THE MECHANISM OF BROMINATION OF 4-QUINAZOLONE AND ITS N-METHYL DERIVATIVES

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To my wife, Prabha

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ABSTRACT

GHANSHYAM VITHAL PATIL

THE MECHANISM OF BROMINATION OF 4-QUINAZOLONE AND ITS N-METHYL DERIVATIVES

The kinetics of bromination of 4-quinazolone, 3-methyl-4-quinazolone, and 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate have been measured in dilute aqueous acid media. For the three substrates second order kinetics are obeyed; first order in substrate, first order in bromine. Consequently, pseudo-first order rates were measured using excess substrate, the decrease in bromine concentration being followed titrimetrically. On the basis of the order of reaction and the acidity dependence of the rates it was concluded that reaction proceeds via slow attack of bromine upon the covalent hydrate (or pseudo base) of the substrate leading, by proton loss, to the corresponding 6-bromo-product.

TABLE OF CONTENTS

Part I - INTRODUCTION

	Page
GENERAL INTRODUCTION	1
QUINAZOLINES	
Introduction	2
Electrophilic Substitution	2
Covalent hydration	3
Nucleophilic addition	5
Pseudo base formation in quinazoline and related compounds	6
4-QUINAZOLONE	
Tautomerism	8
Theoretical aspects	9
Electrophilic substitution	
Nitration	9
Chlorination	10
Sulfonation	10
Bromination	10
Covalent hydration	11
Pseudo base formation	12
ELECTROPHILIC SUBSTITUTION OF PYRIMIDONES	13

Part II - EXPERIMENTAL

INTRODUCTION	14
PREPARATION OF COMPOUNDS	18
MEASUREMENT OF RATE CONSTANTS	25
Kinetic procedure	25
Reagents	28
Acidity	28
Second order rate constant	28
Computer programs	29
Example of a kinetic run	31
Product isolation	32
PSEUDO BASE FORMATION	33

Part III - RESULTS AND DISCUSSION

	Page
INTRODUCTION	35
PRODUCT OF BROMINATION	35
ORDER OF REACTION	37
BROMIDE ION DEPENDENCE	40
ACIDITY DEPENDENCE OF THE BROMINATION OF 4-QUINAZOLONE	47
ACIDITY DEPENDENCE OF THE BROMINATION OF 3-METHYL-4-QUINAZOLONE	51
ACIDITY DEPENDENCE OF THE BROMINATION OF 1,4-DIHYDRO-1,3-DIMETHYL-4-OXO-QUINAZOLINIUM PERCHLORATE	55
CONCLUSION	

Part IV - APPENDIX

ACETATE ION DEPENDENCE	66
MODEL COMPOUND FOR PSEUDO BASE	70
2-QUINAZOLONE Synthesis Model compounds Solubility	74
2,4-QUINAZOLINEDIONES	76

Part V - BIBLIOGRAPHY

78

INDEX TO TABLES

NO	CONTENT	PAGE
1	Ionisation constants and u.v. spectral data of 4-quinazolone substrates and their 6-bromo products.	16
2	P.m.r. spectral parameters of 4-quinazolone substrates and their 6-bromo products.	17
3	Variation of the rate of bromination (k_1) of 4-quinazolone (22) with substrate concentration.	38
4a	Variation of the rate of bromination of 4-quinazolone (22) with [Br^-]	42
4b		43
5a	Variation of the rate of bromination of 4-quinazolone (22) with pH	48
5b		49
6a	Variation of the rate of bromination of 3-methyl-4-quinazolone (36) with pH	52
6b		53
7a	Variation of the rate of bromination of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37) with pH	56
7b		57
8	Variation of the rate of bromination of 4-quinazolone (22) in buffers	67
9	Variation of the rate of bromination of 4-quinazolone (22) with acetate ion concentration	68
10	The rate of bromination of N-methyl-o-methylaminobenzamide in 10N H_2SO_4	73
11	The rate of bromination of N-Methyl anthranilic acid in 10N H_2SO_4	73

INDEX TO FIGURES

FIGURE NO.	TITLE	PAGE
1	A plot of $\ln[Br_2]_t$ against time for 4-quinazolone	27
2	U.v. spectral changes accompanying bromination of 22→38	36
3	Variation of the pseudo first order rate constant (k_1) with substrate concentration	39
4a	Variation of the rate of bromination of 4-quinazolone with Br^-	44
4b	Variation of the rate of bromination of 4-quinazolone with Br^-	46
5	Observed rate profile for 4-quinazolone	50
6	Observed rate profile for 3-methyl-4-quinazolone	54
7	Observed rate profile for 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate with pH	58
8	Observed rate profiles for 4-quinazolone and its N-methyl derivatives	61

INTRODUCTION

GENERAL INTRODUCTION

There has been much research done on the medicinal aspects of quinazolines and their derivatives. Surprisingly though, very little has been done on the mechanistic aspects of their chemistry.

Several quinazolones have been incorporated into the vitamin B_{12} molecule in place of the 5,6-dimethylbenzimidazole moiety. The resulting compounds possessed cobalamine activity.[1-4] 3-Hydroxy-4-quinazolone was found to be useful in protection against x-ray irradiation damage.[5,6] Furthermore, several derivatives of 4-quinazolone have been found to be active against protozones and influenza.[7-12]

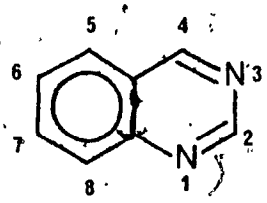
The object of ~~the work described~~ in this thesis was to investigate the mechanism of the bromination[13] of quinazolones, partly for comparison with their non-benzonoid analogues, pyrimidones.[14-16] The kinetic experiments on 4-quinazolones described herein suggest that a covalent hydrate (or pseudo-base) is the reactive species involved in the bromination in the aqueous acid solutions.

Such studies may throw light on the importance of covalent hydration in enzyme catalysed oxidations, since covalent hydrates behave as secondary alcohols which may easily undergo oxidation. For example, the enzyme Xanthine oxidase catalyses the oxidation of aldehydes to acids, purines to hydroxypurines and pteridines to hydroxypteridines[17,18], and it is a reasonable hypothesis that covalent hydrates are involved in these oxidations.

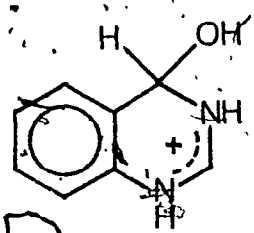
QUINAZOLINES

Introduction

Before the name quinazoline was universally adopted, it was variously called phenminazine, benzaleneamidine, benzo-1,3-diazene, 5-6-benzopyrimidine and 1,3-diazanaphthalene. The numbering system which is currently in use (1) was suggested by Paal and Busch.[19]



(1)



(2)

In quinazoline (1) the two rings are potentially aromatic.[20,21] However since a doubly-bonded nitrogen atom has high electron-affinity, the two nitrogen atoms of the pyrimidine ring of quinazoline polarise the π-electron layer so strongly that normal aromatic stability is reduced.[22,23] The overriding delocalisation of the attached benzene ring of quinazoline also contributes to the localisation of the π-electrons of the 3,4 double bond making it behave more like an isolated double bond. As a result, a weak nucleophile like water adds easily across the 3,4 double bond to produce the cation of structure (2).[20,22]

Electrophilic Substitution

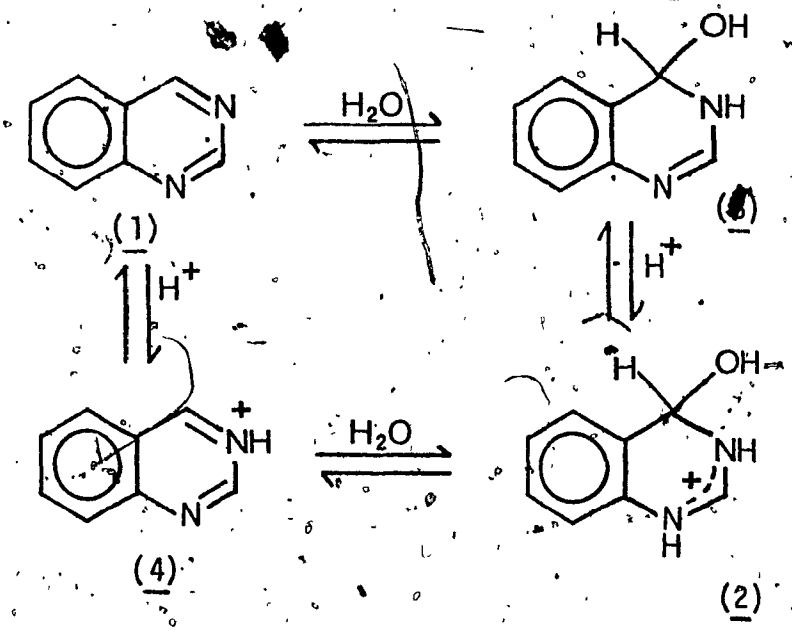
Since quinazoline (1) has an electron deficient π-system,[24] electrophilic substitution occurs with difficulty. Theoretical studies[25] based on localisation energies indicate that the expected order of reactivity of the positions is $8 > 6 > 5 > 7 \gg 4 > 2$. A similar

treatment by Brown,[26] using electron densities reveals the slightly different order of reactivity, 6 > 8 > 5 > 7 ≫ 2 > 4. Nitration is the only known electrophilic substitution reaction of quinazoline and 6-nitroquinazoline is the only isomer reported from the nitration reaction in concentrated sulfuric acid.[27-29] It was suggested,[30] that the nitration proceed via hydrated cation (2), but now it is known that the quinazoline exists as dication in concentrated sulfuric acid,[31] and so this suggestion may be wrong.

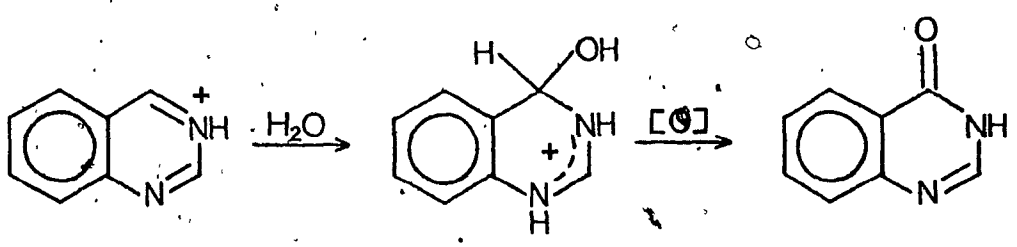
Covalent Hydration

Quinazoline (1), and its cation (4), reversibly add water across the 3,4-NC double bond.[20,21] Such an addition is described as covalent hydration.[22]

Albert and coworkers[32] found that quinazoline is a tenfold stronger base than 4-methylquinazoline. This result was unexpected since a methyl group is base-strengthening. The anomaly was explained by the equilibria (eqn. 1) involving covalent hydrates (3 and 2) of quinazoline (1) and its cation (4).



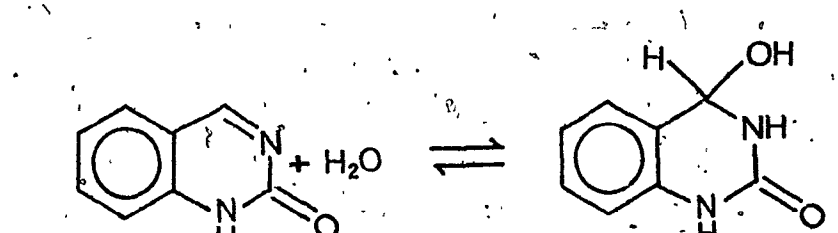
Interestingly, quinazoline hydrochloride (4), which adds water to produce the covalent hydrate (2), undergoes mild oxidation with acidic hydrogen peroxide to produce 4-quinazolone (22) in high yield.[20]



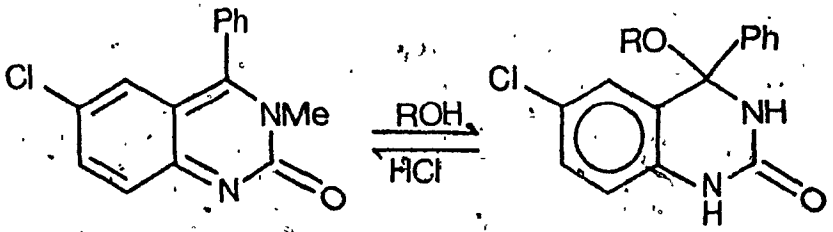
(4)* (2) (22)

* A necessary feature for covalent hydration is the presence of powerful electron withdrawing centers which are capable of depleting the π-electron layer so that a highly polarised bond is isolated from Kekule type conjugation, and its reactivity is enhanced. Thus the 3,4 double bond in 2-hydroxypteridine[34] and 2-aminopteridine[22] add many nucleophilic reagents.

It has been demonstrated[23] that the neutral species of 2-quinazolone(5) in aqueous solution adds water across 3,4 N=C bond, so that about 25% exists as 6. Similarly 6-chloro-3-methyl-4-phenyl-2-



(5) (6)

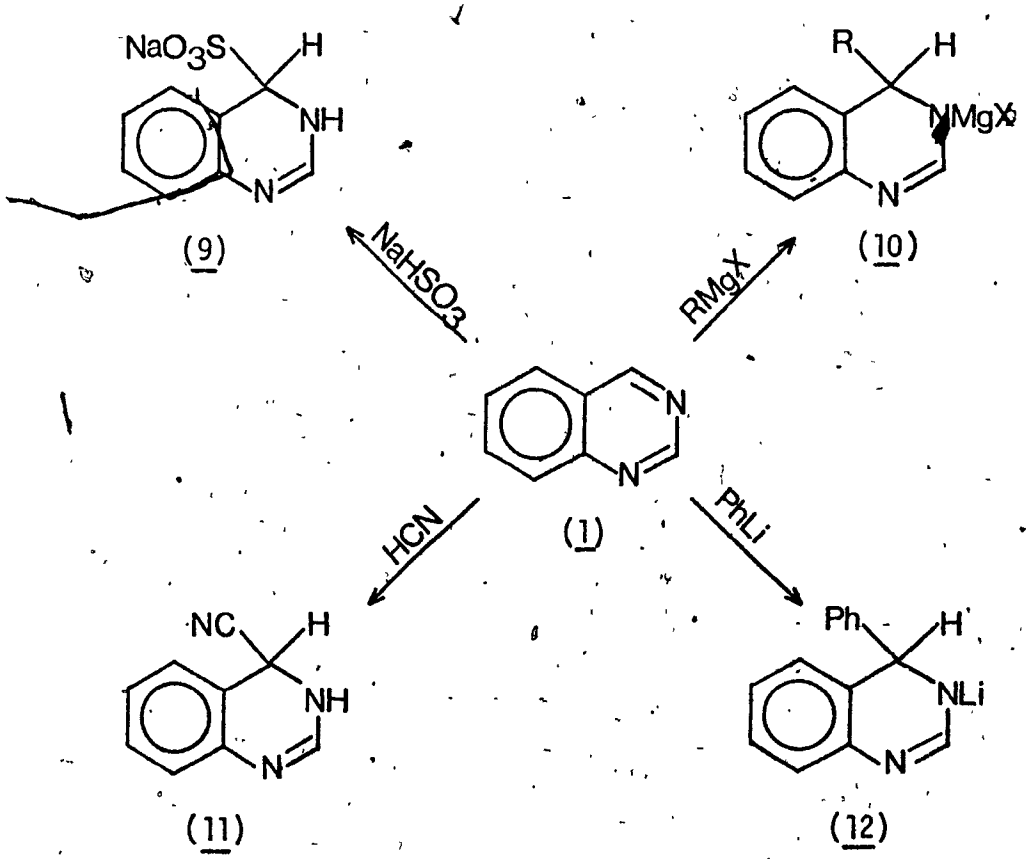


(7) (8)

quinazolone (7) adds water and methanol covalently across the 1,4 positions.[35]

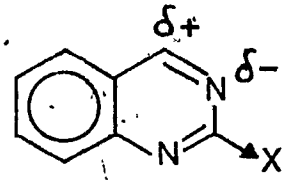
Nucleophilic addition

In addition to water, nucleophilic reagents like sodium bisulfite, hydrogen cyanide, alkyl or aryl magnesium-halide and phenyl lithium add to quinazoline (1) to give the corresponding 4-substituted-3,4-dihydro-quinazolines (9, 10, 11, 12).



