

2-*Acetamido-6-ethylbiphenyl* formed white needles, m.p. 98–99°, also from light petroleum. (Found: C, 80·5; H, 7·3. $C_{16}H_{17}NO$ requires: C, 80·3; H, 7·2%).

2-*Acetamido-6-methylbiphenyl* (obtained from the amine[28] and AcOH at reflux temperature) formed white needles, m.p. 113–114°, from light petroleum. (Found: C, 79·7; H, 6·8. $C_{15}H_{15}NO$: C, 79·9; H, 6·7%).

4-*Ethylfluorenone-1-carboxylic acid* (from 3-phenyl-4-ethylphthalic anhydride[27] and $AlCl_3$ in C_6H_6) formed yellow needles, m.p. 186–187° from xylene. (Found: C, 75·9; H, 4·7. $C_{16}H_{12}O_3$ requires: C, 76·2; H, 4·7%). Decarboxylation of the keto-acid and reduction of the resulting fluorenone with aluminium *iso*propoxide gave 4-*ethylfluorenol*, which formed white prisms, m.p. 114–115°, from light petroleum. (Found: C, 85·1; H, 6·7. $C_{15}H_{14}O$ requires: C, 85·7; H, 6·7%). Essentially the same route was used to obtain 2,7-*dimethylfluorenol* from 2,7-dimethylfluorenone-1-carboxylic acid. The fluorenol formed white platelets, m.p. 159–160°, from light petroleum. (Found: C, 85·7; H, 6·7. $C_{15}H_{14}O$ requires: C, 84·8; H, 6·7%). H, 6·7%).

Phenanthridines from 2-acylaminobiphenyls. 2-Acetamido-6-methyl, 2-formamido-6-ethyl- and 2-acetamido-6-ethylbiphenyl were heated in polyphosphoric acid at 170–180° to give (respectively) 1,6-*dimethylphenanthridine* (73%), white prisms, m.p. 114·5–115°, from light petroleum. (Found: C, 86·7; H, 6·2. $C_{15}H_{13}N$ requires: C, 86·9; H, 6·3%); 1-*ethylphenanthridine* (32%), near white prisms, m.p. 56·5–57°, from light petroleum. (Found: C, 86·7; H, 6·6. $C_{15}H_{13}N$ requires: C, 86·9; H, 6·3%); and 1-*ethyl-6-methylphenanthridine* (54%), white prisms, m.p. 92·5–93°, from light petroleum. (Found: C, 86·3; H, 6·9. $C_{16}H_{15}N$ requires: C, 86·8; H, 6·8%).

3,8-*Dimethylphenanthridine*, (from 2,7-dimethylfluorenol and hydrazoic acid), formed white prisms (45%), m.p. 120–121°, from light petroleum. (Found: C, 86·7; H, 6·4. $C_{15}H_{13}N$ requires: C, 87·0; H, 6·3%).

1,10-*Dimethyl-5,6-dihydrophenanthridine*, previously prepared from the phenanthridone by the action of LAH (and used without purification),[26] was found to be much more stable than 5,6-dihydrophenanthridine, forming white needles, m.p. 100–101°, from light petroleum. (Found: C, 86·2; H, 7·3. $C_{15}H_{15}N$ requires: C, 86·1; H, 7·2%).

1.10-*Dimethylphenanthridine* was obtained by dehydrogenating the dihydro-compound by heating it with a slight excess of chloranil in boiling xylene for 3 hr. This method offers considerable advantages over the Pd–C dehydrogenation previously employed.[26] The base formed white prisms m.p. 54·5–55° (48%) from light petroleum.

6-*Chloro*-3.8-*dimethylphenanthridine*. 2.7-Dimethylfluorenone (1·0 g), trichloracetic acid (35·0 g) and conc H_2SO_4 (6·0 ml) were kept at 60° and stirred continuously during the portionwise addition of NaN_3 (1·0 g) over 1 hr. After stirring for a further 1 hr the mixture was poured over ice, basified with NaOH aq and the solid filtered.

3.8-*Dimethylphenanthridone* (0·5 g; 47%) formed white plates, m.p. 297–299° (from EtOH). (Found: C, 80·4; H, 5·7. $C_{15}H_{19}NO$ requires: C, 80·7; H, 5·9%). On heating the lactam with excess phosphoryl chloride in the presence of dimethylaniline and working up in the usual way 6-*chloro*-3.8-*dimethylphenanthridine* (86%) was obtained. The compound formed white needles, m.p. 129–130° from petroleum ether. (Found: C, 74·3; H, 5·0. $C_{15}H_{12}NCl$ requires: C, 74·6; H, 5·0%).

