Dyes and Pigments 3 (1982) 173–182

THE EFFECT OF 5-SUBSTITUENTS ON THE REACTIVITY OF 2-CHLORO- AND 2-HYDROXY-PYRIMIDINES

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(Received: 16 November, 1981)

SUMMARY

A range of 5-substituted 2-chloropyrimidines has been hydrolysed and the rate constants are shown to vary systematically with para *σ-values. Dissociation constants of the corresponding 2-hydroxypyrimidines, however, vary with* meta *σ-values, confirming tautomerism to 1,2-dihydro-2-oxopyrimidines. There is evidence for slow hydrolysis at the 5-position in 5-substituted 2-chloropyrimidines.*

1. INTRODUCTION

It is well known that chlorinated heterocyclic reactive dyes can show a wide range of reactivity within any one reactive class. This is clearly due to the different chromogens and other groups substituted into the heterocyclic ring exerting different substituent effects on the replaceable chlorine atoms. The general observation is that base-strengthening substituents depress and acid-strengthening substituents enhance the reactivity of the chlorines as would be expected.[1]

It was thought to be of interest to study these effects in a simple series of compounds bearing substituents whose influence on reactivity in aromatic systems (especially benzene) was well established. This would enable the effects of the different substituents to be compared in terms of the Hammett σ constants and also allow a comparison of reactivity in a heterocyclic system with that in benzene by means of the ρ constants.[2]

The compounds (**I**) shown were investigated. The pyrimidine system was chosen because substituents in the 5-position are completely symmetrically placed relative to the ring nitrogens and the 2-position which is the one involved in the combination of chloropyrimidyl reactive dyes with cellulose.

The rates of hydrolysis of the variously substituted 2-chloropyrimidines, followed by the dissociation constants of the corresponding 2-hydroxypyrimidines, were

Dyes and Pigments 0143-7208/82/0003-0173/$02·75 © Applied Science Publishers Ltd, England, 1982
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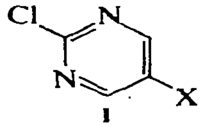


I

$X = -NO_2, -Cl, -Br, -H, -CH_3, -OC_2H_5, -NH_2$

measured. The latter measurements also enabled a check to be made on the existence of 2-hydroxypyrimidines as the tautomeric 1,2-dihydro-2-oxopyrimidines.[3]

2. EXPERIMENTAL

2.1. Synthesis

2-Hydroxy-5-nitropyrimidine and 2-chloro-5-nitropyrimidine: Sodium nitromalonic aldehyde (produced from mucrobromic acid by the action of sodium nitrite[4]) was reacted with guanidine carbonate using piperidine as catalyst to yield 2-amino-5-nitropyrimidine.[5] This in turn was hydrolysed to 2-hydroxy-5-nitropyrimidine by heating for 3 h at 70°C with 0·5 M sodium hydroxide in 85 % aqueous ethanol. Impurities were removed by filtering hot and the 2-hydroxy compound recovered from the filtrate as the sodium salt. It was converted to the acid form (m.p. 203–205 °C) as required by treatment of a solution with a cation exchange resin (Zeo Karb–225). The 2-chloro derivative (m.p. 110–111 °C) was obtained in the usual way by treatment with phosphorus oxychloride.[6]

2-Chloro-5-aminopyrimidine: This was prepared from 2-chloro-5-nitropyrimidine by reduction using iron dust and dilute acetic acid.[6] It had m.p. 185–190 °C.

2-Chloro-5-ethoxypyrimidine: This was prepared from 2-ethylmercapto-5-ethoxy-6-hydroxypyrimidine[7] by hydrolysis to the 2-hydroxy compound using dilute chloroacetic acid followed by chlorination to 2,6-dichloro-5-ethoxypyrimidine with phosphorus oxychloride. Finally, the 6-chloro substituent was removed by reduction using zinc in 50 % ethanol and recrystallisation from dilute ethanol, to give 2-chloro-5-ethoxypyrimidine, m.p. 70 °C.[8] 2-Hydroxy-5-ethoxypyrimidine was prepared from this by hydrolysis in 0·5 M sodium hydroxide for 6 weeks at 60 °C and extracted from the neutralised solution by means of ethyl acetate. Crystallisation from ethyl acetate yielded long needles having m.p. 145–146 °C. Found (%): C, 51·4; H, 5·7; N, 19·7 Calc. for $C_6H_8N_2O_2$: C, 51·42; H, 5·71; N, 20·0.