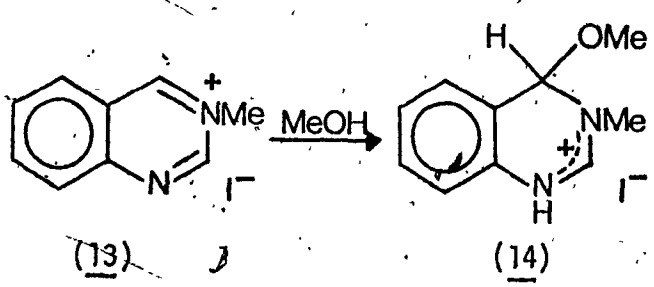
The presence of electron withdrawing groups ($-NO_2$, $-CF_3$) in benzene ring of quinazoline assist nucleophilic addition,[33] but such substituents in the 2-position in the pyrimidine ring of quinazoline

antagonise addition. In the position 2, the substituent attracts electron density from N-3 and so the polarisation required for addition is diminished.[36]

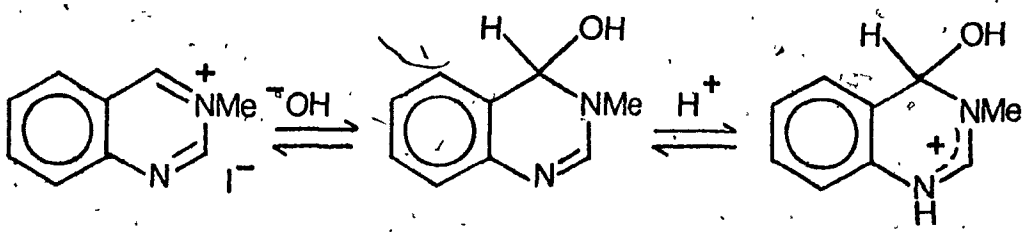


Pseudo base formation in quinazoline and related compounds

German workers[37] observed that crystallisation of the quaternary iodide (13) from methanol-ether affords the methanolate (14). Similarly, aqueous alkali upon 13 affords the pseudo-base (15), which in aqueous acid is converted to the cation (16).[21]

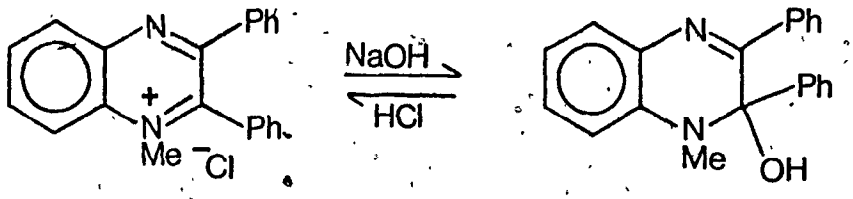


(13) (14)



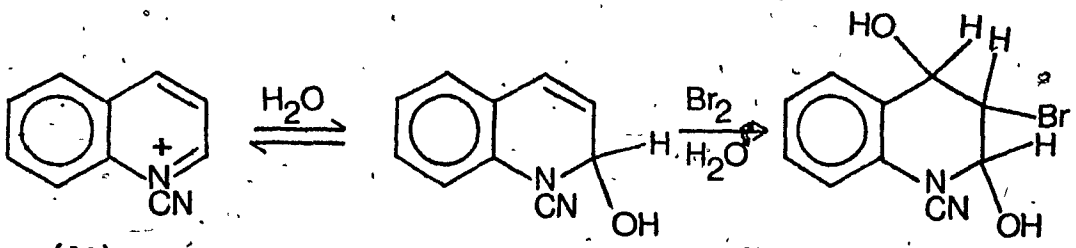
(13) (15) (16)

Also, 1-methyl-2,3-diphenyl-quinoxalinium chloride (17) upon action of dilute alkali affords the pseudo-base (18).[39]



(17) (18)

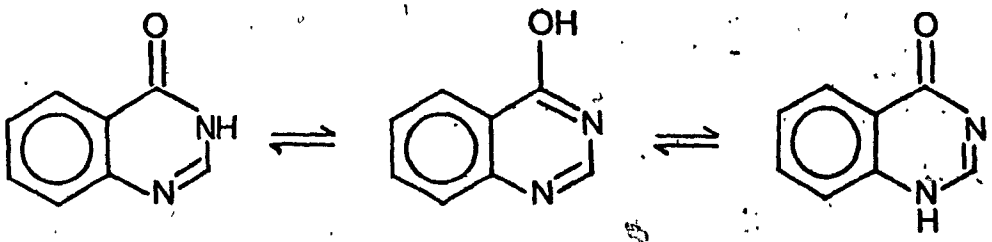
The intermediacy of pseudo-bases in the H-D exchange and bromination of some quaternised pyrimidones has been invoked by Banerjee and Tee.[14,15,16,55,56,60] Also it appears that the bromination of the N-cyano-quinolinium ion (19) occurs via its pseudo-base (20) giving (21) which upon elimination produces 3-bromo product.[40]



(19) (20) (21)

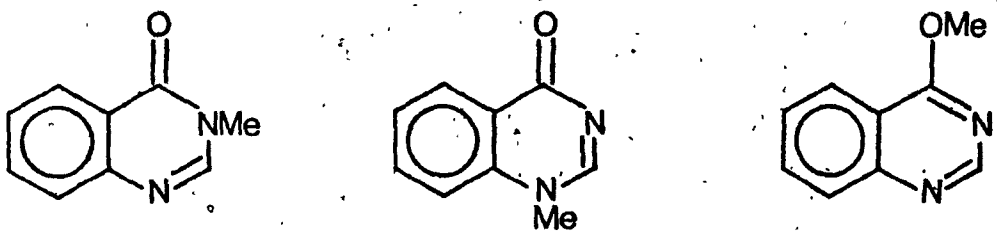
Tautomerism

4-QUINAZOLONE



(22) (23) (24)

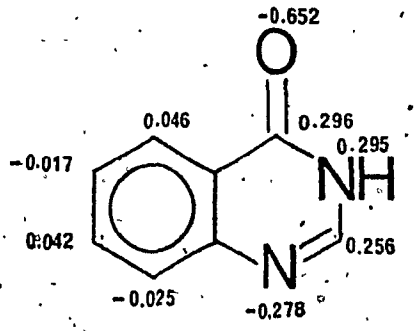
4-Quinazolone (22) exists in three tautomeric forms shown above.[41] From a detail examination of ultraviolet spectra of 4-quinazolone (22), 3-methyl-4-quinazolone (36), 1-methyl-4-quinazolone (25) and 4-methoxyquinazoline (26) (presumably in ethanol since the solvent is unspecified), Hearn and coworkers[41] concluded that (22), (23) and (24) exist in ratio 7:2:1 respectively.



(36) (25) (26)

The predominance of oxo-tautomers is also shown by the presence of strong C=O and N-H stretch vibrations in the infrared spectra.[42,43] Since the oxo forms are the predominant tautomers, the name 4-quinazolone is adopted throughout this thesis.

Theoretical aspects[44]



(22)

The charge densities of (22) obtained by a Huckel molecular orbital treatment indicate that the carbon between the two nitrogen atoms is positive. This makes the 1,2 bond very polarised and thus position 2 is susceptible to the nucleophilic attack.

Electrophilic substitution

Nitration

Reaction of fuming nitric acid and sulfuric acid with 4-quinazolone (22) produces the 6-nitro derivative.[45,46] The yield of this reaction may be improved by keeping the reaction temperature below 95°.[47] 1-Methyl, 2-methyl and 2,3-dimethyl-4-quinazolone also give

6-nitro products upon nitration.[48-51]

Chlorination

Chiang et al[52] carried out the chlorination of 4-quinazolone in acetic acid with $FeCl_3$ at 100°. They noted that absorption of chlorine was relatively fast in first ten minutes upto a mole ratio of 1:1 and that beyond this ratio the rate was considerably decreased. The 6,8-dichloro derivative was isolated after an hour, but direct chlorination of the 6-chloro product was unsuccessful!

Sulfonation

4-Quinazolone (22) upon treatment with chlorosulfonic acid yields a 6-chlorosulfonyl derivative. Similarly 2-methyl and 7-chloro-4-quinazolone in presence of HgO and 10% oleum gives 6-sulfonic acids.[53]

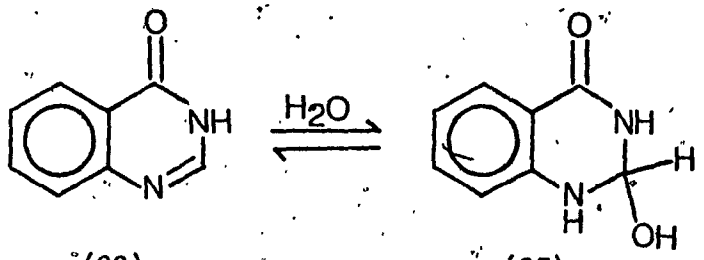
Bromination

Bogert and Geiger[46] reported that all attempts to brominate 4-quinazolone with the bromine in aqueous potassium bromide solution, in glacial acetic acid or in acetic anhydride failed. However, they obtained a monobromo product of 4-quinazolone and its 2-methyl derivative upon bromination in concentrated sulfuric acid. The position of the bromine in their product was not specified.

Contrary to Bogert and Geiger's findings, in this work 4-quinazolone (22) was brominated by aqueous bromine solutions containing potassium bromide and the 6-bromo product was isolated in high yield.

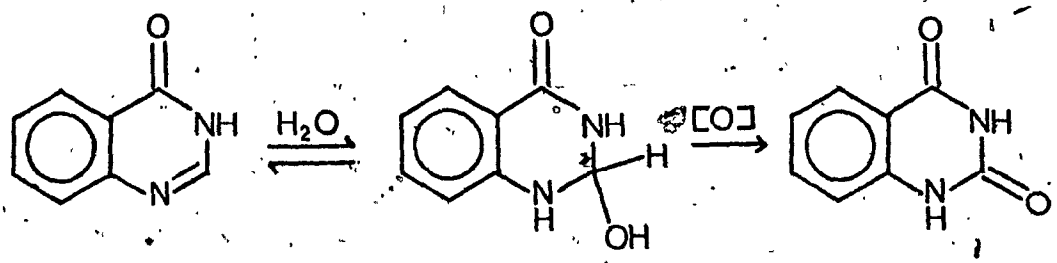
The action of bromine on 2-styryl-4-quinazolone gave rise to substitution and not an addition product.[54]

Covalent hydration



(22) (27)

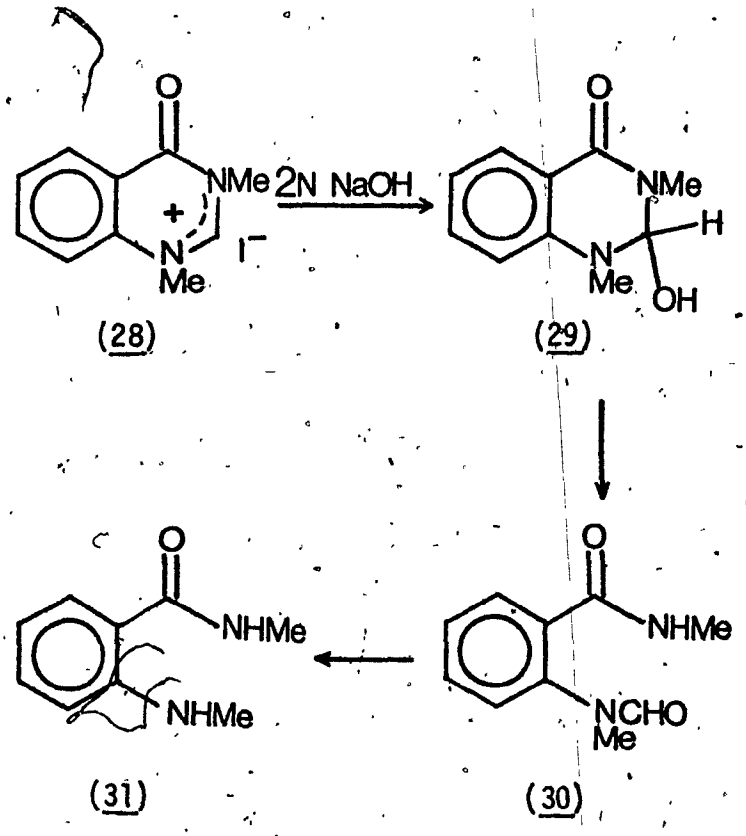
Quinazoline (1) and 2-quinazolone (5) are known to undergo covalent hydration,[20,23] but there is no direct evidence for it occurring with 4-quinazolone (22). However, it is interesting to note that 4-quinazolone (22) upon oxidation with potassium permanganate yields 2,4-quinazolinedione (47) which may possibly occur via the covalent hydrate (27).



(22) (27) (47)

Pseudo base formation

Morley and Simpson[48] treated the quaternary salt (28) with cold 2N sodium hydroxide and obtained an oil. Since the picrate of this oil was found to be different than that of the quaternary salt, they suggested that this might be the pseudo-base (29).

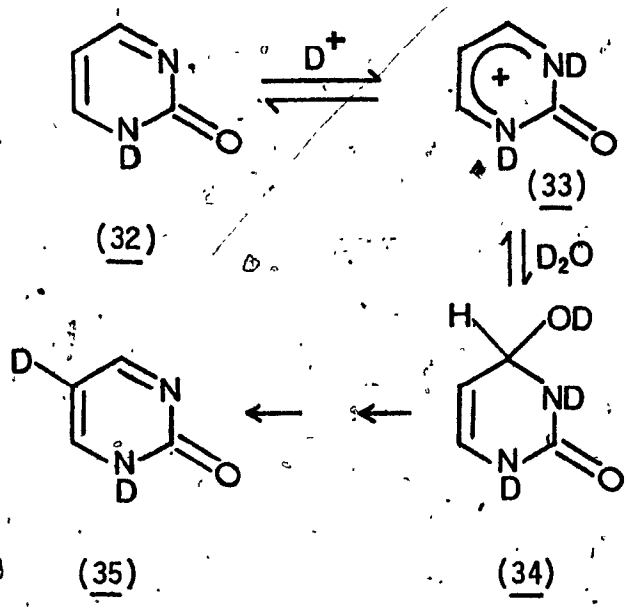


(28) (29) (30) (31)

Later it was shown[38] that the oil Morley and Simpson assumed was the pseudo-base has the open structure 31. It was suggested that the quaternary salt (28) with alkali gives pseudo-base (29) which on ring opening yields (30) and then the formamido group hydrolyses to give (31).

Electrophilic substitution of pyrimidones

Katritzky and coworkers[55,56] studied the hydrogen exchange at 5-position of 2-pyrimidone (32). In view of abnormal reactivity of (32) as compared to that of 2-pyridone, they postulated that the exchange at 5-position occurs via a covalent hydrate (34).



4-Pyrimidone and 1,4-dihydro-1,3-dimethyl-4-oxopyrimidinium iodate are found to undergo facile exchange at 5-position[59] and are more reactive than 4-pyridone. It was therefore suggested by Tee[60] that a similar mechanism involving covalent hydration may be operative there also.

The nitration study[58] of 2-pyrimidone, 1-methyl-2-pyrimidone indicate that they react via their free bases but 1,2-dihydro-1,3-dimethyl-2-oxopyrimidinium ion is unreactive. Here, presumably, reaction via the covalent hydrates or the pseudo-base is precluded by the strong acid.

EXPERIMENTAL

INTRODUCTION

4-Quinazolone (22), 3-methyl-4-quinazolone (36), 3,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37) and their corresponding 6-bromo-derivatives (38), (39) and (41) respectively were required for this investigation. (see scheme 1)

Of these compounds 22, 36 and 38 were prepared according to literature procedures. The perchlorate 37 was easily prepared from the known iodide 28.

Attempts to prepare 6-bromo-3-methyl-4-quinazolone (39) either by methylation of 28 or by cyclisation of 42 with N-methyl-formamide failed, but it was obtained in high yield by direct bromination of 36. Methylation of 39 with iodomethane afforded the iodide 40, which was converted to the perchlorate 41. This material was identical to that obtained by the direct bromination of the parent perchlorate (37).

