1,3-DISUBSTITUTED-1,2-DIHYDRO-2-OXO-PYRIMIDINIUM CATIONS

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ABSTRACT

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1,3-DISUBSTITUTED-1,2-DIHYDRO-2-OXO-PYRIMIDINIUM CATIONS

Quaternary salts of pyrimidine compounds are normally made by alkylation of their parent bases. However, there are limitations to this type of synthesis, in that quaternary salts having a variety of N-substituents are difficult to obtain, because of the suitability of only a few alkylating agents.

It was found, however, that 1,3-dimethyl-2-oxo-pyrimidine quaternary salts could easily be synthesised by direct cyclisation.[5,13] Thus for this thesis various 1,3-dialkyl(aryl)-2-oxo-pyrimidinium salts were made by direct cyclisation of malondialdehyde and appropriate ureas. These quaternary salts underwent pseudo-base formation, and the equilibrium constants between the quaternary cations and their pseudo-bases were determined. In addition, UV and NMR spectra of these quaternary salts and their pseudo-bases will be discussed in this thesis.

Oxidation of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bisulfate by hydrogen peroxide caused a ring transformation giving 3-methyl-oxazolin-2,4-dione in good yield.

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ACKNOWLEDGEMENTS

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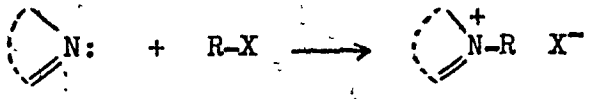
Introduction

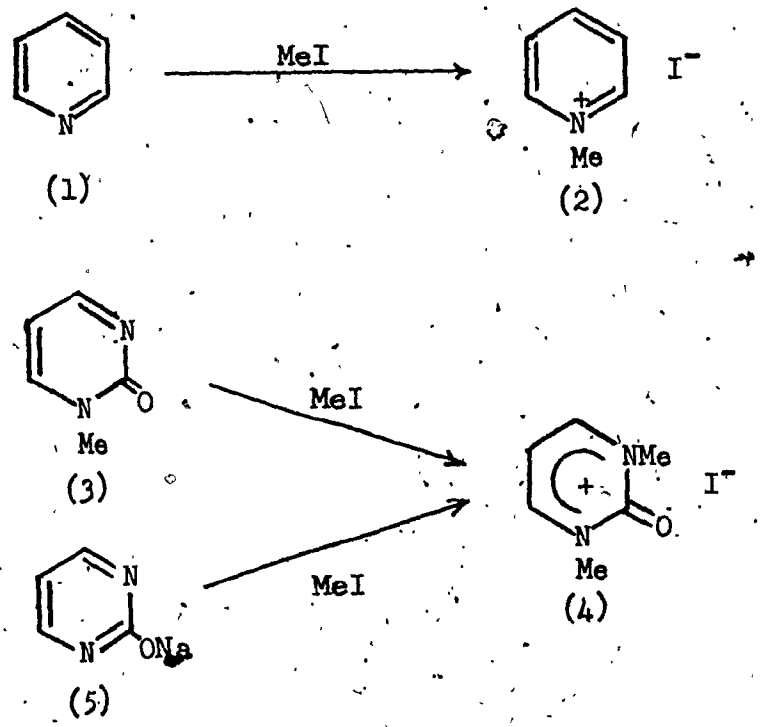
1) Quaternary Compounds

A nitrogen atom in a heterocyclic ring possessing a lone pair of electrons may form a bond between the nitrogen and a carbon atom having a suitable polarization.[1] In the resulting cation the nitrogen is said to be quaternized. N-Heterocyclic compounds are normally quaternized by alkylation of the parent bases.[1]

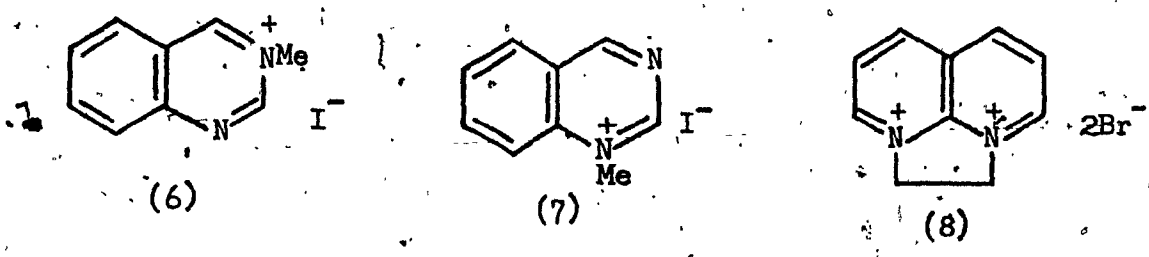


The commonest reagents used for quaternization are alkyl halides of which primary alkyl halides are the more reactive.[2] These reactions presumably proceed via SN2 mechanisms which are strongly affected by steric effects, but much less affected by electronic effects. Secondary alkyl halides, therefore, are less reactive,[2] and tertiary alkyl halides do not react at all to give quaternary salts, but undergo elimination.[3] Also, the longer chain primary alkyl halides commonly undergo elimination rather than quaternization. For example, n-octyl and cetyl iodides give only elimination products when heated with 9-aminoacridine.[4] Therefore, the alkylation method has considerable limitations as a synthetic route to quaternary compounds having various N-substituents.

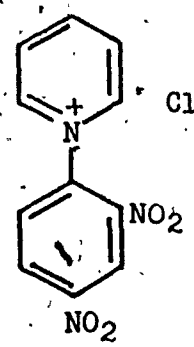
Quaternizations using methyl iodide are well known.[1] For example, pyridine(1) readily reacts at room temperature with methyl iodide to give 1-methylpyridinium iodide(2). Also, 1,2-dihydro-1-methyl-2-oxo-pyrimidine(3) reacts with methyl iodide in a sealed



tube at high temperature to give 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium iodide(4) in good yield.[5] This same compound may also be obtained from the methylation of the sodium salt of 2-hydroxy-pyrimidine(5).[6] Similarly, methyl iodide reacts with quinazoline[7] to give a mixture of the isomers(6) and (7) in the ratio of 5 : 1.



Moreover, 1,2-dibromoethane reacts with 1,8-naphthyridine to give the diquaternary salt(8).[8]



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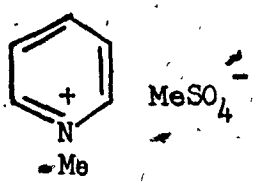

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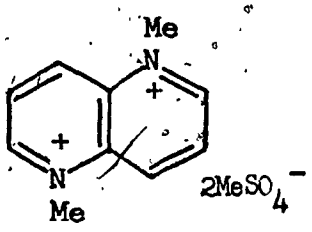

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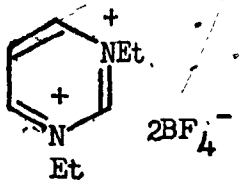

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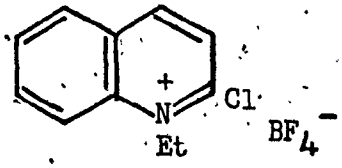


(13)

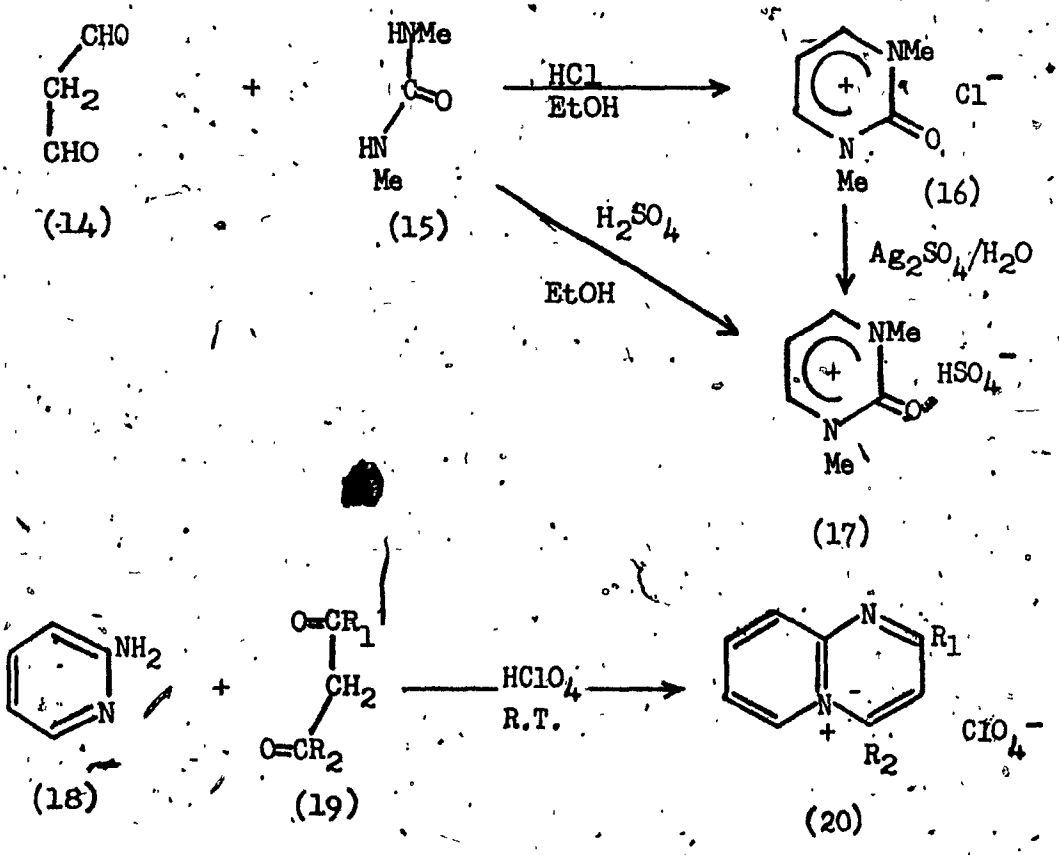
Heterocyclic compounds which readily react with alkyl halides may also react with suitably activated arylhalides to give quaternary salts. As an example, pyridine reacts with 1-chloro-2,4-dinitrobenzene to give 1-(2,4-dinitrophenyl)pyridinium chloride(9).[9]

As other reagents for quaternization, dimethyl sulfate and triethyloxonium tetrafluoroborate have also been used. For example, dimethyl sulfate reacts with pyridine under reflux to give 1-methylpyridinium methyl sulfate(10)[10] and with 1,5-naphthyridine to give a diquaternary salt, 1,5-dimethyl-1,5-naphthyridinedi-ium dimethylsulfate(11).[8] Triethyloxonium tetrafluoroborate readily reacts with pyrimidine to give a diquaternary salt, 1,3-diethylpyrimidinedi-ium difluoroborate(12)[11] and with 2-chloroquinoline to give 2-chloro-1-ethylquinolinium fluoroborate(13).[12]

Most heterocyclic quaternary compounds have been synthesised

by alkylation of the parent bases as shown above. Recently, however, examples of the formation of quaternary salts by direct cyclisation have appeared.

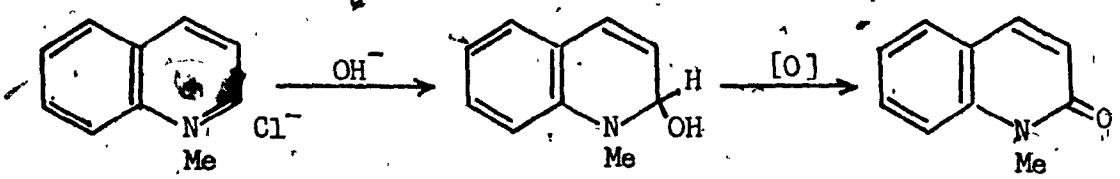
The condensation of malondialdehyde(14) and dimethylurea(15) in ethanolic hydrochloric acid gives 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium chloride(16) in good yield.[5] This chloride may be converted to the corresponding bisulfate(17) in an aqueous silver sulfate solution.[5] However, a better synthesis of this bisulfate(17) is afforded by direct cyclisation in ethanolic sulfuric acid.[13] As another example, 2-aminopyridine(18) readily reacts with various β-dicarbonyl compounds(19) in the presence of perchloric acid to give the pyrido[1,2-a]pyrimidinium perchlorates(20).[14,15]



One of the objectives of this thesis was to exploit the synthetic possibilities of the direct cyclisation method to prepare various quaternary salts related to (16) and (17), but in which N_1 and N_3 carry a variety of substituents.

