280. *ω-Halogenomethyl-pyridines, -quinolines, and* -isoquinolines. *Part IV.* The Mechanism of Halogenation of Quinaldines.*

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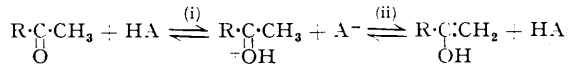
It is found that ωω-dibromoquinaldine in acetic acid containing sodium acetate is brominated at 30° to ωωω-tribromoquinaldine at a rate which is independent of the concentration of bromine and of acetate. The analogy between this phenomenon and the acid-catalysed halogenation of ketones is discussed and conclusions as to the mechanism are drawn.

Many reactions of α- and γ-methyl-pyridines and -quinolines are similar to the prototropic reactions of methyl ketones, *e.g.*, Claisen condensation in presence of a base (Wislicenus and Kleisinger, *Ber.*, 1909, **42**, 140; Bergstrom and Moffatt, *J. Amer. Chem. Soc.*, 1937, **59**, 1494), aldol condensation with an aldehyde in the presence of an acid (Jacobsen and Reimer, *Ber.*, 1883, **16**, 2606), and ready bromination of the methyl group in acetic acid in presence of sodium acetate (Koenigs, *Ber.*, 1898, **31**, 2364; Hammick, *J.*, 1923, **123**, 2882; Brown, Hammick, and Thewlis, Part I, *J.*, 1951, 1145). Mills and Smith (*J.*, 1922, 2724) have suggested that the methylene base (I) is an intermediate in these reactions, analogous to the

(I) (II)

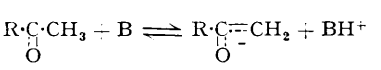
enol form (II) of a ketone. Kinetic investigations of the prototropic reactions of ketones (Bell, " Acid–Base Catalysis, Oxford Univ. Press, 1941, pp. 69, 135) have shown that two mechanisms are applicable :

(1) *Acid-catalysed.*



Further reaction

(2) *Base-catalysed.*



Further reaction

It appeared not improbable that α- and γ-methyl-pyridines and -quinolines might react by similar mechanisms, and the special example of bromination has been investigated kinetically under the preparative conditions, *viz.*, in acetic acid in presence of sodium acetate (Part I, *loc. cit.*).

Experimental

The rate of disappearance of bromine in acetic acid containing bromine, ωω-dibromoquinaldine, and sodium acetate was followed colorimetrically at λ 5200 Å by means of a Hilger–Nutting spectrophotometer. Preliminary experiments showed that the colour density–concentration variation is linear for bromine in acetic acid. The simple Beer's law relation could not, however, be used to ascertain bromine concentrations in the reaction mixtures because, when Br^- ions are produced, residual free bromine is progressively converted into Br_3^- ions; the extinction coefficient of Br_3^- at 5200 Å is less than that of the bromine molecule (Rurakayastha, *J. Indian Chem. Soc.*, 1929, **361**). A series of calibration curves was therefore constructed. Thus the optical density of an initial solution containing bromine $[Br_2]_0$ and sodium acetate $[OAc^-]_0$ was determined. A series of solutions was then made up containing progressively less bromine but with enough sodium bromide added to maintain the quantity $[Br_2] + [Br^-]$ equal to the initial bromine concentration $[Br_2]_0$. Sodium acetate was then added to make the total ionic strength in each solution equal to the original, *i.e.*, $[OAc^-]_0$. The conditions existing in a reaction run were thus duplicated. The optical densities were measured and plotted against bromine concentration giving a smooth curve. If there be present in the original bromine solution $[Br_2]_0$ an appropriate concentration of ωω-dibromoquinaldine, the rate of bromination of the latter can be followed by determinations of optical

* Part III, *J.*, 1952, 1186.

density and reference to the calibration curve, which will give the total concentration of free plus ionic bromine at time t. From the stoicheiometry of the reaction the amount of dibromoquinaldine that has been brominated is obtained.

Kinetic Measurements.—The reaction rates were measured at 30·0°. The initial concentration of each reactant was varied, the other two being constant and in excess. The variations in concentration were: bromine, 0·0175—0·0639M; dibromoquinaldine, 0·0050—0·0300M; anhydrous sodium acetate, 0·0050—0·100M. All reagents and the solvent were purified by normal procedures; control experiments were carried out which showed no appreciable interaction of bromine with solvent either alone or containing sodium acetate. The error in optical density measurement corresponded to an error in estimation of bromine of ±0·0002M. As explained above, the amount of ωω-dibromoquinaldine $(a - x)$ present at time t could be obtained from the optical density and the appropriate calibration curve; these values were substituted in the equation $k_{mono} = (1/t) . \ln a/(a - x)$. The unimolecular constant was sensibly the same in all cases. In Table 1 we give the results obtained in a typical run. In Table 2 the results of all our experiments are summarised.

