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META-SUBSTITUENT EFFECTS ON THE KINETICS OF METHOXYDECHLORINATION OF SOME 2- AND 4-CHLOROQUINOLINES[1]

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Abstract—The kinetic effects of some *meta*-substituents on the methoxydechlorination of 2-chloro and 4-chloroquinolines in methanol have been investigated. For all cases where the data for each substituent were available in both series a linear correlation is observed at 75°. The reaction at the 2-position is appreciably less selective than that at the 4-position. The results are consistent with those obtained for the substituent effects from the heteronuclear positions. It is shown that with electron-releasing substituents, including OR, SCH_3, Cl, the reactions are slower than predicted by Hammett's σ_m constants, at least partly because of mesomeric interaction with an *ortho* or *para* aza-group. The methyl group is affected but slightly by such an interaction. The observed effect of the CN group seems to indicate that in the case of electron-withdrawing groups σ_m constants may still predict reactivities correctly in aromatic nucleophilic substitutions. The activation entropies were found to vary at least as widely as the activation enthalpies.

INTRODUCTION

SPECIAL emphasis has been given in recent years to the importance of the knowledge of *meta*-substituent effects in the field of structural correlations with reactivity. For example, convenient sets of supposedly invariant constants have served as a base for the evaluation of the enhanced electron-releasing power of some *para*-substituents in such reactions as the solvolysis of phenyldimethylcarbinyl chlorides[3] and the aromatic halogenation of methylbenzenes[4] in an extension of the classical form of the Hammett equation.[5] Also, critical statistical analyses[6,7] of reactivity data have led to an accurate selection of substituents the σ_m constants of which can be used as a firm and convenient base of discussion of the effects of any given substituent with various forms of linear free-energy relationships.[5,8]

These analyses and previous review articles[5b,9] have revealed that *meta*-reactivity data are generally scarcer than the corresponding *para* data and that little quantitative information concerning *meta* and *para* substituent effects in the whole category of aromatic nucleophilic substitutions is available.

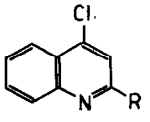
Meta-substituent effects are also in the latter reaction those which have been

[1] Electronic transmission through condensed-ring systems. IV. For the preceding papers in this series see ref. (13).
[2] To whom correspondence should be addressed.
[3] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.* **79**, 1913 (1957).
[4] G. Illuminati, *J. Amer. Chem. Soc.* **80**, 4941, 1945 (1958); see especially, p. 4944.
[5] (a) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, N.Y., 1940. (b) H. H. Jaffè, *Chem. Revs.* **53**, 191 (1953).
[6] R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.* **81**, 5343 (1959).
[7] H. van Bekkum, P. E. Verkade and B. M. Wepster, *Rec. trav. chim.* **78**, 815 (1959).
[8] R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.* **80**, 2436 (1958); ref. (6); R. W. Taft, Jr., S. Ehrenson, I. C. Lewis and R. E. Glick, ibid., **81**, 5352 (1959); R. W. Taft, Jr., *J. Phys. Chem.* **64**, 1805 (1960); R. W. Taft, I. R. Fox and I. C. Lewis, *J. Amer. Chem. Soc.* **83**, 3349 (1961).
[9] J. Miller, *Austral. J. Chem.* **9**, 61 (1956).

investigated least. Bevan[10] examined the effect of the *m*-nitro group in the methoxydehalogenation of non-activated fluorobenzene. Dealing with the more familiar substrates involving activation by *o-p*-withdrawing groups, Miller *et al.*[11] carried out a more extensive investigation of the same reaction in the series of 5-R-2,4-dinitrochlorobenzene.

Except for 2-nitrohalogenobenzenes, *meta* substituents in all *ortho* and/or *para* nitro and dinitro aryl halides are adjacent to a nitro group which may thus become subject to steric inhibition of resonance. The electrically similar aza-activation is free from such a molecular complexity. This point was clearly illustrated by comparison of the effects of a *m*-alkyl group on the piperidinodehalogenation of 2,4-dinitrochlorobenzene and the diaza-analog 4-chloropyrimidine.[12]

The preceding papers of this series[13] have dealt with substituent effects from the heteronuclear positions of the 1-*aza*-naphthalene system as part of a program including extension to other *aza*-activated aromatic systems and to homonuclear substituent effects. Here we wish to report the preparative and kinetic results concerning the effects on methoxydehalogenation of a number of substituents of varying types at the *meta* positions of 4-chloro and 2-chloroquinolines (series I and II, respectively).



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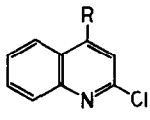


II

The final objects of this and subsequent papers will be

(1) to see to what an extent in the above systems and for this category of reactions substituent effects resemble those found in benzoic reactivities which are taken as the arbitrary base in empirical free-energy relationships;

(2) to establish a select group of substituents, if any, for use in the evaluation of reaction constants;

(3) to determine the substituent parameters related to homonuclear as well as heteronuclear positions.