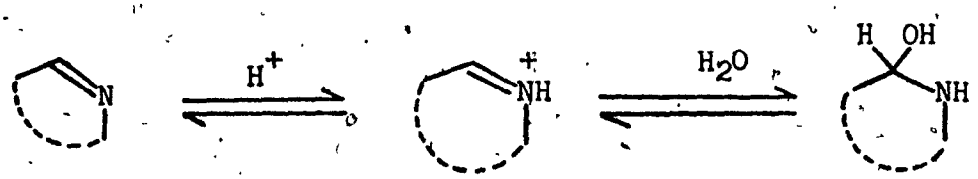
2) Pseudo-base formation

In 1899, Hantzsch[16] found that when a cold aqueous solution of N-methylquinolinium chloride(21) is basified, the initial high alkalinity slowly decreases, and there is a parallel drop in conductance. The product, 1,2-dihydro-2-hydroxy-N-methylquinoline(22), which he termed the "pseudo-base" of (21), is formed by attack of hydroxide ion at the 2-position of (21). Moreover, the pseudo-base(22) is easily oxidized by potassium ferricyanide to N-methyl-2-quinolone(23).[16] Since the work of Hantzsch, the phenomenon of pseudo-base formation from nitrogen heterocyclic quaternary salts has generally been accepted,[17,18] and the structures of the pseudo-bases have been discussed in theoretical organic chemistry.[19] However, in most instances their existence was never actually demonstrated, and only recently has evidence of pseudo-base formation been demonstrated by Albert,[20] Katritzky,[5] Bunting,[21] and others[22] for a variety of systems.

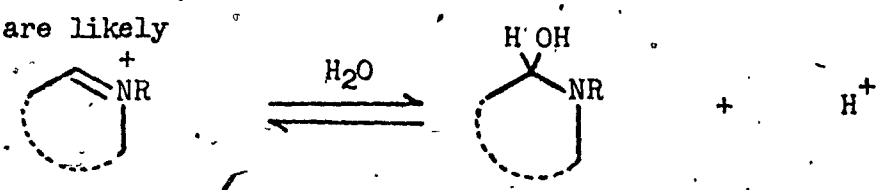


(21) (22) (23)

In 1955, Albert et al. showed that water can add across the C-N double bonds of certain heterocycles to give covalently hydrated forms,[23,24]

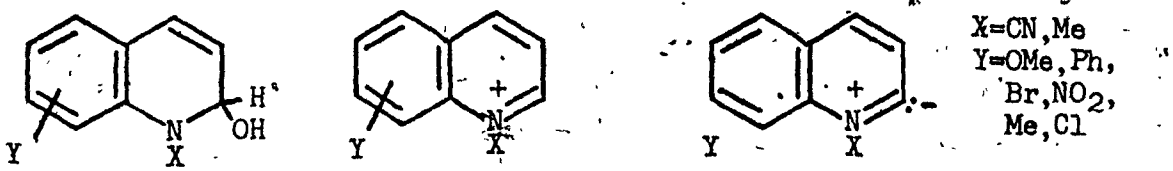


Clearly, systems whose quaternary ions readily undergo pseudo-base formation are likely



to be susceptible to covalent hydration.

The effect of substitution on the equilibrium between substituted quinolinium cations(25) and their pseudo-bases(24) has been studied by Cooksey and Johnson.[22] According to their studies, substituents at

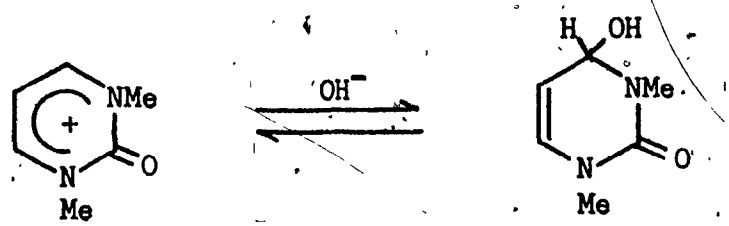


(24) (25) (26)

the 3-,5-,6-,7-,and 8-positions have a large effect on the position of equilibrium, and substituents on the nitrogen have an even larger effect. The substituents effects are so large that hydroxide ion addition is preferred to loss of a proton to give a nucleophilic carbene(26).

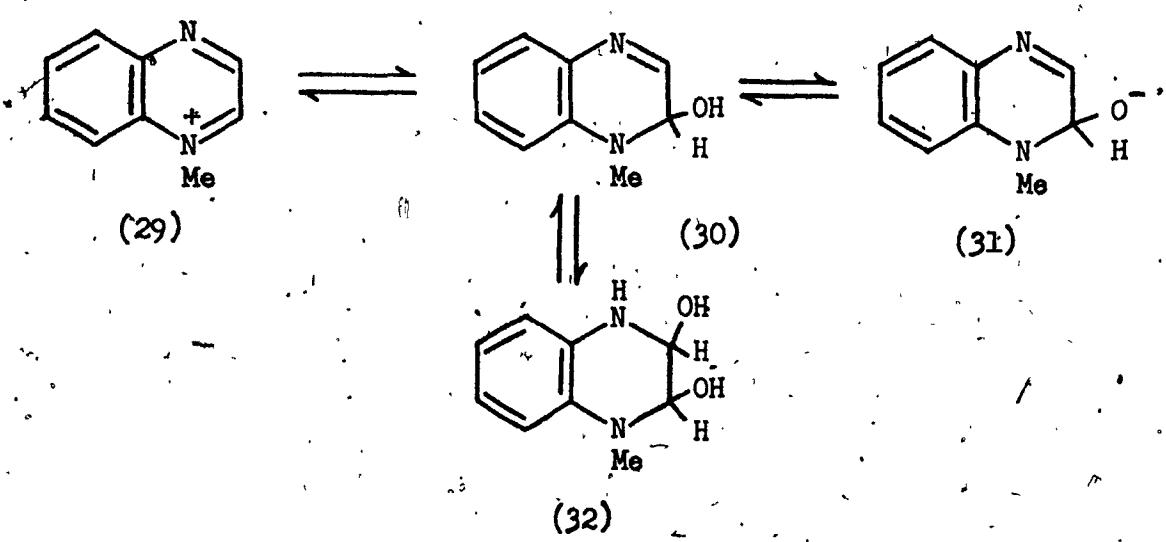
Also, in 1968, Katritzky et al.[5] suggested that 2-oxo-pyrimidines might undergo isotope exchange at the 5-position via covalent hydrates, and it was shown that 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium ion(27) readily formed the pseudo-base(28).

Recently, equilibrium constants of the pseudo-base formation for several naphthyridinium, quinolinium, phthalazinium and (iso)quinolinium cations were determined by Bunting and Meathrel.[21] Ionization constants for ionization of some of these pseudo-bases to alkoxide



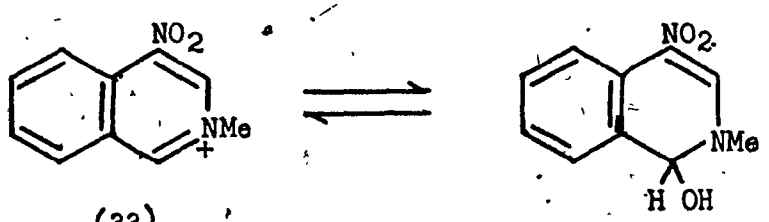
(27) (28)

anions(e.g. 30→31) were also determined. One of them, the pseudo-base(30) of the 1-methylquinoxalinium cation(29), exists in equilibrium with a considerable amount of its covalent hydrate(32) which is formed by addition of water across the C_3-C_4 double bond of (30). In other cases, however, only one major pseudo-base is present in solution.

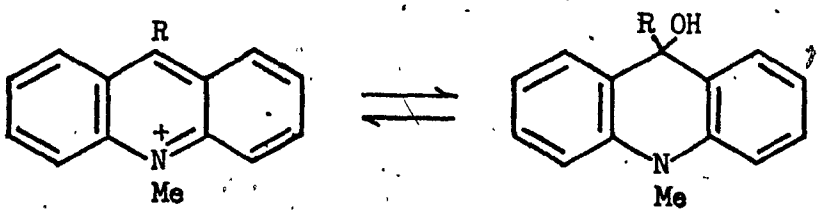


(29) (30) (31) (32)

Bunting and Meathrel have also reported[25] comprehensive kinetic studies of the pseudo-base formation and decomposition of quaternary N-methyl heterocyclic cations(33) and (35). According to the pH-rate studies, pseudo-base formation(e.g. 33→34) may kinetically occur through either attack of a water molecule or of hydroxide ion on the heterocyclic cation depending upon the pH of the reaction medium. Conversely, pseudo-base decomposition(e.g. 34→33) may occur through



(33) (34)

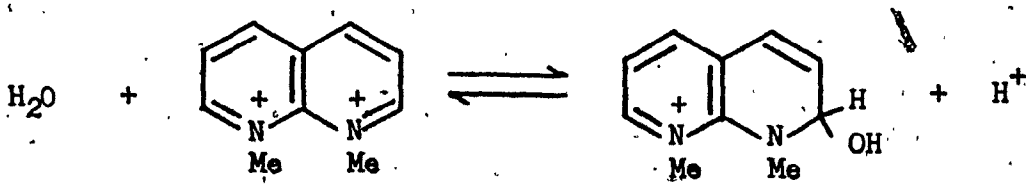


(35) (36)

R=H, Ph

either the neutral or protonated pseudo-base species or their kinetic equivalents.

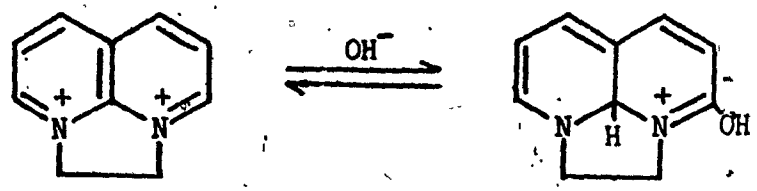
The pseudo-base formation of diquaternary salts was very recently reported by Pokorny and Paudler.[26] 1,8-Dimethyl-1,8-naphthyridinium dication(37) undergoes pseudo-base formation(37⇌38) at the 2-position more easily than other naphthyridinium dications give their pseudo-bases.



(37) (38)

However, Summers et al.[27] studied the pseudo-base formed from the dication (39) and concluded that it has a different type of structure, namely, (40). The difference in the structure of the pseudo-base(38) as compared with (40) is presumably due to the presence of the two methyl

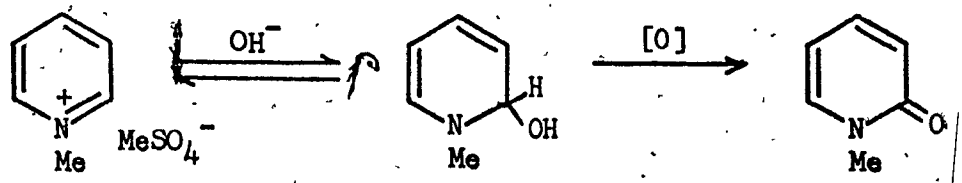
groups in (38), which sterically hinder the formation of the fully conjugated tautomer analogous to (40).[27]



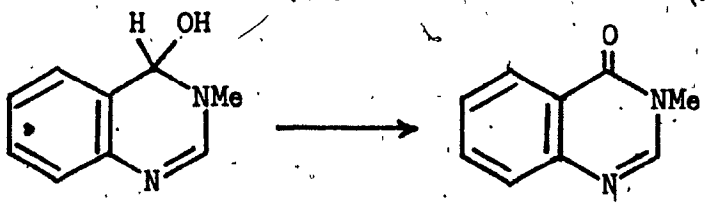
(39) (40)

3) Oxidation of pseudo-bases

Oxidation of quaternary cations might be a useful method of proving the structure of pseudo-bases, since such oxidation to keto-compounds can be normally expected to occur at the position in the pseudo-base bearing the hydroxyl group. For example, it was already mentioned(p.6) that the pseudo-base(22) of 1-methylquinolinium chloride (21) is easily oxidized by potassium ferricyanide to 1-methyl-2-quinolone(23). Also, well-known is the oxidation of 1-methyl-pyridinium methyl sulfate(10) by alkaline potassium ferricyanide which gives 1-methyl-2-pyridone(42).[10] The mechanism[28] proposed for this reaction requires the formation of the pseudo-base(41), which is in equilibrium with the pyridinium salt(10). Similarly, the pseudo-



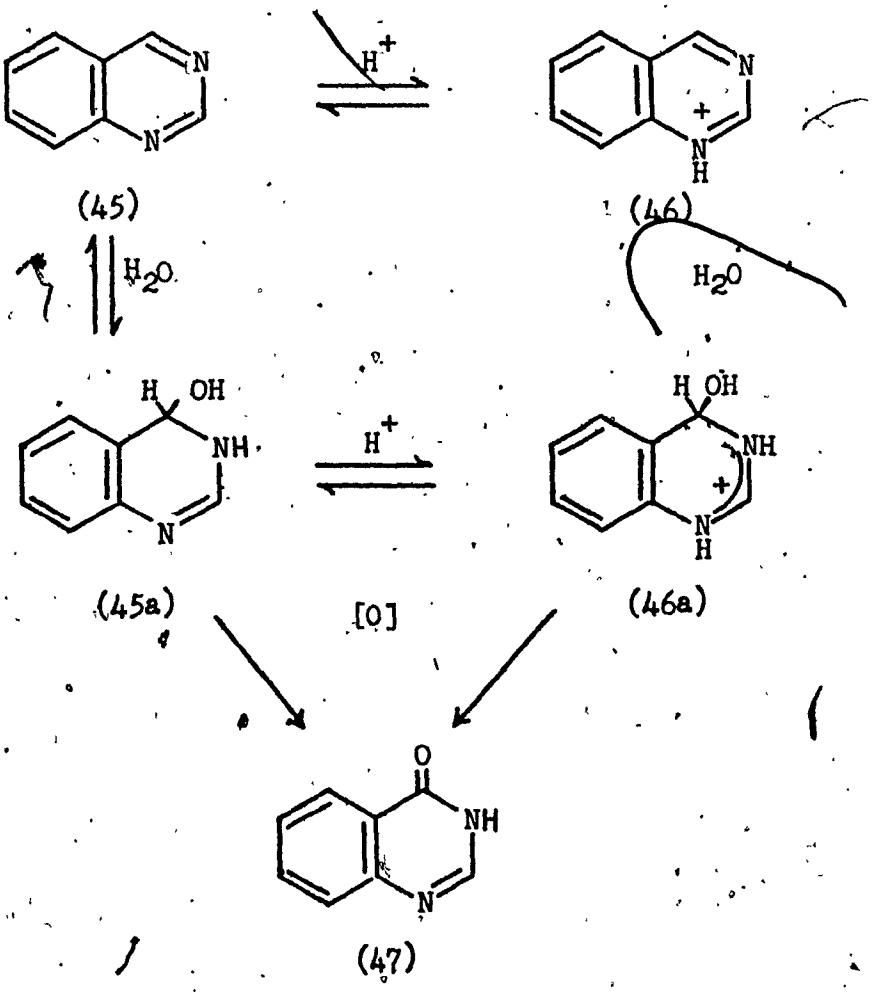
(10) (41) (42)



