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HALOGEN REACTIVITIES. III. KINETIC STUDY OF DISPLACEMENT REACTIONS OF HALOQUINOLINES WITH PIPERIDINE

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Previously published papers in this series have dealt with the kinetics of halide removal in pyridines (1) and in naphthalene (2). The present paper discusses the anionoidal displacement reactions of the seven haloquinolines with piperidine.

The parent compounds, to which all haloquinolines may be referred for comparison, are 1-bromo- and 2-bromo-naphthalene. It has been shown earlier (2) that the $E_{act.}$ for bromide replacement with piperidine for the bromonaphthalenes are identical (24.9 ± Kcal.) within experimental error. The spatial steric effects operating in the haloquinolines may be assumed to be the same (excepting possibly for 2-haloquinolines and to a lesser extent for 8-haloquinolines) as those operating in the halonaphthalenes. It is believed therefore that any differences in $E_{act.}$ for the haloquinolines as compared to the halonaphthalenes may be ascribed to the electronic influences of the nuclear nitrogen atom. One of the prime reasons for the present work was to discover if and to what extent these electronic influences extend to the 3-, 5-, 6-, 7-, and 8- positions of quinoline.

In order to strengthen our supposition that cine- substitution does not occur, the piperidinoquinolines obtained from 2-, 3-, 4-, 6-, and 8-haloquinolines have been isolated and characterized. Proof of structure of the 6- and 8-piperidinoquinolines rests on independent synthesis from *o*- and *p*-piperidinoaniline by means of the Skraup reaction. It is safe to assume that the highly reactive 2- and 4-chloroquinolines give rise to substitution at the 2- and 4-positions, and it was found that 3-bromoquinoline gave a product not identical with 2- or 4-piperidinoquinoline.

Energies and entropies of activation for the reactions of various haloquinolines with piperidine have been assembled in Table II.[3]

It has been shown that 2-chloroquinoline reacts by a bimolecular process, and we assume that the other compounds react similarly. Attempts to measure second order rate constants for 6-bromoquinoline were foiled by the same liquid phase separation observed in the case of the bromonaphthalenes (2). It is possible that second order conditions could be applied to 4-chloroquinoline, but it is so similar to 2-chloroquinoline in reactivity that the determination of its kinetic order would not strengthen our conclusions concerning the benz-bromoquinolines. The fairly good agreement between the activation energies determined for

[1] Taken in part from the Ph.D. thesis of K. R. Brower, June 1953.

[2] Taken in part from the M.S. theses of J. W. Way, June 1951; and W. P. Samuels, June 1952.

[3] The data presented here include redeterminations and refinements of that presented at the Atlantic City convention of the American Chemical Society, September 14–19, 1952. Our conclusions here presented are intended to supercede those given at the above meeting.

TABLE I

PSEUDO-UNIMOLECULAR REACTION RATE CONSTANTS

COMPOUND	TEMP., °C.	k (sec^{-1}) × 10^4
3-Bromoquinoline	194.5 ± .2	0.104 ± .002
	201.0 ± .1	.138 ± .003
	205.4 ± .1	.166 ± .003
	207.2 ± .2	.180 ± .003
	222.0 ± .2	.375 ± .005
4-Chloroquinoline	99.6 ± .1	.171 ± .001
	116.9 ± .1	.449 ± .001
	124.1 ± .1	.659 ± .001
5-Bromoquinoline	193.5 ± .2	.0272 ± .0002
	197.5 ± .2	.0339 ± .0003
	213.7 ± .2	.0698 ± .0006
	224.2 ± .2	.115 ± .002
	225.1 ± .2	.131 ± .002
	232.7 ± .2	.181 ± .002
6-Bromoquinoline	195.6 ± .2	.0592 ± .0015
	201.6 ± .2	.0890 ± .0015
	211.6 ± .2	.146 ± .003
	223.1 ± .2	.253 ± .006
7-Bromoquinoline	181.4 ± .2	.109 ± .002
	186.4 ± .2	.147 ± .002
	203.5 ± .2	.338 ± .005
	210.7 ± .2	.462 ± .004
8-Bromoquinoline	173.7 ± .2	.130 ± .002
	178.6 ± .2	.159 ± .002
	189.7 ± .3	.311 ± .005
	200.0 ± .3	.531 ± .007

The pseudo-unimolecular rate constants were put into the form of second order rate constants by dividing by the concentration of piperidine (10 mol./l.) in order that all entropies of activation might have the same standard state.