With regard to the first point, it is of interest to note that in acid-base equilibria there is indeed found a common base of substituent effects between benzoic reactivities and basic strengths of pyridine[14] and quinoline[13a] derivatives.

RESULTS

The 15 chloroquinolines examined in this paper were prepared according to previously reported procedures, except for the methylthio and methoxy derivatives which were synthesized for the first time. Vapor phase chromatography proved to be a valuable technique for the characterization, structural assignment and quantitative product analyses of some of these compounds and of the reaction mixtures therefrom. Thus, by this method it was possible to confirm the structural assignment of the isomeric

[10] C. W. L. Bevan and G. C. Bye, *J. Chem. Soc.* **3091** (1954).

[11] M. Liveris, P. G. Lutz and J. Miller, *J. Amer. Chem. Soc.* **78,** 3375 (1956).

[12] B. Capon and N. B. Chapman, *J. Chem. Soc.* 600 (1957).

[13] (a) E. Baciocchi and G. Illuminati, *Gazz. Chim. Ital.* **87,** 981 (1957); (b) G. Illuminati and G. Marino, *J. Amer. Chem. Soc.* **80,** 1421 (1958); (c) E. Baciocchi, G. Illuminati and G. Marino, *J. Amer. Chem. Soc.* **80,** 2270 (1958).

[14] H. H. Jaffè and G. O. Doak, *J. Amer. Chem. Soc.* **77,** 4441 (1955).

methoxy chloroquinolines, to obtain information on the course of methoxydechlorination in the case of the following members of series I and II: 2,4-diCl, 2-OCH_3-4-Cl, 4-OCH_3-2-Cl, 2-CN-4-Cl, 4-CN-2-Cl and, finally, to determine the exact isomeric distribution in the reaction product from the 2,4-diCl member at all required temperatures according to a recently developed technique.[15]

It is interesting to note, however, that the cases of anomalous course of reaction experienced in these series were first discovered from the preliminary kinetic results. Such cases include the 2-$CO_2C_2H_5$-4-Cl, 4-$CO_2C_2H_3$-2-Cl and 2-CN-4-Cl derivatives. The methoxydechlorination of chloroquinolines in methanol is a 2nd order reaction and proceeds smoothly to completion.[13b] The carbethoxychloro-isomers were both found to follow an irregular kinetic course consisting of low reproducibility of the individual runs, erratic character of titers as a function of time and arrest of the reaction well before completion (64–76%) under the general conditions used for all the experiments reported herewith. This behavior is attributed to a specific interaction of the carbethoxy group with the reagent,[16] which would make the chloride ion release to slow down.

As to the 2-CN-4-Cl compound, the kinetic course was essentially normal, the 2nd order plots being linear within the precision of the measurements, but the apparent rate constants thus obtained was abnormally low, in fact lower than that for the 2,4-diCl compound in striking contrast with the order expected from the known electronic

TABLE 1. KINETIC DATA FOR THE METHOXYDECHLORINATION OF SOME *meta*-SUBSTITUTED CHLOROQUINOLINES IN METHYL ALCOHOL

R	10^4k, l.mole^{-1} sec^{-1}, at various temps						E_{exp} kcal/mole	$\Delta H‡$ kcal/mole	$-\Delta S‡$ *e.u.*
	30·0°	43·5°	60·8°	75·2°	86·5°	99·5°			
Series I: 2-R-4-Cl									
OC_2H_5				0·159[a]	0·409	1·17	21·3	20·4	22·3
OCH_3				0·143	0·403	1·21	22·7	22·0	18·0
SCH_3				1·17[a]	3·17[a]	6·82	18·7	18·0	22·1
CH_3				0·776	2·12	6·23	22·1	21·4	16·2
H				2·47[a]	6·305[a]	17·81	21·2	20·3	17·2
Cl[b]	1·00		21·08	74·7			20·0	19·4	13·0
CN				9925[c]					
Series II: 2-Cl-4-R									
OC_2H_5				0·478[a]	1·13	2·98	19·5	18·7	24·9
OCH_3				0·486	1·27[a]	3·21	20·0	19·3	23·1
SCH_3				1·94	5·56	15·08	21·8	21·0	15·4
CH_3				0·877	2·42	6·52[d]	21·4	20·8	17·8
H				2·22[a]	6·76[a]	19·38	24·2	23·9	7·0
Cl[b]	0·58		11·32	39·4			19·6	18·9	15·6
CN	12·80[a]	56·44	318·8	1190[e]			21·1	20·4	4·7

[a] Run in duplicate; [b] Partial rate constant (see Experimental); [c] Value estimated from that for the 2-Cl-4-CN isomer and from the slope of the linear plot in Fig. 1; [d] At 99·2°; [e] Value calculated from the activation parameters.

[15] G. Marino, *Ricerca Sci.* **30**, 2094 (1960).