(43) (44)

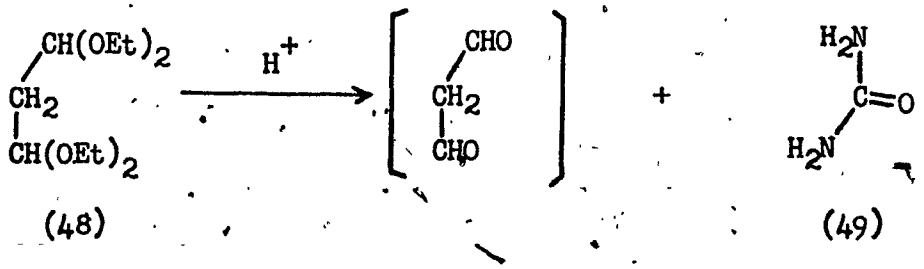
base(43) of 3-methylquinazolinium iodide(6) is readily oxidised to 3-methyl-4-quinazolone(44).[7] The oxidation of quinazoline(45) is interesting in relation to the oxidation of the pseudo-base(43) above,

since reaction of quinazoline with H_2O_2 in dilute aqueous acid gives 3,4-dihydro-4-quinazolone(47) in good yield.[29] This oxidation may proceed via the covalent hydrate(45a) or the hydrated cation(46a) since the latter is known to be the predominant cation in aqueous media.

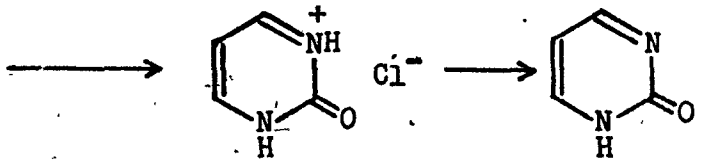


4) Synthesis of 2-pyrimidones

1,2-Dihydro-2-oxo-pyrimidine derivatives are commonly synthesised by condensation of ureas with β-dialdehydes, β-ketoaldehydes or β-diketones in the presence of an acid catalyst in alcohol. For example, the reaction of malondialdehyde tetraethylacetal(48) and urea(49) in ethanolic hydrochloric acid gives 1,2-dihydro-2-oxo-pyrimidine hydrochloric acid salt(50), which may be neutralized in an aqueous solution to give the neutral species(51),[30] the parent base of 2-oxo-pyrimidine derivatives.

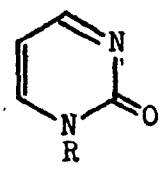


(48) (49)



(50) (51)

Similarly, N-alkyl(aryl)-1,2-dihydro-2-oxo-pyrimidines(52) are obtained as salts from the reaction of (48) and 1-alkyl(aryl)ureas in alcoholic hydrochloric acid, and those salts are converted by neutralization to their neutral forms(52).[31] Also, the reaction of acetylacetone with ureas gives 1,2-dihydro-4,6-dimethyl-2-oxo-pyrimidines(53; R=H,Ph),[32,33] and the reaction of 2-methylmalondialdehyde tetraethylacetal with 1-methylurea gives 1,2-dihydro-1,5-dimethyl-2-oxo-pyrimidine



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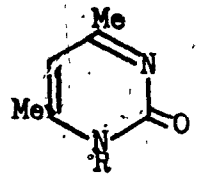

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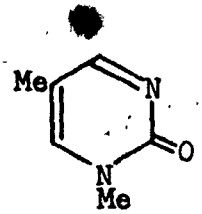
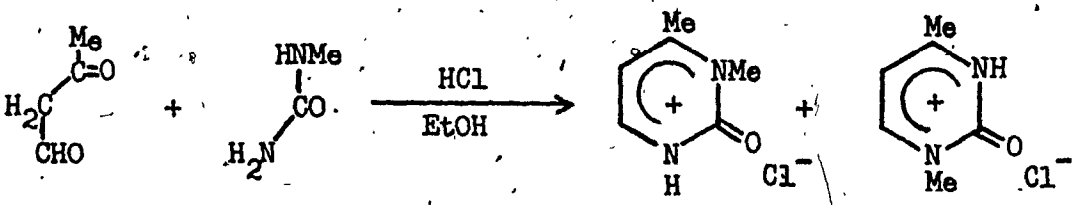


(54)

(54).[31] These reactions do not result in any isomers, since the 2-oxo-pyrimidine molecule is symmetrical about the C_2-C_5 axis. However, the reaction of formylacetone with 1-methylurea in alcoholic hydrochloric acid give two isomers of (55) and (56),[34] of which (55) is the major product.



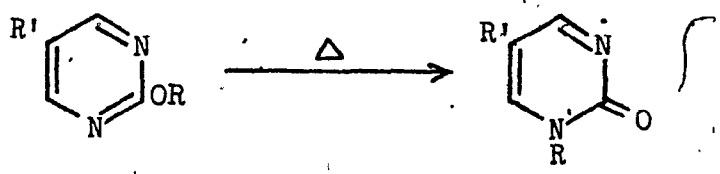
(55) (56)

N-Alkyl-2-oxo-pyrimidine derivatives are also obtained by alkylation of 2-hydroxy- and alkoxypyrimidines. The reaction of either 2-hydroxy- or methoxypyrimidine with diazomethane gives 1,2-dihydro-1-methyl-2-oxo-pyrimidine(52;R=Me),[35] which is also obtained by the alkylation of 2-hydroxypydimidine using methyl iodide in alcohol.[36]

Brown[31,37] has studied the amine-catalysed thermal rearrangement of 2-alkoxypyrimidines(57), a reaction which may also be used to synthesize N-alkyl-2-oxo-pyrimidines. Electron-withdrawing substituents(R=Br, NO_2) at the 5-position of (57) enhance the rate of rearrangement, whereas when R'=Me, the rate is retarded (see overleaf).

As mentioned previously(p.4), 1,3-dimethyl-2-oxo-pyrimidinium salts(16 and 17) have also been made, both by alkylation methods and

by direct cyclisation of 1,3-dimethylurea.[5,13]



(57) (58)

R=Me,Et,Pr,iso-Pr,Bu,iso-Bu

R'=NO_2,Br,Me

Results and Discussion

1) Introduction

As discussed earlier, quaternary salts of pyrimidine compounds are normally made by alkylation of their parent bases. However, there are limitations to this type of synthesis, in that quaternary salts having a variety of N-substituents are difficult to obtain, because of the suitability of only a few alkylating agents.[1]

It was found, however, that 1,3-dimethyl-2-oxo-pyrimidine quaternary salts could easily be synthesised by direct cyclisation.[5,13] The ease of these syntheses suggested that the method might be extended. Thus for this thesis various 1,3-dialkyl(aryl)-2-oxo-pyrimidinium salts were made by direct cyclisation of malondialdehyde and appropriate ureas. These quaternary salts undergo pseudo-base formation, as was confirmed by UV and NMR spectroscopies. In addition, equilibrium constants(K) between the quaternary cations(Q^+) and their pseudo-base (QOH) were determined by potentiometric titration.[38] These equili-

$$Q^+ + H_2O \rightleftharpoons QOH + H^+$$

$$K = \frac{[H^+][QOH]}{[Q^+]}$$

brium constants were expressed as pK values following eqn.1, and which denote the pH at which the quaternary cation and its pseudo-base exist at equal concentration.

$$pK = pH - \log \frac{[QOH]}{[Q^+]} \qquad \ldots\ldots\ldots (1)$$

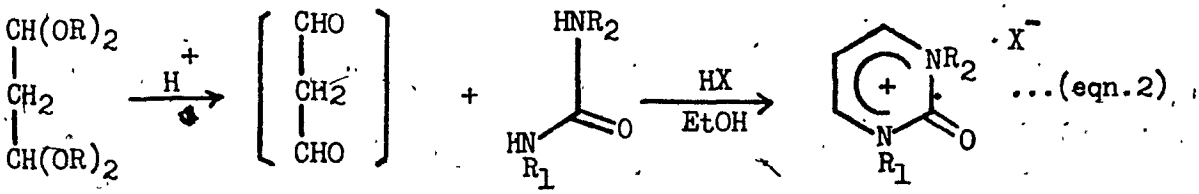
Oxidation of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bisulfate

by potassium ferricyanide in an alkaline solution was expected to give 1,3-dimethyluracil, but gave only intractable oils. However, oxidation by hydrogen peroxide in either alkaline, acidic or neutral solution caused a ring transformation giving 3-methyl-oxazolidin-2,4-dione in good yield.

2) Synthesis

As discussed earlier, the synthesis of quaternary heterocyclic compounds by alkylation methods is limited by the relatively few suitable alkylating agents.[1] In some instances, however, this limitation may possibly be avoided by use of a direct cyclisation route.

Brown[31] and earlier workers showed that 1,2-dihydro-1-alkyl-2-oxo-pyrimidinium salts(62;R_1=alkyl,R_2=H,X=Cl) may be made from malondialdehyde tetraalkyl acetals(59;R=Me,Et) and N-alkylureas(61;R_1=alkyl,R_2=H) in ethanolic hydrochloric acid. This suggested to Tee[5,13] that



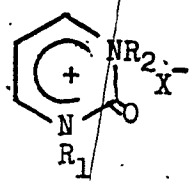
...(eqn.2)

(59) (60) (61) (62)

1,3-dialkyl salts(62;R_1,R_2=H) might be made similarly from 1,3-dialkylureas(61;R_1,R_2=H). Indeed, reaction of 1,1,3,3-tetraethoxypropane (59;R=Et) with 1,3-dimethylurea in ethanolic hydrochloric acid(or sulfuric acid) gave the desired chloride[5](or bisulfate[13])(62;R_1=R_2=Me,X=Cl or HSO_4) in very good yield.

For this work the 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts(62) shown in Table 1 were synthesised in the manner outlined above (eqn..2). Most of the compounds were prepared relatively easily in good yield, and without special difficulties in their isolation. It is significant that quaternary salts having tertiary alkyl,phenyl, or other bulky substituents were made, since these substituents are very

Table 1



1,2-Dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts made by direct cyclisation(eqn.2)

R_1	R_2	X	Temp.	Time(hr)	Yield(%)	M.p.(°C)	Remarks
Me	Me	Cl	60°C	1	85	245-50(dec.)	ref. 5
Me	Me	HSO_4	50°C	0.5	95	204-6	ref. 13
Me	Et	Cl	reflux	4.5	74	217-9	hygroscpic
Me	Et	HSO_4	"	2	50	-	deliquescent
Me	Et	I	"	2	72	210-3	
Me	i-Pr	HSO_4	room	36	68	136-7	
Me	t-Bu	HSO_4	"	96	54	145-7	
Me	c-Hex	I	reflux	2	88	205-8	
Me	Ph	Cl	"	9	64	109-13	hygroscopic
Me	Ph	I	"	6	64	129-32	
Me	$PhCH_2$	HSO_4	"	2	96	250-5(dec.)	
Et	Et	Cl	"	2	21	-	hygroscopic
Et	Et	HSO_4	"	2.8	40	87-94	hygroscopic
Et	Et	I	"	4	81	208-12	
Pr	Pr	Cl	"	1.5	85	138-41	hygroscopic
Pr	Pr	I	"	6.3	69	153-5	
i-Pr	i-Pr	$EtSO_4$	"	6	73	209-12	
n-Bu	n-Bu	Cl	"	3	91	122-5[a]	hygroscopic
n-Bu	n-Bu	HSO_4	"	2	99	108-9	
$PhCH_2$	$PhCH_2$	HSO_4	"	4	70	175-7	
c-Hex	c-Hex	$EtSO_4$	"	52	94	177-9	

a. sealed tube

difficult to introduce by alkylation.