SECOND ORDER RATE CONSTANTS

COMPOUND	TEMP., °C.	k (l./mol-sec.) × 10^4
2-Chloroquinoline in pet. ether solution	123.0 ± .1	0.375 ± .004
	130.0 ± .1	.531 ± .005
	137.0 ± .1	.714 ± .007
2-Chloroquinoline in toluene solution	75.7 ± .1	.092 ± .001
	80.4 ± .1	.116 ± .001
	86.3 ± .1	.154 ± .001
	90.4 ± .1	.195 ± .002

2-chloroquinoline under pseudo-unimolecular (1) and second order conditions indicates that complicating factors such as solvolysis by piperidine are probably absent.

The great reactivity of 2-chloroquinoline and 4-chloroquinoline is easily explained by reference to the following structure diagrams for the transition states:

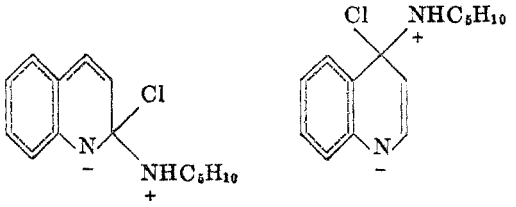


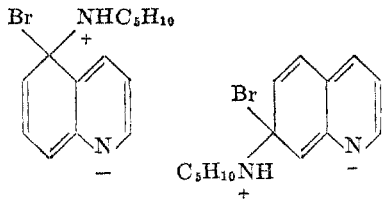
TABLE II

ENERGIES AND ENTROPIES OF ACTIVATION FOR REACTIONS OF HALOQUINOLINES WITH PIPERIDINE

COMPOUND	ΔE*	ΔS*
2-Chloroquinoline (1)	13.8 ± 0.4	−43.2
2-Chloroquinoline (toluene sol'n)	12.9 ± 1.0	−45.2
2-Chloroquinoline (pet. ether sol'n)	14.9 ± 1.0	−44.0
3-Bromoquinoline	21.6 ± 0.9	−43.6
4-Chloroquinoline	16.1 ± 1.1	−44.5
5-Bromoquinoline	22.0 ± 0.7	−44.6
6-Bromoquinoline	23.9 ± 0.7	−39.1
7-Bromoquinoline	21.6 ± 0.7	−41.5
8-Bromoquinoline	23.3 ± 0.7	−37.2
1-Bromonaphthalene (2)	25.0 ± 0.8	−39.8
2-Bromonaphthalene (2)	24.9 ± 1.0	−39.0

The negative charge generated by the approach of the unshared electron pair of piperidine may be imposed largely on the nuclear nitrogen atom to produce polarized structures of relatively low energy content. Of the two, one would expect the more extensive conjugation of the transition state for 2-chloroquinoline to make it less energetic, and this expectation is confirmed by experiment.

It is probable that the nuclear nitrogen exerts an activating influence on nucleophilic substitution at the 5- and 7-positions as illustrated by the following resonance forms:

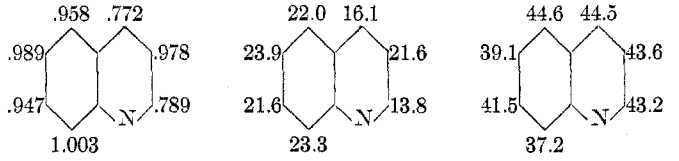


The contribution of such forms could not be very great since both rings are quinonoid, but the experimental activation energies for the benz-bromoquinolines suggest strongly that the effect operates to a measurable extent. The close agreement between the activation energies of the 5- and 7-isomers and between those of the 6- and 8-isomers serves to substantiate our previous finding that the activation energies for 1- and 2-bromonaphthalene do not differ appreciably.

The low reactivity of 3-bromoquinoline follows naturally from the impossibility of transferring the unit negative charge to the nuclear nitrogen, and its transition state should resemble that of 2-bromonaphthalene.