6-*Chloro*-3.8-*dibromophenanthridine*. 2.7-Dibromofluorenone[29] with HN_3 (as above) gave 3.8-*dibromophenanthridone* (71%) as white needles, m.p. 330–333° from EtOH. (Lit.[30] 320–321°). The dihalogenophenanthridone gave, with phosphoryl chloride and dimethylaniline, 6-*chloro*-3.6-*dibromophenanthridine* (76%) as white needles, m.p. 216–217°, from EtOH. (Found: C, 41·9; H, 1·6. $C_{13}H_6NCl\,Br_2$ requires: C, 42·0; H, 1·6%).

3.6.8-*Trichlorophenanthridine* 2.7-Dichlorofluorenone,[29] treated as above, gave 3.8-*dichlorophenanthridone* (70%) as white platelets, m.p. 355–358° from EtOH. (Lit.[30] 348–349°). With phosphoryl chloride and dimethylaniline the lactam gave 3.6.8-*trichlorophenanthridine*. (62%), which formed white needles, m.p. 196–197° from EtOH. (Found: C, 55·5; H, 2·2; Cl, 37·2. $C_{13}H_6N\,Cl_3$ requires: C, 55·3; H, 2·1; Cl, 37·6%).

6-*Chloro*-3.8-*dinitrophenanthridine*, prepared as described by Albert *et al.*[31] m.p. 226°, from $CHCl_3$. (Lit. 225°).

6-*Chloro*-1.10-*dimethylphenanthridine*. Difficulty was encountered in preparing this compound from the corresponding lactam[26] owing to rapid hydrolysis, especially in the presence of mineral acid. The procedure adopted was: 1.10-dimethylphenanthridone (4·0 g), phosphoryl chloride (25 ml) and PCl_5 (1·0 g) were refluxed for 6 hr. After removing excess phosphoryl chloride by distillation (finally azeotropically with dry C_6H_6) the residue was extracted twice with hot, dry, light petroleum and the combined extracts evaporated. The residual clear yellow oil was taken up in dry C_6H_6 (15 ml), chromatographed twice over alumina and finally purified by distillation. 6-*Chloro*-1.10-*dimethylphenanthridine* was obtained as a colourless oil, b.p. 150°/0·05 mm (2·7 g, 62%) which solidified slowly on standing: trituration with petroleum ether gave a white solid, m.p. 74·75°. (Found: C, 74·9; H, 5·2; N, 5·8. $C_{15}H_{12}NCl$ requires: C, 74·5; H, 5·0; N, 5·8%).

Kinetic procedures

Quaternisation. 'Analar' nitrobenzene was used throughout: preliminary experiments showed further purification to be unnecessary. MeI was dried ($CaCl_2$) and fractionally distilled twice: material obtained had b.p. 42·5 ± 0·1/760 mm. The phenanthridine bases were recrystallised to constant m.p. and purities checked titrimetrically with acetous $HClO_4$ prepared from 'Analar' AcOH, 70% $HClO_4$ and Ac_2O standardised with potassium hydrogen phthalate. Preliminary experiments with phenanthridine itself showed that at the 0·01M level (since only small quantities of some of the alkyl-substituted compounds were available) both Crystal Violet and Oracet Blue B gave endpoints less satisfactory than those obtained potentiometrically, owing partly to the development of the characteristic yellow colour of the quaternary salts. Endpoints were therefore determined using an E.I.L. (Model 23A) pH meter equipped with calomel and glass electrodes: the potential drop over the endpoint was normally 400–500 mV. Appropriate volumes of stock solutions of base and MeI were mixed at 25° to give 50·0 ml of reaction mixture: 5·0 ml aliquots were transferred with a pressure-pipette to ampoules cooled in dry ice-acetone which were then sealed and transferred to the thermostat bath. In the case of the unreactive 6-methyl compounds the reacting solutions were 0·100M with respect to MeI and 0·010M with respect to base. In all other cases the reactants were equimolar (0·010M). At measured intervals the ampoules were withdrawn, rapidly cooled, opened and the contents rinsed into 'Analar' AcOH. The final solution (10–15 ml) was titrated with acetous $HClO_4$ from a microburette. Temperature corrections for the expansion of nitrobenzene were applied, extrapolated where necessary:[7] when equimolar concentrations of base (b) and halide (a) were employed specific rate constants were obtained from plots of $1/b-x$ against t and where excess halide was used values were obtained from plots of $\log b(a-x)/a(b-x)$ against t. The reactions were established as clean in all cases by assaying

with standard KIO_4 the quaternary iodide obtained from preparative runs: in the kinetic runs reactions were not usually taken further than 50% completion, although second-order behaviour was invariably observed throughout specimen reactions taken to 80% completion. The rates quoted (Table 1) are mean values from duplicate runs (all agreed within 2%).