Attempts to prepare the 1,3-diphenyl- and the 1,3-di-t-butyl-2-oxo-pyrimidinium salts(62;R_1=R_2=Ph,t-Bu,X=Cl,HSO_4 or I) were not successful. The difficulty in preparing the 1,3-diphenyl compound is probably due to the low nucleophilicity of the PhNH- group of the urea(61;R_1=Ph,R_2=Ph). The easy preparation of the 1-methyl-3-phenyl-2-oxo-pyrimidinium salts(62;R_1=Me,R_2=Ph,X=Cl,I) from the urea(61;R_1=Me, R_2=Ph) suggests that in this case the cyclisation may begin by attack of the MeNH- group of the urea upon a carbonyl group of malondialdehyde (60) rather than by initial attack of the ArNH- group. The reason why 1,3-di-t-butylurea did not react with malondialdehyde(60) is probably steric hindrance.

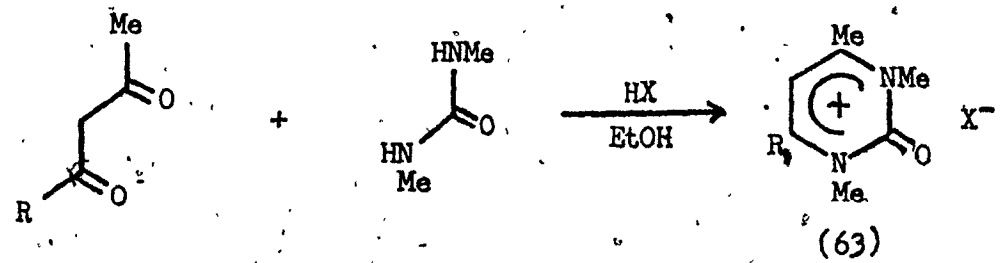
For ureas having larger alkyl and aryl substituents, the rate of the condensation is apparently slower (See Table 1), so that higher reaction temperatures and/or longer reaction times were required. Under these conditions, however, the reactions often resulted in tarry and dark-colored products which were more difficult to purify and to recrystallise. This is almost certainly due to side reactions and/or self-condensations of malondialdehyde.

When either hydrochloric acid or sulfuric acid was used as an acid catalyst, those pyrimidinium chlorides or bisulfates obtained were often hygroscopic or even deliquescent, so that it was hard to purify them and to completely remove water from them. This drawback was later overcome by using hydriodic acid, in that none of the iodides so obtained were hygroscopic. Also the reactions resulted in much less tarry materials which were easier to recrystallise. Therefore,

hydriodic acid should be used in the condensation(eqn.2) as the acid catalyst of choice.

Cyclisation of 1,3-di-isopropylurea and 1,3-dicyclohexylurea with malondialdehyde tetraalkyl acetal(59) was carried out using conc. sulfuric acid. However, from the analysis, IR spectra, NMR spectra and chemical reactions of the products(62;R_1=R_2=i-Pr, c-Hex, X=$EtSO_4$), it was apparent that the anion in these salts was ethylsulfate($EtSO_4^-$) and not bisulfate(HSO_4^-). For example, the NMR in D_2O showed peaks of ethyl group(δ 1.30(Me), δ 4.08(CH_2)) which were identical with those of ethyl potassium sulfate($EtOSO_3K$).[55] Also these salts did not give a white precipitate of barium sulfate with aqueous barium chloride solution, as is the case when the anion is bisulfate ion. The ethylsulfate anion in these salts is obviously derived from ethylsulfuric acid which is easily produced by the reaction of ethanol and conc. sulfuric acid.

Analogous condensations have previously been carried out with 1,3-dimethylurea and either acetyl acetone or 3-ketobutyraldehyde[39], but the cited literature gives scant details and no physical properties of the salts. Therefore, these condensations were carried out again to give the salts(63;R=Me,X=Cl,HSO_4;R=H,X=HSO_4) in good yield.



(63)

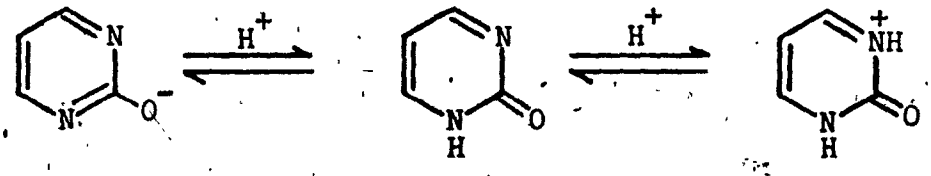
R=H,Me, X=HSO_4,Cl

All three of the compounds made were obtained as hydrates(See Experimental).

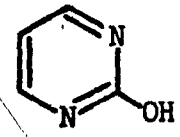
3) Spectral data

i) UV spectra

As with many heterocyclic compounds, pyrimidines may possess basic centers(e.g. 65→66) and/or acidic hydrogens(e.g. 65→64) and/or be potentially tautomeric(e.g. 65⇌67). Therefore, in taking spectra of such compounds, it is important to know in what form the molecule exists, and to choose solution conditions such that one form predominates. For example, 2(1H)-pyrimidone in neutral aqueous solution exists potentially in the tautomeric forms(65) and (67).

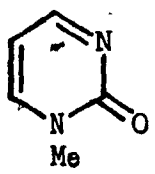


(64) (65) (66)

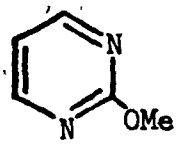


(67)

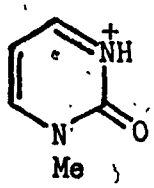
Of these, the oxo-form(65) is largely favored,[35,41] since its UV spectra resemble those of N-methyl-2(1H)-pyrimidone(68) more closely than those of 2-methoxypyrimidine(69).[35] On the other hand, the anionic form (64) exists in basic solution, and the cationic form(66) exists in acidic solution.[42]



(68)

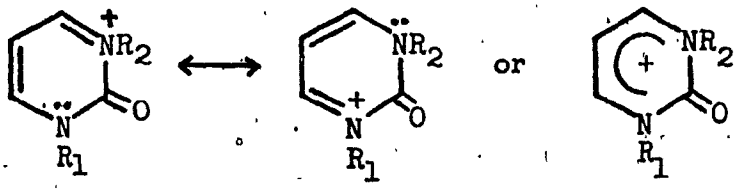


(69)



(70)

UV spectra of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts were measured in an acidic solution(1N.H_2SO_4)(See Table 2) in which they exist in a simple cationic form(71). For the structures of the cations, we can write two principal canonical structures(71a)



(71a) (71b) (71)

and (71b). However, so long as R_1 and R_2 are either the same or quite similar, the contributions of these two will be essentially equal, and so in general we prefer to write the structure as (71).

The absorption spectra[42] of the 2-oxo-pyrimidinium cations(See Table 2) consist of two bands: an intense band below 210 nm due to the $\pi \rightarrow \pi^*$ transition, and a less intense band ~320 nm due to the $n \rightarrow \pi^*$ transition(N.B. Iodide salts also have a band at ~225 nm). The effect of methyl substitution in pyrimidines is generally to cause bathochromic shifts and to cause an increase in intensity.[42] These effects are well shown by the cations (66), (70) and (71) (see p.26).

The UV spectra of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts were also measured in basic solutions of pH 9.18(See Table 2).

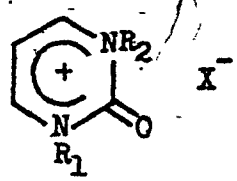
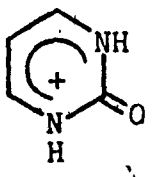


Table 2

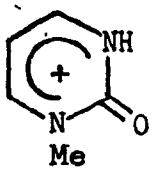
UV spectra of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts

R_1	R_2	X	λmax(nm)(logε) at pH 0.29[a]		λmax(nm)(logε) at pH 9.18[b]	
Me	Me	HSO_4		316 (3.93)	239 (3.93)	296 (2.70)
Me	Et	I	225 (4.16)	316 (3.93)	228 (4.23)	296 (3.27)
Me	i-Pr	HSO_4		317 (3.92)	238 (3.76)	298 (3.02)
Me	t-Bu	HSO_4		316 (3.92)	236 (3.61)	308 (3.22)
Me	c-Hex	I	223 (>4.00)	319 (3.96)	227 (4.16)	300 (3.21)
Me	Ph	Cl		326 (3.91)	235 (3.85)	335 (1.66)
Me	Ph	I	225 (4.15)	325 (3.95)	227 (4.33)	338 (2.00)
Me	$PhCH_2$	HSO_4		318 (3.95)	239 (3.69)	299 (2.51)
Et	Et	Cl		317 (3.91)	238 (3.71)	300 (2.84)
Et	Et	HSO_4		317 (3.92)	238 (3.69)	300 (2.83)
Et	Et	I	223 (>4.00)	317 (3.90)	225 (>4.00)	299 (3.12)
Pr	Pr	I	223 (4.09)	320 (3.89)	227 (>4.00)	303 (3.50)
i-Pr	i-Pr	$EtSO_4$		319 (3.95)	237 (3.62)	305 (3.31)
n-Bu	n-Bu	HSO_4		319 (3.95)	240 (3.61)	301 (2.88)
$PhCH_2$	$PhCH_2$	HSO_4		321 (3.99)	241 (-)	*
c-Hex	c-Hex	$EtSO_4$		322 (4.02)	239 (3.73)	*

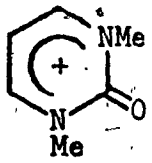
a. 1.00N. sulfuric acid.
b. sodium borate buffer.
* in 95% ethanol.



(66)

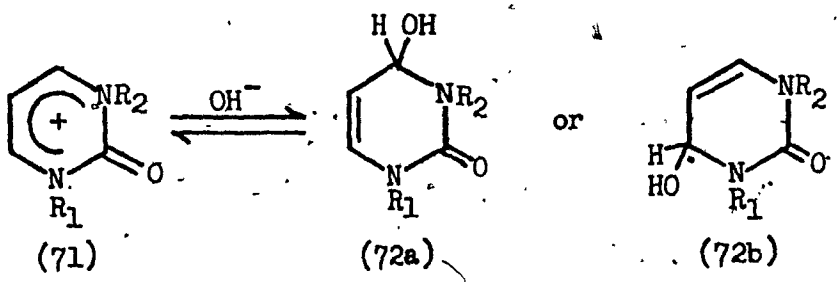


(70)

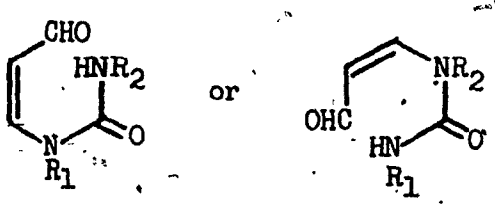


(71)

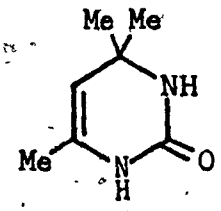
λmax	309	313	316 nm
log ε	3.77	3.85	3.93
ref.	40	40	5



(71) (72a) (72b)



(73a) (73b)



(74)

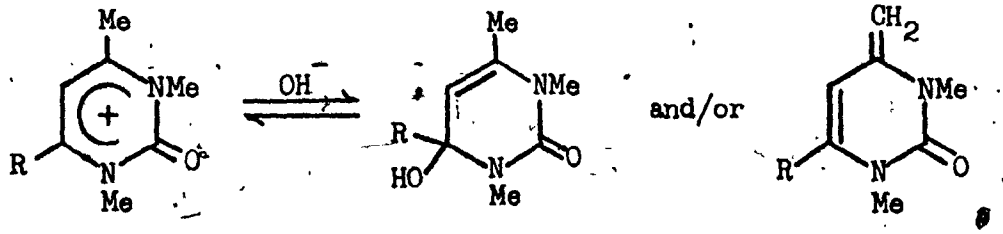
λmax	log ε	solvent	ref.
236 nm	3.51	MeOH	52
235	3.47	?	53
246	3.28	pH 5	54

In this medium the cations(71) exist as pseudo-bases (72a) or (72b), rather than the ring-opened forms (73a) or (73b)(see p.26). This contention is supported by NMR spectra(See next section) and by the UV data in Table 2. The pseudo-bases(72) all show a band at ~238 nm(logϵ~3.70) except where masked by an iodide band at ~225 nm. The 238 nm band is consistent with the proposed structure(72) in that the compound(74) shown above (see p.26) has a very similar UV.

The pseudo-bases(72;R_1 =R_2=c-Hex or $PhCH_2$) precipitated from aqueous solution and so their UV spectra were taken in 95% ethanol. The isolation of these pseudo-bases(as oily, glassy materials) enabled other evidence for their structures to be obtained(See Experimental).

The problem of orientation which accrues when in (71) and (72) $R_1 \neq R_2$ is discussed in the next section (on NMR).

In basic solution the C-Me cations(63) may form pseudo-bases(75) and/or anhydrobases(76). The German workers,[39] who previously made salts of (63), claim to have isolated the anhydrobases(76;R=H,Me), but offer no physical data to support this. Their claim seems to rest on the basis of various chemical reactions involving condensations at the exocyclic methylene of (76). Since it is not inconceivable that they had in fact isolated the pseudo-bases(75), it seemed necessary to try to



(63) (75) (76)

R=H,Me

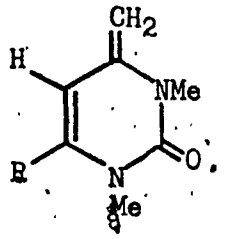
repeat their isolations and characterise the materials obtained.