2-Chloro-5-methylpyrimidine: Thymine was converted to 2,6-dichloro-5-methylpyrimidine by treatment with phosphorus oxychloride.[9] An attempt to remove the 6-chloro substituent by the method of Gerngross[10] was unsuccessful but the required 2-chloro-5-methylpyrimidine, m.p. 96–94 °C (petroleum ether), was finally obtained by refluxing the 2,6-dichloro compound with zinc dust and water for 3 h and extracting with ether. Found (%): N, 27·7. Calc. for $C_5H_5N_2Cl$: N, 27·79. Hydrolysis of 2-chloro-5-methylpyrimidine for 2 weeks at 40 °C in 0·4 M sodium hydroxide yielded the 2-hydroxy derivative which was extracted into ethyl acetate and recrystallised from ethanol. M.p. 212–214°C. Found (%): C, 54·2; H, 5·6; N, 25·2. Calc. for $C_5H_6N_2O$: C, 54·45; H, 5·45; N, 25·45.

2-Chloro-pyrimidine and 2-hydroxypyrimidine: These were prepared from 2-aminopyrimidine. Diazotisation using excess of hydrochloric acid followed by neutralisation with ammonia gas leads to a mixed precipitate of the 2-chloro compound and ammonium chloride,[11] from which 2-chloropyrimidine, m.p. 63·4–64·4 °C, can be extracted with benzene and purified from petroleum ether. Hydrolysis under reflux with 0·5 sodium hydroxide for 6 h yielded 2-hydroxypyrimidine, which was extracted from the neutralised solution and then crystallised using ethyl acetate. The 2-hydroxy compound was also prepared by hydrolysing 2-aminopyrimidine[12] in 10 M sodium hydroxide. 2-Hydroxypyrimidine exists in two forms having m.p. 160 °C and 180 °C.[13] The low melting form was first obtained but on seeding with crystals of high melting point (supplied by D. J. Brown) the high-melting form was obtained then and in all subsequent preparations, even without seeding.

2-Hydroxy-5-chloropyrimidine and 2,5-dichloropyrimidine: These were both prepared from 2-aminopyrimidine. Direct chlorination in water at 70–80 °C gave 2-amino-5-chloropyrimidine. This in turn was diazotised in 30 % sulphuric acid solution and the diazo compound decomposed by heating and treatment with ammonia yielding the ammonium salt of 2-hydroxypyrimidine.[14] It was purified (m.p. 237 °C) by dissolving in water and precipitating by adding acetic acid. It was converted to 2,5-dichloropyrimidine in the usual way by refluxing with phosphorus oxychloride;[14] 2,5-dichloropyrimidine, m.p. 57 °C, was recovered from the neutralised reaction mixture by steam distillation.

2-Hydroxy-5-bromopyrimidine and 2-chloro-5-bromopyrimidine: These compounds were also prepared from 2-aminopyrimidine in the same way as the 5-chloro derivatives except that in the conversion of 2-hydroxy to 2-chloro-5-bromopyrimidine a small amount of *N,N*-diethylaniline was used as catalyst. 2-hydroxy-5-bromopyrimidine had m.p. 241–243 °C[15] and 2-chloro-5-bromopyrimidine had m.p. 78–79 °C. Found (%): C, 25·0; H, 0·90; N, 14·2; Hal 58·97. Calc. for $C_4H_2N_2ClBr$: C, 24·8; H, 1·03; N, 14·47; Hal, 59·68.