Scheme I

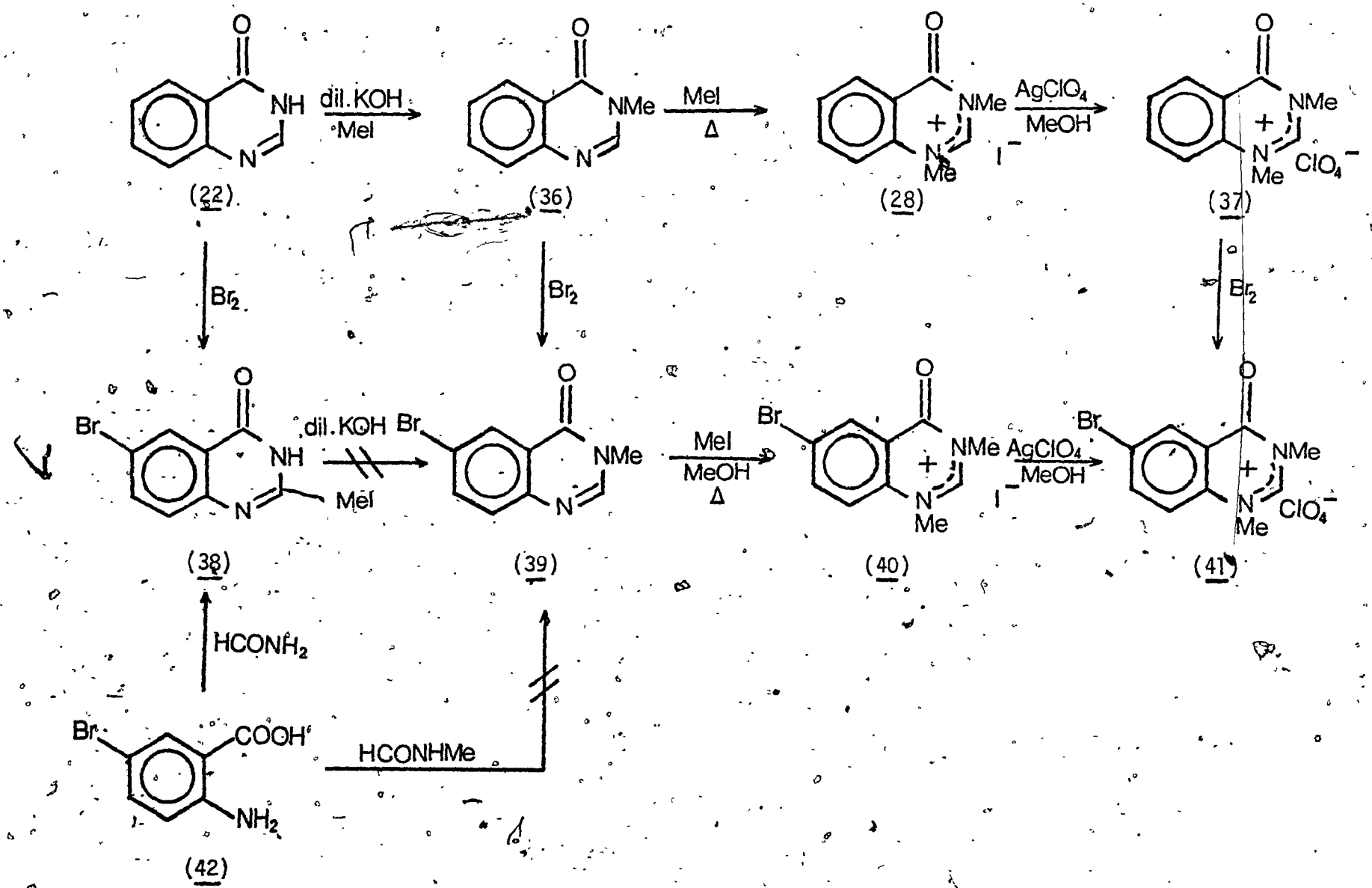

(22)
dil.KOH
MeI
(36)
MeI
Δ
(28)
AgClO4
MeOH
(37)
Br2
Br2
Br2
dil.KOH
MeI
(38)
(39)
MeI
MeOH
Δ
(40)
AgClO4
MeOH
(41)
HCONH2
HCONHMe
(42)

TABLE 1

IONISATION CONSTANTS AND U.V. SPECTRAL DATA OF 4-QUINAZOLONE SUBSTRATES AND THEIR 6-BROMO PRODUCTS

Substrate or Product	pK_a	pH	λmax, nm; (log ε)	Ref.
4-Quinazolone (22)	2.12	2.23	255(3.76), 261(3.77), 283(3.68), 291(3.65)	This work
		7.00	226(4.42), 231(4.39), 263(3.75), 269(3.71), 292(3.46), 311(3.61), 313(3.54)	41
3-Methyl-4-quinazolone (36)	2.18	1.0	229(4.34), 234(4.39), 279(3.78), 293(3.74), 303(3.59)	79
		7.0	225(4.42), 266(3.80), 272(3.78), 290(3.43), 301(3.56), 313(3.49)	41
1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37)	-	2.10	273(3.77), 283(3.77), 294(3.67)	This work
6-Bromo-4-quinazolone (38)	-	0.29	266(3.97), 293(3.72), 302(3.56)	This work
6-Bromo-3-methyl-4-quinazolone (39)	-	2.10	264(3.85), 297.5(3.37), 311.3(2.23)	This work
1,4-Dihydro-6-bromo-1,3-dimethyl-4-oxoquinazolinium perchlorate (41)	-	2.10	274(3.96), 294(3.80), 305(3.66)	This work

TABLE 2

P.M.R. SPECTRAL PARAMETERS OF 4-QUINAZOLONE SUBSTRATES AND THEIR 6-BROMO PRODUCTS*

	Signals (δ)			
Substrate or Product	1-CH_3 s	2-H s	3-CH_3 s	Aromatic H's m
4-Quinazolone (22)	-	hidden in aromatic H's	-	7.43-8.25
3-Methyl-4-quinazolone (36)	-	8.38	3.50	7.40-8.27
1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37)	4.06	8.85	3.65	7.86-8.46
6-Bromo-4-quinazolone (38)	-	hidden in aromatic H's	-	7.54-8.23
1,4-Dihydro-6-bromo-1,3-dimethyl-4-oxoquinazolinium perchlorate (41)	4.06	9.93	3.65	7.94-8.49

* In DMSO-d_6/TMS internal standard.

Preparation of Compounds

The melting points were obtained on Gallenkamp m.p. apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, 37921, U.S.A.

The u.v. spectra in Table 1 were recorded on Cary Model 14 spectrophotometer. The p.m.r. data in Table 2 and below were taken on a Varian A-60 instrument in DMSO-d_6, DCl/D_2O, CCl_4 and the data are quoted as δ values relative to TMS internal standard. The i.r. spectra were obtained on Perkin-Elmer 425 spectrophotometer using KBr discs.

4-Quinazolone (22) was prepared by the reaction of anthranilic acid with formamide.[64] Methylation of 22 gave 3-methyl-4-quinazolone[46] (36). 6-Bromo-4-quinazolone was prepared by cyclisation[65], and by direct bromination of 22 (vide infra).

5-Bromo-anthranilic acid (42)

This compound was prepared by modification of method described by Wheeler and Oates.[66]

Anthranilic acid (13.7 g, 0.1 mole) was added to glacial acetic acid (120 ml) and the mixture was stirred for 1/2 hr. until all the solid had dissolved. To the resulting solution was added dropwise bromine solution (16.0 g, 0.1 mole Br_2 in 50 ml glacial acetic acid) over the period of 1.25 hr. The resulting light yellow colored slurry was filtered off, washed with water and then with benzene. Recrystallised from 95% ethanol resulted in a crystalline solid (yellow plates), weight = 15.4 g, yield = 71.4%, m.p. 210-13° (Lit.[67] 213°)

I.R. spectra: Identical to that in the Sadtler index.[67] (No. 39347)

3,5-Dibromoanthranilic acid

To anthranilic acid (13.7 g, 0.1 mole) dissolved in glacial acetic acid (200 ml) was added dropwise bromine solution (32.0 g, 0.2 mole in 50 ml glacial acetic acid). The resultant slurry was stirred for 40 hrs., and then heated on waterbath for two hrs. The yellow colored precipitate was filtered off, washed with benzene and dried at 75°. This solid was recrystallised from ethanol-water (90:10). Weight = 21.9 g, yield = 74.5%, m.p. 229-31 (Lit[67]: 230-32°).

I.R. spectra: Identical to that in the Sadtler index.[67] (No. 43810)

6-Bromo-4-quinazolone (38). (By bromination)

To a bromine solution (1.6 g, 0.01 mole Br_2 in 30 ml water containing 1.19 g KBr) was added 4-quinazolone (1.46 g, 0.01 mole) and the mixture was stirred overnight. The resulting orange-white slurry was heated until the orange color of bromine had disappeared. After cooling to room temperature, the precipitate was filtered off, washed with little acetone and dried at 75°. Recrystallisation from methanol-DMF gave, fine, white crystalline substance. Weight = 2.1 g, yield = 94.0%, m.p. 260-64° (Lit.[65]: 261-73°)

I.R. spectra: (cm^{-1}) 3198 (weak), 3030 (weak, bonded, NH) 1672 (strong, broad, C=O), 1600 (strong, -C=N). Identical to that of the material obtained by Baker's cyclisation.[65]

6,8-Dibromo-4-quinazolone (44)

3,5 Dibromoanthranilic acid (14.7 g, 0.05 mole) and formamide (6.75 g, 0.15 mole) were heated together at 210° for 30 minutes. After cooling the crystalline slurry obtained was filtered off, washed with

water, then with ethanol and recrystallised from DMF-methanol. Weight = 16.0 g, yield = 86.3%, m.p. 340d (Lit.[67]: 337°).

I.R. spectra: Identical to that of Sadtler[67] spectrum No.45518.

6-Bromo-3-methyl-4-quinazolone (39) (as HBr salt)

To 3-Methyl-4-quinazolone (0.80 g, 0.005 mole) dissolved in methanol-water (80:20, 10 ml) was added bromine solution (0.80 g, 0.005 mole in 10 ml 80:20 methanol-water).

This yellow solution was stirred at room temperature and within 5 hrs., the white precipitate obtained was filtered off, washed with water and recrystallised from 95% ethanol. Weight = 1.1 g, yield = 68.8%, m.p. 338-40°.

I.R. spectra: (cm^{-1}), 1700 (strong, broad, C=O) 1610 (strong, C=N), 1360 (medium, N-CH_3).

U.V. spectra: See Table 1 (p.16).

N.M.R. spectra: See Table 2 (p.17).

Analysis: $C_9H_8N_2OBr_2$ Required C, 33.78%; H, 2.52; N, 8.75

Found C, 33.79%; H, 2.67; N, 8.76

1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium iodide (28)

This was prepared by slight modification of the method described by Bogert and Geiger.[68]

3-Methyl-4-quinazolone (11.6 g, 0.072 mole) and iodomethane (14.2 g, 0.1 mole) were heated in sealed tube at 100° for 10 hours. The brownish-yellow crystalline substance obtained was washed thoroughly with methanol to give a creamy colored substance upon filtration. This product was recrystallised from methanol-water. Weight = 13.0 g,

yield = 59.4%, m.p. 270-73° (Lit[68]: 273°).

N.M.R. spectra: δ 4.17 (s, $-N_3-CH_3$), 4.57 (s, $-N_1-CH_3$), 8.48-9.11 (m, aromatic H's), 10.09 (s, 2H). (D_2O/DCl, TMS) (Compare spectra of 37 in Table 2).

1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37)

To a solution of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium iodide (6.04 g, 0.02 mole) in warm absolute methanol (40°, 200 ml) was added silver perchlorate solution (4.15 g, 0.02 mole in 10 ml absolute methanol). Upon addition a yellowish precipitate of silver iodide was immediately obtained. The mixture was stirred for half an hour at 40°, cooled to room temperature and the AgI was filtered off. The filtrate was evaporated and the residue obtained was recrystallised from ethanol-water. Weight = 4.67 g, yield = 85.0%, m.p. 254-7°.

I.R. spectra: (cm^{-1}) 1715 (broad, strong C=O), 1654 (broad, strong, C=N), 1386 (strong, $N-CH_3$), 1110-1060 (very broad, strong, $^-ClO_4$).

U.V. spectra: See Table 1 (p.16).

N.M.R. spectra: See Table 2 (p.17).

Analysis: $C_{10}H_{11}N_2O_5Cl$ Required C, 43.73%; H, 4.04; N, 10.20

Found C, 43.90%; H, 3.91; N, 10.20

1,4-Dihydro-6-bromo-1,3-dimethyl-4-oxoquinazolinium iodide (40)

6-Bromo-3-methyl-4-quinazolone (1.20 g, 0.005 moles) and iodomethane (1.0 g, 0.704 moles) were heated together in the sealed tube at 120° for 12 hours. The crystalline mass was washed with methanol and recrystallised from ethanol-water (80:20). Weight = 1.64 g, yield = 86.3%, m.p. 287-88°.

I.R. spectra: (cm^{-1}) 1700 (strong, broad, C=O), 1645 (strong, broad, C=N), 1375 (strong, N-CH_3).

N.M.R. spectra: δ 3.66 (s, -3N-CH_3), 4.08 (s, -1N-CH_3), 7.96-8.49 (m, aromatic H's), 9.99 (2H). (DMSO-d_6, TMS) (Compare spectra of 41 in Table 2).

Analysis: $C_{10}H_{10}N_2OBrI$ Required C, 31.52%; H, 2.65; N, 7.35

Found C, 31.58%; H, 2.62; N, 7.32

1,4-Dihydro-6-bromo-1,3-dimethyl-4-oxoquinazolinium perchlorate (41)

(a) From the iodide 40.

1,4-dimethyl-6-bromo-1,3-dimethyl-4-quinazolinium iodide (0.381 g, 0.001 moles) was dissolved in hot aqueous ethanol (25 ml). To this was added silver perchlorate solution (0.207 g, 0.001 moles in 10 ml ethanol), and the silver iodide precipitate that resulted was filtered off. This clear solution, upon cooling to room temperature, yielded white needles which were recrystallised from aqueous ethanol. Weight = 0.332 g, yield = 94.0%, m.p. 395-7°.

I.R. spectra: (cm^{-1}) 1708 (broad, strong, C=O), 1650 (strong, broad, C=N), 1381 (medium, N-CH_3), 1100-1050 (strong, very broad, $^-ClO_4$).

U.V. spectra: See Table 1 (p.16).

N.M.R. spectra: See Table 2 (p. 17).

Analysis: $C_{10}H_{10}N_2O_5BrCl$ Required C, 33.97%; H, 2.85; N, 7.92.

Found C, 34.23%; H, 2.71; N, 7.94.

(b) By bromination of 37.

1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (1.37 g, 0.005 mole) was added to a methanol-water mixture (80:20, 20 ml) and was warmed to dissolve. To this was added bromine solution (0.8 g,

0.005 mole, in 10 ml methanol) and the mixture was stirred until the yellow color disappeared. (About 2 hours). The crystalline substance which had appeared was filtered off, washed with methanol and recrystallised from 80% ethanol. Weight = 1.62 g, yield = 91.5%, m.p. 394-97°.

Spectral properties: Identical to those of the compound obtained from the iodide (see (a) above).

N-Methyl-o-methyl-aminobenzamide (31)

(a) By action of dilute sodium hydroxide on 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium iodide.[48,69]

To a solution of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium iodide (1.51 g, 0.005 mole) in 20 ml water was added 20 ml 2N sodium hydroxide solution and the mixture was stirred at 40° for 1 hour. The solution was allowed to cool to room temperature, and the white shiny precipitate obtained was filtered, washed with water and recrystallised from cyclohexane. Weight = 0.80 g, yield = 97.6%, m.p. 83-85° (Lit.[38,69]: 43-45°, 70-72°).

Spectral properties: Identical to those given below in (b).

(b) By action of methylamine on N-methyl-isatoic anhydride[38].

To N-methyl-isatoic anhydride (11.7 g, 0.066 moles) was added water (30 ml), methylamine (30%, 15 ml) and the stirred mixture was heated for 30 minutes. The clear top layer was decanted off and on cooling white needles were obtained which were filtered off and recrystallised from cyclohexane. Weight = 10.25 g, yield = 94.7%, m.p. 84-86° (Lit.[38]: 43-45°).