Chloroform(or CCl_4) extraction of a basic solution of (63;R=H,anion=HSO_4^-) provided an oil for which UV and NMR spectra(Table 3) were obtained and to which is assigned the anhydrobase structure(73a). When the tetramethyl salt(63;R=Me,anion=HSO_4^-) was dissolved in a solution of KOH (or NaOH), a white precipitate was formed and for which UV,NMR,IR, and mass spectral data were also consistent with the anhydrobase structure (73b)(See Table 3). Both the oil(73a) and white solid (73b) are difficult materials to work with, since they are very sensitive to oxidation in air, and give rise to deep red-coloured products.

The relative ease with which a C-Me proton may be abstracted from (63)⟶(76) may be observed in another way. Solutions of the cations (63) in D_2O show expected NMR peaks, but with time the signal due to the C-Me protons decreases in intensity due to exchange with the deuterated solvent. Similar observations have been made by Batterham et al.[46] for various other pyrimidines bearing methyl groups at 2-,4-, and 6-positions.

Table 3

Spectral properties of Anhydrobases(76)



(76a) R=H

(76b) R=Me

UV(95% EtOH) λmáx (logϵ)

(76a) 250 nm (3.85), 297(3.53)

(76b) 247 nm (3.95), 292(3.33)

NMR(δ)	C-Me	N-Me	=CH2	5-H	6-H	J5,6
(76a)(CCl_4)	-	3.08;3.10	3.62,3.65	5.38	6.06	8Hz
(76b)($CDCl_3$)	2.00	3.13,3.20	3.63,3.68	5.40	-	8Hz

IR(KBr)

(76b) No significant -OH bands

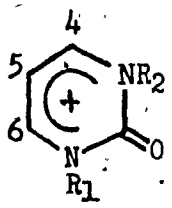
MS

(76b) m/e 152, 137, 124, 109, 94

ii) NMR spectra

Further evidence of the structure of the salts synthesised in this work, and of the structure of their pseudo-bases is provided by their NMR spectra.

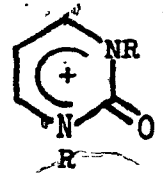
The ring protons(4-H,5-H, and 6-H) of the 2-oxo-pyrimidinium cations give characteristically simple signals. When $R_1=R_2$, the



(71)

cation(71) is symmetrical about on a C_2–C_5 axis, so that the 4-H and 6-H are magnetically equivalent to each other, and so the NMR shows a first-order spectrum consisting of a doublet for the 4,6-Hs at about δ 7 and a triplet for the 5-H at about δ 9(See Table 4). If $R_1 \neq R_2$, the cation(71) is not symmetric and so more complex spectra would be anticipated(See Table 5). However, in the cases where R_2=Me, R_1=Et, $PhCH_2$ the effect of the different alkyl groups are so similar that the spectra resemble those of the symmetrical cations. In the cases where R_2=Me, R_1=i-Pr, t-Bu, or c-Hex the 4- and 6-Hs are no longer equivalent and so they appear as a complex multiplet at $\sim\delta$ 9. However, the coupling constants $J_{4,5}$ and $J_{5,6}$ are still so similar that the 5-H appears as a triplet. For the case where R_2=Me, R_1=Ph the signals of the 4- and 6-Hs are well separated, each appearing as a doublet of doublets with $J_{4,5}=J_{5,6}=6$Hz, $J_{4,6}=2$Hz, and again the 5-H as a triplet.

Table 4



X^-

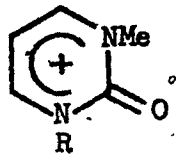
NMR spectra of 1,2-dihydro-1,3-di-(sym.)-alkyl-2-oxo-pyrimidinium salts in D_2O (reference DSS)

R	X	4-H(δ)	6-H(δ)	5-H(δ)	other(δ)
Me	Cl *	8.90	8.90	7.00	3.82(NMe)
Me	HSO_4 *	8.95	8.95	7.12	3.85(NMe)
Et	Cl	8.97	8.97	7.08	1.45(CH_3),4.28(CH_2)
Et	HSO_4	8.95	8.95	7.07	1.47(CH_3),4.27(CH_2)
Et	I	9.00	9.00	7.10	1.48(CH_3),4.28(CH_2)
Pr	Cl	8.97	8.97	7.20	0.98(CH_3),1.80(CH_2),4.17(NCH_2)
Pr	I	8.94	8.94	7.00	0.97(CH_3),1.80(CH_2),4.15(NCH_2)
i-Pr	$EtSO_4$	8.99	8.99	7.18	1.30($\underline{CH_3}CH_2SO_4$),1.55(CH_3);4.10($CH_3\underline{CH_2}SO_4$),5.06(CH)
n-Bu	HSO_4	8.95	8.95	7.08	0.95(CH_3),4.23(NCH2)
$PhCH_2$	HSO_4	9.24	9.24	7.15	5.34(NCH_2),7.42(Ph)
c-Hex	$EtSO_4$	8.88	8.88	7.09	1.30(CH_3),4.08(CH_2)

coupling constant $J_{5,6} = J_{4,5} = 6.5$Hz ; $J_{4,6} = 2$Hz where observable

* ref.5

Table 5



NMR spectra of 1,2-dihydro-1-alkyl(aryl)-3-methyl-2-oxo-pyrimidinium salts in D_2O(reference DSS)

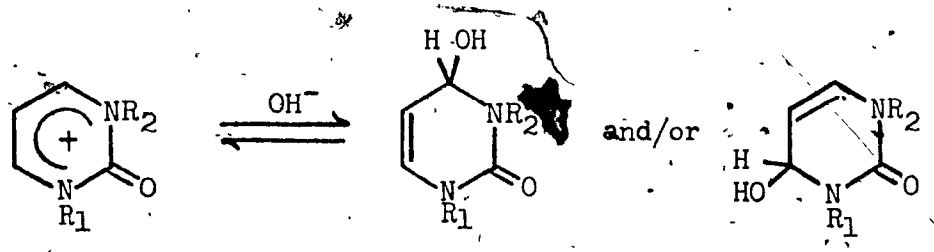
R	X	4-H(δ)	6-H(δ)	5-H(δ)	NMe(δ)	other(δ)
Me	Cl[a]	8.90	8.90	7.00	3.82	
Me	HSO_4[a]	8.95	8.95	7.05	3.85	
Et	Cl	9.02	9.02	7.12	3.88	1.49(CH_3),4.31(CH_2)
Et	HSO_4	9.02	9.02	7.10	3.86	1.47(CH_3),4.29(CH_2)
Et	I	9.02	9.02	7.10	3.87	1.47(CH_3),4.30(CH_2)
i-Pr	HSO_4	multiplet at	9.02	7.15	3.88	1.56(CH_3),5.08(CH)
t-Bu	HSO_4	multiplet at	9.00	7.03	3.82	1.75(CH_3)
c-Hex	I	multiplet at	8.95	7.06	3.82	
Ph	Cl[b]	9.25	9.63	7.21	3.80	7.62(Ph)
Ph	I[b]	9.25	9.37	7.23	3.78	7.65(Ph)
$PhCH_2$	HSO_4	9.03	9.03	7.10	3.84	5.42(CH_2),7.53(Ph)

coupling constant $J_{4,5} = J_{5,6} = 6.5$Hz ; $J_{4,6} = 2$Hz where observable

a. ref.5

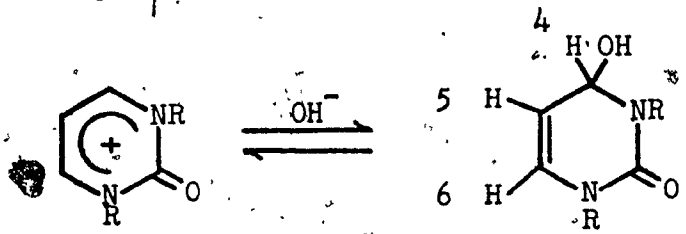
b. in DMSO-d6(reference TMS)

The formation of pseudo-bases from the cations(71) was clearly observed by NMR, since in the pseudo-bases(72a and/or 72b) the signals due to the 4-H, 5-H and 6-H are well separated and to higher field than those of the cations(71). Also upfield shifts are apparent for the groups R_1, R_2, particularly for those protons on the carbon bonded to nitrogen. The splitting of the 4-H, 5-H and 6-H signals



(71) (72a) (72b)

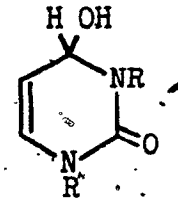
is also consistent with the structures(72). For the symmetrical cations(71c) only one pseudo-base(72c) is possible. and so simple NMR spectra are obtained(See Table 6). The 4-H appears as a doublet (J=4.5 Hz) at ~δ 5.3, the 6-H as a doublet(J=8Hz) at ~δ 6.4, and the 5-H as a doublet of doublets(J=4.5, 8 Hz) at ~δ 5.0. Appropriate signals are obtained for the groups R.



(71c) (72c)

The spectra of the pseudo-bases(72c;R=i-Pr or $PhCH_2$) are interesting in that they show diastereotopism.[56] In the case of (72c;R=$PhCH_2$) one benzyl CH_2 group appears as a singlet(area 2) at δ 4.67, whereas the other appears as two separate signals (δ 4.20,4.45).

Table 6



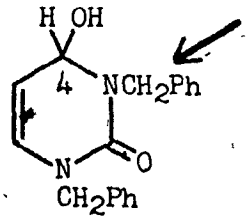
NMR spectra of the pseudo-bases of 1,2-dihydro-1,3-di-(sym.)-alkyl-2-oxo-pyrimidinium salts in D_2O (reference DSS)

R	6-H(δ)	4-H(δ)	5-H(δ)	other(δ)
Me	6.25	5.39	5.07	3.04(N_1,Me), 2.97(N_3,Me)
Et	6.39	5.48	5.11	3.49, 3.45(CH_2), 1.17, 1.13(CH_3)
Pr	6.44	5.47	5.17	0.98, 0.86(CH_3)
i-Pr	6.50	5.48	5.23	1.36, 1.30(N_3,CH_3), 1.17, 1.13(N_1,CH_3)
n-Bu	6.34	5.34	4.93	
* $PhCH_2$	6.42	5.21	4.93	7.28, 7.25(Ph), 4.67(N_1,CH_2), 4.45, 4.20(N_3,CH_2)
* c-Hex	6.41	5.33	4.99	

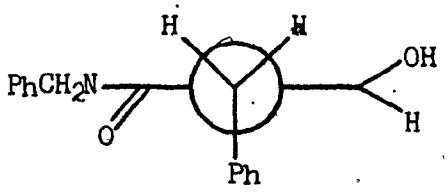
coupling constant $J_{4,5}$=4.5Hz; $J_{5,6}$=8Hz where observable

* These pseudo-bases precipitate from aqueous solution. For R=$PhCH_2$-, spectrum was run in DMSO-d6. For R=c-Hex, spectrum was run in acetone-d6 (reference TMS).

Presumably, the latter is due to the $PhCH_2$ group closest to the asymmetric centre(C-4). Clearly from structure(72d) the environment of the two benzylic protons is quite different.



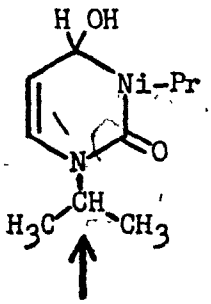
(72d)

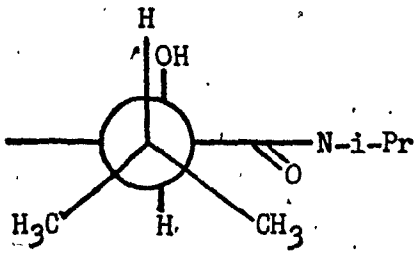


(72d)

For the diisopropyl pseudo-base(72c;R=i-Pr) it is in the methyl signals where the diastereotopism is evident. Each isopropyl methyl doublet shows further splitting, one by about 4Hz, the other by about 2Hz. Presumably the larger of these splitting is associated with the isopropyl proximal to the asymmetric centre, while the smaller is that of the distal isopropyl group. This latter group, though some way removed from the asymmetric centre, should still have diastereotopic methyls(See 72e).