2.2. *Measurement of rate of hydrolysis*

Hydrolyses of the 2-chloro compounds were carried out in a 20 % dioxan–water mixture at 40 °C. The concentration of chloropyrimidine was 2×10^{-3} M whilst the concentration of sodium hydroxide was varied between 5×10^{-2} M and 1·6 M. The reactions were followed by removing aliquots into a slight excess of nitric acid, to quench the hydrolysis, followed by electrometric titration of the liberated chloride against 1×10^{-2} M silver nitrate. In all cases (apart from the 5-nitro derivative, which reacted too rapidly to be measured) plots of log ([unreacted chloropyrimidine]) against time were linear, yielding first-order rate constants (k_1) in the usual way and hence second-order constants ($k_2 = k_1/[\text{NaOH}]$). At least five determinations (at different concentrations of sodium hydroxide) were made for each compound, each reaction being followed up to 70% completion.

2.3. *Dissociation constants*

Solutions of the 2-hydroxypyrimidines (*ca.* 0·01 M in water) were titrated against sodium hydroxide (0·01 M) in the normal way using a glass indicating electrode. Even for the most weakly acidic compounds it was possible to locate the end-point on the titration curve. The pH at half neutralisation was taken as pK_A.

3. RESULTS AND DISCUSSION

3.1. *Rates of hydrolysis*

Typical first-order log plots are shown in Fig. 1, and Table 1 gives the derived second-order rate constants for all the compounds other than 2-chloro-5-nitropyrimidine, which was completely hydrolysed within the analysis time (0·5 min) even in the most dilute alkali. The rate constants cover a wide range of values and are in the order expected for a nucleophilic reaction. Figure 2 shows the values of $\log k_2$ plotted against the Hammett substituent constants (σ) for *para* substituents. The point for the 5-nitro compound is the theoretical point using the normal σ value of + 0·78.

The experimental points are a good fit to a straight line, indicating clearly that the substituents are exerting exactly the same electronic influences on the 2-chlorine as would be the case in benzene. The point for the nitro derivative indicates a value for k_2 of 263 litre min^{-1} mol^{-1} which corresponds to a time of half reaction of about 3 s at the lowest concentration of sodium hydroxide and explains our inability to follow this particular hydrolysis. The slope of the line in Fig. 2 gives the reaction constant (ρ), which is found to be +5·25. This value is much higher than is found for similar reactions of substituted chlorobenzenes (for the reaction of *p*-substituted 2-nitro- and 2,6-dinitro-chlorobenzenes with methoxide ion +3·9 and 4·3 respectively[16]), showing the pronounced effect of the heterocyclic nitrogens in polarising the π electrons and thus enhancing the relative effects of the substituent.

TABLE 1
SECOND-ORDER RATE CONSTANTS

5-substituent	$k \times 10^3$ (*litre mol^{-1} min^{-1}*)
$-NH_2$	0·035
$-OC_2H_5$	0·047
$-CH_3$	1·870
—H	20·76
—Cl	207·00
—Br	277·00