I.R. spectra: (cm^{-1}) 3280 (strong, -C(=O)-NH-), 2870 (weak, $N-CH_3$), 2800 (weak, $N-CH_3$), 1610 (strong C=O). Spectra of compounds obtained

by both methods were identical.

N.M.R. spectra: δ 2.87 (s, $-NHCH_3$), 2.78 (s, $-CONHCH_3$), 7.60 (s, $-NHCH_3$), 6.17 (s, $-CONHCH_3$), 6.27-7.32 (m, ring protons).

Measurement of Rate Constants

Initial experiments using a titrimetric method of determining bromine concentrations indicated that second order kinetics were being followed in the brominations of 22, 36 and 37. Consequently, it was desirable to carry out experiments under pseudo-first order conditions to simplify both procedures and the calculation of rate constants. Under such conditions, however, the u.v. spectrophotometric method used earlier in this laboratory[16] was not applicable. The substrates and products have very similar absorption curves, and the bromine absorption maximum lies in the same region. Therefore, the presence of an excess of substrate, as required for pseudo-first order kinetics, obscures measurement of either product increase or bromine decrease by u.v. spectrophotometry.

Attempts to follow the brominations by potentiometric methods[62,63] also were unsuccessful largely because of instrumental problems.

Surprisingly, it was found that the titrimetric method could be used conveniently and that it afforded tolerably accurate results.

Kinetic Procedure

A stock solution (1 litre) containing KBr (1.0×10^{-2} M) in the desired acid or buffer solution was prepared. Using this medium separate 50 ml solutions of bromine ($1.0\text{-}1.6 \times 10^{-3}$ M) and of substrate (1.0×10^{-2} M) were then prepared. The pH of the substrate solution was recorded. The flasks containing the substrate and bromine solutions were wrapped in aluminium foil to prevent deterioration due to light, and were then equilibrated in a constant temperature bath at 30 ± 0.2^{o}C for at least 15 minutes.

A timer was started as the substrate solution was added to the bromine solution, and the mixture was thoroughly shaken. (N.B. The concentrations of substrate and of bromine in the reaction mixture are thus half what they were in the initial solutions). At appropriate intervals 5 ml aliquots of the reaction mixture were withdrawn and added to 20 ml of 5% KI. The liberated iodine was titrated immediately against standard sodium thiosulfate solution (1.0×10^{-2} M) contained in a Metrohm No. E274 semi-automatic microburette (5 ml capacity, graduated in 0.005 ml) using 1% starch indicator. Altogether between 7 and 17 aliquots were taken over a period extending well beyond one half-life.

For fast runs, where time did not allow titration of each aliquot as drawn, the aliquots were quenched with 5% KI solution as before, and then stored in the dark. When time permitted they were titrated in sequence as fast as possible.

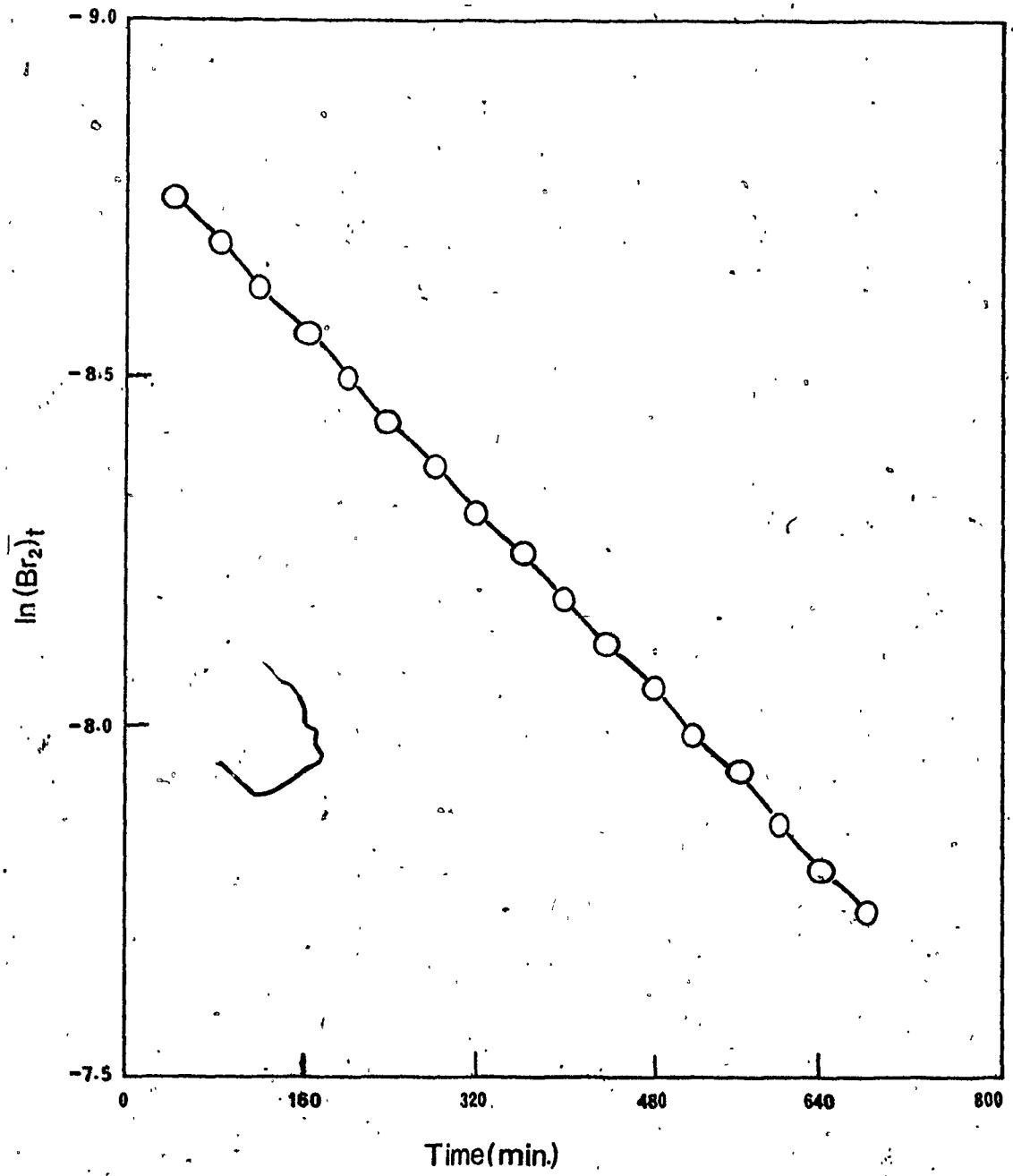
From the titration of each aliquot drawn at time t the concentration of bromine $[Br_2]$ was calculated, and $\ln[Br_2]$ was plotted versus t . Such a plot is shown in Fig. 1. Least square analysis of the data by the computer program TITR was used to obtain the pseudo-first order rate constants k_1 corresponding to the equation

$$\ln[Br_2] = \ln[Br_2]_0 - k_1 t$$

All kinetic runs were carried out at least twice, and only those were accepted which gave correlation coefficients > 0.9998 in the least square analysis.

Figure 1

A plot of $\ln (Br_2)_t$ against time for 4-quinazolone



Reagents

All the inorganic reagents used were of analytical reagent grade. Sulfuric acid, sodium thiosulfate and starch solutions were prepared from standard volumetric concentrates. Bromine in the aqueous sulfuric acid solutions was estimated by titration against standard sodium thiosulfate.

Buffer solutions (0.2 M) were prepared as described by Vogel[78] and Perrin.[79]

Acidity

The acidities of all substrate solutions were measured using a Beckmann Expandomatic pH meter. The pH values thus obtained for sulfuric acid solutions were, within experimental error, the same as those calculated on the basis of the known pK_a values[72] of 22 and of 36 where applicable.

The hydronium ion concentration of sulfuric acid solutions was calculated as described previously.[71] The effect due to the substrate was then calculated using

$$[H_3O^+] = \frac{-([B_o]-[H_o^+]+ K) + \sqrt{([B_o] - [H_o^+] + K)^2 + 4K[H_o^+]}}{2} \qquad (2)$$

where $[B_o]$ is the substrate concentration, K is the dissociation constant of substrate conjugate acid, and $[H_o^+]$ is the hydronium ion of the acid solution before addition of the substrate.

The necessary computations were carried out using the program PHCAL.

Second Order Rate Constant

The reaction being following is of the form

$$S + Br_2 \xrightarrow{k_2} P$$

$$\text{Rate} = k_2 [S][Br_2]$$

For a large excess of the substrate S, this becomes pseudo-first order situation in which

$$\text{Rate} = k_1[Br_2]$$

and

$$\ln[Br_2] = \ln[Br_2]_o - k_1 t$$

Thus, by following the decrease in bromine concentration, the pseudo first order rate constant k_1 may be easily obtained. Strictly speaking, the second order rate constant k_2 should be obtainable from $k_2 = k_1/[S]$. However, following Bell[62], the expression

$$k_2 = k_1/([S] - [Br_2]_o)$$

was used to give a better estimate of k_2, since the excess of substrate S is not exceedingly large.

Computer Programs

A Hewlett-Packard 2114A computer was used for various calculations using the following programs written either in BASIC or FORTRAN by Dr. O.S. Tee, Dr. S. Banerjee, and by the author.

TITR: This program does the least-square calculations on given titration data points and computes the first order rate constant (k_1), its standard deviation, the initial bromine concentration $[Br_2]_o$, the second order rate constant (k_2) and the correlation coefficient for the plot of $\ln[Br_2]$ versus time (t). An example of the output of this program is shown on page 31.

LESQ: A linear least-square treatment on given data points can be obtained using this program. It was used for the substrate dependence and for the potassium bromide dependence of the rates of bromination of 22 and acidity dependence of the rate of bromination of compound 37.

CONT: This program is written to obtain the best curve fitting for log rate-pH profiles for compounds 22 and 36.

$$k_2^{obs} = \frac{k_2 K}{K + H^+} = \frac{\text{Constant}}{K + H^+}$$

$$\text{Constant} = k_2^{obs}(K + H^+) \qquad (3)$$

For a given pK_a, using sets of k_2^{obs} and pH, this program calculates the constant from the equation 3 . Then it averages the constant values obtained at each pH and computes the standard deviation. Incorporating this average constant value back into equation 3 , it calculates the second order rate constant (k_2^{cal}). This procedure is repeated for various values of pK_a, and the best pK_a value is chosen such that the standard deviation of the constant value is a minimum.

PHCAL: Used for pH calculations using the quadratic equation 2 (P. 28).

DM40Q: This program was specifically written for analysis of the data obtained from the quaternary salt 37. Assuming $k_2^{obs} = kK/[H^+]$, it calculates $k_2^{obs}[H^+] = kK$ = constant for each pH. It then averages these constant and from this calculates k_2^{cal} for each pH, and hence the difference between k_2^{obs} and k_2^{cal}.

Example of a Kinetic Run (No. A64)

Substrate: 4-Quinazolone (22)

Substrate concentration = 5.0×10^{-3} M

Bromine concentration = 4.6×10^{-4} M

KBr concentration = 1.0×10^{-2} M

Sulfuric acid: 1.0N, pH = 0.29

Time (Min)	$[Br_2]_t \times 10^3$(M)	$\ln[Br_2]_t$
40	0.432	-7.74708
80	0.405	-7.81162
120	0.380	-7.87534
160	0.356	-7.94058
200	0.334	-8.00437
240	0.313	-8.06931
280	0.294	-8.13193
320	0.275	-8.19874
360	0.260	-8.25483
400	0.243	-8.32245
440	0.228	-8.38616
480	0.214	-8.44953
520	0.200	-8.51719
560	0.190	-8.56849
600	0.176	-8.64503
640	0.165	-8.70957
680	0.155	-8.77209

These data are plotted in Figure 1 (P. 27)

Least-square analysis gave the following: $k_1 = -1.60 \times 10^{-3} min^{-1}$

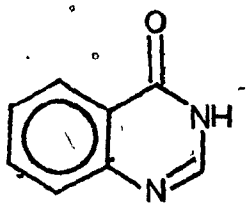
S.D. = 0.004×10^{-3} Intercept = $\ln[Br_2]_o$ = -7.684 S.D. = 0.0008

$[Br_2]_o = 4.46 \times 10^{-4}$ M. Corr. Coeff = 0.99995

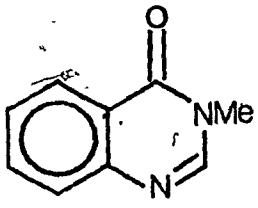
Half life = $t_{1/2}$ = 434 min.

$k_2^{obs} = k_1/([S] - [Br_2]_o) = 0.352\ M^{-1}min^{-1}$

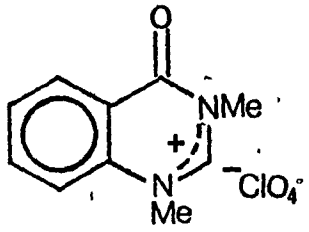
Product Isolation



(22)



(36)



(37)

(a) On synthetic scale: Bromination of 22, 36 and 37 in aqueous methanol afforded the corresponding 6-bromo-derivative (see pages 19, 20, and 22 respectively).

(b) In the reaction flask: If a high substrate concentration (0.01 M) is used the 6-bromo-products precipitate from solution and can be isolated in quantitative yield from all the three substrates.

(c) Identification by u.v. spectra: The following stock solutions were made.

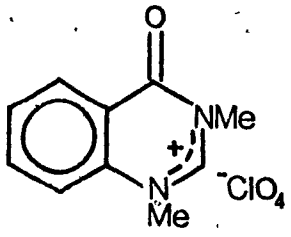
A 100 ml of 1.0×10^{-4} M substrate in 0.01 M H_2SO_4 contains 0.01 M KBr

B 100 ml of 1.0×10^{-4} M bromine in the same medium.

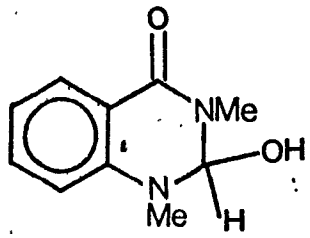
Solution A and B were mixed thoroughly and the reaction was carried out well beyond 10 half lives. The u.v. spectra of resulting solution was identical to that of corresponding 6-bromo-product (5.0×10^{-5} M in 0.01 M H_2SO_4/0.01 M KBr).

N.B. U.v. spectral data for the substrates and their bromo derivatives are presented in Table 1 (P. 16)

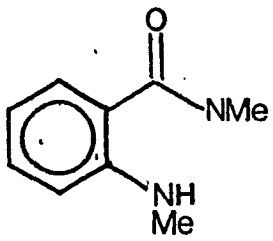
Pseudo base Formation (37 ⇌ 29)



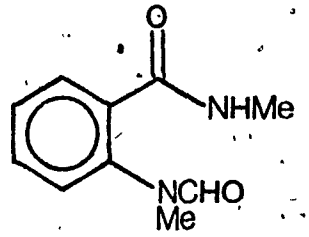
(37)



(29)



(31)



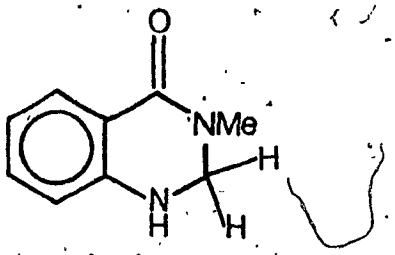
(30)

Later in this thesis it will be postulated that the bromination of 37 occurs via its pseudo base 29. Consequently attempts were made to observe 29, and to measure the equilibrium 37 ⇌ 29.

The perchlorate salt 37 is not soluble enough in D_2O to obtain a reasonable p.m.r. spectrum and therefore to observe the equilibrium 37 ⇌ 29. The salt is, however, soluble in dilute NaOD solution, but in this medium ring opening occurs irreversibly to give 31. (cf. Morley and Simpson[47]).

On the other hand, the solubility of 37 in water is sufficient to permit the study of the equilibrium 37 ⇌ 29 by u.v. spectrophotometry. A spectrum of 37 at 1.0×10^{-3} M in water was first recorded. To this solution was added 0.025N NaOH (to give 8.3×10^{-5} M NaOH in the cell) and immediately a peak at 330 nm appeared. On addition of an equivalent amount of dilute HCl this peak disappeared and the

original spectrum of 37 was retraced.