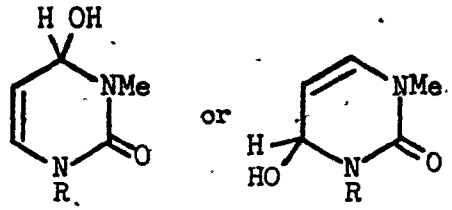
(72e)





(72e)

For the unsymmetrical cations(71a) two possible pseudo-bases(72a and 72b) may be formed. Indeed, from the NMR spectra(See Table 7) obtained after adding NaOD to D_2O solutions of (71a) it is evident that in most instances, both pseudo-bases are formed, though in unequal amounts. The problem is to decide which set of signals belongs to



(a) or (b)

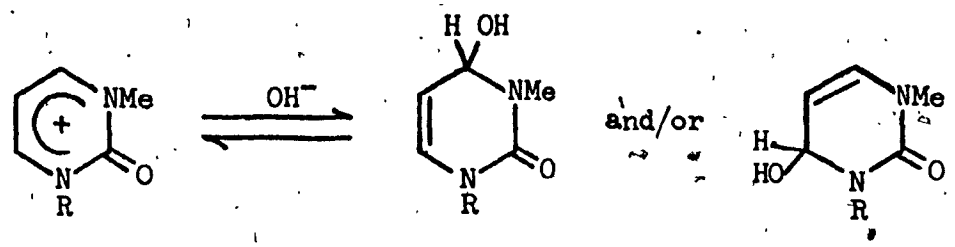
Table 7

NMR spectra of the pseudo-bases of 1,2-dihydro-1-alkyl (aryl)-3-methyl-2-oxo-pyrimidinium salts in D_2O (reference DSS)

R	6-H(δ)	4-H(δ)	5-H(δ)	NMe(δ)	other(δ)
Me	6.25	5.39	5.07	2.97 3.04	
Et	a) 6.30 b) 6.27	5.38 5.38	5.10 5.08	2.97 3.03	1.11(CH_3) 1.14(")
i-Pr	a) 6.55 b) 6.53	5.41 ?	5.18 ?	3.02 3.08	1.20,1.17(CH_3) **
t-Bu	6.58	5.27	5.04	2.94	1.43(CH_3)
c-Hex	6.59	5.43	5.17	3.03	
Ph	a) 6.30 b) 6.33	complex		3.04 3.11	7.42(Ph) 7.38(")
* $PhCH_2$	a) 6.41 b) 6.37	5.22 5.13	4.88 4.86	2.90 3.03	7.26(Ph),4.63(CH_2) 7.26("),4.38,4.13(CH_2)

coupling constant $J_{4,5}$=4.5Hz; $J_{5,6}$=8Hz where observable

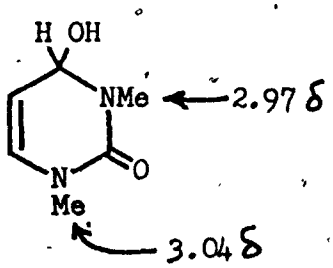
* in DMSO-d6, ** trace, a) major, b) minor



(71a) (72a) (72b)

which pseudo-base.

If we assume that NMe protons adjacent to the hydroxyl position

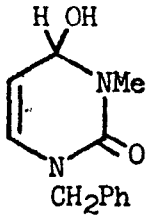


always occur to higher field than those adjacent to the 5,6-double bond, a consistent pattern of behaviour emerges. Given this assumption it appears that the predominant pseudo-base is always the one (72a) in which hydroxide attack on (71a) has occurred preferentially next to the less bulky methyl group.

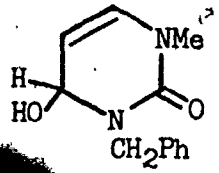
For example from the cation(71a;R=Et) the major pseudo-base(72a; R=Et) has the NMe signal at δ 2.97, whereas the minor pseudo-base(72b; R=Et) has it at δ 3.04. From the cation(71a;R=i-Pr) one pseudo-base greatly exceeds the other, with the major one having the NMe at δ 3.02, the minor one($\sim$6%) having the NMe at δ 3.08. Added confirmation of the structure of the major pseudo-base as (72a;R=i-Pr) is afforded by the splitting of the isopropyl Me signals due to diastereotopism(See p. 33 and 35). The magnitude of this splitting($\sim$2Hz) is consistent with the isopropyl group being distal to the hydroxyl

group(c.f. p.35).

A similar situation arises for the pseudo-bases derived from the methyl-benzyl cation(71a;R=$PhCH_2$). The major component(72a;R=$PhCH_2$) shows the NMe at δ 2.90, and a singlet(δ 4.63) for the benzylic protons. The minor component(72b;R=$PhCH_2$) shows its NMe at δ 3.03, and the benzylic protons as <u>two</u> signals at δ 4.13 and 4.38 due to the diastereotopism induced by the adjacent asymmetric centre(c.f. p.33 and 35).



(72a;R=CH_2Ph)



b;R=CH_2Ph)

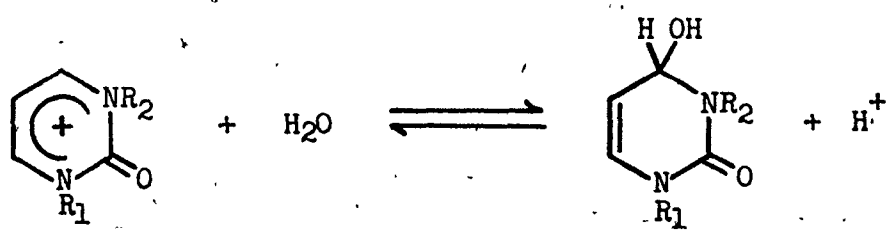
Of the two pseudo-bases derived from th[redacted]l-phenyl cation (71a;R=Ph), the major one has the NMe at δ 2.90 and is, presumably, (72a;R=Ph), while the minor one(72b;R=Ph) has its NMe at δ 3.03.

The remaining unsymmetrical cations(71a;R=t-Bu, c-Hex) each give only one observable pseudo-base which presumably have the structure (72a;R=t-Bu, c-Hex).

In summary, then, it appears that where two conceivable pseudo-bases may arise, the preferred one derives from hydroxide attack adjacent to less bulky substituent(i.e. 72a rather than 72b).

4) Pseudo-base Equilibria

In aqueous solution the cations(71) behave as weak acids due to their equilibria with their pseudo-bases(72), evidence for which is presented in the previous section. For these equilibria we may



(71) (72)

define $K=\frac{[72][H^+]}{[71]}$, and $pK=pH-\log\frac{[72]}{[71]}$.

Values of pK for various cations(71) were determined by the potentiometric method of Albert and Serjeant[38], and are presented in Table 8. The trends evident in these data are easily rationalized in terms of electronic and steric effects.

For progressively larger alkyl groups(Me,Et,i-Pr,t-Bu;Me,Et,n-Pr, n-Bu) two effects are anticipated. Firstly, the increasing electron-releasing capability of the substituent should stabilize the cation(71), and so increase the pK value. Secondly, the increasing steric bulk of the substituent should destabilize the pseudo-base(72) if the OH group is adjacent to that substituent, since from NMR evidence(previous section) it was concluded that the predominant pseudo-base formed from non-symmetric cations(71;$R_1 \neq R_2$) is that in which the hydroxy group is adjacent to the least bulky N-substituent. A bulky group, then, should also contribute to an increase in the value of pK.

These trends are amply demonstrated by the data in Table 8.

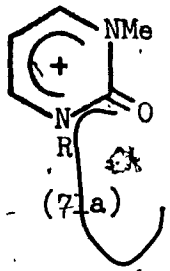
Table 8

pK values of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium[a] salts

temperature: 23-4°

R_1	R_2	X	pK	SD[b]	points
Me	Me	Cl	7.03[c]	—	—
Me	Me	HSO_4	7.12	0.04	10
Me	Et	I	7.20	0.03	13
Me	i-Pr	HSO_4	7.49	0.03	12
Me	t-Bu	HSO_4	8.41	0.07	18
Me	c-Hex	I	7.62	0.03	14
Me	Ph	Cl	4.87	0.01	8
Me	Ph	I	4.86	0.02	10
Me	CH_2Ph	HSO_4	6.49	0.02	6
Et	Et	HSO_4	7.49	0.03	12
Et	Et	I	7.50	0.03	14
Pr	Pr	I	7.42	0.03	14
i-Pr	i-Pr	$EtSO_4$	7.94	0.01	7
n-Bu	n-Bu	HSO_4	7.59	0.02	10

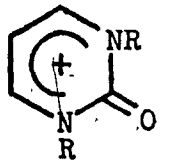
a. pK values could not be obtained for $R_1=R_2$=c-Hex and $R_1=R_2=CH_2Ph$, since the corresponding pseudo-bases precipitated from solution during attempted titration.
b. SD=standard deviation from least squares analysis.
c. ref.5, at 20°C.



(71a)

R =	Me	Et	i-Pr	c-Hex	t-Bu
pK =	7.12	7.20	7.49	7.62	8.41

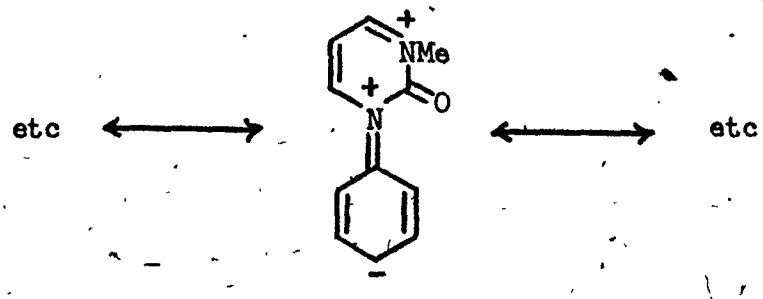
For the cations(71a) the value of the pK increases as anticipated. The effects are less well shown by the symmetrical cations(71c) since the alkyl groups cover a smaller range of electron-releasing ability and steric size.



(71c)

R =	Me	Et	n-Pr	n-Bu	i-Pr
pK =	7.12	7.50	7.42	7.59	7.94

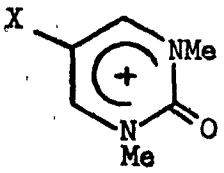
The effect of a phenyl substituent is evidently to <u>destabilize</u> the cation(71a;R=Ph), since its pK is reduced to 4.87. This may be attributed to the electron-withdrawing ability of a phenyl ring, as expressed by canonical structures such as -



A benzyl substituent is also slightly electron-withdrawing[57], and so the pK value of the cation(71a;R=CH_2Ph) is also reduced (to 6.49). The steric effects of these substituents(R=Ph or CH_2Ph) which are discernible from NMR spectra of the appropriate pseudo-base mixtures(vide

supra, p.36) would tend to increase the value of the pK. However, in view of the observed pK values, it is evident that the electronic effects of these substituents(which affect the overall electronic structure of the cations), overide their steric effects (which are site specific).

The presence of an electron-withdrawing substituent at the 5-position of a cation also serves to destabilize it, and hence to reduce its pK value. Here the reduction is quite dramatic, perhaps because the effect is totally electronic in nature, and lacks a countervailing steric component.

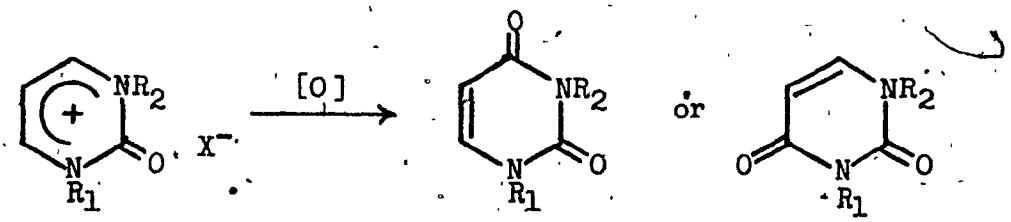


X =	H	Br
pK =	7.12	3.08

5) Oxidative ring transformation

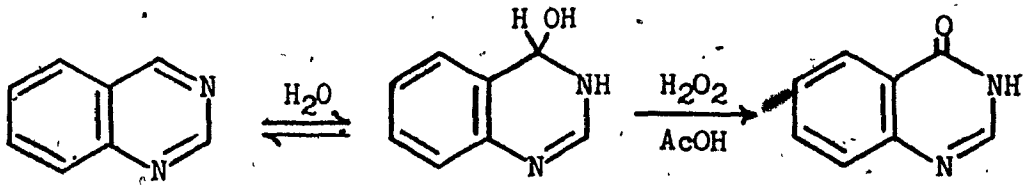
N-Heterocyclic quaternary salts with the potential for pseudo-base formation are often easily oxidised by potassium ferricyanide in alkaline solution to the oxo-derivatives, presumably via pseudo-base formation.[7]

Therefore, alkaline oxidation of 1,3-dialkyl-1,2-dihydro-2-oxo-pyrimidinium salts(62) was expected to give 1,3-dialkyluracils(80a or 80b). However, attempted oxidation of the 1,3-dimethyl cation(62; R_1=R_2=Me) using alkaline potassium ferricyanide gave only intractable oils.



(62) (80a) (80b)

Hydrogen peroxide is a useful reagent for oxidation of some heterocyclic compounds. For example, quinazoline(81) is oxidised to 4-quinazolone(83) by hydrogen peroxide in acetic acid.[29] Presumably

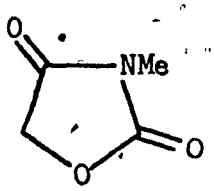


(81) (82) (83)

the easy formation of the covalent hydrate(82) facilitates this oxidation.