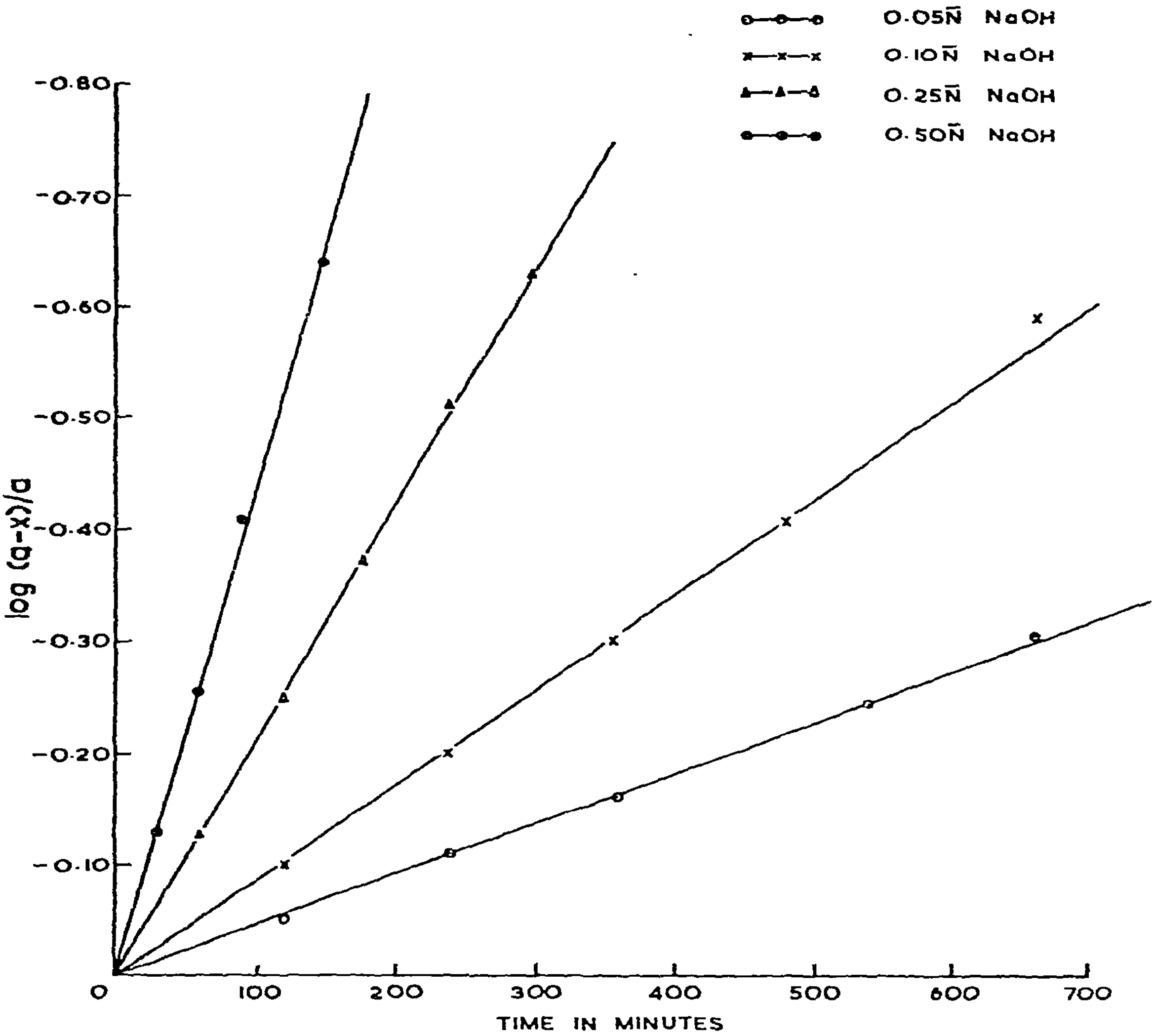


Fig. 1. Typical first-order plots. Reactions of 2-chloropyrimidine.

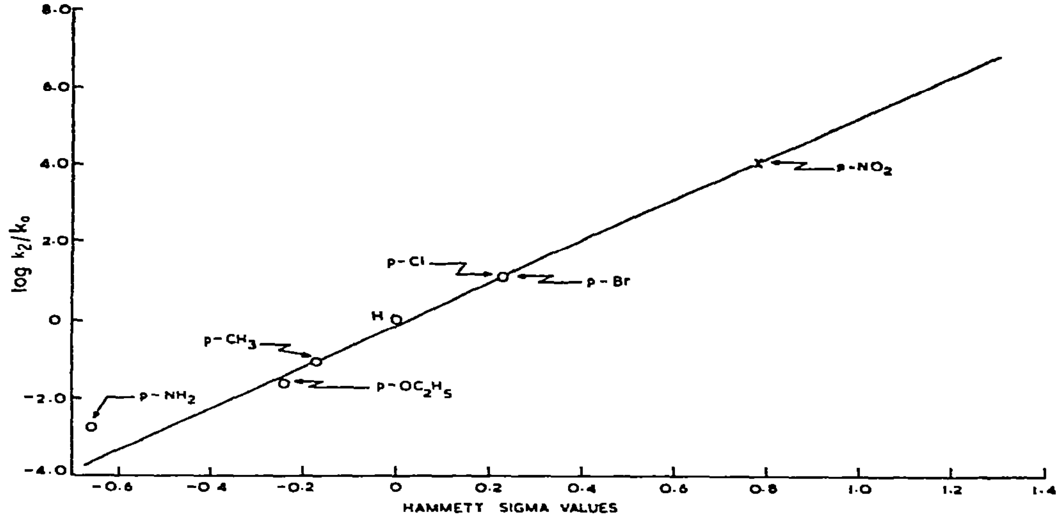


Fig. 2. Plot of log k_2/k_0 against Hammett σ-values. ×, theoretically expected point for the nitro compound.