[16] J. F. Bunnett, M. M. Robinson and F. C. Pennington, *J. Amer. Chem. Soc.* **72**, 2378 (1950) and refs. thereof.

effects of the substituents. Product analysis based on elemental analysis, V.P. chromatography and comparison of the corresponding data for the 4-CN isomer indeed indicated that a reaction other than the expected methoxydechlorination for the 2-CN had occurred. The 4-CN isomer behaved instead normally. The expected competing reaction is the amido-ester formation that has been described in detail recently in connection with similar studies.[17] It may be worth noting that amido-ester formation is known as a reaction sensitive to steric hindrance, a property which might explain why a 2-CN rather than a 4-CN group should be more susceptible to the reaction (*peri*-effect).

From the above, there is enough evidence to discard the anomalous kinetic data just described as unreliable for our present purposes. The kinetic results for the methoxydechlorination reaction are reported in Table 1 and include the 2nd order rate constants at various temperatures and the energies and entropies of activation. The probable errors in k and E_{exp} were found to be 2·3% and 0·3 kcal/mole respectively. The rate constants of series I and II for R = Cl were obtained as partial rate constants of 2,4-dichloroquinoline. A plot of log k values for series I vs. log k values for series II at the same temperature is linear (Fig. 1) and allows to estimate the rate constant

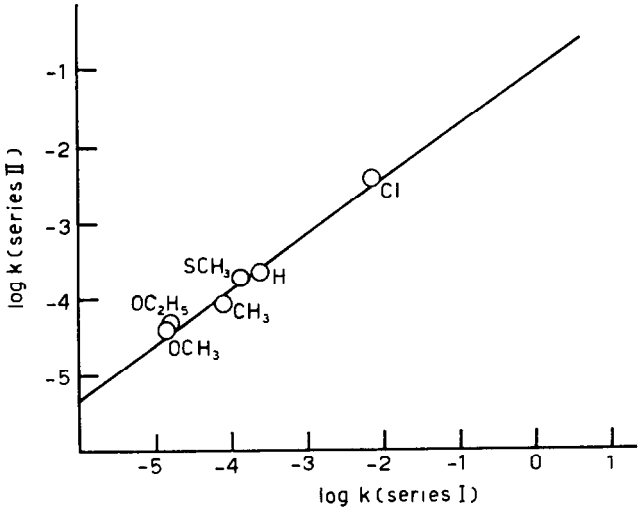


FIG. 1. Correlation of reactivity data (log k) for the methoxydechlorination of some 4-Cl-2-R (Series I) and 2-Cl-4-R-quinolines (Series II) in methanol at 75·2°.

for the 2-CN-4-Cl derivative from the value observed for the other isomer. Such an estimated rate has been included in Table 1.

DISCUSSION

Enhanced electron-releasing effects of meta *substituents*

Reactivities relative to the reference compound (k/k_0) in each of the series I and II are reported in the 2nd and 4th columns of Table 2. They involve appreciably different spreads in the rate constants, i.e., by factors of 8·4 × 10^4 and 3·0 × 10^3, respectively,

[17] N. S. Bayliss, R. L. Heppolette, L. H. Little and J. Miller, *J. Amer. Chem. Soc.* **78**, 1978 (1956).

TABLE 2. RELATIVE REACTIVITIES AND SUBSTITUENT PARAMETERS FOR THE METHOXYDECHLORINATION OF CHLOROQUINOLINES I AND II, AT 75·2°

	Series I		Series II		Mean values for	
$m-R$	k/k_0	$\frac{1}{\rho}\log(k/k_0)$	k/k_0	$\frac{1}{\rho}\log(k/k_0)^a$	$\frac{1}{\rho}\log(k/k_0)$	$\sigma_m{}^b$
H	1	0	1	0	0	0
CH_3	0·314	−0·086	0·395	−0·096	−0·091	−0·07
OCH_3	0·0579	−0·213	0·219	−0·157	−0·185	+0·08
OC_2H_5	0·0644	−0·205	0·215	−0·159	−0·182	+0·1
SCH_3	0·474	−0·056	0·874	−0·014	−0·035	+0·15
Cl	30·24	+0·254	17·75	+0·298	+0·276	+0·37
CN	4070	+0·620	536·0	+0·650	+0·635	+0·62

[a] As ρ (series II) the value +4·2, which is independent of the data for the CN group, was used. [b] The σ_m values for CH_3, OCH_3, Cl and CN were taken from refs. 6 and 7, and those for OC_2H_5 and SCH_3 from D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).

from methoxy to cyano. The most striking feature in these data is that alkoxy groups are markedly deactivating from the *meta* position in contrast with their normal behavior (positive σ_m values). This enhanced conjugation effect confirms the similar inversion of reactivity observed from *meta*-like heteronuclear positions (*epi*) in the methoxydechlorination of 4-chloroquinolines. From the homonuclear positions (*meta*) the effect is stronger and can also be detected with substituents having a lower mesomeric electron-releasing power. It is still evident with the methylthio group which also shows inversion of reactivity, but less so in the case of Cl for which no inversion is observed. That the latter substituent is subject to the same kind of interaction is indicated by a $\rho - \sigma_m$ analysis for the series I as based on the ρ value of +5·8 which was independently estimated from a correlation of the present reaction with the basic strength.[13c] This analysis is shown in Fig. 2 and reveals that the electron-releasing groups deviate from the calculated line of slope +5·8 and made to pass through H, in accordance with the expected order of the mesomeric electron release