The oxidation of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium

bisulfate(62;R_1=R_2=Me,X=HSO_4) by hydrogen peroxide(2.3 equivalents) in acetic acid at 60-65° for 2 hours gave a sublimable white powder in good yield. This, however, was not 1,3-dimethyluracil as expected, but 3-methyloxazolidine-2,4-dione(84) which was identified

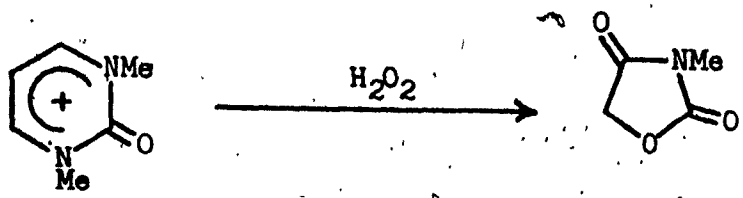


(84)

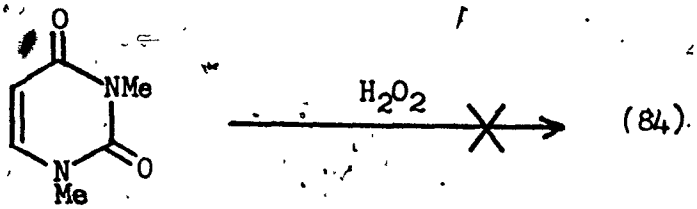
from its elemental analysis, IR, NMR and mass spectra, and by comparison with an authentic sample synthesised by a literature method.[43]

The same product(84) was obtained from oxidations carried out using 2.3 equiv. hydrogen peroxide in water or in basic solution(pH ~9). However, if only 1.15 equiv. of peroxide were used no product was obtained, even though, the reaction time was considerably extended(from 2 → 21 hours).

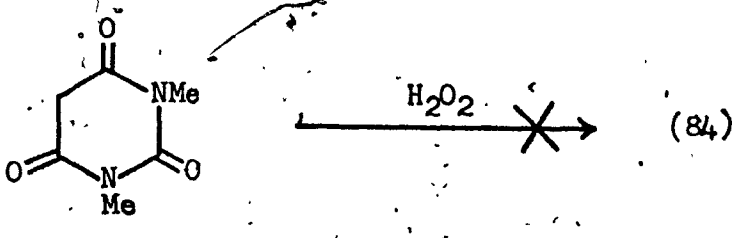
The oxazolidine product(84) is not derived from further oxidation of the expected product 1,3-dimethyluracil(85), since the latter is unaffected by hydrogen peroxide under the same reaction conditions.



(27) (84)



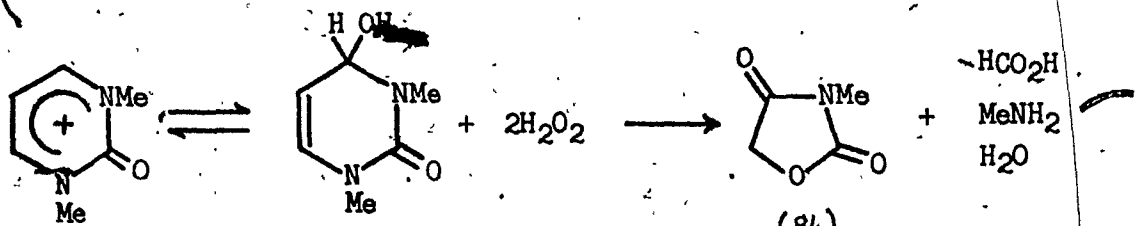
(85)



(86)

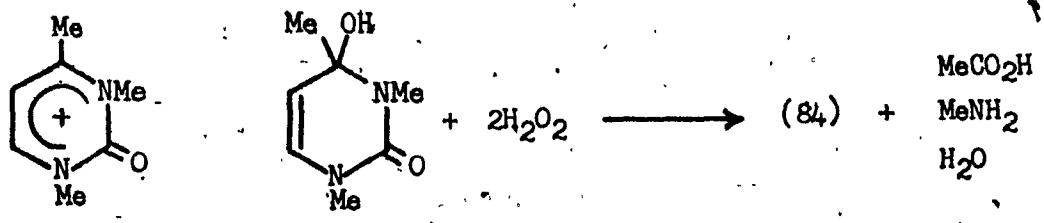
Similarly, another potential oxidation product 1,3-dimethylbarbituric acid(86)[40] when submitted to the oxidation condition did not give (84).

It appears that the stoichiometry of the oxidation of (27) is:



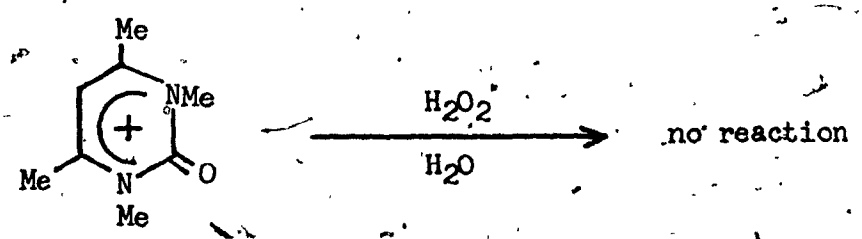
(27) (28) (84)

NMR spectra of reaction mixtures show a peak attributable to formic acid. Moreover, oxidation of the trimethyl cation(63a) in water



(63a) (75a)

gives the same oxazolidine(84) and NMR spectra show the presence of acetic acid. These observations suggest that oxidation of these cations(27) and (63a) proceeds in some way upon the pseudo-bases(28) and (75a), even though uracil derivatives do not appear to be involved. Somewhat surprisingly the tetramethyl cation(63b) does not undergo oxidation under the conditions used for the other cations. All the oxidation experiments are summarised in Table 11, p.54.



(63b)

The elucidation of the mechanisms of these interesting oxidations must await some future detailed study.

Experimental

Experimental

All melting points given below are uncorrected. UV spectra were taken in solutions of pH 0.29(1.0N. H_2SO_4) and pH 9.18(sodium borate buffer) on a Cary 14 instrument. NMR spectra were obtained from a Varian A-60 spectrometer. IR spectra(KBr) were obtained from a Perkin-Elmer 457 model. Mass spectra were run on a Perkin-Elmer-Hitachi RMU-6E mass spectrometer by Dr.R.T.Rye and Dr.T.J.Adley.

The following compounds were commercial samples used without further purification: malondialdehyde tetramethyl acetal, 1,3-dimethyluracil, acetylacetone, acetylacetaldehyde dimethyl acetal. The following ureas were also commercial in origin: 1,3-dimethyl, 1,3-diethyl, 1,3-diphenyl, 1,3-dicyclohexyl,1,3-dibenzyl. Commercial isocyanates used were: methyl, n-propyl, iso-propyl, n-butyl, t-butyl.

The following compounds were made by literature methods: 1,3-dimethylbarbituric acid,[58] 3-methyloxazolidin-2,4-dione,[43] 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bisulfate.[13]

5-Bromo-1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bromide was kindly supplied by Mr.S.Banerjee.

Synthesis of ureas

The other ureas required in this work were synthesised from isocyanates and amines(See Table 9). The general method used was as follows:

In an ice-cooled 100 ml 3-neck round-bottom flask fitted with a dropping funnel and $CaCl_2$ tube was placed 0.05 mole amine in 20 ml of either dry ether or dry benzene. To this was added dropwise

Table 9

1,3-disubstitutedurea $R_1\text{-NCO} + R_2\text{-NH}_2 \rightarrow R_1\text{NHCONHR}_2$

R_1	R_2	Temp.	Time(hr)	Yield(%)	M.p.(°C)	Solvent	Remarks	ref.
Me	Et	room	24	86 90	53-6	ether benzene	hygroscopic	47
Me	i-Pr	"	27	91.4	105-7	ether	lit. m.p.94-6°	48
Me	t-Bu	"	6	90.8	147-8	"	lit. m.p.146°	49
Me	Ph	"	18 24	61.5 89.5	148-50	"	lit. m.p.149-50°	47
Me	$PhCH_2$	"	17.5	91.5	97-8	"	lit. m.p. 98-9°	47
Pr	Pr	"	44	93	97-9	"	lit. m.p. 100°	50
i-Pr	i-Pr	"	24	89	188-90	"	lit. m.p. 192°	50
Bu	Bu	"	24	64.5	68-70	"	lit. m.p. 71°	50
t-Bu	t-Bu	"	24	89	222-24 *	"	lit. m.p. 242°	51

* in sealed tube

with stirring 0.05 mole of the isocyanate in 20 ml dry ether(or dry benzene). In most cases the urea started to precipitate from solution after a few minutes. To ensure complete reaction the mixture was stirred at room temperature for several hours(See Table 9). After this time the precipitate was filtered off, washed with ether and then dried.

All the reactions proceeded readily, and good to excellent yields of the ureas were obtained(See Table 9). Recrystallisation was usually from ligroin/benzene.

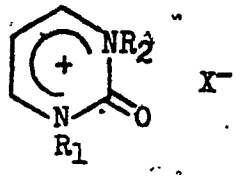
The only urea which was at all problematical was 1-ethyl-3-methylurea, which is hygroscopic.

Preparation of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts

General method: to a mixture of a 1,3-dialkylurea(0.025 mole) and malondialdehyde tetramethyl acetal(0.025 mole) in 25 ml either ethanol or methanol was added conc. acid(0.03 mole of hydrochloric acid, sulfuric acid or 47% hydriodic acid). When the acid used was sulfuric acid, the mixture was precooled in ice-water. After addition of the acid the mixture was stirred and heated at the temperature shown in Table 1, and the solvent was then removed on a rotary evaporator. The residue was recrystallised from appropriate solvents.

The NMR spectra of those salts showed the expected results (See Table 4 and 5). Also, the elemental analyses gave satisfactory results(See Table 10). The 1-methyl-3-phenyl-2-oxo-pyrimidinium chloride contains one molecule of water of crystallisation. Also, the 1,3-dibenzyl-2-oxo-pyrimidinium bisulfate

Table 10



Elemental analyses of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts

				Calc.(%)			Found(%)		
R_1	R_2	X	Formula	C	H	N	C	H	N
Me	Et	Cl	$C_7H_{11}N_2OCl$	48.14	6.35	16.05	47.91	6.25	15.90
Me	Et	I	$C_7H_{11}N_2OI$	31.60	4.17	10.53	31.31	4.32	10.44
Me	i-Pr	HSO_4	$C_8H_{14}N_2O_5S$	38.39	5.64	11.20	38.54	5.56	11.22
Me	t-Bu	HSO_4	$C_9H_{16}N_2O_5S$	40.90	6.10	10.60	40.75	6.14	10.60
Me	c-Hex	I	$C_{11}H_{17}N_2OI$	41.27	5.35	8.75	41.43	5.32	8.78
Me	Ph	Cl	$C_{11}H_{11}N_2OCl.H_2O$	54.89	5.44	11.64	54.23	5.56	11.37
Me	Ph	I	$C_{11}H_{11}N_2OI$	42.06	3.53	8.92	41.80	3.83	8.73
Me	$PhCH_2$	HSO_4	$C_{12}H_{14}N_2O_5S$	48.31	4.73	9.39	48.44	4.78	9.41
Et	Et	HSO_4	$C_8H_{14}N_2O_5S$	38.39	5.64	11.20	38.35	5.45	11.01
Et	Et	I	$C_8H_{13}N_2OI$	34.30	4.64	10.00	34.40	4.73	9.96
Pr	Pr	I	$C_{10}H_{17}N_2OI$	38.98	5.56	9.09	39.02	5.42	8.94
i-Pr	i-Pr	$EtSO_4$	$C_{12}H_{22}N_2O_5S$	47.04	7.24	9.14	47.24	7.39	9.22
n-Bu	n-Bu	HSO_4	$C_{12}H_{22}N_2O_5S$	47.04	7.24	9.14	46.98	7.22	9.07
$PhCH_2$	PhCH2	HSO_4	$C_{18}H_{18}N_2O_5S.1/2H_2O$	56.38	5.00	7.31	56.35	5.46	6.96
c-Hex	c-Hex	$EtSO_4$	$C_{18}H_{32}N_2O_5S$	55.65	8.30	7.21	55.83	7.82	7.33

contains 1/2 H_2O. On the other hand, the 1,3-diethyl-2-oxo-pyrimidinium chloride, the 1-ethyl-3-methyl-2-oxo-pyrimidinium bisulfate, the 1,3-di-n-propyl-2-oxo-pyrimidinium chloride and the 1,3-di-n-butyl-2-oxo-pyrimidinium chloride are highly hygroscopic and were not submitted for analysis.

Preparation of 1,2-dihydro-2-oxo-1,3,4-trimethyl- and 1,3,4,6-tetramethylpyrimidinium salts

These compounds were made in the manner outlined by Bauman et al.[39]

Reaction of 1,3-dimethylurea and acetylacetaldehyde dimethyl acetal in the presence of conc. sulfuric acid at room temperature for 22 hours gave 1,2-dihydro-2-oxo-1,3,4-trimethylpyrimidinium bisulfate. One recrystallisation from ethanol/acetone gave colourless needles, m.p. 120-121°. Second recrystallisation gave colourless plates, m.p. 106-107°. Analysis of these plates corresponded to a hydrate $C_7H_{12}N_2O_5S \cdot H_2O$: Calc. C,33.07;H,5.55;N,11.02. Found: C,33.34; H,5.73;N,10.78. NMR(D_2O): δ 2.75(CMe),* δ 3.74(NMe), δ 6.96(5-H), δ 8.66 (6-H). See Table 2 for UV data.