The results from a typical run (3,8-dimethylphenanthridine with MeI, both 0·01M, at 75°) are:

Time (mins)	Titre (ml)	$\frac{1}{b-x}$ (1 mole^{-1})
0	4·50	100·0
48	4·21	106·9
102	3·92	114·8
150	3·71	121·3
204	3·48	129·3
264	3·24	138·9
312	3·10	145·2
372	2·91	154·6
426	2·78	161·9

$k_2 = 2{\cdot}56 \times 10^{-3}$ l mole^{-1} sec^{-1} (corrected for thermal expansion, factor 1·046).[5]

Energies of activation were obtained from plots of log k against $1/T$.

Nucleophilic replacements. 'Analar' grade MeOH and dioxan were dried, redistilled and stored under N_2. Fresh solutions of NaOMe were prepared for each run and standardised with HCl. Piperidine (b.p. 106·6/760 mm), pyrrolidine (b.p. 88·8–89·0°/760 mm) and morpholine (b.p. 128·4–128·7°/760 mm) were dried and purified by repeated distillation and stored under N_2: solutions in MeOH were prepared by weight immediately before use and checked by titration with HCl. Reactions were followed by titrating the liberated chloride with $Hg(NO_2)_2$ in the presence of diphenylcarbazone. This method has been used infrequently in organic systems[32] but here gave consistently better results than the Volhard method. For reactions carried out wholly or partly in MeOH at above 45° sealed ampoules were employed. Thermal expansion corrections for MeOH were obtained from the literature,[33] and the following factors for MeOH–40% dioxan mixtures were obtained experimentally: 1·000 (20·0°); 1·004 (25·0°); 1·020 (36·6°); 1·031 (45°); 1·045 (55·2°). All reactions were established as 'clean' by carrying out preparative runs: analytical data for all new products are given in Table 4.

As in related studies[34] no evidence for competing methanolysis was found in the reactions with amines in MeOH. (Cavell and Chapman have likewise concluded[36] that ethanolysis does not occur in ethanolic solutions of piperidine at temperatures below 100°).

Good second-order plots were obtained for all reactions except those showing autocatalysis, for which initial pseudo-first order rate constants were obtained.

Results of specimen runs. The methoxydechlorination of 6-chlorophenanthridine (b = 0·01M) with methanolic NaOMe (a = 0·01M) at 45·0°.

Time (hr)	Corrected titre (ml)	$\frac{1}{b-x}$ (1 mole^{-1})
14·7	0·85	119·8
22·0	1·18	129·7
38·7	1·75	151·5
47·5	1·98	162·5
62·8	2·34	183·3
72·0	2·49	193·6
87·2	2·78	217·3
110·6	3·05	245·2
∞	5·15	

Blank titre: 0·01 ml. Thermal expansion factor: 1·031. $k_2 = \frac{1}{t}\left(\frac{1}{b-x} - \frac{1}{b}\right)$: from the plot of $\frac{1}{b-x}$ against t. k_2 (45°) = $3{\cdot}76 \times 10^{-4}$ l mole^{-1} sec^{-1}.

The piperidinodechlorination of 6-chloro-3,6-dimethylphenanthridine (b = 0·01M) with methanolic piperidine (a = 0·10M) at 55·2°.

Time (hr)	Corrected titre (ml)	x (mole l^{-1})	$\log \frac{b(0{\cdot}5a - x)}{0{\cdot}5a(b - x)}$
4·3	0·22	0·000457	0·0163
16·9	0·51	0·001060	0·0394
28·5	0·78	0·001622	0·0625
41·2	1·04	0·002162	0·0866
46·9	1·15	0·002391	0·0974
65·8	1·52	0·003160	0·1366
74·9	1·66	0·003451	0·1528
112·7	2·23	0·004636	0·2283
∞	4·81		

Blank titre: 0·03 ml. Thermal expansion factor: 1·045.

$k_2 = \frac{2{\cdot}303}{2t(0{\cdot}5a - b)} \cdot \log \frac{b(0{\cdot}5a - x)}{0{\cdot}5a(b - x)}$: from the plot of $\log \frac{b(0{\cdot}5a - x)}{0{\cdot}5a(b - x)}$ against t.

k_2 (55·2°) = 1·64 × 10^{-5} 1 $mole^{-1}$ sec^{-1}.

Ionization constants. Spectra of the bases and their conjugate acids were determined in aqueous solution at 25° using a Unicam SP500 spectrophotometer fitted with a thermostatted cell compartment. pK_a values were obtained from the extinction coefficients of these species and from solutions at several intermediate buffered pH values at two or more suitable wavelengths.[37]

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