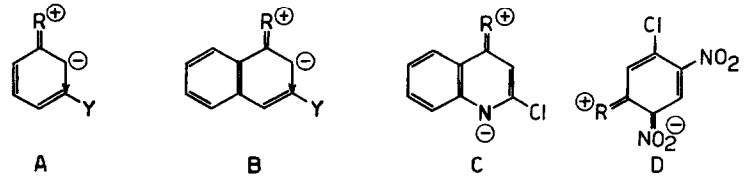
$$OCH_3, OC_2H_5 > SCH_3, Cl > CH_3$$

The deviation in the case of CH_3 is so slight that it hardly exceeds the range of precision of its σ_m value, but in the case of Cl it is quite definite. Electron releasing substituents display a closely similar behavior in series II as shown by the fairly linear reactivity correlation between the two series (Fig. 1).

The position of the electron-accepting cyano group in Fig. 2 is interesting because it is precisely consistent with the used value of ρ. This latter point will be further discussed in the next section.

An enhanced electron-releasing effect cannot be promoted in the transition state because of the electron-repelling nature of the reagent. Therefore, the observed effect is more likely to be connected with the ground state structure of the heteroaromatic substrate. The transmission of resonance effects from the *meta* position to a reaction

center Y is believed to occur by a resonance-inductive mechanism[6] as illustrated by structure A,



which represents the normal mode of transmission in the reactions of monosubstituted benzene derivatives.

For Cl and, even, alkoxy groups, the extent of this interaction has been found to be rather insensitive to change in the nature of the reaction and to be conveniently expressed by a σ_m constant. In fused-ring systems (B), however, the extent of the interaction may be different because of the differences in aromatic character among fundamental hydrocarbons, and σ_m constants may not predict naphthalene reactivities correctly. Thus, differences in bond orders between naphthalene and benzene[18] may

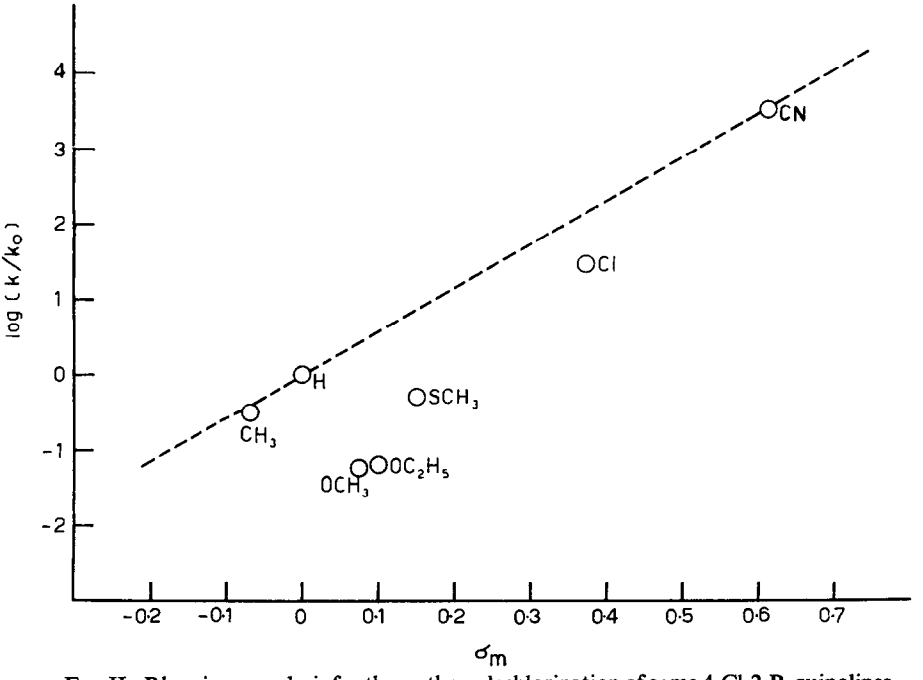


FIG. II. Rho-sigma analysis for the methoxydechlorination of some 4-Cl-2-R-quinolines as based on a predetermined ρ value of $+5{\cdot}8$.

explain why inversions with respect to expected "benzoic" reactivities are observed when a methoxy group is located at a *meta*-like heteronuclear position (*epi* or *pros*), as in the cases of the alkaline hydrolysis of 7-methoxy-2-carbethoxy-naphthalene[19] and the solvolysis of 6-methoxy-1-bromomethylnaphthalene[20].

[18] A. Streitweiser, *Molecular Orbital Theory* p. 170. Wiley and Sons, New York (1961).
[19] C. C. Price and R. H. Michel, *J. Amer. Chem. Soc.* **74**, 3652 (1952).
[20] K. C. Schreiber and R. G. Byers, *J. Amer. Chem. Soc.* **84**, 859 (1962).

