

### A KINETIC STUDY OF THE REACTION OF TRIOLS WITH HALOGEN HYDRACIDS IN NON-AQUEOUS MEDIA

KINETICS of the reaction of diols with halogen hydracids in pure acetic acid and binary mixtures of acetic acid and with some dipolar aprotic solvents has been reported earlier<sup>1,2</sup>. It was thought worthwhile to investigate the action of halogen hydracids on triols to follow the rate of the reaction for the 3 steps.

With this end in view, the substitution of 1, 2, 3-propanetriol with halogen hydracids has been investigated. The reactions of 1, 2, 3-propanetriol with HCl, HBr, HI (aq) have been studied at 80° C in glacial acetic acid and in binary mixtures of acetic acid with benzene, dimethyl formamide, acetonitrile and toluene.

The second order rate constants of the first step in the case of the three halogen hydracids at 80° C in pure acetic acid are given in Table I.

TABLE I

Temperature 80° C	10 × litre mole <sup>-1</sup> min <sup>-1</sup>
HCl	1.87
HBr	34.00
HI	45.02

The rate constants are reproducible to ± 1%. It is seen that the trend is quite in accordance with the nucleophilicity of the halide ions.

The second order rate constants (litre mole<sup>-1</sup> min<sup>-1</sup>) for the three steps of substitution of glycerol with HBr in 100% acetic acid are given in Table II.

TABLE II

K <sub>1</sub>	K <sub>2</sub>	K <sub>3</sub>
3.40	7.89	20.94

The rate constants are reproducible to ± 1%.

A plot of 1/a-x vs. t gave distinct straight lines and the values of K<sub>1</sub>, K<sub>2</sub>, K<sub>3</sub> have been calculated from the slopes of these lines.

The increasing rate suggests that the monobromo substituted product formed at the first step favour the formation of dibromo substituted product which in turn favour the formation of tribromo substituted product. This type of anchimeric assistance is observed in the cleavage of dicarboxylic esters with HBr in non-aqueous media earlier<sup>3</sup>.

The effect of variation of dielectric constant has also been studied, by investigating the reaction in

acetic acid-benzene, acetic acid-toluene, acetic acid-dimethyl formamide, acetic acid-acetonitrile mixtures. It is observed that the decrease of dielectric constant favours the reaction, an observation made in ester cleavages with HBr<sup>3</sup>. The second order rate constants (l.mole<sup>-1</sup> min<sup>-1</sup>) for the displacement in glycerol with HBr at 80° C at these mixtures are given in Table III.

In this investigation, the plot of log<sub>10</sub>K<sub>1</sub> vs. 1/D are all linear indicating the reactions to be positive ion-dipole type.