(46)

Since the u.v. spectrum of 2,3-dihydro-3-methyl-4-quinazolone (46) (in methanol) has an absorption band[80] at 338 nm, the band at 330 nm suggests the existence of the pseudo base (29) in the solution. Moreover, the disappearance of the band at 330 nm upon addition of dilute HCl confirms the reversibility of the equilibrium 37 ⇌ 29. Note, however, that the addition of excess dilute NaOH solution again results in irreversible ring opening, and the formation of 31.

Potentiometric titration of 37 with dilute NaOH after the method of Albert and Serjeant[81] suggested that the equilibrium constant $K = [29][H^+]/[37] = 10^{-7.54}$ (i.e. pK = 7.54). However, this value is suspect since towards the end of the titration there is probably sufficient base present to promote irreversible ring opening to 31.

RESULTS AND DISCUSSION

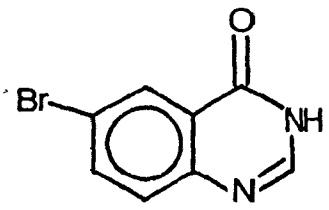
Introduction

Previous studies in this laboratory by Tee and Banerjee[14,15,16] pointed to the involvement of covalent hydrates in the bromination of 2-pyrimidones and 4-pyrimidones carried out in aqueous acidic media.

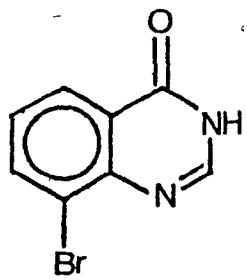
The object of the present work was to study the bromination of the benzo analog of 4-pyrimidone, namely, 4-quinazolone (22), and, if possible, to arrive at a mechanistic scheme consistent with the kinetic results. The involvement, or otherwise, of a covalent hydrate in this reaction might have ramifications with respect to oxidations such as those catalysed by Xanthine oxidase. (see page 1).

Product of Bromination

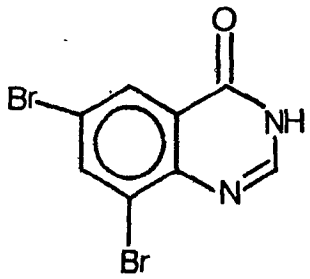
The most likely products formed from the bromination of 4-quinazolone (22) are 6-bromo-derivative (38), the 8-bromo-derivative (44), and the 6,8-dibromo-derivative (45) shown below.



(38)



(44)



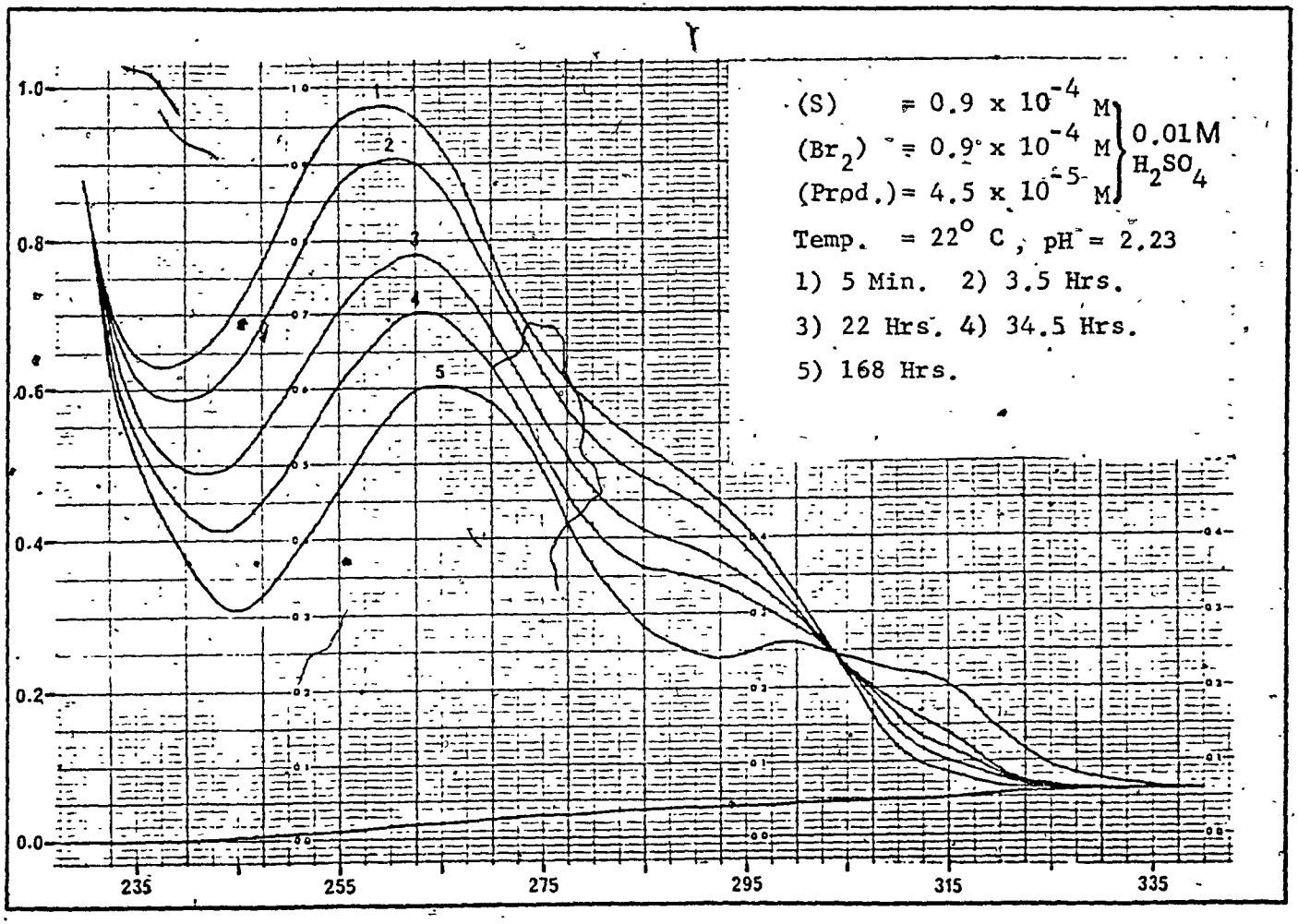
(45)

Synthetic scale bromination of 4-quinazolone (22) in aqueous solution gave only the 6-bromo compound (38) in high yield (94% after recrystallisation). Moreover, the u.v. spectral changes occurring during a bromination carried out in dilute solution were completely consistent with the simple conversion (22)→(38).

Figure 2 shows spectra traced at various times following

Figure 2

U.v. spectral changes accompaning bromination of 22 → 38



the mixing of equimolar quantities of 22 and bromine. The absorption due to both of these substrates gradually diminished and new absorptions appeared, most noticeably above 310 nm. After 1 week the spectrum traced was identical to that of an authentic sample of 6-bromo-4-quinazolone (38) of the appropriate concentration. In neither the synthetic work, nor in the spectral studies was there any evidence of the formation of the 8-bromo-compound (44).

The possible formation of the 6,8-dibromo-compound (45) during the bromination 22 was also considered. However, it was found that the apparent rate of bromination of 38→45 is very much slower than that of parent 22. For example, at 30°, 38 did not decolorise an equivalent amount of bromine, even after 4 days. On a synthetic scale, attempted dibromination of 22 (at 85°, 10 hrs) was unsuccessful, and only the 6-bromo-product (38) was obtained. The 6,8-dibromo-4-quinazolone (45) was obtained, however, by prolonged heating of 38 and bromine for 1 week at 50°. From the above observations the possibility of significant formation of 45 during the course of the kinetic studies of the bromination of 4-quinazolone (22) can be safely eliminated, particularly since these were carried out with about a 10-fold excess of 22 over bromine.

Similar observations for 3-methyl-4-quinazolone (36), and the 1,3-dimethyl salt (37) also exclude the formation of 8-bromo- and 6,8-dibromo-derivatives during the course of bromination of these substrates.

Order of Reaction

Initial titration kinetics suggested a second order reaction; first order in substrate, and first order in bromine. For

Table 3

Variation of the rate of bromination (k_1) of 4-quinazolone (22) with substrate concentration

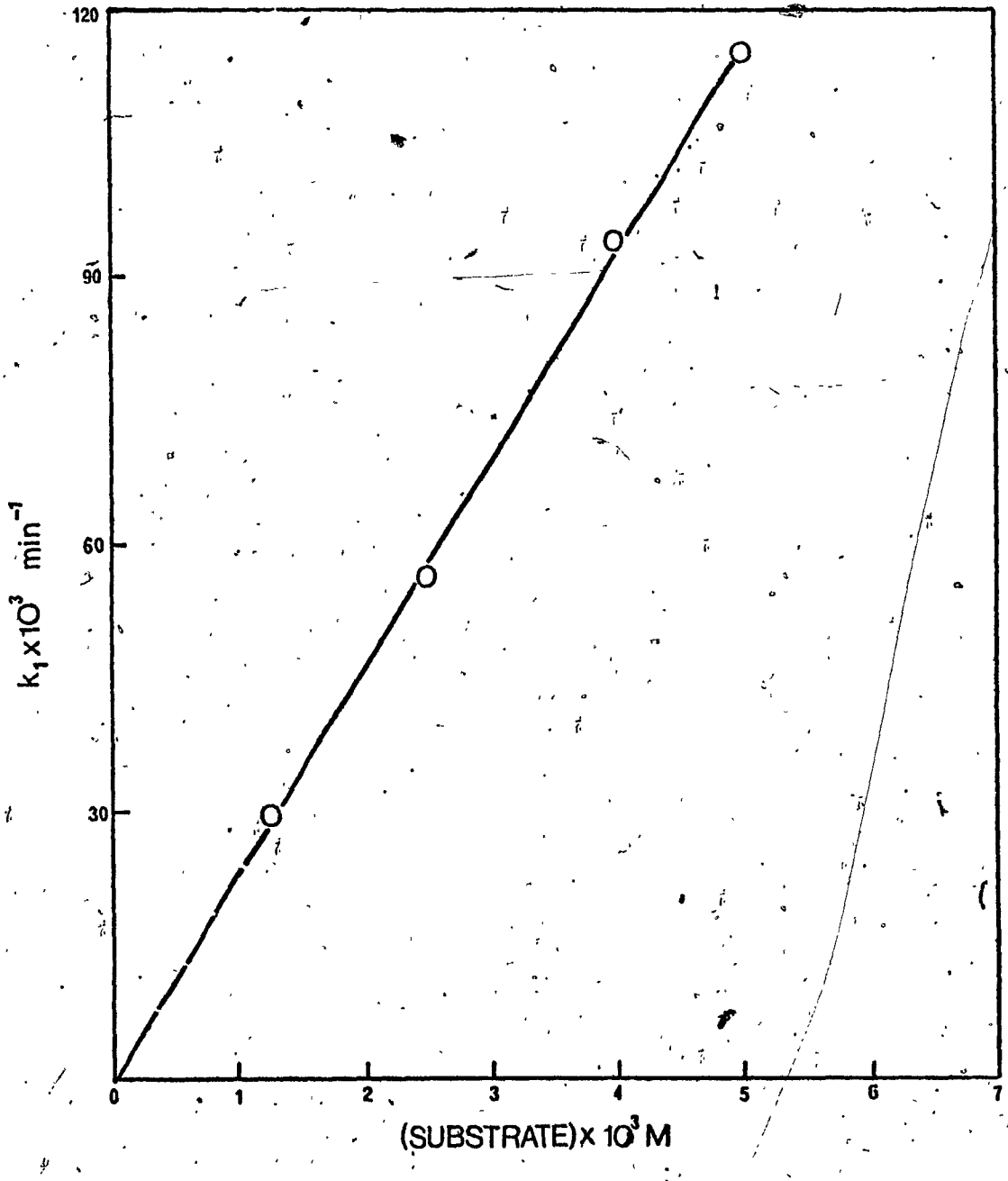
KBr concentration = 0.01 M
Acetate buffer pH = 3.97

Run No.	[22] x 10^3 M	[Br_2] x 10^4 M	k_1 x 10^3 min^{-1}	Ave k_1 x 10^3 min^{-1}
A-72	5.0	4.91	114	115
A-73	"	6.51	115	
S-20	4.0	4.94	93.7	94.0
S-21	"	5.20	94.3	
S-30	2.5	2.91	56.5	56.3
S-31	"	2.27	56.0	
S-40	1.25	1.22	30.9	29.7
S-41	"	1.33	28.4	

Slope = 2nd order rate constant = 23.07 $M^{-1}min^{-1}$ SD = 0.58
Intercept = 0.20 SD = 0.83
Corr. Coeff. = 0.9994

Figure 3

Variation of the pseudo first order rate constant (k_1) with substrate concentration



convenience, therefore, subsequent kinetics were measured under pseudo-first order conditions, with an approximate ten fold excess of substrate over bromine. Rate constants (k_1) thus obtained are for the pseudo-first order disappearance of bromine (due to the reaction 22 → 38).

That this reaction is truly second order is shown by the data in Table 3 (plotted in Figure 3). The pseudo-first order rate constant (k_1) diminish linearly with the substrate concentration, and within experimental error, the least squares line in Figure 3 goes through the origin.

Note also from the data in Table 3 , that the pseudo first order rate constant are independent of initial bromine concentration, as they should be if the reaction is first order in bromine.

Bromide Ion Dependence

Bromination of the type being studied i.e. $ArH + Br_2 \longrightarrow ArBr + H^+ + Br^-$ produce bromide ion which complicates the observed kinetics since there is reduction in the bromine concentration due to the formation of tribromide ion.

$$Br_2 + Br^- \rightleftharpoons Br_3^-$$

While tribromide ion is generally a very poor electrophile, there are examples known where 1-3% of bromination occurs via this ion.[74,75]

To swamp the effect of bromide ion produced during kinetic runs an approximate 20 fold excess of KBr was present in all solutions used. Also, to check that molecular bromine (Br_2) is the sole brominating agent the variation of rate with bromide ion concentration was studied.

For the equilibrium

$$Br_2 + Br^- \rightleftharpoons Br_3^-$$

we define the dissociation constant

$$K = [Br_2][Br^-]/[Br_3^-] \qquad (4)$$

For the reaction being followed by a titrimetric determination of bromine

$$\text{rate} = k_2^{obs}[S][Br_2]_s = k_2[S][Br_2] \qquad (5)$$

and so

$$k_2^{obs} = k_2[Br_2]/[Br_2]_s \qquad (6)$$

where k_2^{obs} is the observed 2nd order rate constant

k_2 is the true 2nd order rate constant

$[Br_2]_s$ is the stoichiometric concentration of Br_2

$[Br_2]$ is the true concentration of Br_2

Now $[Br_2]_s = [Br_2] + [Br_3^-]$

and since Br^- is present in large excess,

$$[Br^-]_s = [Br^-] + [Br_3^-] \simeq [Br^-]$$

then equation (6) may be replaced by

$$k_2^{obs} = k_2K/(K + [Br^-]) \qquad (7)$$

Thus the apparent rate of bromination should diminish as the concentration of bromide ion is increased. This trend is evident in the data of Table 4a.