A second mode of transmission leading to an enhanced electron-releasing effect involves direct interaction of the activating group (i.e., the *aza*-group) with the substituent according to structure C, thereby reducing the electron-accepting capacity of the latter in the rate-determining step of the reaction. This effect needs not be specific for the systems under examination and can in fact be expected to be general for most familiar activated substrates occurring in aromatic nucleophilic substitutions. It was observed in the methoxydechlorination of 5-substituted-2,4-dinitrochlorobenzenes[11] as the methoxy derivative was found to react about one third as fast as the reference compound, thus showing inverted reactivity also in this case. This result is not completely unequivocal in this series, because of the superimposition of steric inhibition of resonance involving the nitro group adjacent to the substituent, but is likely to be largely due to an enhanced resonance effect of the kind illustrated by structure D.[21]

To sum up, we may state that the enhanced electron-releasing effects from the *meta*-position observed in the *aza*-naphthalene series, may result from two factors, the one involving the change in aromatic character from the benzene ring to the fused-ring system, and the other the direct interaction of the substituent with the *aza*-group. Since the *aza*-group is strongly perturbing, it is believed that in *aza*-naphthalene reactivity the latter factor is also important. The present research suggests that, outside the *aza*-naphthalene area, more information along the lines of *meta*-substituent effects in non-activated naphthalene and in *aza*-activated benzene systems is needed.

The knowledge of the dissociation constants of 4-R-2-naphthalene carboxylic acids, offering the most direct link to the substituent effects in benzoic reactivity, seems to be particularly desirable in this connection.

The Hammett parameters

In the preceding section we have shown that the effects of electron-releasing *m*-substituents (CH_3O, Cl, etc.) on the reactivity of halogeno heteroaromatic substrates toward the methoxide ion are not additive to the effects of the *aza*-group *ortho* or *para* to the reaction center and, therefore, cannot be properly predicted by Hammett's σ_m constants even though some of such constants have been found "invariant" for all other reaction types tested in the course of recent statistical analyses.[6,7] For these reasons these constants cannot be taken as a base for the evaluation of the reaction constants (ρ) in the general reaction type under examination. Probably, however, the effect of hyperconjugation of the methyl group is generally small enough to let this group behave normally (see next section).

Electron-withdrawing substituents, such as NO_2, $COCH_3$, CF_3, CN, cannot interact with the *aza*-group and are expected to affect reactivities without enhancement of resonance. That this is the case is indicated by the data for the CN group reported in the present paper which indeed appear to be suitable for a reliable evaluation of reaction constants. This can be seen in two independent ways.

(1) The position of CN in Fig. 2 as obtained from the rate constants estimated for the 4-Cl-2-CN derivative (see Results Section) is precisely consistent with the ρ value of $+5{\cdot}8$ previously obtained from the kinetic effects of the heteronuclear substituents in the 4-chloroquinoline series. Alternatively, from this ρ value and from the slope of

[21] However, inverted reactivity was not observed in the piperidinodechlorination of 5-alkoxy-2-nitrochlorobenzene (W. Greizerstein, R. A. Bonelli and J. A. Brieux, *J. Amer. Chem. Soc.* **84**, 1026 (1962).

the plot reported in Fig. 1 (0·723), which does not include the CN group, the ρ constant for the 2-chloroquinoline series is found to be 4·2.

$$\rho \text{ (series II)} = \rho \text{ (series I)} \times \text{slope} = 5{\cdot}8 \times 0{\cdot}723 = 4{\cdot}2$$

(2) From the reactivity of 2-chloro-4-cyanoquinoline and from σ_m(CN) value, the ρ constant for the 2-chloroquinoline series is found to be 4·4.

$$\rho \text{ (series II)} = \frac{1}{\sigma_m} \log (k/k_0) = \frac{1}{0{\cdot}62} \times 2{\cdot}73 = 4{\cdot}4$$

The latter ρ (series II) value is in satisfactory agreement with the former and further confirms the ρ (series I) value. These values give a measure of how less selective is the reaction of series II as compared with the reaction of series I.

The above results suggest that in aromatic nucleophilic substitution with *o,p*-aza-activated substrates the existence of a select group of *meta*-substituents, although more limited than in other reaction types, is still possible for a reliable determination of reaction constants and that such a group should be sought among electron-withdrawing substituents. The scope of this suggestion will be the object of further investigations.

The above ρ values can be tentatively used as normalizing factors to express substituent effects in terms of readily comparable substituent parameters in "σ units" $\left(\frac{1}{\rho} \log (k/k_0)\right)$. These parameters, which are reported in columns 3 and 5 of Table 2, need not be considered as generally valid "constants", but are useful in discussing mechanism-dependent and/or substrate-dependent substituent effects relative to the ionization of benzoic acids. As anticipated by the linear plot in Fig. 1, the two sets of parameters corresponding to series I and II are in satisfactory agreement with each other. Their mean values (column 6) can be compared with the σ_m constants. The major features of this comparison are the inverted signs for the methoxy, ethoxy and methylthio groups and differences ranging from 0·10 to 0·25 σ units. It is interesting to note that the substituent effects of these groups and of Cl are intermediate between normal *meta*- and *para*-effects and resemble more closely the latter. The mean value for the methyl group is slightly more negative (by 0·02 units) than the σ_m constant and that for the cyano group shows a difference by only 0·01.