In addition to the specific alternating effects discussed above, the nuclear nitrogen appears to exert a generalized activating influence on nucleophilic substitution in which both mesomeric and inductive type displacements play their parts. Work in progress at this laboratory shows that the activation energy of 3-bromopyridine in its reaction with piperidine is less than that of bromobenzene, and the same relationship holds between 2-chloroquinoxaline and 2-chloroquinoline. It is not unexpected, therefore, that 3-bromoquinoline has a lower activation energy than 2-bromonaphthalene probably by operation of an inductive displacement of electrons from the 3-position. It is possible that the effect extends weakly to the benzene ring of quinoline, although the lowering of the activation energies of 6- and 8-bromoquinoline relative to those of the bromonaphthalenes is too small to permit a definite conclusion.

It is interesting to correlate the energies and entropies of activation with the electron densities calculated by Longuet-Higgins and Coulson (3) for the various positions on the quinoline nucleus.



Electron Densities ΔE^* $-\Delta S^*$

It is clear that the general correlation between calculated electron densities and ΔE^* is quite good. In particular, the iminohalide vinylogous positions are found to be activated as theory predicts. One minor discrepancy is noticed in the reversal of the electron densities of the 2 and 4 positions. A method is decsribed by Longuet-Higgins (4) for calculating the lowering of the activation energy of substitution reactions on certain types of nuclei when one carbon atom is replaced by an aza-nitrogen. The result is obtained in terms of a parameter the value of which depends on the particular substitution made. In the case of the haloquinolines the lowering of the activation energy relative to the halonaphthalenes should be as follows: 2-, .20 α; 3-, 0; 4-, .20 α; 5-, .05 α; 6-, 0; 7-, .05 α; 8-, 0. Evaluation of α from the average observed lowerings of 2- and 4-chloroquinoline leads to the results given in Table III. The agreement is fairly good except for the 3-isomer which is thought to exhibit inductive activation not taken into account in the calculation referred to above.

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EXPERIMENTAL

Preparation of Reagents. Piperidine was purified in the manner described previously (2).

2-Chloroquinoline (Eastman "White Label" product), m.p. 36.0–37.0°, was used without further purification.

3-Bromoquinoline was obtained in 66% yield as a light yellow oil, b.p.$_{3.0}$ 116.0–116.5°, by means of the Sandmeyer reaction on 3-aminoquinoline.

TABLE III

ACTIVATION ENERGY INCREMENT LOWERING UPON REPLACEMENT OF CARBON BY AZA-NITROGEN

POSITION:	2	3	4	5	6	7	8
Predicted $\Delta\Delta E^*$ (kcal).....	(10)	0	(10)	2.5	0	2.5	0
Observed $\Delta\Delta E^*$.....	11.1	3.3	8.9	3.0	1.0	2.6	1.7

TABLE IV

PROPERTIES OF NEW PIPERIDINOQUINOLINES

COMPOUND	B.P., °C.	MM.	M.P., °C.	ANALYSES	
				C[a]	H[a]
2-Piperidinoquinoline (12)			49–50	—	—
3-Piperidinoquinoline	140–145	0.2	75–76	78.9	7.82
4-Piperidinoquinoline	214–216	14	90–91	79.4	7.77
6-Piperidinoquinoline	138–140	0.2	42–43	78.9	7.84
8-Piperidinoquinoline	155–160	1.7	77–78	79.2	7.60

[a] *Anal.* Calc'd for $C_{14}H_{16}N_2$: C, 79.2; H, 7.59.

4-Chloroquinoline was obtained by the action of phosphorus oxychloride on 4-hydroxyquinoline which was prepared according to the procedure used by Price and Roberts (5) for the synthesis of 7-chloro-4-hydroxyquinoline. A 45% yield of material melting at 30.0–30.2° resulted.

5-Bromoquinoline was prepared by reduction of the diazonium salt of 5-bromo-8-aminoquinoline with hypophosphorous acid according to the procedure used by Kornblum (6) for the preparation of 3,3-dimethoxybiphenyl. A 55% yield of material, b.p.$_{1.2}$ 104.5–107°, m.p. 45–47°, was obtained.

6-Bromoquinoline was obtained in 30% yield as a low-melting, light yellow solid, b.p.$_{15}$ 155–156°, m.p. 21.5–21.7°. The method of La Coste (7) was followed.

7-Bromoquinoline was prepared by the method of Bradford, Elliott, and Kowe (8) through the Skraup reaction on *m*-bromoaniline. The dichromates of the mixed 5- and 7-isomers were separated by fractional recrystallization and the 7-bromoquinoline was recovered from its dichromate by treatment with strong alkali. A 20% yield of material, m.p. 30–34°, was obtained.