A more accurate analysis of the validity of equation (7) requires a value for the dissociation constant K. Several such values

Table 4a

Variation of the rate of bromination of 4-quinazolone (22) with $[Br^-]$

Substrate concentration = 5.0×10^{-3} M
Acetate buffer pH = 3.55

Run No.	[KBr](M)	$[Br_2] \times 10^4$ M	$k_1 \times 10^3 min^{-1}$	$k_2 M^{-1} min^{-1}$
A-230	0.01	5.26	116	25.9
A-231	"	4.84	115	25.5
KB-20	0.02	5.73	96.4	21.8
KB-21	"	5.63	98.7	22.3
KB-30	0.03	5.38	86.9	19.5
KB-31	"	5.06	88.0	19.6
KB-40	0.05	5.81	70.6	16.0
KB-41	"	5.40	70.7	15.9
KB-50	0.10	5.39	47.8	10.7
KB-51	"	4.94	48.8	10.8
KB-60	0.15	6.23	35.8	8.17
KB-61	"	5.67	36.1	8.14

Table 4b

Variation of the rate of bromination of 4-quinazolone (22) with $[Br^-]$

$K = [Br_2][Br^-]/[Br_3^-] = 0.0562$ M

KBr (M)	k_2^{obs} ($M^{-1}min^{-1}$)*	$1/k_2^{obs}$	$k_2^{obs}(K+[Br^-])$	$K/(K+[Br^-])$
0.01	25.7	0.03891	1.701	0.849
0.02	22.1	0.04525	1.684	0.738
0.03	19.6	0.05102	1.690	0.652
0.05	16.0	0.06250	1.699	0.529
0.10	10.8	0.09259	1.687	0.360
0.15	8.16	0.12255	1.682	0.273
		Ave	1.691	

* An average of two determinations (see Table 4a)

Least squares for k_2^{obs} vs $K/(K + [Br^-])$ gives

slope = k_2 = 30.2 ± 0.2 $M^{-1}min^{-1}$

Intercept = -0.06 ± 0.04, Corr. Coeff. = 0.999914

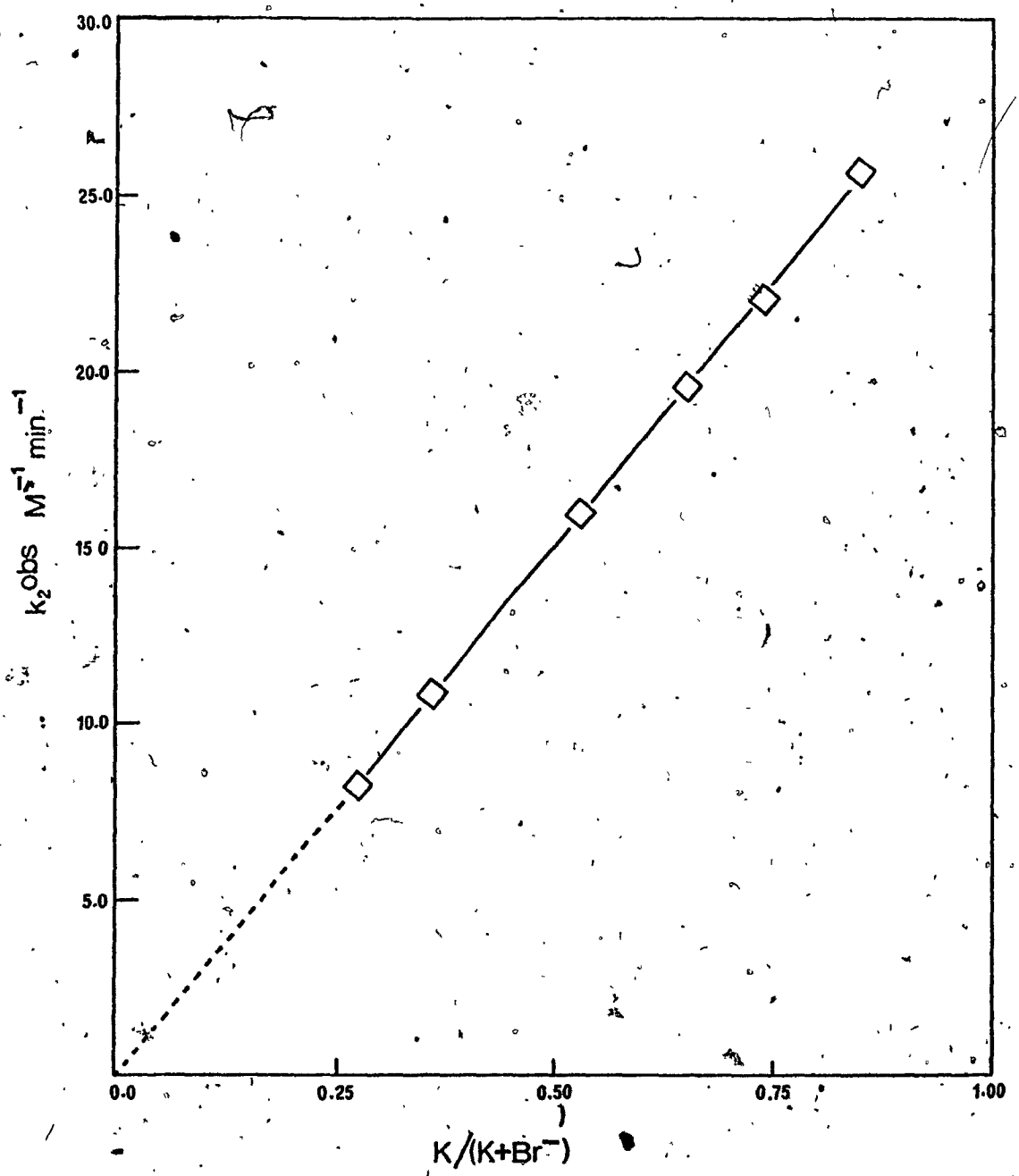
Least squares for $1/k_2^{obs}$ vs $[Br^-]$ gives

k_2 = 1/Intercept = 30.3 $M^{-1}min^{-1}$

$$K = \frac{\text{Intercept}}{\text{slope}} = 0.0554 \text{ M}$$

Figure 4a

Variation of the rate of bromination of 4-quinazolone with $(Br)^{-}$



are to be found in the literature,[62,76] but that most appropriate for the present study is the value K = 0.0562 M due to Bell and Ramsden.[62]

Clearly equation (7) requires that the term $k_2^{obs}(K + [Br^-]) = k_2K$ = constant. Values of this term calculated using Bell's value of K are shown in column 4 of Table 4b, and are essentially constant as required. Similarly equation (7) requires that a plot of k_2^{obs} versus $K/(K + [Br^-])$ gives a straight line of zero intercept and slope = k_2. This requirement is also met by the data in Table which is plotted in Figure 4a. Least squares analysis gives slope = $k_2 = 30.2 \pm 0.2\ M^{-1}min^{-1}$, intercept = -0.06 ± 0.04.

The data may be analysed in another way such that a value of K need not be assumed. Inversion of equation 7 yields

$$\frac{1}{k_2^{obs}} = \frac{1}{k_2} + \frac{[Br^-]}{k_2K} \qquad (8)$$

and thus from the slope and intercept of a plot of $1/k_2^{obs}$ versus $[Br^-]$ one can calculate both k_2 and K. The present data plotted in this way is shown in Figure 4b. From the least squares slope and intercept $k_2 = 30.3\ M^{-1}min^{-1}$, K = 0.0554 M. The value of k_2 from this analysis hardly differs from that given in the previous paragraph. The value of K is very close to that of Bell.[62] However, the difference between the two numbers (0.0562 versus 0.0554) may be real, since the former applies to 25°C, the latter to 30°.

The very good straight lines shown in Figures 4a and 4b, and the consistency of the above analyses means that the bromination by Br_3^- is not significant in the reaction being studied.

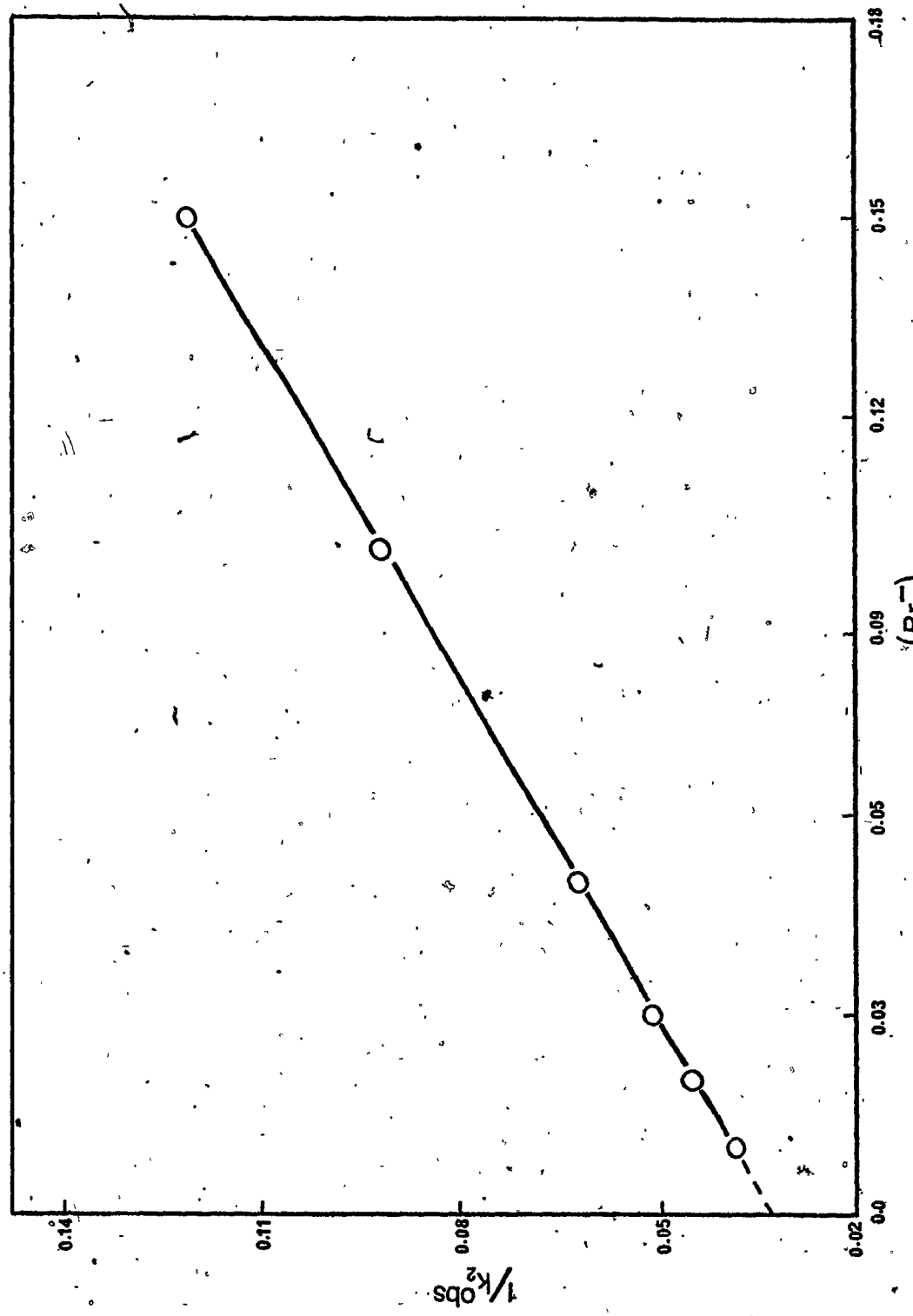


Figure 4b
Variation of the rate of bromination of 4-quinazolone with (Br^-)

Acidity Dependence of the Bromination of 4-Quinazolone (22)

The rate of bromination of 22 was studied at various acidities in dilute sulfuric acid and in the buffer solutions (chloroacetate and acetate buffers). The data obtained is presented in Tables 5a and 5b, and is plotted in Figure 5 as $\log k_2^{obs}$ versus pH. Since the known pK_a value[72] for the protonation of 4-quinazolone is 2.12 (at 20°C), the shape of the rate profile in Figure 5 suggests that reaction is occurring on the free base form of 22.

For the scheme

$$SH^+ \underset{}{\overset{K_a}{\rightleftharpoons}} H^+ + S \xrightarrow[Br_2]{k_2} \text{Product}$$

$$\text{rate} = k_2^{obs}[S]_s[Br_2] = k_2[S][Br_2]$$

and $$k_2^{obs} = k_2 \frac{[S]}{[S]_s} \quad \text{where } [S]_s = [S] + [SH^+]$$

is the stoichiometric concentration of the substrate (here 4-quinazolone). From the definition of the dissociation constant $K_a = [S][H^+]/[SH^+]$ it can easily be shown[56] that $[S]/[S]_s = K_a/(K_a + [H^+])$ and hence

$$k_2^{obs} = \frac{k_2 K_a}{(K_a + [H^+])} \qquad (9a)$$

The logarithmic form of this equation is

$$\log k_2^{obs} = \log k_2 K_a - \log(K_a + [H^+]) \qquad (9b)$$

which describes a curve such as that shown in Figure 5. The solid curve drawn through the experimental points was calculated from

Table 5a

Variation of the rate of bromination of 4-quinazolone (22) with pH

Substrate Concentration: 5.0×10^{-3} M

KBr Concentration: 0.01 M

Run No.	H_2SO_4(M)	pH	$Br_2 \times 10^4$(M)	$k_1 \times 10^3$(min^{-1})	k_2^{obs}($M^{-1}min^{-1}$)
A-61	1.0	0.29	4.49	1.41	0.309
A-63	"	"	4.87	1.53	0.339
A-64	"	"	4.60	1.60	0.352
A-51	0.5	0.59	4.55	3.06	0.673
A-53	"	"	4.89	3.06	0.678
A-54	"	"	5.41	3.14	0.705
A-41	0.2	0.98	4.99	6.90	1.53
A-42	"	"	5.06	6.90	1.54
A-43	"	"	5.42	7.10	1.59
A-32	0.1	1.27	5.08	10.7	2.38
A-33	"	"	5.25	10.8	2.41
A-34	"	"	4.86	10.7	2.38
A-200	0.03	1.66	8.80	27.5	6.64
A-201	"	"	5.04	28.5	6.33
A-11	0.02	1.94	4.28	42.9	9.38
A-12	"	"	4.31	42.5	9.29
A-13	"	"	5.13	41.6	9.28
A-3	0.01	2.23	5.11	73.2	16.3
A-5	"	"	4.41	70.5	15.5
	Buffer				
A-214	Cl-acet.	2.63	4.76	96.9	21.4
A-215	"	"	5.07	91.8	20.4
A-216	"	"	5.41	95.4	21.4
A-242	"	2.80	4.81	94.8	21.0
A-243	"	"	5.38	95.1	21.3
A-220	"	3.07	5.72	113	25.6
A-221	"	"	5.34	112	25.2
A-230	Acetate	3.55	5.26	116	25.9
A-231	"	"	4.84	115	25.5
A-72	"	3.97	4.91	114	25.3
A-73	"	"	6.51	115	26.4

Table 5b

Variation of the rate of bromination of 4-quinazolone (22) with pH

H_2SO_4(M)	pH	k_2^{obs} ($M^{-1}min^{-1}$)≠	log k_2^{obs}
1.0	0.29	0.333	-0.476
0.5	0.59	0.685	-0.164
0.2	0.98	1.55	0.190
0.1	1.27	2.39	0.378
0.03	1.66	6.49	0.812
0.02	1.94	9.32	0.969
0.01	2.23	15.9	1.20
Buffer			
Cl-Acet.	2.63	21.1	1.32
"	2.80	21.2	1.33
"	3.07	25.4	1.40
Acetate*	3.55	25.7	1.41
" *	3.97	25.9	1.41

≠ An average from 2 or more determinations. (see Table 5a).

* In acetate buffers with higher acetate concns. (and thus pH > 4) the rate decreases due to the formation of acetylhypobromite . (see Appendix p. 66).

