The Mechanism of Bromination of Pyrimidin-2(1*H*)-one, its *N*-Methyl and *NN'*-Dimethyl Derivatives

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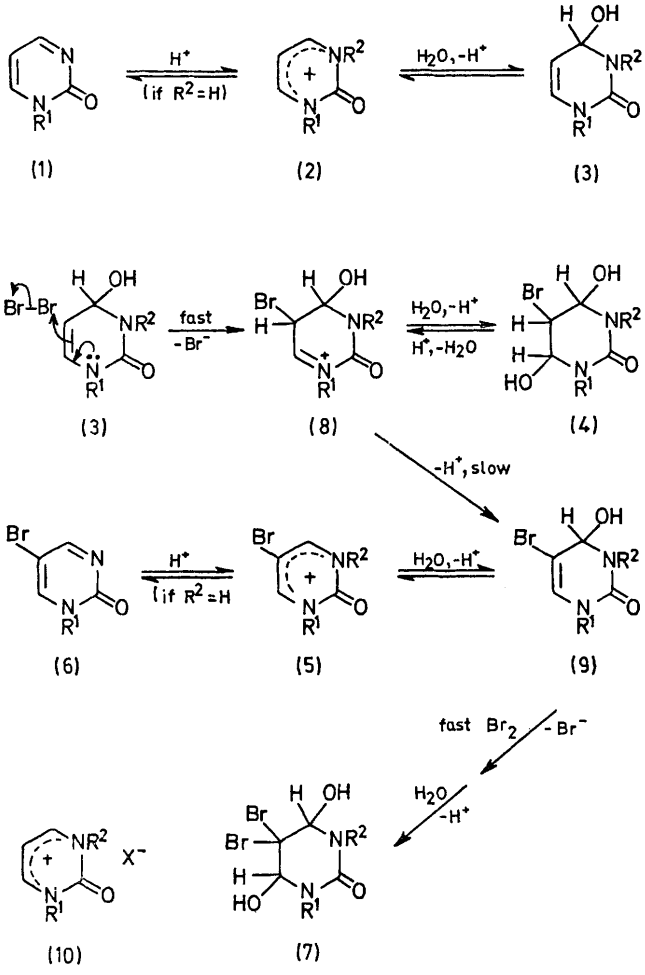
Summary Bromination at the 5-position of the title compounds in aqueous sulphuric acid solutions involves rapid formation of an addition compound which undergoes slow acid-catalysed elimination to form the substitution product, which in turn may react further with an excess of bromine.

KATRITZKY *et al.*[1] studied deuteriation at the 5-position of pyrimidin-2(1*H*)-one (**1**; R = H) and of its 1-methyl (**1**; R^1 = Me) and 1,3-dimethyl (**2**; $R^1 = R^2$ = Me) derivative in acidic D_2O solutions. It was concluded[1] that these exchanges occur *via* the covalent hydrates (**3**; $R^1 = R^2$ = H) and (**3**; $R^1 = R^2$ = H) and the pseudo-base (**3**; $R^1 = R^2$ = Me), respectively. On the other hand, nitration of these derivatives[2] in strong acid appears to occur by conventional mechanisms, the cation (**2**; $R^1 = R^2$ = Me) being unreactive.



In aqueous solution at room temperature the compounds (**1**; R^1 = H), (**1**; R^1 = Me), and the cation (**2**; $R^1 = R^2$ = Me) (as the chloride or hydrogen sulphate) react rapidly with 1 mol. equiv. of bromine to give, after work-up, the 5-bromo-derivatives: (**6**; R^1 = H), (**6**; R^1 = Me), and (**5**; $R^1 = R^2$ = Me) (as the bromide).† The u.v. spectrum of an aqueous acid solution of the cation (**2**; $R^1 = R^2$ = Me) has λ_{max} 316 nm (log ϵ 3·93), whereas that of the 5-bromo-cation (**5**; $R^1 = R^2$ = Me) has λ_{max} 222 and 346 nm (log ϵ 4·10 and 3·85). The solution obtained from mixing equimolar quantities of solutions of (**2**; $R^1 = R^2$ = Me) and bromine had no significant u.v. absorption above 220nm. However, upon the addition of acid, absorptions appropriate to the 5-bromo-cation (**5**; $R^1 = R^2$ = Me) appeared. The rate of this appearance was measured spectrophotometrically and first-order kinetics were observed at fixed acid concentrations. The measured rates were independent of bromine concentration but dependent upon acid concentration. Similar behaviour and rates were observed for (**2**; $R^1 = R^2$ = H) and (**2**; R^1 = H, R^2 = Me). The data shown in the Table emphasise the similarity in rate and the acidity dependence.

In explanation we suggest the mechanism set out in the Scheme. This involves fast irreversible attack by bromine upon the covalent hydrate (or pseudobase) (**3**) to give the ion (**8**) which rapidly reacts with water to produce an addition compound (**4**). The latter derivative (**4**) then undergoes slow acid-catalysed dehydration (*via* **8**) to form the 5-bromo-product (**5**) [or (**6**), if R^2 = H]. Our identification of the slow step as the deprotonation (**8**) → (**9**) is supported by the slower rate of reaction of 5-deuterio-(**2**; $R^1 = R^2$ = Me) from which we obtain k_H/k_D = 6. There are precedents for compounds of the type (**4**). Barbieri *et al.* have isolated derivatives similar to (**4**) from the bromination of some 2-sulphonamidopyrimidines.[3] Thymine undergoes addition of "HOBr" across the 5,6-double-bond,[4] and similar intermediates have been postulated for the bromination of uracils.[4] Our attempts to isolate and characterise compounds (**4**) have so far been unsuccessful. We obtain white labile materials which are readily transformed to the 5-bromo-products (**5**) or (**6**).

Variation of the rate of appearance of product with acidity for (**10**)

R^1 R^2 X	$[H_2SO_4]$ (N)	$[H_3O^+]$[a] (M)	$k_{obs} \times 10^4$ (min^{-1})
H H Cl	0·5	0·261	1·88
	0·6	0·311	2·19
	0·8	0·411	3·19
	1·0	0·511	4·11
Me H Cl	0·5	0·261	6·10
	0·7	0·361	7·95
	0·8	0·411	9·50
	1·0	0·511	12·0
Me Me HSO_4	0·5	0·261	28·3
	0·6	0·311	34·1
	0·86	0·411	53·3
	1·00	0·511	63·8

[a] Calculated from the normality assuming the second dissociation constant of H_2SO_4 is $K_2 = 1·2 \times 10^{-2}$ (ref. 5).

It is well known that uracils, cytosine, and isocytosine give 5,5-dihalogeno-6-hydroxy-derivatives in the presence of an excess of halogen.[4] We observe that the 5-bromo-derivatives (**5**) and (**6**) themselves react with bromine to produce materials with no u.v. absorption above 220 nm. These we believe to be (**7**), and for (**7**; $R^1 = R^2$ = Me) we have obtained spectra and an elemental analysis consistent with this structure.

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† This new derivative gave satisfactory elemental analysis and spectra.

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