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Chimica. — *Solvent Effects on the Reactivity of 2, 4–Dichloroquinoline with Dimethylamine. Application to Syntheses* (*). Nota di GABRIELLO ILLUMINATI e GIANLORENZO MARINO, presentata (**) dal Corrisp. L. PANIZZI.

INTRODUCTION.

Recently [1] we have shown that the rate of aminodechlorination at a quinoline system is influenced by the nature of the solvent to a markedly different extent depending on whether the halogen is displaced from a position α or γ to the *aza*–group. Whereas 4–chloroquinoline becomes much less reactive on going from a hydroxylic to a non–polar solvent, the reactivity of 2–chloroquinoline keeps at a relatively high level even in the latter solvent.

It may be predicted [2] that a similar phenomenon would also occur if both reactive positions were occupied by potential leaving groups for nucleophilic displacements by amines. If so, the choice of the solvent and other experimental conditions would lead to reactions of synthetic value for the preparation of isomeric 2, 4–disubstituted quinolines. With these expectations in mind, we have now investigated the kinetics of the reaction of 2, 4–dichloroquinoline with dimethylamine in methanol and toluene.

RESULTS AND DISCUSSION.

The displacement of one chlorine of 2, 4–dichloroquinoline by dimethylamine is first-order in each reactant in both investigated solvents, methanol and toluene, and in the concentration range 0.05 to 0.15 M. Unlike 4–chloroquinoline [1], the reaction at the position 4 of 2, 4–dichloroquinoline with an amine is not subject to autocatalysis. This is expected from the diminished basicity of the ring nitrogen due to the presence of an electron–withdrawing substituent (the second chlorine) at position 2. As to the reaction at position 2, since 2–chloroquinoline itself is not subject to autocatalysis, *a fortiori* 2, 4–dichloroquinoline is not expected to be so either, which is in complete agreement with experiment.

The observed rate constants for the above reactions at varying temperatures are reported in Table I (column 2). This table also includes another independent set of data, the isomer composition of the reaction mixtures as obtained

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(**) Nella seduta del 10 aprile 1965.

at all investigated conditions (columns 3 and 4). Quantitative product analysis was carried out by V. P. chromatography and the individual isomers identified by comparison with authentic specimens [3]. Combination of these data with the observed rate constants yields the partial rate constants k_α and k_γ (Table I, columns 5 and 6). The activation parameters for the reactions in both solvents and at each reacting center are reported in Table II.

Table I shows that, in close analogy with the behavior observed for the reactions of monochloroquinolines with piperidine, the reactivity at the position 4 of 2,4–dichloroquinoline is more sensitive to solvent effects than that at position 2. Thus, at 86,5°, the decrease in rate on going from methanol to toluene is 250–fold at position 4 and only 8–fold at position 2. This behavior is attributed to a specific α effect probably related to differences in the solvation requirements at the positions α and γ to the *aza*–group in the transition state [1]. It is of interest to note that, although there is evidence for a different selectivity in the nucleophilic displacements of chlorine in the series 2–Cl–4–X–and 4–Cl–2–X–quinolines [4], the presence of a second chlorine acting as a substituent does not alter the essential picture of the solvent effect on the relative reactivities at the two positions examined.

TABLE I.

Reaction of 2,4–Dichloroquinoline with Dimethylamine in Methanol and Toluene.

Solvent and Temperature (°C)	Observed $k \times 10^4$ $l \cdot m^{-1} \cdot sec^{-1}$	Isomer Distribution (%)		Partial Rate Constants ($l \cdot m^{-1} \cdot sec^{-1}$)		k_α/k_γ
		2–NMe_2–4–Cl	4–NMe_2–2–Cl	$k_\alpha \times 10^4$	$k_\gamma \times 10^4$	
Methanol, 75.2	4.17	27.7	72.3	1.16	3.01	0.383
86.5	8.26	31.6	68.4	2.61	5.65	0.463
99.5	18.2	34.4	65.6	6.24	11.9	0.524
Toluene 86.5	0.354	93.6	6.4	0.331	0.0225	14.7
99.5	0.780	94.5	5.5	0.737	0.0429	17.2
115.7	1.691	95.6	4.4	1.615	0.0747	21.6