The energies and entropies of activation

In the methoxydechlorination of 6- and 7-substituted 4-chloroquinolines, the entropy of activation showed fairly large changes along the series[13b]. This is now also observed for the reaction of series I and II. The over-all changes in enthalpy and entropy of activation are 4 kcal/mole and 9·3 *e.u.*, respectively, for the former series and 2·3 kcal/mole and 20·1 *e.u.* for the latter series. The most reactive compound in the latter series, i.e., the 4-CN-2-Cl derivative, is the one with the highest entropy value but not with the lowest enthalpy value. Within the limited number of compounds examined in each series, the reaction rate constants, which can be well accounted for in terms of the electronic structure of the reacting substrates, appear to result from not as yet understood compensating changes in the two activation parameters.

While we are recording more data of this kind in our current research in an attempt to obtain a better understanding of this phenomenon, we wish to refer to Part II[13b] for a brief comment on the subject.

EXPERIMENTAL

The preparation of 2-chloro and 4-chloroquinolines

The following quinoline derivatives were prepared according to previously described procedures (original refs. and m.ps. are given): 4-Cl,[13a] 27–29°; 2-CH_3-4-Cl,[22] 37·2–40·0°; 2-$CO_2C_2H_5$-4-Cl,[23] 85·5–86°; 2-CN-4-Cl,[24] 107·5–108°; 2,4-diCl,[25] 83·5–84°; 2-OC_2H_5-4-Cl,[25,26] 41–41·5°; 2-Cl (commercial sample Eastman Kodak) 36·5–37·5°; 2-Cl-4-CH_3[27], 57·5–58; 2-Cl-4-$CO_2C_2H_5$,[26a,28] 64–64·5°; 2-Cl-4-CN,[26b] 155·5–156°; 2-Cl-4-OC_2H_5,[25] 83·5–84°.

In the following the syntheses of previously unreported quinoline derivatives are described.

2-Methylthio-4-chloroquinoline

2-Methylthiocinchoninamide. An ethanolic solution of methyl mercaptan (3 g, 0·062 mole) was added to a sodium ethoxide solution (containing 0·942 g, 0·039 mole Na). 2-Chlorocinchoninamide[23a] (8·2 g, 0·039 mole) was added to the resulting sodium thiomethoxide solution and the mixture was refluxed and stirred for 2½ hr. After cooling at room temp, the mixture was poured into an excess of water and the white product filtered and crystallized from ethanol, yielding 7·4 g (88%), m.p. 228·5–229·5°. (Found: N, 12·86; $C_{11}H_{10}N_2OS$ requires: N, 12·8%).

2-Methylthio-4-aminoquinoline. A solution of potassium hypobromite (prepared by adding 2 ml bromine (0·039 mole) to a KOH solution) was added to 8·5 g (0·039 mole) 2-methylthiocinchoninamide (prepared as described in the previous paragraph). The mixture was stirred for 1 hr, filtered and then heated at 70° for 45 min. The solution was concentrated and cooled down; the amine was collected and crystallized from water, yielding 1·9 g (26%), m.p. 99–100°.

2-Methylthio-4-chloroquinoline. The preceding compound (1·9 g, 0·010 mole) was dissolved in conc HCl (27 ml) and the mixture was cooled at −5°. A 3·37N $NaNO_2$ solution (0·010 mole) was added dropwise and the resulting red solution kept for ½ hr at the same temp, then warmed to room temp and stirred until the development of nitrogen ceased.

The solution was neutralized by adding 10N NaOH and the precipitate filtered. The crude product (1·15 g) was purified by chromatography through aluminum oxide (using pet ether as eluent) and subsequent crystallization from 95% ethanol, yielding 1 g (50%), m.p. 53–53·5°. (Found: C, 57·23; H, 3·79; N, 6·70. $C_{10}H_8ClNS$ requires: C, 57·27; H, 3·84; N, 6·68%).

2-Chloro-4-methylthioquinoline

2-Ethoxy-4-methylthioquinoline. Methyl mercaptan (5 g, 0·104 mole) was dissolved in 100 ml 0·71M EtONa and 2-ethoxy-4-chloroquinoline (14·2 g, 0·0674 mole) was added. The solution was refluxed for 2½ hr; most of the solvent removed by distillation and water added to the residual mixture. The product was collected by filtration and crystallized from ethanol until a constant m.p. was obtained, yielding 10·4 g (70·3%), m.p. 86·5–87°. (Found: C, 65·83; H, 6·06; N, 6·36. $C_{12}H_{13}NOS$ requires: C, 65·71; H, 5·93; N, 6·39%).