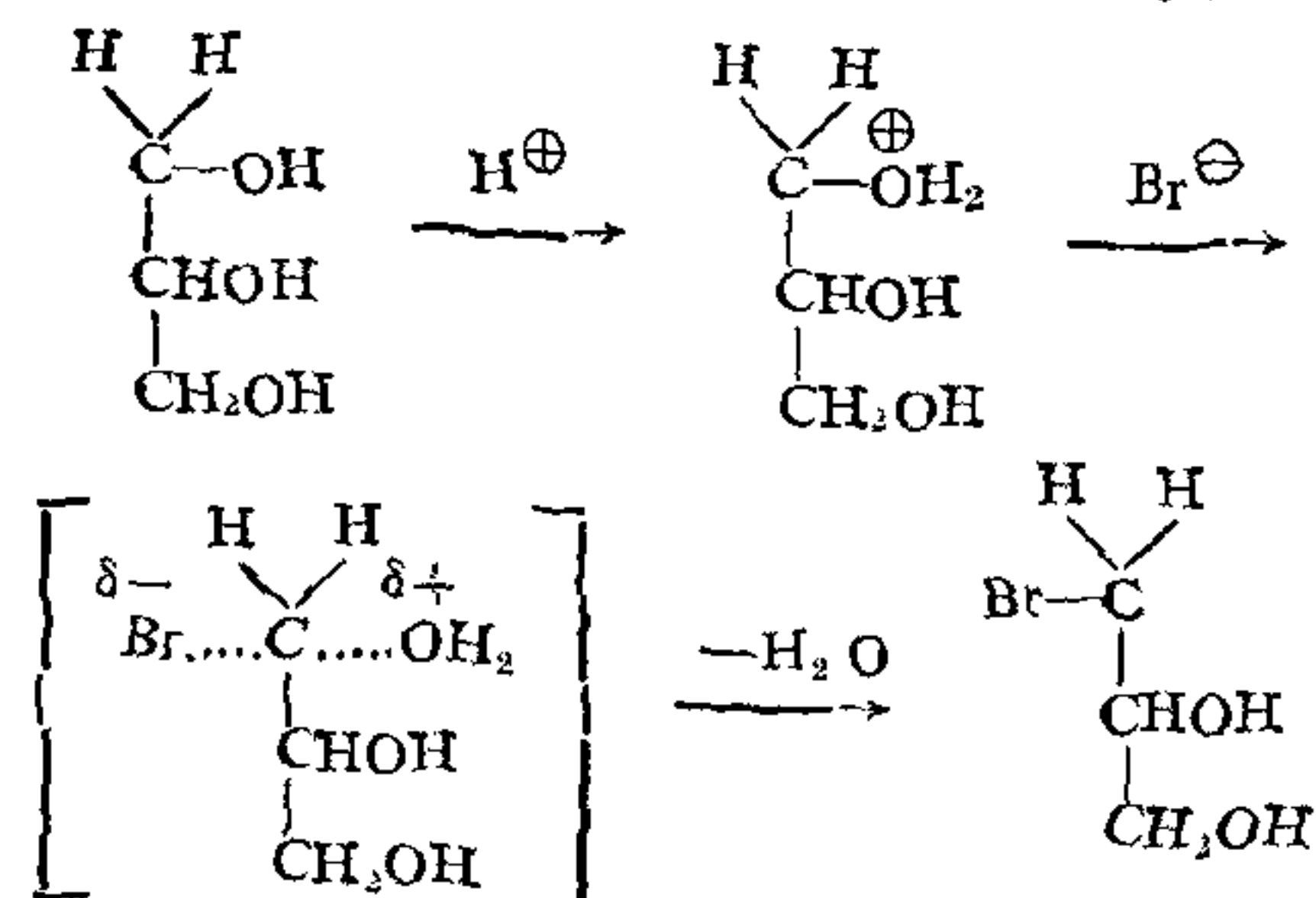
TABLE III  
(Temperature 80° C)

Solvent mixture (v/v)	Dielectric constant	K <sub>1</sub> l. mole <sup>-1</sup> min <sup>-1</sup>
100% HOAc	6.15	3.40
90% HOAc-10% C <sub>6</sub> H <sub>6</sub>	5.76	4.15
85% HOAc-15% C <sub>6</sub> H <sub>6</sub>	5.57	6.87
80% HOAc-20% C <sub>6</sub> H <sub>6</sub>	5.28	9.60
90% HOAc-10% C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	5.77	4.26
85% HOAc-15% C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	5.61	6.72
80% HOAc-20% C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	5.40	9.56
97.5% HOAc-2.5% DMF	7.06	0.286
95% HOAc-5% DMF	7.97	0.115
92.5% HOAc-7.5% DMF	8.87	0.076
95% HOAc-5% CH <sub>3</sub> CN	7.09	2.431
90% HOAc-10% CH <sub>3</sub> CN	8.02	1.709
85% HOAc-15% CH <sub>3</sub> CN	8.96	0.844

The rate constants are reproducible to ± 1%.

#### Mechanism

The reactions under investigation are SN<sub>2</sub> process bordering on SN<sub>1</sub> in as much as the rate determining step is the formation of a conjugate acid, at the hydroxylic oxygen, which tends to produce an incipient and transient carbonium ion. The transition state for the I step can be depicted as follows :



The rate has been studied for all the three halogen hydracids in pure HOAc at 60°, 70°, 80° C. The  $K_1$  values (litre mole<sup>-1</sup> min<sup>-1</sup>) are given in Table IV.