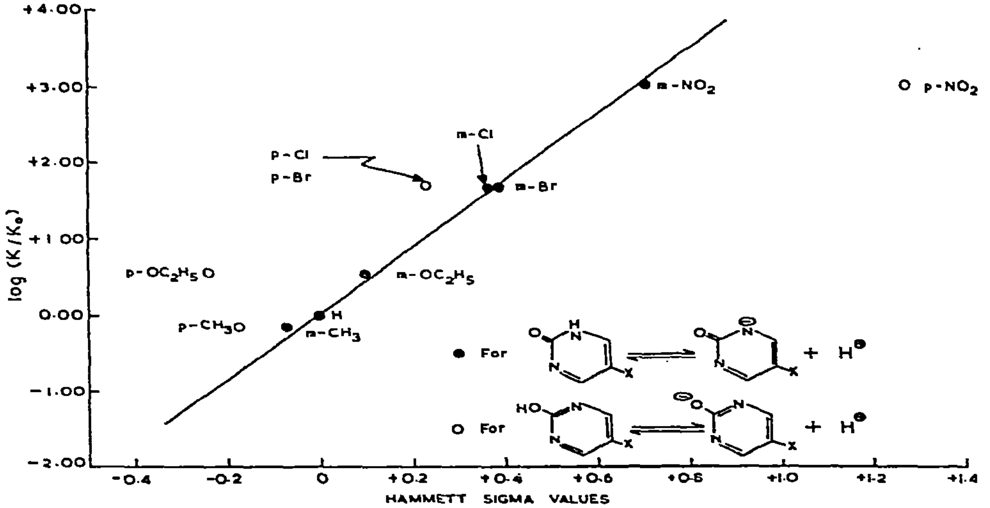
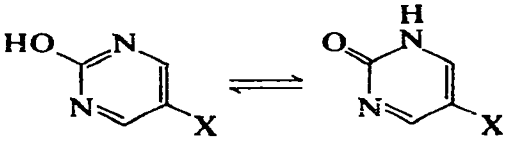


Fig. 3. Plot of the ionisation constants of 2-hydroxypyrimidines against Hammett σ-values.

3.2. Dissociation constants

The values of pK_A are given in Table 2, ranging from 6·0 for the nitro derivative to 9·35 for methyl. 2-Hydroxypyrimidines tautomerise to the corresponding oxo forms (II) and p.m.r. measurements for a number of naturally occurring 2- and 4-hydroxypyrimidines indicate that the equilibrium is almost exclusively in favour of the oxo form.[3]



II

The values in Table 2 are in the expected range for ionisation of HN rather than an activated phenolic —OH (e.g. picric acid has pK_A 0·38) and the supposition that the compounds exist virtually entirely in the oxo form is supported by the plot of pK_A versus σ in Fig. 3, which shows a good linear relationship for *meta* σ-values (oxo form) but not for *para* σ-values. The value for ρ is again high at +4·5.

TABLE 2
VALUES OF pK_a

5-substituent	pK_a
—OC_2H_5	8·50
—CH_3	9·35
—H	9·05
—Cl	7·35
—Br	7·35
—NO_2	6·00

3.3. Absorption spectra

The spectra of all the fully hydrolysed solutions from the kinetic runs were measured and compared with those of solutions of the authentic 2-hydroxy compounds. Good agreement was observed except for a slightly increased absorption of the hydrolysed solutions in the 270–280 nm region. Figure 4 gives the spectra for the 5-bromo compound and shows that the increased absorption is enhanced with increasing concentration of sodium hydroxide in the hydrolysing solution. Two possible reasons for this behaviour may be put forward; either 2-hydroxy-5-bromopyrimidine decomposes slowly in sodium hydroxide, presumably to yield 2,5-dihydroxypyrimidine, or alternatively 2-chloro-5-bromopyrimidine is slowly hydrolysed to 2-chloro-5-hydroxypyrimidine which then hydrolyses to 2,5-dihydroxypyrimidine.