Let us now see how this effect is related to the energies and entropies of activation. Inspection of the data reported in Table II can be made in either of the following ways: (*a*) by noting the effect of the solvent on the changes in enthalpies ($\Delta\Delta H^{\neq}$) and entropies ($\Delta\Delta S^{\neq}$) of activation when reactions at centers α and γ are compared; or (*b*) by noting the effect of the reaction center on the $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ values when reactions in the two investigated solvents are compared. In both cases, the $\Delta\Delta H^{\neq}$ values only vary within the limits of expe-

rimental error, whereas the $\Delta\Delta S^{\neq}$ values show differences in the order of 8 e.u. The least change in $\Delta S^{\neq}$ is observed in the more solvating solvent (method *a*), or for the reaction center α (method *b*).

TABLE II.

Activation Parameters for the Reaction of 2,4-Dichloroquinoline with Dimethylamine.

Solvent	Position of Substitution	E_{att} Kcal/mole	$\Delta H^{\neq}$ Kcal/mole	$-\Delta S^{\neq}$ e. u.
Methanol . . .	2	17.9	17.2	27.6
	4	14.6	13.9	35.0
Toluene	2	15.0	14.3	39.6
	4	11.4	10.6	55.1

Method (*) Activation enthalpy changes, $\Delta\Delta H^{\neq}$ (Kcal/mole)
(*a*) : 3.2 (in methanol) and 3.7 (in toluene)
(*b*) : 2.9 (at position α) and 3.3 (at position γ)
Activation entropy changes, $\Delta\Delta S^{\neq}$ (e.u.)
(*a*) : 7.4 (in methanol) and 15.5 (in toluene)
(*b*) : 12.0 (at position α) and 20.1 (at position γ)

(*) Methods (*a*) and (*b*) are defined in the text.

If this behavior is combined with the observation that reactivity at position 2 is relatively high, no matter which of the two solvents is used, it may be concluded that the reactions at position α involve a less extensive solvent participation than the reaction at position γ. This is consistent with several possible models for the reaction at position α, which may alternatively involve " built-in " solvation [5], internal H-bonding or H-bonding with a third molecule [1].

APPLICATION TO SYNTHETIC WORK.

Table I shows that the reaction takes place predominantly at position 4 in methanol and at position 2 in toluene. Furthermore, since the activation energy is lower for the reaction at position 4 in either solvent, the best yield in the 2-chloro-4-dimethylamino derivative is obtained when 2, 4-dichloroquinoline is made to react in methanol solution at the lowest practicable temperature; in contrast, the other isomer is obtained in toluene solution in excellent yields

especially at the higher temperatures. Some preliminary experiments have shown that use of an excess of the nucleophilic reagent is harmful since the subsequent reaction of each isomer, which leads to 2, 4–bisdimethylaminoquinoline, has a tendency to level off the composition of the reaction product.

It may be worth mentioning here that in the displacement of chlorine of 2, 4–dichloronitrobenzene by amines, solvent effects, although similar to those found by us in *aza*–activated systems, do not seem to alter the composition of the mixture to the point that both isomers can be conveniently made if appropriately different conditions are used, since in this case the reaction at the position *ortho* to the nitro group will remain predominant (2,6).

Experimental part.

Materials.—2, 4–Dichloroquinoline was prepared in a single step by a modification of the method described by Ziegler and Gelfert [7] for the preparation of 4–hydroxycarbostyril. Aniline (22.4 g, 0.24 mole), malonic acid (25 g, 0.24 mole) and phosphorus oxychloride (294 g, 1.92 mole) were mixed together and heated under stirring for 4 hours at 90–100° C. After cooling, the reaction mixture was poured into an excess of a sodium hydroxide solution and crushed ice. The solid was extracted with toluene and the organic layer was washed with water and dried over sodium sulphate. On removal of the solvent by distillation, the residue was applied on chromatographic alumina column, benzene being the eluent. The product was recovered from this treatment in 44 % yield (20.5 g) and recrystallized from aqueous ethanol to constant melting point, 66.5–67°.

Reagent-grade dimethylamine was used without further purification. Methanol was purified as described previously [8]. Toluene (A.S.D.) was dried over calcium sulphate and sodium, then fractionated in a Todd column at atmospheric pressure using a reflux ratio of about 10. The middle fraction, b.p. 110°, was used.