TABLE IV  
1, 2, 3-Propanetriol

Temperature	HCl	HBr	HI
60° C	0.3175	8.571	15.44
70° C	0.8121	17.18	26.27
80° C	1.872	34.08	45.02

The rate constants are reproducible to  $\pm 1\%$ .

The plot of  $\log_{10}K_1$  vs.  $1/T$  are all linear suggesting that the reactions are bimolecular.

The substrate was of imported quality. The halogen hydracids were azeotropic mixtures (with water) distilled just before use. The solvents were purified by the usual procedure and distilled before use. The kinetics has been followed by the usual Argentimetric procedure, *i.e.*, Volhards' method.

Authors' thanks are due to the Principal, Regional Engineering College, Tiruchirapalli, for providing facilities for the work.

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August 18, 1977.

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#### SYNTHESIS OF 7-CHLORO-2, 3-DIHYDRO-4 (IH)-QUINOLONE—AN IMPORTANT INTERMEDIATE IN THE SYNTHESIS OF CHLOROQUINE

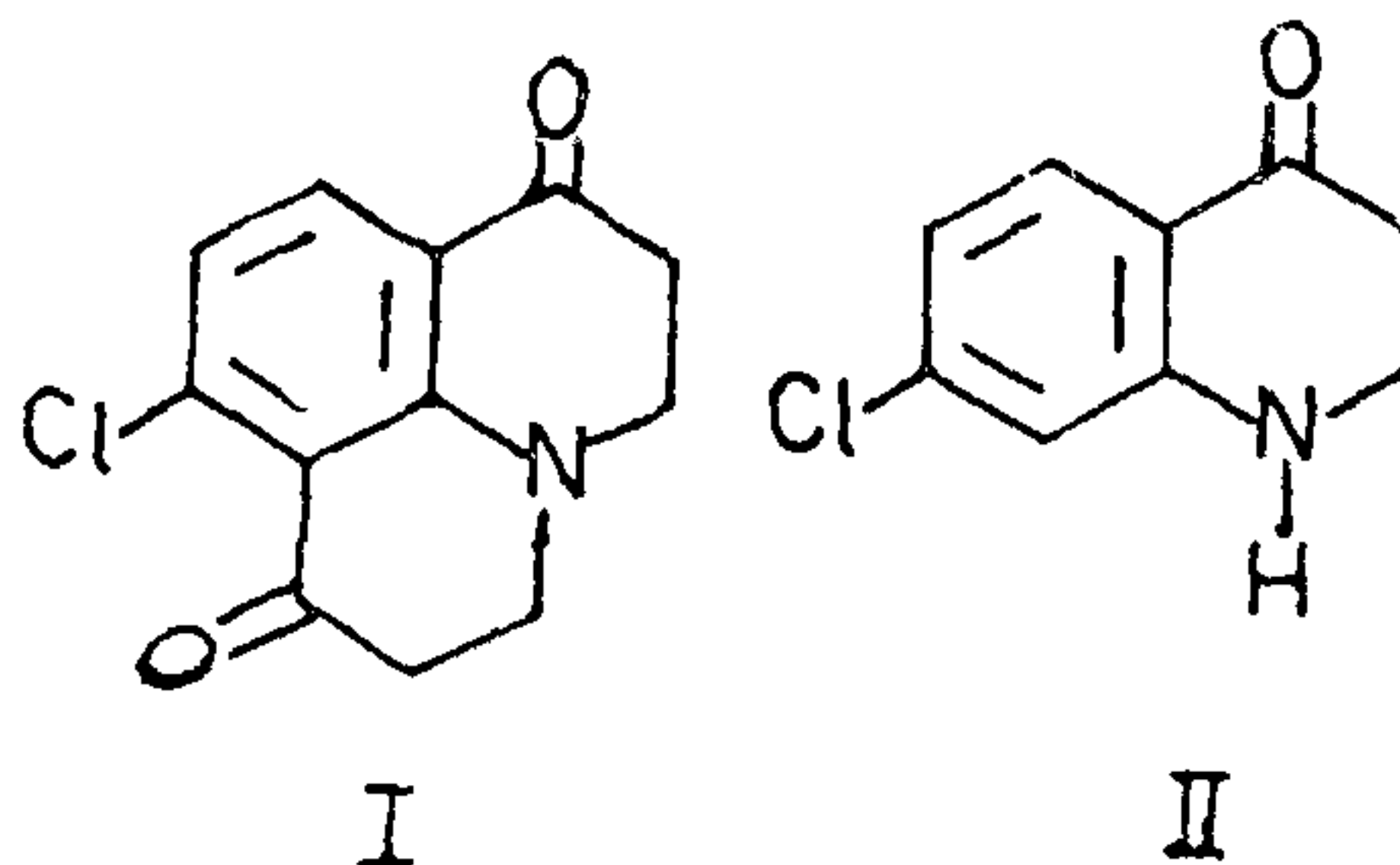
CHLOROQUINE is an important antimalarial and an antiamebic drug which has been synthesised by different workers<sup>1,2</sup>. However, the simplest method appears to be the one described by Johnson and Buell<sup>2</sup> who have synthesised it by the condensation of *m*-chloroaniline with methyl acrylate to yield methyl- $\beta$ -anilinopropionate. The tosyl derivative of the latter was hydrolysed to the corresponding propionic acid and then cyclised to yield *N*-tosyl-4-keto-7-chloro-1, 2, 3, 4-tetrahydroquinoline which on subsequent acid