The first alternative was quickly disproved by treating authentic 2-hydroxy-5-bromopyrimidine with sodium hydroxide solutions under the conditions used for

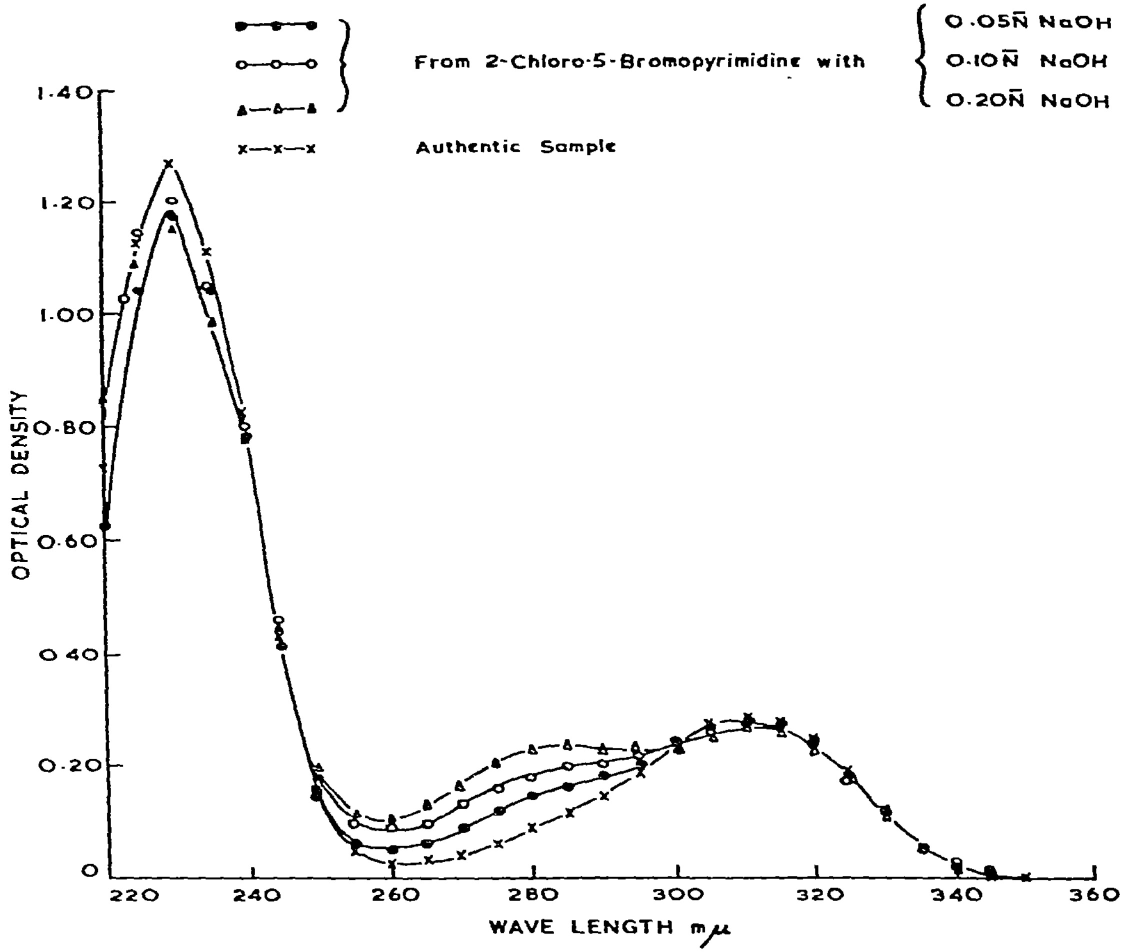


Fig. 4. Ultraviolet spectra of 2-hydroxy-5-bromopyrimidine.

the hydrolysis experiments. No change was observed even after several hours and no bromide ions could be detected. However, it has been reported that 5-bromouracil (5-bromo-2,4-dihydroxypyrimidine) is hydrolysed to 2,4,5-trihydroxypyrimidine in sodium bicarbonate, but not in sodium carbonate or sodium hydroxide.[17] 2-Hydroxy-5-bromopyrimidine was therefore refluxed with 0·1 M sodium bicarbonate solution for 12 h and showed the same increased absorption at 270–280 nm (see Fig. 5). At the same time branched ions could be detected in the solution as could development of phenolic —OH reactivity (colour with ferric chloride). Presumably in sodium bicarbonate solution 2-hydroxy-5-bromopyrimidine remains largely unionised (pK_A 7·35; Table 2) but is fully ionised in sodium hydroxide