2-Hydroxy-4-methylthioquinoline. 2-Ethoxy-4-methylthioquinoline was hydrolyzed quantitatively by refluxing in 6N HCl for 8 hr. The product was crystallized from ethanol until constant m.p., 245·5–246·5° (monoaquo). After removal of water by heating at 110° followed by weight decrease with time, the resulting constant weight dehydrated product was analysed. (Found: C, 62·77; H, 4·83; N, 7·35. $C_{10}H_9NOS$ requires: C, 62·80; H, 4·74; N, 7·32%).

2-Chloro-4-methylthioquinoline. 2-Hydroxy-4-methylthioquinoline (7·6 g, 0·0365 mole) and phosphorus oxychloride (33·4 g, 0·2183 mole) were heated under reflux for 3 hr. The mixture was

[22] *Organic Syntheses* Coll. Vol. 3; p. 593. Wiley and Sons, New York (1955); W. L. Glen, M. M. J. Sutherland and F. J. Wilson, *J. Chem. Soc.* 491 (1939).

[23a] G. F. Lisk and W. Stacy, *J. Amer. Chem. Soc.* **67,** 2686 (1946); [b] E. Compaigne, R. E. Cline and C. E. Kaslow, *J. Org. Chem.* **15,** 600 (1950).

[24] M. Henze, *Ber. Dtsch. Chem. Ges.* **69,** 1566 (1936); H. Rupe and A. Gassmann, *Helv. Chim. Acta* **22,** 1241 (1939).

[25] F. J. Buchmann and C. S. Hamilton, *J. Amer. Chem. Soc.* **64,** 1358 (1942).

[26a] J. A. Aeschlimann, *J. Chem. Soc.* 2909 (1926); [b] Hans Wojahn, *Arch. der Pharm.* **274,** 83 (1936).

[27] *Organic Syntheses,* Coll. Vol. 3; p. 194. Wiley and Sons, New York (1955).

[28] W. Borsche and W. Jacobs, *Ber. Dtsch. Chem. Ges.* **47,** 359 (1914).

cooled and poured into excess of iced water and the chloroquinoline extracted twice with ether. The combined extracts were washed with water until the last traces of acid were removed and, then, dried (Na_2SO_4). The crude product, after removal of solvent (8·3 g) was chromatographed on alumina, eluted with a 1:1 pet ether–ethyl ether mixture and, after recovery, crystallized from absolute ethanol, yielding 6·5 g (85·5%), m.p. 106·5–107°. (Found: C, 57·28; H, 3·79; N, 6·66. $C_{10}H_8ClNS$ requires: C, 57·27; H, 3·84; N, 6·68%).

2-Chloro-4-methoxyquinoline and 2-methoxy-4-chloroquinoline. 2,4-Dichloroquinoline (40·5 g, 0·270 mole) was added to a solution containing 15 g commercial potassium hydroxide in 400 ml methanol and the resulting solution refluxed for 2 hr. Most of the solvent was distilled off and the solution diluted with water and kept in a refrigerator for 2 hr. The solid product was filtered off and steam-distilled. Ten fractions were collected, the total volume being more than 16 liters. The intermediate fractions were steam-distilled once more. The first group of fractions, containing the more volatile isomer, were combined and the product was crystallized from 80% ethanol until constant m.p. 72·5–73°, yielding 10·8 g (25%) (Found: C, 62·05; H, 4·43; N, 7·27. $C_{10}H_8ClNO$ requires: C, 62·02; H, 4·16; N, 7·23%).

The second group of fractions containing the less volatile compound were also combined and crystallized from the same solvent, yielding 8·5 g (21%), m.p. 77–77·5°. (Found: C, 60·50; H, 4·43; N, 7·00. $C_{10}H_8ClNO$ requires: C, 62·02; H, 4·16; N, 7·23).

On the base of the analogous behaviour in steam-distillation and of the close similarity of the retention times in gas-chromatography through several different columns, when compared with the corresponding ethoxy compounds, the structures of 2-methoxy-4-chloro and 2-chloro-4-methoxyquinoline were assigned to the products melting at 73 and 77·5°, respectively.

Product analyses of the reaction mixtures

2,4-Dichloroquinoline. The reaction mixtures obtained from experiments carried out at 30·0 and 60·8° were analysed by vapor phase chromatography according to the same conditions used at 75·2°.[15] The results are as follows: 2-Methoxy-4-chloro and 2-chloro-4-methoxy: 36·7 and 63·3% (at 30·0°); 35·0 and 65·0% (at 60·8°); 34·3 and 65·7% (at 75·2°), respectively.