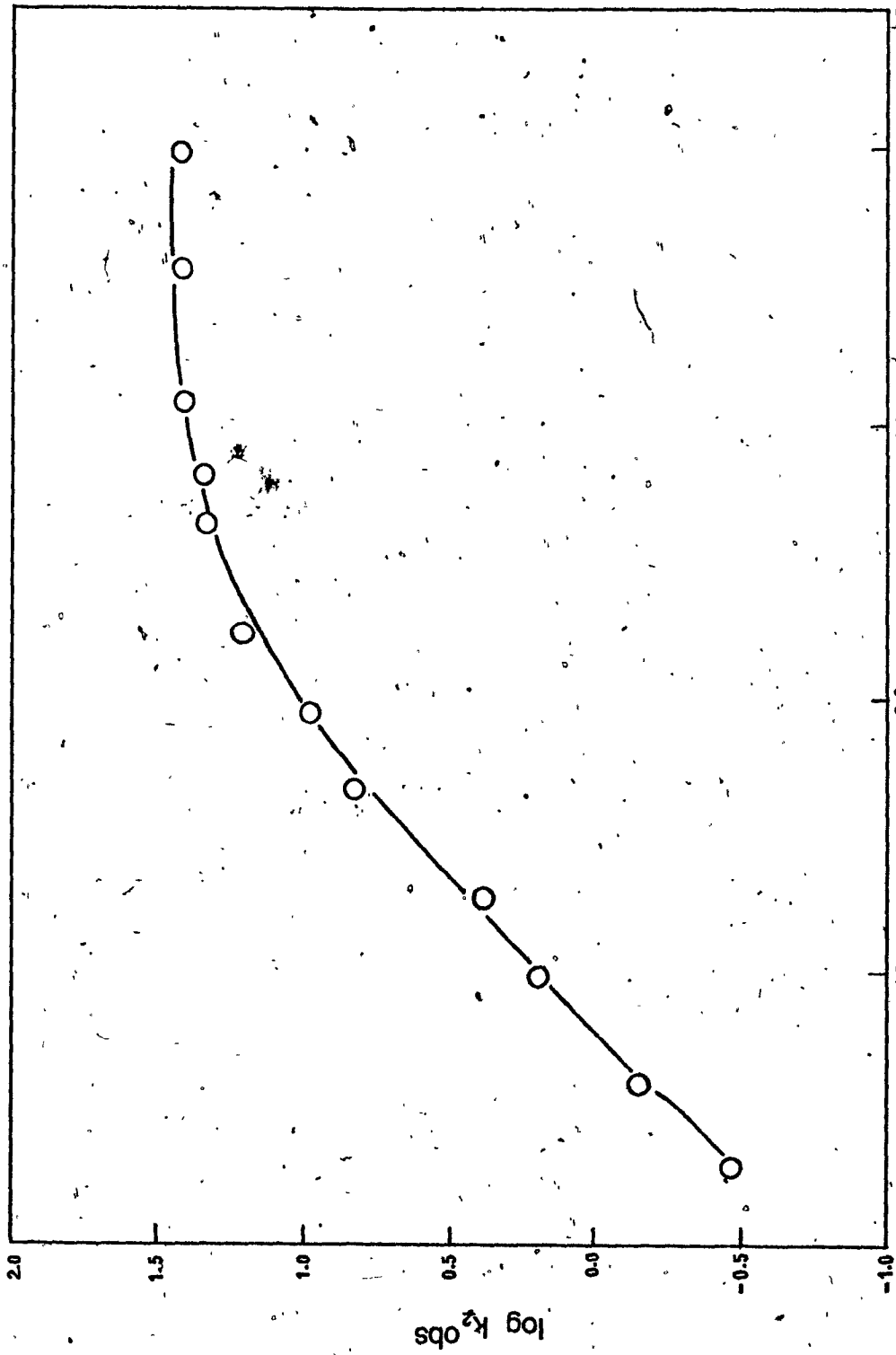


Figure 5

Observed rate profile for 4-quinazolone

equation (9b) using $k_2 = 27.79\ M^{-1}min^{-1}$, and $K_a = 10^{-2.21}$ (pK_a = 2.21), these values being obtained from the program CONT as described in the experimental section. The agreement between the calculated curve and the experimental points is excellent. The difference in value between the pK_a used here (2.21) and that determined[72] experimentally (2.12) is probably a reflection of the difference in temperature (30° versus 20°C).

The observed rate profile, then, is consistent with the bromination of 22 taking place on the free base form. However, it is also consistent with the reaction taking place on any species (such as a covalent hydrate) that is related to the free base in a manner that is independent of acidity.[56]

Acidity Dependence of the Bromination of 3-Methyl-4-Quinazolone (36)

Analogous bromination data which was obtained for 36 is shown in Tables 6a and 6b and plotted in Figure 6 . Again the shape of the rate profile is consistent with equations 9a and 9b . The curve drawn through the experimental points was calculated using $k_2 = 41.47\ M^{-1}min^{-1}$ and $pK_a = 2.21$. (Literature $pK_a = 2.18$ at 20°C).[77]

The curve in Figure 6 is slightly displaced from that shown in Figure 5 for the parent compound 22. This is due to the slightly larger value of k_2 and is in the direction expected for the effect of a methyl group upon an electrophilic substitution.

Table 6a

Variation of the rate of bromination of 3-methyl-4-quinazolone (36) with pH

Substrate Concentration: 5.0×10^{-3} M

KBr Concentration: 0.01 M

Run No.	H_2SO_4(M)	pH	$Br_2 \times 10^4$(M)	$k_1 \times 10^3$ (min^{-1})	k_2^{obs} ($M^{-1}min^{-1}$)
Z-11	1.0	0.30	5.47	2.30	0.516
Z-12	"	"	4.94	2.29	0.507
Z-21	0.5	0.60	5.14	4.13	0.921
Z-22	"	"	5.54	4.31	0.969
Z-31	0.2	0.99	4.91	10.3	2.29
Z-32	"	"	5.13	10.6	2.35
Z-41	0.1	1.27	5.06	19.9	4.42
Z-42	"	"	5.37	19.4	4.35
Z-51	0.05	1.60	5.77	36.5	8.25
Z-52	"	"	5.60	37.8	8.51
Z-61	0.03	1.78	5.35	57.6	12.9
Z-62	"	"	5.13	56.1	12.5
Z-71	0.01	2.24	5.38	87.0	19.5
Z-72	"	"	4.87	86.3	19.1
	Buffer				
Z-81	Cl-acet.	2.40	5.19	117	26.2
Z-82	"	"	5.35	111	25.0
Z-91	"	2.82	5.24	132	29.5
Z-92	"	"	5.06	139	31.0
Z-101	Acetate	3.14	5.24	161	36.0
Z-102	"	"	4.80	165	36.5
Z-111	"	3.38	5.68	183	41.3
Z-112	"	"	5.26	182	40.8
Z-121	"	3.61	5.36	176	39.5
Z-122	"	"	5.04	184	41.0

Table 6b

Variation of the rate of bromination of 3-methyl-4-quinazolone with pH

H_2SO_4 (M)	pH	k_2^{obs} ($M^{-1}min^{-1}$)≠	$\log k_2^{obs}$
1.0	0.30	0.512	-0.291
0.5	0.60	0.945	-0.025
0.2	0.99	2.32	0.365
0.1	1.27	4.39	0.642
0.05	1.60	8.38	0.923
0.03	1.78	12.7	1.10
0.01	2.24	19.3	1.29
Buffer			
Cl-acet.	2.40	25.6	1.41
"	2.82	30.3	1.48
Acetate	3.14	36.3	1.56
"	3.38	41.1	1.61
"	3.61	40.0	1.61

≠ An average of two determinations. (see Table 6a).

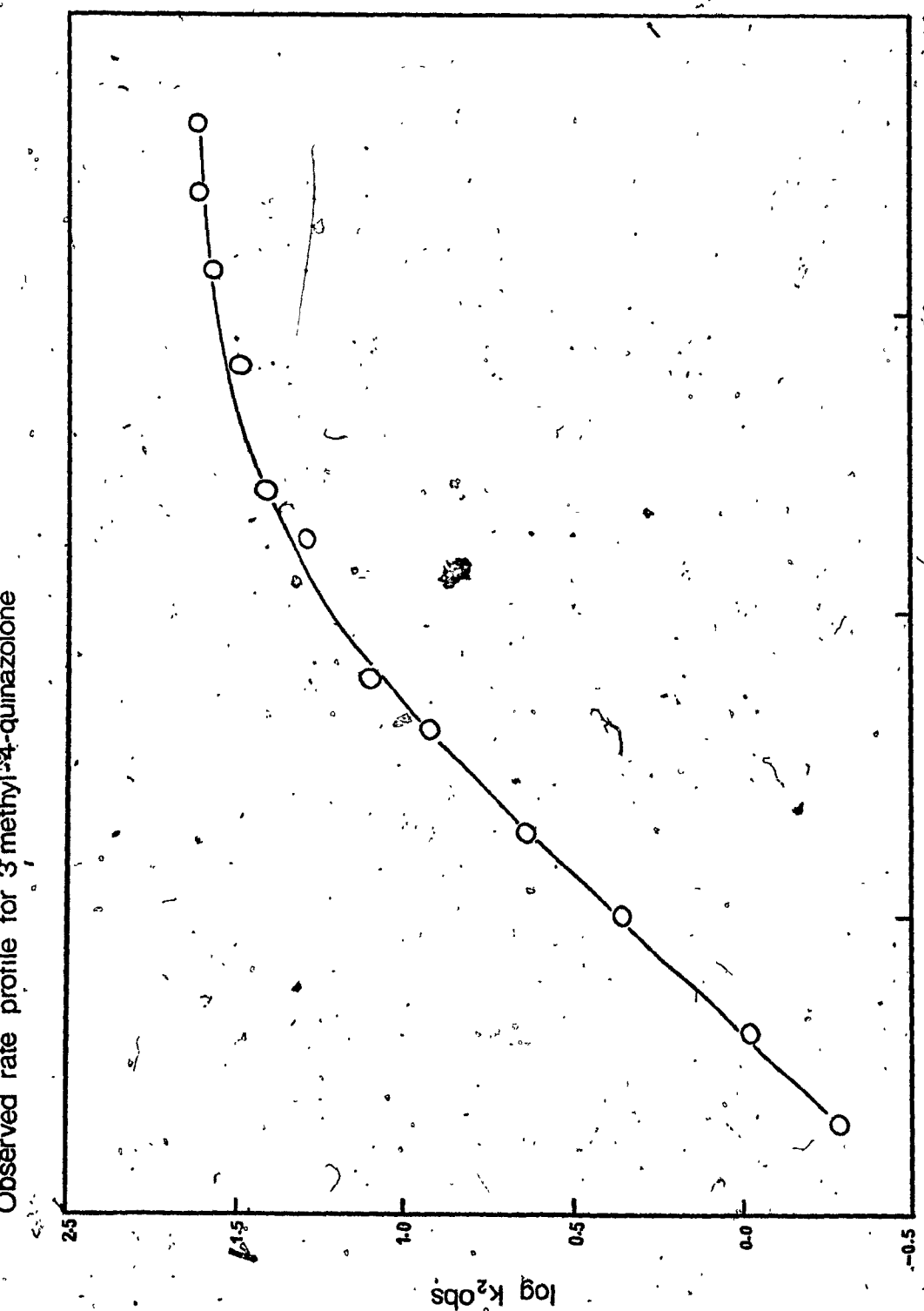
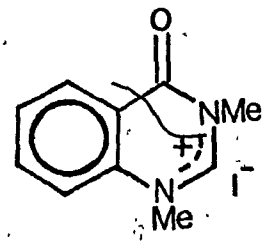


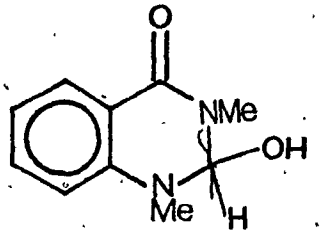
Figure 6

Observed rate profile for 3-methyl-4-quinazolone

Acidity Dependence of the Bromination of 1,4-Dihydro-1,3-Dimethyl-4-Oxoquinazolinium Perchlorate (37)



(28)



(29)

The methylation of 3-methyl-4-quinazolone (36) with methyl-iodide produced the quaternary iodide (28). In the bromination of such iodide salts complications may arise due to the formation of interhalogen complexes.[82,83] To avoid all such complications, the quaternary iodide salt (28) was converted to the corresponding perchlorate (37).

The rate data obtained for the bromination of the perchlorate (37) are shown in Tables 7a and 7b and plotted in Figure 7. The rate increases linearly with pH in the manner required for bromination taking place upon a species whose concentration is related to that of the cation in 37 through an acid dependent equilibrium. This species is most probably the pseudo base 29.

For the scheme

$$37 + H_2O \underset{}{\overset{K}{\rightleftharpoons}} H^+ + 29 \xrightarrow[Br_2]{k_2} \text{Products}$$

one can easily derive the expression

$$k_2^{obs} = \frac{k_2 K}{(K+[H^+])} \qquad (10)$$

Table 7a

Variation of the rate of bromination of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37)

Substrate Concentration : 5.0×10^{-3} M

*Substrate Concentration : 2.5×10^{-3} M

KBr Concentration: 0.01 M

Run No.	H_2SO_4 (M)	pH	$Br_2 \times 10^4$(M)	$k_1 \times 10^3$(min^{-1})	k_2^{obs}($M^{-1}min^{-1}$)
DM-10	1.0	0.29	7.08	6.57	1.53
DM-11	"	"	5.60	7.05	1.59
DM-12	"	"	5.44	7.03	1.58
DM-14	"	"	5.00	6.96	1.55
DM-20	0.5	0.58	4.91	15.9	3.52
DM-21	"	"	5.11	16.1	3.58
DM-22	"	"	6.01	15.4	3.50
DM-23	"	"	4.76	16.0	3.54
DM-30	0.2	0.96	4.35	32.5	7.12
DM-31	"	"	5.68	34.2	7.71
DM-40	0.1	1.23	8.23	62.7	15.0
DM-41	"	"	8.50	62.2	15.2
*DM-50	0.05	1.50	3.06	60.6	27.6
*DM-51	"	"	4.38	60.4	29.3
*DM-60	0.02	1.84	3.72	147	69.1
*DM-61	"	"	3.05	137	62.4
*DM-62	"	"	3.69	155	72.7
*DM-63	"	"	4.32	141	68.3

Table 7b

Variation of the rate of bromination of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate (37).

H_2SO_4(M)	pH	k_2^{obs}($M^{-1}min^{-1}$)≠	log k_2^{obs}
1.0	0.29	1.56	0.193
0.5	0.58	3.53	0.548
0.2	0.96	7.41	0.870
0.1	1.23	15.1	1.18
0.05	1.50	28.5	1.46
0.02	1.84	68.1	1.83

≠ An average of 2 or more determinations. (see Table 7a).

Least square for log k_2^{obs} vs pH gives

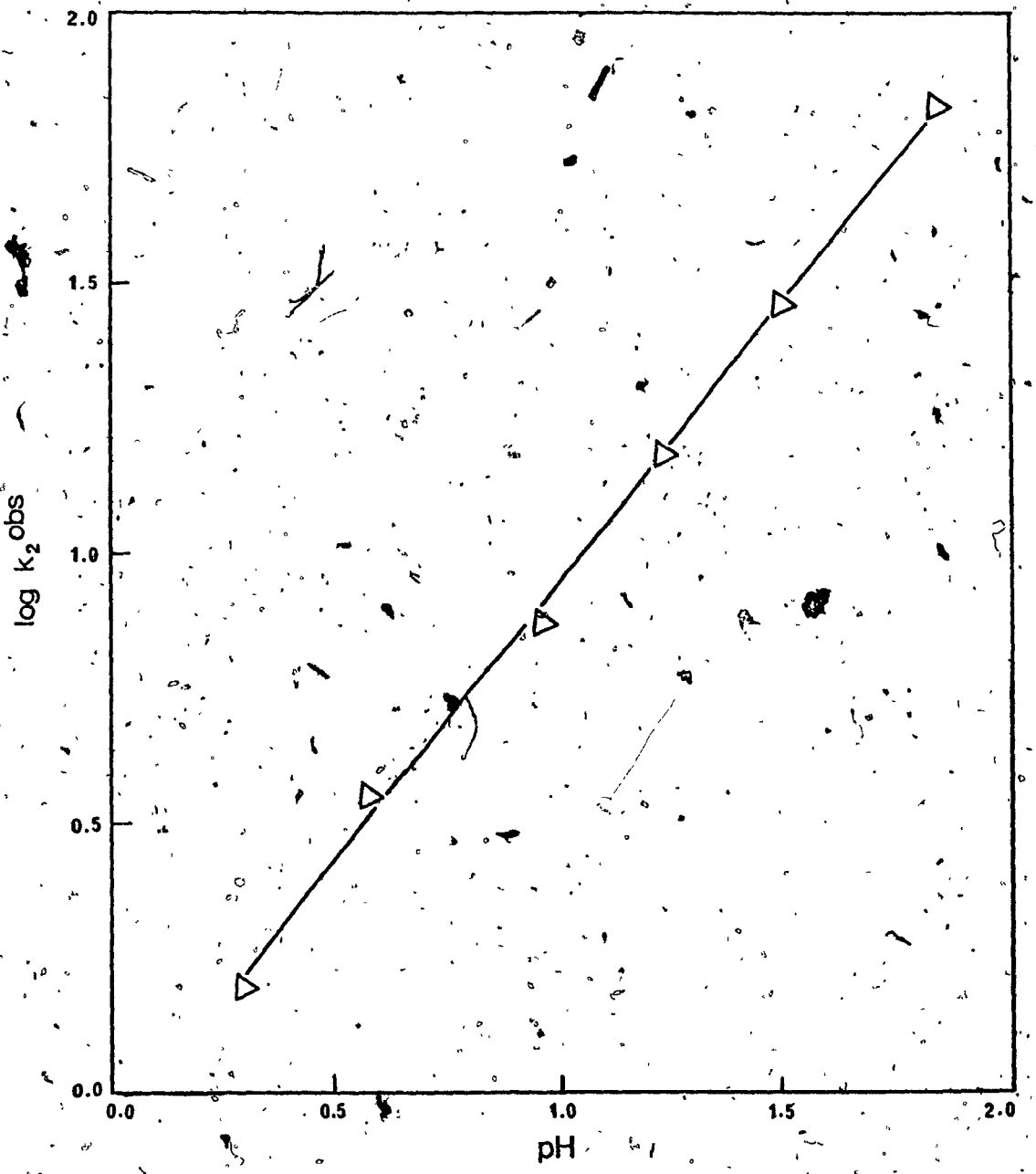
slope = 1.04 S.D. = 0.02

Intercept = -0.096 S.D. = 0.011

Corr. Coeff. = 0.9992

Figure 7

Variation of rate of bromination of 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate with pH.



in a similar manner to that outlined above (see p.47). Here $K = [29][H^+]/[37]$.