TABLE 1. *Initial concs. : dibromoquinaldine,* 0·0100M; *sodium acetate,* 0·0200M.

t (sec.)	Br (mole/l.)	x	$(a - x)$	10^4k (sec.$^{-1}$)	t (sec.)	Br (mole/l.)	x	$(a - x)$	10^4k (sec.$^{-1}$)
0	0·0433	—	—	—	3,900	0·0384	0·0049	0·0051	1·75
300	0·0428	0·0005	0·0095	1·70	4,500	0·0380	0·0053	0·0047	1·70
600	0·0423	0·0010	0·0090	1·70	5,100	0·0373	0·0060	0·0040	1·80
900	0·0419	0·0014	0·0086	1·70	6,000	0·0367	0·0066	0·0034	1·80
1200	0·0415	0·0018	0·0082	1·65	6,900	0·0363	0·0070	0·0030	1·75
1500	0·0413	0·0020	0·0080	1·50	7,800	0·0356	0·0077	0·0023	1·90
2100	0·0405	0·0028	0·0072	1·60	8,700	0·0352	0·0081	0·0019	1·90
2700	0·0400	0·0033	0·0067	1·50	10,500	0·0349	0·0084	0·0016	1·75
3300	0·0391	0·0042	0·0058	1·65					

$k = 1·70 \times 10^{-4}$ sec.$^{-1}$

TABLE 2.

Variation of initial bromine concentration.

Initial concns. : sodium acetate, 0·070M; dibromoquinaldine, 0·070M.

Initial Br concn. (mole/l.)	0·0175	0·0331	0·0433	0·0545	0·0639
10^4k (sec.$^{-1}$)	1·90	1·70	1·80	1·80	1·80

Variation of initial dibromoquinaldine concentration.

Initial concns. : sodium acetate, 0·020M; bromine, 0·0433M.

Initial dibromoquinaldine concn. (mole/l.)	0·0050	0·0100	0·0200	0·0300
10^4k (sec.$^{-1}$)	1·60	1·70	1·55	1·70

Variation of initial sodium acetate concentration.

Initial concns. : bromine, 0·0433M; dibromoquinaldine, 0·020M.

$[NaOAc]_0$ (mole/l.)	0·0050	0·0100	0·0200	0·0400	0·0600	0·100
10^4k (sec.$^{-1}$)	1·80	1·80	1·55	1·70	1·80	1·70

ωω-*Dibromo*-8-*nitroquinaldine* (Hammick, *J.*, 1926, 1302).—The compound separated from ethanol as pale yellow needles, m. p. 184°.

ωω-*Dibromo*-5-*nitroquinaldine*.—5-Nitroquinaldine (Gerdiessen, *Ber.*, 1889, **22**, 245) (6·0 g.) and anhydrous sodium acetate (20 g.) were dissolved in glacial acetic acid (30 ml.), and bromine (3·25 g.) in acetic acid (25 ml.) was added with stirring, the temperature not being allowed to rise above 70°. Towards the end of the reaction yellow ωω-*dibromo*-5-*nitroquinaldine* separated. The mixture was cooled and the dibromonitro-compound (5·0 g.) separated. Three recrystallisations from ethanol yielded pale yellow needles, m. p. 161° (Found: C, 34·7; H, 1·6; N, 7·8; Br, 46·9. $C_{10}H_6O_2N_2Br_2$ requires C, 34·7; H, 1·7; N, 8·0; Br, 46·2%).