Chloromethoxyquinolines. Solutions 0·066 M with respect to both reagents, the chloroquinoline and the sodium methoxide, were refluxed for about one month, then poured into excess water. The organic product was extracted 3 times with benzene and the combined benzene layers washed twice with water and then dried (Na_2SO_4). The solution was filtered; most of the solvent was removed by distillation and the residue analysed employing a C. Erba Mod. B Fractometer operated with a 1 m column packed with Craig Polyesther Succinate (Wilkens) at 195°, using hydrogen as carrying gas. The chromatograms consisted in both cases of 2 well resolved peaks, one of which being the starting chloroquinoline. While the retention times of the starting materials were very different (2·8 and 17·4 min, respectively) for the 2-methoxy and 4-methoxy isomers) the retention times for the reaction products were exactly the same in the two cases (6·9 min). The same result was obtained by using a completely different kind of stationary phase, silicone oil. The identity of the retention times is ascribed to the identity of the reaction products. The only common product which could be reasonably formed in both cases is indeed 2,4-dimethoxyquinoline. All the other hypothetical reactions (cine-substitution via benzyne-type intermediates, hydrolysis, etc.) would produce different isomers.

Chlorocyanoquinolines. In preparative batches carried out under conditions similar to the kinetic runs (as to reagent concentrations and temp) with 2-chloro-4-cyano and 2-cyano-4-chloroquinoline, the reaction mixtures were poured into water and the resulting solids filtered, washed, dried and analyzed without any purification. The elementary analysis gave the following results: reaction product from 2-Cl-4-CN quinoline (Found C, 72·71; H, 4·60; N, 14·99%) reaction product from 2-CN-4-Cl quinoline (Found C, 65·80; H, 5·42; N, 12·70; $C_{11}H_8ON_2$ requires C, 71·71; H, 4·38; N, 15·21%). V.P. chromatography was then carried out with a 1-meter silicone column at 195°. Whereas a single peak was obtained in the case of 2-chloro-4-cyanoquinoline, no peak could be detected in the case of the other isomer, even on prolonged elution, indicating the formation of much less volatile products.

Kinetic experiments

Dry methanol and sodium methoxide solution were prepared as described in a previous paper.[18b] The chloroquinolines were all purified by crystallization to constant m.p. from the appropriate solvent.

The kinetic runs at 30·0° were carried out in a volumetric flask, whereas all experiments at higher temp were performed by using the sealed tubes technique. Details concerning the analytical procedure of chloride ions determination were reported previously.[13b]

In order to avoid scarcely reproducible results possibly due to some interaction of 2-chloro-4-methylthioquinoline with silver ions, a modified procedure was used in this case. The tubes were crushed under a mixture of about equal amounts of benzene and distilled water and the organic material was extracted in a separatory funnel. The aqueous layers were acidified with nitric acid and analysed in the usual way.

The concentrations used were in the range 0·025–0·050 M for the chloroquinoline compound and 0·065–0·120 M for the sodium methoxide reagent. The second order rate constants were graphically determined from the plots $\lg \frac{a-x}{b-x}$ vs. time.

A total of 66 independent kinetic runs was carried out, and two typical experiments are included in Table 3.

TABLE 3. TYPICAL METHOXYDECHLORINATION KINETIC EXPERIMENTS

Compound and conditions	Time mins	NH_4CNS ml	Reaction %	$\lg \frac{a-x}{b-x}$
	0	5·37	0	0·24018
2-chloro-4-methylquinoline	120	5·27	9·64	0·25944
$a = [CH_3ONa] = 0·07121$	332	5·10	26·04	0·30067
$b = 0·04096$	555	4·96	39·54	0·34659
$k_2 = 2·42 \times 10^{-4}$	1480	4·67	65·57	0·49767
Temp 86·5°	1778	4·62	70·40	0·54356
	2035	4·58	74·22	0·58741
	2917	4·50	81·97	0·77015
	∞	4·32	101·2	—
	0	4·13	0	0·36167
4-chloro-2-methoxyquinoline	266	4·01	13·76	0·39925
$a = [CH_3ONa] = 0·09900$	535	3·88	28·67	0·45068
$b = 0·04304$	1385	3·65	55·04	0·59017
$k_2 = 1·21 \times 10^{-4}$ l.mole^{-1}	1665	3·60	60·78	0·63500
sec^{-1}	1960	3·56	65·37	0·66995
Temp. 99·5°	2825	3·46	76·68	0·82038
	3255	3·43	80·27	0·88031
	∞	(3·26)		

The activation energies, E_{exp} were calculated by the least square method from the equation

$$2·303 \log k = 2·303 \log A - \frac{E_{exp}}{RT}$$

Activation enthalpies and entropies, $\Delta H‡$ and $\Delta S‡$ were calculated from the equation[29]

$$\log \frac{k}{T} = 10·319 - \frac{\Delta H‡}{4·574T} + \frac{\Delta S‡}{4·574}$$

Partial rate constants for 2,4-*dichloroquinoline.* The overall rate constants for the methoxydechlorination of 2,4-dichloroquinoline, $1·58 \times 10^{-4}$ (at 30·0°), $3·24 \times 10^{-3}$ (at 60·8°) and $1·14 \times 10^{-2}$ (at 75·2°) and the isomer distributions reported in a preceding section allowed to calculate the partial rate constants for substitution at the 2- and 4-positions as reported in Table 1. A more detailed description of this procedure was reported elsewhere.[15]

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[29] E. W. Cagle and H. Eyring, *J. Amer. Chem. Soc.* **73**, 5628 (1561).