hydrolysis afforded 7-chloro-2, 3-dihydro-4 (IH)-quinolone. The latter on reaction with 4-diethylamino-1-methylbutylamine gives chloroquine.

In an earlier publication<sup>3</sup> we have reported the formation of some 2, 3-dihydro-4 (IH) quinolones in a single step by reacting aniline derivatives with  $\alpha$ ,  $\beta$ -unsaturated acids in the presence of polyphosphoric acid (PPA). It was, therefore, of interest to see if 7-chloro-2, 3-dihydro-4 (IH) quinolone could be obtained in a single step by the reaction of *m*-chloroaniline (1 mole) with acrylic acid (1 mole) in the presence of PPA at 100° for 5 hr. However, the reaction afforded only a single crystalline compound (TLC), m.p. 164.5°, in 25% yield. Its m.p. as well as the analytical and spectral data indicated that it was different from the expected quinolone, though it formed a crystalline 2, 4-DNP. Its mass spectrum showed a large molecular ion peak at  $M^+$  235 and the UV of the compound showed  $\lambda_{\max}^{\text{MeOH}}$  at 230, 270, 300 and 410 nm whereas 2, 3-dihydro-4 (IH) quinolones generally showed  $\lambda_{\max}^{\text{MeOH}}$  at 235, 255 and 375 nm.

Further, in the IR (KBr) spectrum the -NH band was completely absent while other bands were obtained at 1660 ( $>C=O$ ), 1580, 1550, 1500 (ar)  $\text{cm}^{-1}$ . Its NMR ( $\text{CDCl}_3$ ) spectrum integrated for a total of ten protons including two aromatic protons appearing as an AB pattern at  $\delta$  6.5 and  $\delta$  7.6.

The above evidence is fully consistent with the structure 8-chloro-benzo (*i, j*) quinolizine-1, 7-dione (I) which was assigned to the reaction product.



7-Chloro-2, 3-dihydro-4 (IH) quinolone was, however, prepared by us by a simplified procedure as follows:

*m*-Chloroaniline was cyanoethylated by heating it with acrylonitrile and cupric acetate when  $\beta$ -(3-chloroanilino)-propionitrile was obtained as a crystalline solid in 60% yield<sup>4</sup>. This on alkaline hydrolysis yielded the corresponding propionic acid which was cyclodehydrated with PPA to give 7-chloro-2, 3-dihydro-4 (IH) quinolone (II) as a yellow crystalline solid in 50% yield. It was characterized by the