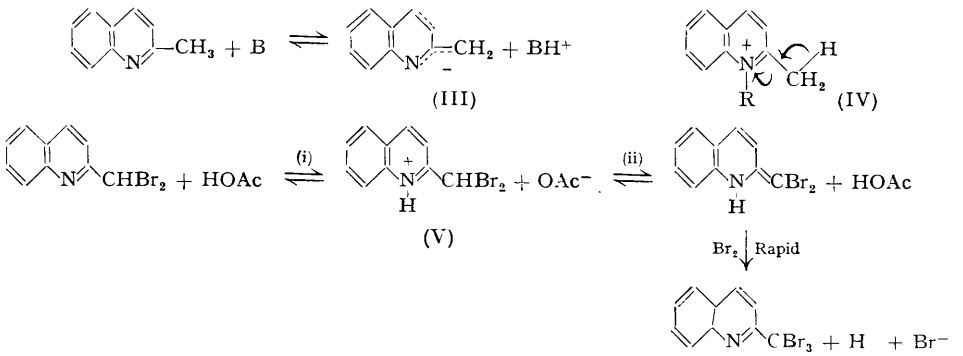
The rate constants for the bromination of these two dibromonitroquinaldines were determined at 30·0° as for dibromoquinaldine itself. Mean values were: ωω-dibromo-8-nitroquinaldine, $8·0 \times 10^{-4}$ sec.$^{-1}$; ωω-dibromo-5-nitroquinaldine, $0·40 \times 10^{-4}$ sec.$^{-1}$

DISCUSSION

The rate of bromination of ωω-dibromoquinaldine in acetic acid in presence of sodium acetate is independent of the bromine concentration (Table 2). This is exactly analogous to the acid- or base-catalysed bromination of ketones and indicates that the rate-

determining step is probably a catalysed prototropic change followed by rapid bromination of the intermediate. Also the rate is independent of the concentration of acetate ion (Table 2). The reaction does not therefore involve a rate-determining base-catalysed prototropic change of the dibromoquinaldine molecule as was previously thought (Part I, *loc. cit.*).

In the light of other reactions of the α- and γ-methylquinolines this result appears less surprising, since the majority of the base-catalysed reactions, *e.g.*, the Claisen condensation (Wislicenus and Klesinger, Bergstrom and Reimer, *locc. cit.*), require much stronger bases than the acetate ion to produce the intermediate mesomeric ion (III). Also, the aldol condensation with aldehydes does not occur with basic catalysts (Mills and Roper, *J.*, 1925, 2466). On the other hand, in the quaternary salts (IV) the nitrogen atom carries a fixed positive charge which should facilitate the release of a proton from the α-carbon atom. Thus quinaldine condenses with benzaldehyde in the presence of acids (Jacobsen and Reimer, *loc. cit.*), and quinaldine ethiodide condenses with benzaldehyde in the presence of piperidine whereas quinaldine itself does not (Mills and Roper, *loc. cit.*). Furthermore, ω-bromination of lepidine has not proved possible, but its methiodide is smoothly brominated in aqueous sodium acetate (Part I, *loc. cit.*).



Since ωω-dibromoquinaldine must exist mainly as the quaternary salt (V) in excess of glacial acetic acid, its bromination is interpreted as an acid-catalysed prototropic change followed by rapid bromination of the intermediate methylene base, a process entirely analogous to the acid-catalysed bromination of ketones. The function of the sodium acetate is thus to remove hydrogen bromide, which, in the absence of acetate, causes a reduction in the rate of bromination by the removal of the reactant dibromoquinaldine as its insoluble hydrobromide. In the analogous reaction with ketones [(1), p. 1369] Zucker and Hammett (*J. Amer. Chem. Soc.*, 1939, **61**, 2785) have obtained evidence that step (ii) is rate-determining, since the rate constants are independent of the basic strengths of a series of ketones. Thus, as Zucker and Hammett (*loc. cit.*) point out, the rate-determining step of this acid-catalysed mechanism is one in which a base removes a proton from a point remote from the basic centre. A similar effect may occur with the quinaldines, since, as was inferred in Part I (*loc. cit.*), the progressive ω-substitution of halogen atoms, which decreases the basic strength, increases the rate of substitution. This is readily explained if the rate-determining step is the removal of a proton by a base from the α-carbon atom.

The rates of reaction of ωω-dibromoquinaldine and of its 5- and 8-nitro-derivatives with bromine in acetic acid in presence of sodium acetate are in the predicted order of proton release from the α-carbon atom, but since the basic strengths of these compounds are unknown, it cannot be said that this represents unequivocal evidence for the rate-determining step of the bromination.

It has not been possible to investigate the catalytic effect of strong acids in acetic acid since their addition results in precipitation of the reactant as an insoluble acid salt. Acetic acid was chosen as solvent since it is itself not attacked by bromine under the experimental conditions; it was moreover desirable to investigate the reaction under the preparative

conditions. It is not possible to investigate the reaction in water because in that solvent the salts of dibromoquinaldine are partly hydrolysed with precipitation of the base. However, the investigation of a suitable soluble quaternary salt in water should reveal a reaction which shows general basic catalysis.

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