Kinetic measurements.—The stock solutions of the nucleophile were prepared by dissolving the content of a 25 ml ampoule of pure–grade dimethylamine (C. Erba) in about 1000 ml of purified solvent. For the reactions in toluene, because of the volatility of dimethylamine in this solvent, the stock solutions were prepared at –10°, stored in a refrigerator at about 0° and titrated just before each kinetic experiment. Similar precautions were unnecessary when methanol was used as solvent, since methanolic solutions of dimethylamine are much more stable.

The reaction mixtures were prepared by weighing a calculated amount of dichloroquinoline in a 25 ml volumetric flask, then adding 15–20 ml of the solvent, a known volume of dimethylamine stock solution and solvent again to the mark. After shaking, 2–ml aliquots of the solution were pipetted into 10–12 tubes which were quickly sealed. For the reactions in toluene, all the operations from the addition of the dimethylamine solution to the sealing of the

tubes were carried out at 0°. The reagent concentrations used were about 0.05 M for 2, 4–dichloroquinoline and in the range of 0.10 to 0.16 M for dimethylamine.

The tubes were immersed simultaneously in a thermostat, removed at convenient time intervals and quickly crushed under a 0.3 N nitric acid solution (20 ml.). Zero–times were taken at about 8 minutes after immersion. The chloride ion content was determined by the Vohlard method. The reactions were followed to approximately 60–70 % completion and the overall second order rate constants obtained graphically from the plots based upon the kinetic equation

$$\log \frac{0.5\ a - x}{b - x} = (a - 2\ b)\ kt + C.$$

All the rate constants were multiplied by a thermal factor consisting of the ratio of the density of solvent at 20° (or 0° for the reactions in toluene) to that at the reaction temperature.

Isomer distributions.—The isomer distributions were determined for reactions carried out under kinetic conditions. In order to avoid disubstitution, the heterocyclic substrate was kept in excess in all the experiments.

The reactions were allowed to proceed to completion, most of the solvent was removed by evaporation and the residue was analyzed by vapor phase chromatography. A variety of column packings was tested; the best resolution of the reaction mixture was achieved with a 1 m column of Diethylen Glycol Succinate or a 1 m column of Silicone D.C. 710 operated at 195° and 1.5 atm. H_2. With both these columns, the components of the reaction mixtures were eluted in the following order: 2, 4–dichloro–, 4–chloro–2–dimethylamino– and 2–chloro–4–dimethylaminoquinoline. The latter two isomeric compounds were identified by comparison with authentic specimens as obtained in the course of related work [3].

Partial rate constants and Arrhenius parameters.—The partial rate constants for the reaction at each individual position, k_α and k_γ, were determined by solving the following system of two equations [9]:

$$k_\alpha + k_\gamma = k_T$$

$$k_\alpha / k_\gamma = r$$

where k_T is the overall, observed rate constant and r is the ratio of the concentrations of the two isomeric chlorodimethylaminoquinolines, as determined by V.P.C. for reactions at the same temperature.

Activation energies and entropies were calculated from the plots of log k and log k/T (where k's are the partial rate constants) *vs.* 1/T, by using the least square method.

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[9] For a previous application of this procedure, see G. MARINO, «Ricerca Sci.», *30*, 2094 (1960).

RIASSUNTO. — È stata studiata la reattività della 2,4–dichlorochinolina presso le posizioni 2 e 4 nella reazione con dimetilammina in alcool metilico e in toluene. A tal fine sono state determinate le costanti di velocità del secondo ordine e le composizioni delle miscele isomeriche a varie temperature, e da questi dati sono state dedotte le costanti parziali di velocità e le energie ed entropie di attivazione presso ciascun centro di reazione. I risultati mostrano effetti del solvente sulla reattività del tutto simili a quelli precedentemente osservati per le analoghe reazioni delle monoclorochinoline isomere, la reazione in posizione 2 essendo relativamente veloce e assai meno sensibile alla natura del solvente della reazione in posizione 4. Pertanto anche in questo caso si osserva un effetto interpretabile in termini dei diversi requisiti di solvatazione nello stato di transizione delle reazioni nelle due posizioni. Il vistoso effetto del solvente sulla composizione del prodotto di reazione permette di sintetizzare uno qualsiasi dei due isomeri in base a una scelta sistematica delle condizioni sperimentali.