From the reaction of acetylacetone, 1,3-dimethylurea and conc. hydrochloric acid at 70° for 5 hours was obtained 1,2-dihydro-2-oxo-1,3,4,6-tetramethylpyrimidinium chloride. Yield 85%. Colourless needles from ethanol/acetone which upon heating became semiliquid at 80° and appeared to lose water. The material remaining melted with decomposition at 209-211°. Analysis of these needles approximately

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* The C-Me groups underwent facile H/D exchange with the solvent.[46]

corresponded to a hydrate $C_8H_{13}N_2OCl \cdot 2.5H_2O$: Calc. C,41.12;H,7.77; N,11.99. Found: C,41.07;H,7.08;N,12.23. A second recrystallisation followed drying in vacuo over silica gel gave needles, m.p. 210°, which analyzed for a different hydrate $C_8H_{13}N_2OCl \cdot 1/2\ H_2O$: Calc. C,48.61;H,7.14;N,14.17. Found: C,48.72;H,7.24;N,14.07. NMR(D_2O): δ 2.70(CMe), δ 3.70(NMe), δ 6.92(5-H). The corresponding tetramethylpyrimidinium bisulfate was obtained in 64% yield from reaction in the presence of conc. sulfuric acid at room temperature for 21 hrs. Colourless needles from ethanol/acetone, m.p. 144-145°. Analysis for $C_8H_{14}N_2O_5S \cdot H_2O$: Calc. C,35.82;H,6.01;N,10.44. Found: C,35.75; H,5.98;N,10.39. This material is slightly hygroscopic. NMR(D_2O): δ 2.69(CMe), δ 3.72(NMe), δ 6.92(5-H).

The UV data for these compounds may be found in Table 3.

Oxidation of 1,2-dihydro-1,3-dimethyl-2-oxo-pyrimidinium bisulfate

To a solution of 2.22g(0.01 mole) of the pyrimidinium bisulfate in 20 ml of glacial acetic acid was added 2 ml(0.023 mole) of 30% hydrogen peroxide at room temperature. The solution was then warmed at 60-65° on a water-bath for 2 hours. Acetic acid was evaporated on a rotary evaporator and to the residue was added 10 ml of water to remove the solvent completely and evaporated again. White crystals were filtered off and dried in a desiccator. Wt. 0.8g(70%). Recrystallised from ligroin/anhyd. ethanol and sublimed under 20 mmHg at 110°, m.p. 130-133°. Analysis for $C_4H_5NO_3$: Calc. C,41.75;H,4.38;N,12.17. Found C,41.80;H,4.42;N,12.30. IR(KBr): νCO, 1823,1711 cm^{-1}. NMR(D_2O): δ 2.94(NMe), δ 4.70(5-H). Mass spectrum: m/e 115.

This material was identical to 3-methyloxazolidin-2,4-dione.[40]

Reactions in water or alkaline aqueous solution(~pH9) instead of acetic acid gave the same product as above.

Oxidation of 1,2-dihydro-2-oxo-1,3,4-trimethylpyrimidinium bisulfate

A mixture of 2.36g(0.01 mole) of the pyrimidinium bisulfate in 10 ml of water and 2 ml of 30% hydrogen peroxide was warmed at 70-75° for 6 hours. Water was evaporated under reduced pressure and the residue was distilled with benzene added in order to remove water. Benzene was then evaporated on a rotary evaporator to give oily crystals, which were recrystallised from ligroin/ethanol. Yield 0.5g (43%), m.p. 130-133°. The compound was also identical with 3-methyloxazolidin-2,4-dione.

Preparation of 3-methyloxazolidin-2,4-dione[40]

A mixture of 3.5g(0.034 mole) of ethylmethylcarbamate and 3.9g (0.035 mole) of chloroacetyl chloride was heated at 180-190° for 1 hour. The reaction mixture solidified on cooling, and was washed with ligroin and then filtered. Wt. 2.6g(66.5%). Recrystallised from ligroin/ethanol, white triangular plates, m.p. 133-134°.

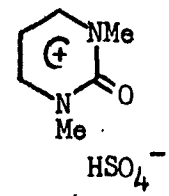
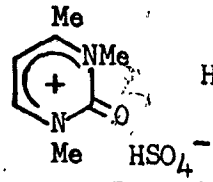
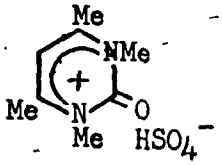
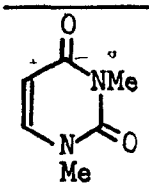
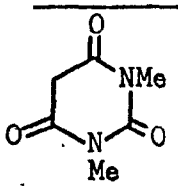
Isolation of pseudo-bases of 1,2-dihydro-1,3-disubstituted-2-oxo-pyrimidinium salts

The pseudo-bases of 1,3-dibenzyl- and 1,3-dicyclohexyl-1,2-dihydro-2-oxo-pyrimidinium salts were isolated as glassy solids from aqueous solution by the addition of alkali.

General method: to a concentrated aqueous solution of the pyrimidinium salt was added 1N. sodium hydroxide dropwise until the precipi-

Table 11

Oxidation reactions of pyrimidine derivatives

compound	reagent	solvent	time (hr)	temp. (°C)	yield (%)	remarks
	H_2O_2 (2.3)*	AcOH	2	60–65	70[b]	(84)
	" (1.15)	AcOH	2	60–65		no reaction
	" (2.3)	AcOH	1	60–65	44[a]	(84)
	" (1.15)	AcOH	21	60–65		no reaction
	" (2.3)	H_2O	4 days	R.T.	100[b]	(84)
	" (2.3)	H_2O, pH9	3	60–65	52[b]	(84)
	" (2.3)	H_2O	6	70–75	61[b]	(84)
	$K_3Fe(CN)_6$ (1.8)	NaOH	6	R.T.		unidentified products
	" (1.1)	NaOH	6	R.T.		
	H_2O_2 (2.3)	H_2O	6	70–75	43[a]	(84)
	"	H_2O	6	70–75		no reaction ? recovered starting material
	"	AcOH	2	60–65		no reaction ? recovered starting material
	"	AcOH	2.5	65–70		unidentified product

* equivalent; a. after recrystallisation ; b. crude (84) is 3-methyloxazolidin-2,4-dione.

tation was complete. The pale yellow sticky precipitate was collected and dried in air to a glassy solid. They could not be recrystallised.

The pseudo-base of 1,3-dibenzyl-1,2-dihydro-2-oxo-pyrimidinium bisulfate: NMR(DMSO-d6/TMS) δ 6.42(6-H), δ 5.21(4-H), δ 4.93(5-H), δ 7.25,7.28(Ph's). UV(95% ethanol) λ max 241 nm. Mass spec. m/e 292.

The pseudo-base of 1,3-dicyclohexyl-1,2-dihyro-2-oxo-pyrimidinium ethylsulfate: NMR(acetone-d6/TMS) δ 6.41(6-H), δ 5.33(4-H), δ 4.99(5-H). UV(95% ethanol) λ max 239 nm(log 3.73). Mass spec. m/e 278.

The other pseudo-bases were not isolated except those of 1-benzyl-1,2-dihyro-3-methyl-2-oxo-pyrimidinium bisulfate and 1,3-di-n-butyl-1,2-dihyro-2-oxo-pyrimidinium bisulfate which were obtained as oils. The NMR spectra of those oil products gave the satisfactory results(See Table 6 and 7).

Isolation of the anhydrobase of 1,2-dihydro-2-oxo-1,3,4,6-tetramethyl-pyrimidinium bisulfate

As soon as 1.0g(0.004 mole) of 1,2-dihyro-2-oxo-1,3,4,6-tetramethylpyrimidinium bisulfate was dissolved in 40 ml of 1N. potassium hydroxide or sodium hydroxide at room temperature, the solution became turbid and deposited a white precipitate, which was filtered off, washed with water and dried in a vacuum desiccator. Yield 0.442g (73%). The anhydrobase is very unstable in air, in that it becomes red and sticky. NMR($CDCl_3$) δ 5.40(5-H), δ 3.68,3.63(=CH_2), δ 3.20,3.13(NMe), δ 2.00(CMe). Mass spec. m/e 152. IR(KBr) did not show any hydroxyl bands.

Measurement of pKs

Ionization constants of the 2-oxo-pyrimidinium salts were determined by the potentiometric method:[38] 25 ml of a solution(0.01 mole) of the pyrimidinium salt was titrated against a standard potassium hydroxide solution(0.05N. or 0.01N.) at 23-24° by using a Potentiograph E436(Metrohm Herisau) previously calibrated using suitable standard buffer solutions. Back-titration was carried out using a standard hydrochloric acid solution(0.01N.). From the titration curve obtained, volumes of the titrant and pH corresponding to the volume of titrant added were read, and pK values were then calculated by using a computer program(See Appendix).

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Appendix

The following computer programs (in BASIC) were written by Mr.S.Banerjee and Dr.O.S.Tee, and utilise the method of calculation suggested by Albert and Serjeant.[38]

PK (without correction for bisulfate)

```
1  DIM F[50]
2  PRINT
3  PRINT
4  PRINT
6  LET S=0
10  DATA
11  DATA
29  DATA -1,-1
31  LET T=1
36  LET V=25
40  PRINT "CONC. OF TITRANT, SUBSTRATE (N) ";
41  INPUT N0,N1
43  PRINT  "PH/DIV,BASE";
44  INPUT D,B
50  PRINT
51  PRINT
52  PRINT
60  PRINT "MLS.",TAB(16),"PH",TAB(20),"PK"
65  PRINT
70  LET N=Z=Q1=0
100  FOR I=1 TO 100
105  READ M,P
106  LET P=P*D+B
110  IF M<0 THEN 300
120  LET N2=N0*M/(M+V)
125  LET N3=N1*V/(V+M)-N2
126  IF N2=0 THEN 105
127  IF N3<=0 THEN 105
130  LET H=EXP(-LOG(10)*P)
132  LET O=1.00000E-14/H
135  IF S>0 THEN 180
145  IF T<1 THEN 160
150  LET Q=(N3-H+O)/(N2+H-O)
155  GOTO 250
160  GOTO 190
180  IF T>0 THEN 150
190  LET Q=(N2-H+O)/(N3-O+H)
250  LET P[I]=LOG(Q)/(LOG(10))+P
260  PRINT M,P,P[I]
```

```
265  LET N=N+1
270  NEXT I
280  PRINT
281  PRINT
300  FOR J=1 TO N
301  LET P[J]=EXP(-P[J]*LOG(10))
305  LET Z=Z+P[J]
310  NEXT J
315  LET P=Z/N
320  FOR I=1 TO N
325  LET Q=P[I]-P
330  LET Q1=Q1+Q↑2
335  NEXT I
339  PRINT
340  LET S=(Q1/(N-1))↑(.5)
341  LET S=-LOG(P-S)/LOG(10)
343  LET P=-LOG(P)/LOG(10)
344  LET S=S-P
345  PRINT "AVE=";P;"SD=2;S
350  PRINT
351  PRINT
999  END
```

PK (correction for bisulfate)

```
1   DIM P[50]
2   PRINT
3   PRINT
4   PRINT
6   LET S=0
10  DATA
11  DATA
29  DATA -1,-1
31  LET T=1
36  LET V=25
40  PRINT "CONC. OF TITRANT, SUBSTRATE (N)";
41  INPUT NO,N1
42  LET V=V+250*N1
43  PRINT "PH/DIV,BASE";
44  INPUT D,B
50  PRINT
51  PRINT
52  PRINT
60  PRINT "MLS.",TAB(16),"PH",TAB(20),"PK"
65  PRINT
70  LET N=Z=Q1=0
100 FOR I=1 TO 100
105 READ M,P
106 LET P=P*D+B
107 LET M=M-250*N1
110 IF M<0 THEN 300
```

```
120  LET N2=NO*M/(M+V)
125  LET N3=N1*V/(V+M)-N2
126  IF N2=0 THEN 105
127  IF N3 <= 0 THEN 105
130  LET H=EXP(-LOG(10)*P)
132  LET O=1.00000E-14/H
135  IF S>0 THEN 180
145  IF T<1 THEN 160
150  LET Q=(N3-H+O)/(N2+H-O)
155  GOTO 250
160  GOTO 190
180  IF T>0 THEN 150
190  LET Q=(N2-H+O)/(N3-O+H)
250  LET P[I]=LOG(Q)/(LOG(10))+P
260  PRINT M+250*N1,P,P[I]
265  LET N=N+1
270  NEXT I
280  PRINT
281  PRINT
300  FOR J=1 TO N
301  LET P[J]=EXP(-P[J]*LOG(10))
305  LET Z=Z+P[J]
310  NEXT J
315  LET P=Z/N
320  FOR I=1 TO N
325  LET Q=P[I]-P
330  LET Q1=Q1+Q↑2
335  NEXT I
340  LET S=(Q1/(N-1))↑(.5)
341  LET S=-LOG(P-S)/LOG(10)
343  LET P=-LOG(P)/LOG(10)
ΣΣ   LET S=S-P
345  PRINT "AVE=";P;"SD=";S
350  PRINT
351  PRINT
352  PRINT
999  END
```