8-Bromoquinoline was prepared by the Skraup reaction on *o*-bromoaniline according to the method of Claus and Tornier (9). A 40% yield of material, b.p.$_{0.7}$ 117.0–117.5° was obtained.

Isolation of reaction products. The haloquinolines were allowed to react with piperidine under the conditions used for rate determinations until the time calculated for 80–90% reaction had elapsed. The reaction mixtures were made neutral by addition of acid, and the piperidinoquinolines were taken up in ether, concentrated, and fractionally distilled in a vacuum. The physical properties and analyses are listed in Table V.

Skraup synthesis of 6- and 8-piperidinoquinoline. The method of Lellman and Geller (10) was used to prepare 40 g. of *p*-piperidinonitrobenzene which was reduced by low pressure hydrogenation using alcohol as solvent and a palladuim-on-charcoal catalyst to *p*-piperidinoaniline. The crude *p*-piperidinoaniline obtained by evaporation of the solvent was converted to 6-piperidinoquinoline by the method used by La Coste (11) to prepare 6-dimethylaminoquinoline. A 20% yield of 6-piperidinoquinoline, b.p.$_{0.1}$ 125–129°, m.p. 42–43°, was obtained. A mixture melting point with the product of the reaction of 6-bromoquinoline with piperidine showed no depression. 8-Piperidinoquinoline was prepared by the same procedures starting with *o*-chloronitrobenzene and piperidine. A 30% yield of 8-piperidinoquinoline, b.p.$_{1.7}$ 155–160° was obtained. After recrystallization from alcohol the m.p. was 77–78°, and a mixture melting point with the reaction product of 8-bromoquinoline and piperidine showed no depression.

Pseudo-unimolecular rate determination procedure. The procedure did not differ from that previously described (2). The result of a typical determination is as follows:

7-BROMOQUINOLINE, T = 186.4 ± .2

Time (hr.)	(Fraction unreacted)$^{-1}$	k (hr.$^{-1}$)
0	1.0016	—
1.5	1.086	0.0539
1.5	1.082	.0526
2.0	1.112	.0523
2.0	1.113	.0526
3.0	1.168	.0517
3.0	1.172	.0524
3.5	1.212	.0549
3.5	1.207	.0537
	k av. = .0530, mean dev. =	.0008

Second order rate determination procedure. A solution of 0.5 *M* in 2-chloroquinoline and 1.0 *M* in piperidine in purified petroleum ether, b.p. 95–100°, was divided into 2-ml. portions which were sealed in Pyrex test tubes and immersed in the constant temperature oil-bath. Sample tubes were withdrawn at regular intervals and opened. The contents were washed into a flask with water, acidified with nitric acid, and titrated electrometrically or by the Volhard method for free chloride ion. Since the reaction proceeds according to the equation:

$$RCl + 2\ C_5H_{11}N \rightarrow C_5H_{10}NR + C_5H_{12}N^+Cl.$$

the rate equation becomes:

$$1/x - 1/a = 2k(t - t_0)$$

where x is the concentration of RCl at time t and a is the concentration at time t_0.

Estimation of precision of activation energies. The method previously described (2) was used without modification.

SUMMARY

Rate constants, activation energies, and entropies of activation are reported for the reactions of 2-chloroquinoline, 3-bromoquinoline, 4-chloroquinoline,

5-bromoquinoline, 6-bromoquinoline, 7-bromoquinoline, and 8-bromoquinoline with piperidine. When compared with the standard compounds 1-bromo- and 2-bromo-naphthalene a marked lowering of $E_{act.}$ is noticed for the 2- and 4-haloquinolines. This is caused by the operation of the electromeric effect of the nuclear nitrogen atom located in the same ring. The $E_{act.}$ of the 5- and 7-bromoquinolines is likewise lowered but to a lesser extent, the electromeric effect in these cases requiring a quinoidation of both rings. $E_{act.}$ for 3-bromoquinoline is significantly lower than that for 2-bromonaphthalene due ostensibly to an inductive displacement.

2-Chloroquinoline reacts by a true second order process in which solvent effects are small or non-existent.

BETHLEHEM, PENNA.

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