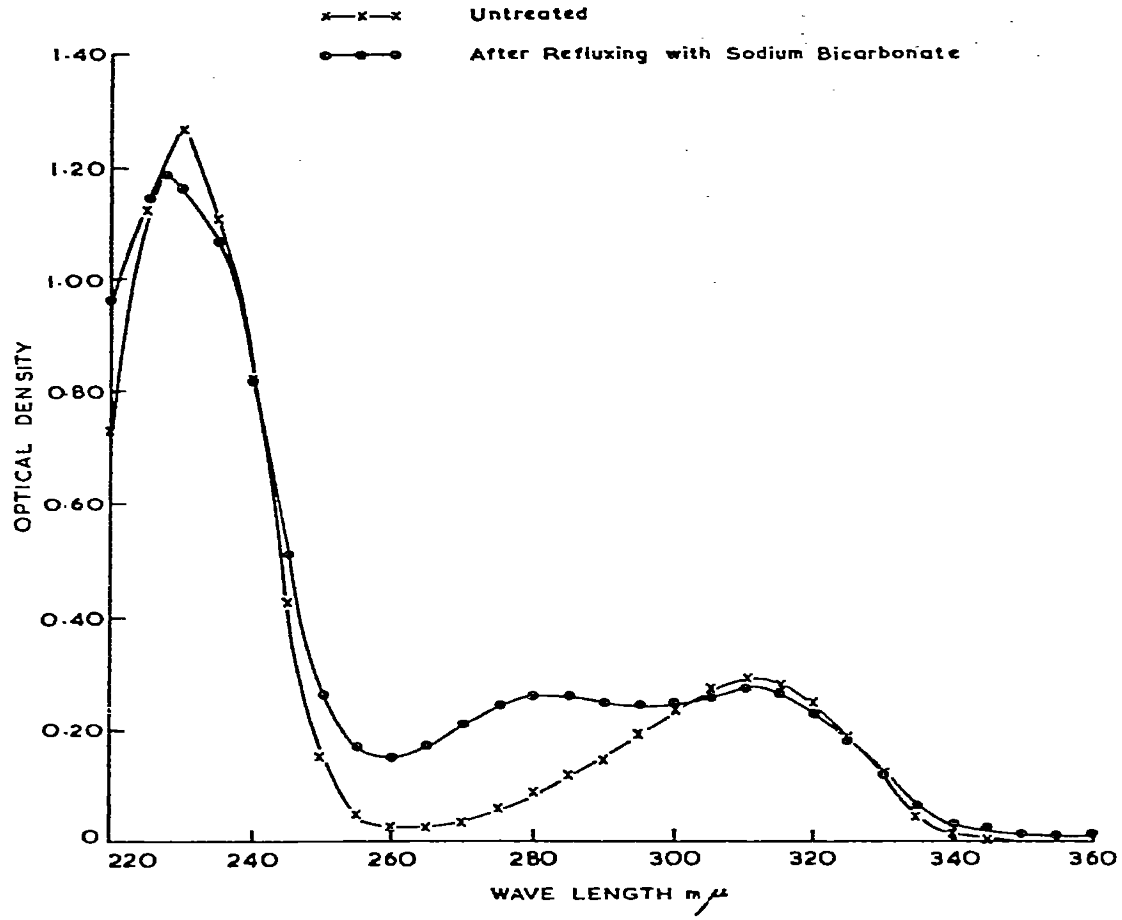


Fig. 5. Ultraviolet spectra of 2-hydroxy-5-bromopyrimidine.

so that the 5-position is strongly deactivated against hydrolysis with hydroxide ion. In 2-chloro-5-bromopyrimidine no such deactivation occurs and slow hydrolysis at the 5-position is possible. The spectra in Fig. 4 show that this hydrolysis is only slight and not sufficient to have any significant effect in the kinetic experiments.

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