As was discussed in the Experimental Section (p.34), the value of K seems to be about 10^{-7}. Thus, in the region of acidity studied (pH = 0.29-1.84) 37 largely exists as the cation and equation 10 becomes $k_2^{obs} = k_2K/[H^+]$, since $[H^+] \gg K$. Alternatively

$$\log k_2^{obs} = \log k_2K + pH$$

Therefore, for the scheme above a plot of $\log k_2^{obs}$ versus pH should give a straight line of slope 1. Least squares analysis of the data in Table 7b and plotted in Figure 7 gives a slope of 1.04 (standard deviation 0.02).

In summary, the rate data obtained for the bromination of the quaternary salt (37) are consistent with the reaction taking place on its pseudo base 29*.

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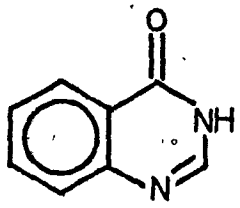
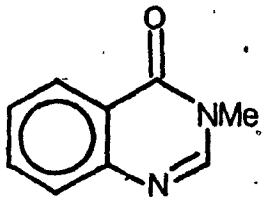
* Attempts to obtain rate data for a compound to act as a model for 29 are described in the Appendix p. 70.

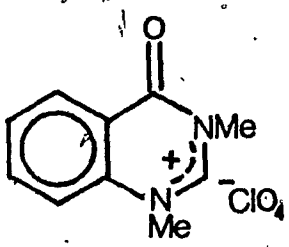
CONCLUSION



(22)



(36)



(37)

The three substrates 22, 36, 37 brominate at very similar rates in the region where all exists predominantly as cations (see Figure 8). For example at pH = 0.29

Substrate	22	36	37
k_2^{obs}	0.333	0.512	1.56 $M^{-1}min^{-1}$

These similarities are strongly suggestive that the three substrates react via similar mechanisms, with the small rate enhancements of the methyl derivatives being attributable to the normal activating effect of methyl groups upon electrophilic substitution.

Since, in the previous section, it was concluded that the quaternary cation 37 reacts via its pseudo base 28, it is now suggested that the substrates 22 and 36 react via their covalent hydrates. These conclusions may be presented in the form of one overall scheme, as shown on page 62.

In this scheme, the cations 51 in equilibrium with the covalent hydrates or pseudo base 52 react with bromine to give the intermediate 53 in the rate determining step. Proton loss from 53 gives the covalent hydrates or pseudo base 54 of the final product cation 55. By analogy with most aromatic bromination,[84,85] the proton loss

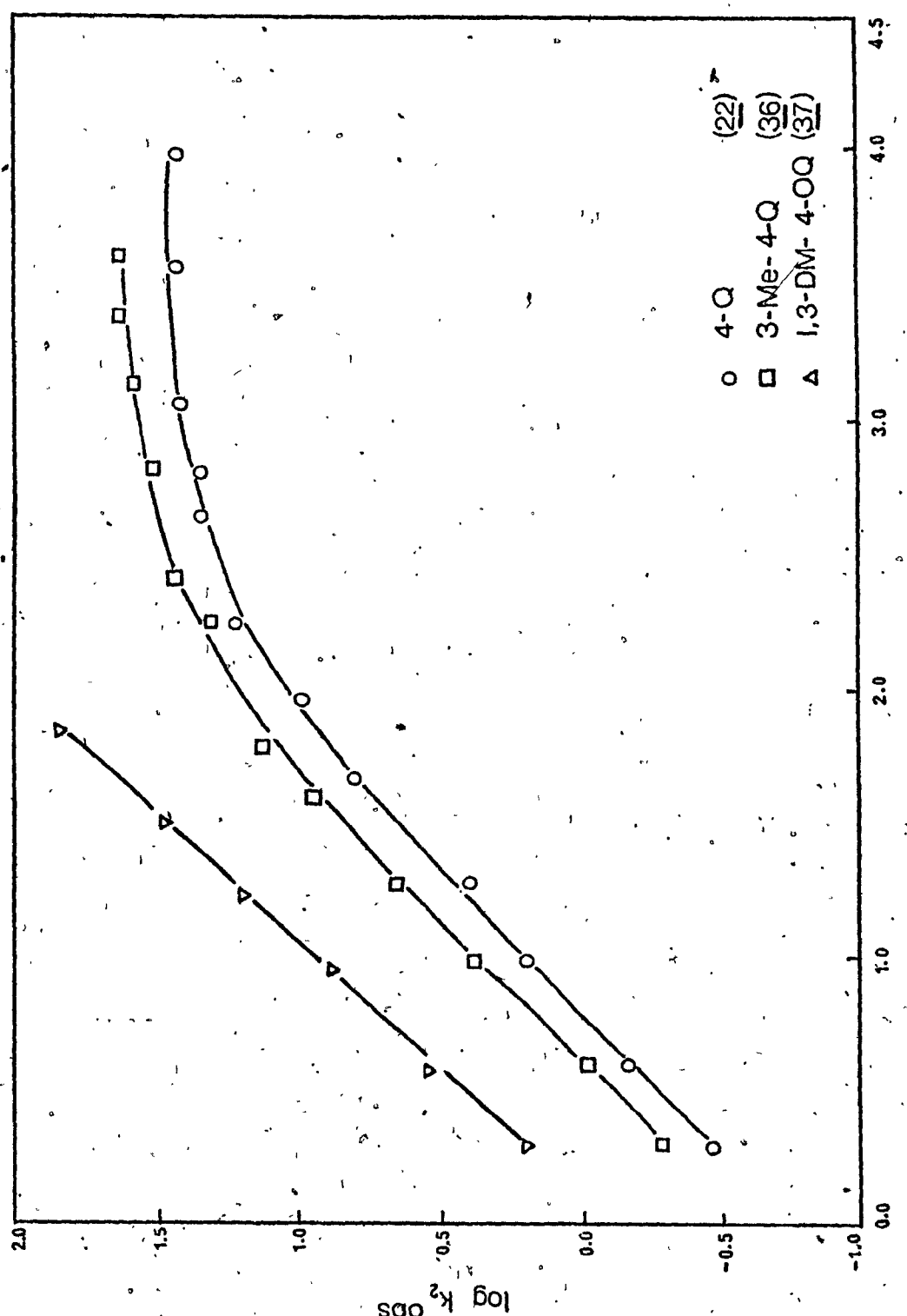
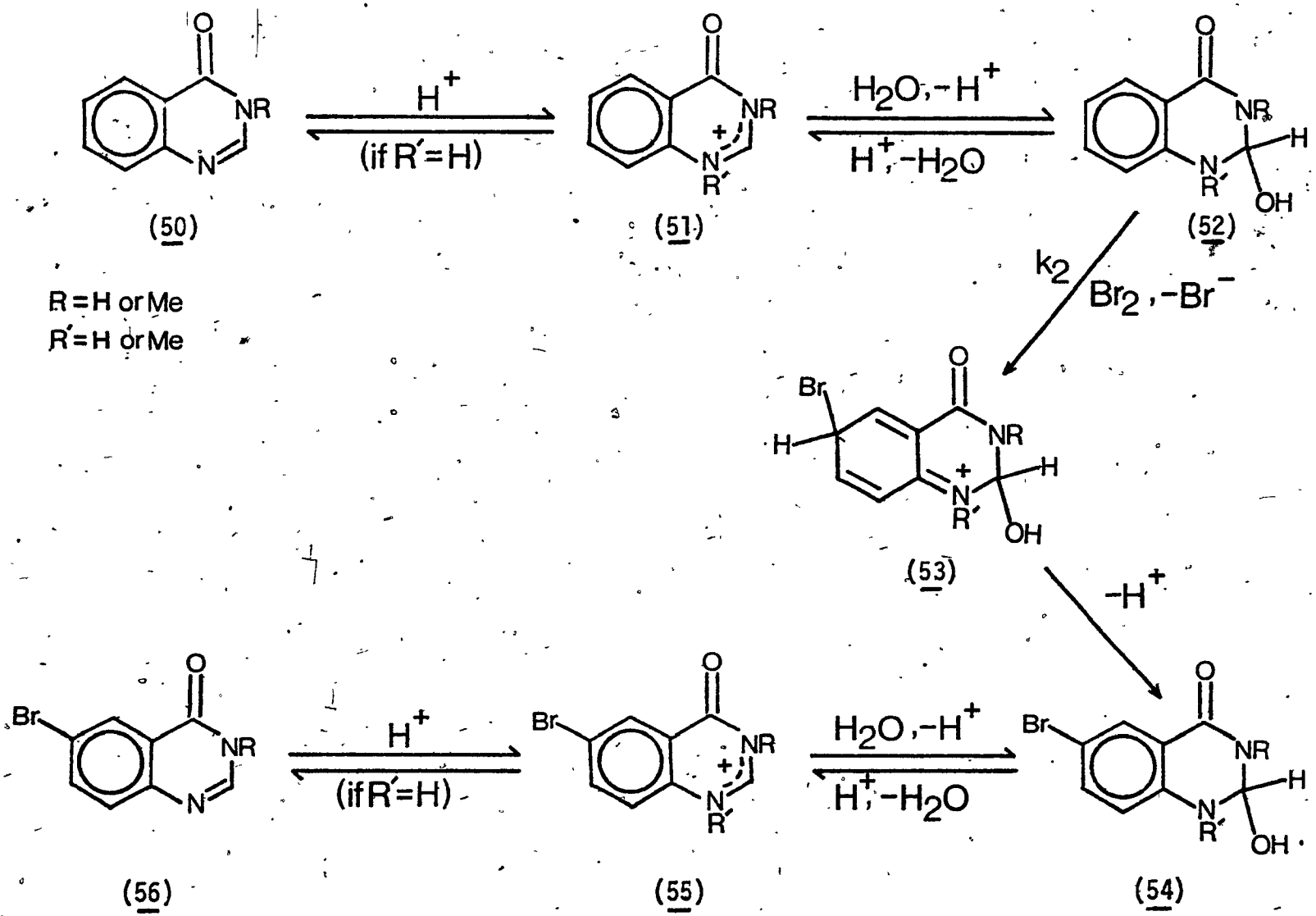


Figure 8

Observed rate profiles for 4-quinazolone and its N-methyl derivatives.

Scheme II



53 → 54 is probably quite fast, and so no attempt was made to determine H-D isotope effects in these brominations.

For the sequence

$$\underline{50} + H^+ \underset{}{\overset{Ka}{\rightleftharpoons}} \underline{51} \overset{K}{\rightleftharpoons} H^+ + \underline{52} \xrightarrow[\text{slow}]{k_2, Br_2} \underline{53} \xrightarrow[\text{fast}]{} \underline{55}$$

$$\text{rate} = k_2^{obs}[51]_s[Br_2] = k_2[52][Br_2]$$

where $[51]_s$ is the stoichiometric concentration of the cation, (=[50] + [51] + [52]).

$$o^o o\, k_2^{obs} = k_2[52]/[51]_s \qquad (11)$$

Define $K_a = [50][H^+]/[51]$, and $K = [52][H^+]/[51]$.

Then

$$\frac{[51]_s}{[52]} = \frac{[50] + [51] + [52]}{[52]}$$

$$= \frac{K_a}{K} + \frac{[H^+]}{K} + 1$$

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

Thus the equation 11 may be rewritten as

$$k_2^{obs} = k_2K/(K_a + [H^+] + K) \qquad (12)$$

(a) For the quaternary cation 51 (R = R' = Me), the equilibrium 50 ⇌ 51 does not exist and thus equation 12 loses the term K_a. Moreover, the equilibrium constant $K \simeq 10^{-7}$ for this cation, and so in the region of observation equation 12 becomes

$$k_2^{obs} = k_2K/[H^+]$$

or $\log k_2^{obs} = \log k_2K + pH$

as the observed data support (see Figure 8)

(b) For the substrates 50 (R = H, or R = Me), $K_a \simeq 10^{-2}$. Since for the dimethyl cation 51 (R = R' = Me) $K \simeq 10^{-7}$, here it is probably 10^{-5}-10^{-6}, i.e. $K \ll K_a$. Thus equation 12 now reduces to

$$k_2^{obs} = k_2K/(K_a + [H^+]) \qquad (13)$$

or $$\log k_2^{obs} = \log k_2K - \log (K_a + [H^+]) \qquad (14)$$

This equation generates curves such as observed in Figure 8 for the substrates 50 (R = H and R = Me, respectively). In the region $pH < pK_a$ (or $[H^+] \gg K_a$) equation 14 approximates to:

$$\log k_2^{obs} = \log k_2K + pH$$

and so the rate increases linearly with acidity. However, in the region $pH > pK_a$ (or $K_a \gg [H^+]$) equation 14 approximates to

$$\log k_2^{obs} = \log k_2K + pK_a = \text{constant}$$

and so the rate is essentially invariant with acidity.

In summary, then, the observed kinetic data are entirely consistent with the substrates 4-quinazolone (22 or 50, R = H) and 3-methyl-4-quinazolone (36 or 50, R = Me) reacting with bromine via their covalent hydrates 52 (R = H or Me, R' = H), and the dimethyl cation 37 (or 51, R = R' = Me) reacting via its pseudo base 52 (R = R' = Me). Similar conclusions were arrived at earlier[14,15,16,55,56,60] for the H-D exchanges and brominations of 2-pyrimidones and 4-pyrimidones.

As a final point, the relative reactivities of the three substrates are again considered. In equation 12 the numerator term k_2K is not separable except for the dimethyl cation 50 (R = R' = Me). However, this composite term may be obtained and compared for the

three substrates.

Substrate	50 (R = H) (22)	50 (R' = Me) (36)	51 (R = R' = Me) (37)
k_2K	0.171	0.256	0.886 min^{-1}
Rel.	1	1.50	5.18

Note that there is only a slight increase due to the introduction of R = Me at N-3. This will principally affect the equilibrium constant K (for 51⇌52). However, the introduction of R' = Me at N-1 causes a more substantial increase. Here the effect is not only to affect 51⇌52, but also to stabilise the intermediate 53 and hence to increase k_2. In short, the observed relative reactivities are readily rationalised in terms of the proposed mechanism in scheme 2.

APPENDIX

Acetate ion dependence

Inspection of Table 8 reveals that the rate constant for bromination of 4-quinazolone (22) gradually falls beyond pH = 3.97. This may be due to the increase in the acetate ion concentration in the buffers used in that region.

To confirm this suspicion, a few kinetic runs were obtained at constant pH (5.32), where the relative concentration of acetate ion is quite large. The rate of bromination is found to decrease with the increase in acetate ion concentration (see Table 9). This decrease in rate may possibly be due to acetyl hypobromite formation according to the equilibrium

$$AcO^- + Br_2 \rightleftharpoons AcOBr + Br^-$$

No values for an equilibrium constant were found in the literature. In one instance[86] it is reported that the addition of acetate ion to a reaction solution lead to a decrease in the bimolecular rate constant for bromination.

A similar, but different, reduction in rate was obtained for brominations carried out in a phosphate buffer (Table 8 , last entry). The second order rate constant (k_2^{obs}) obtained is higher than that obtained in acetate buffers, but is still lower than expected. Hypobromous acid is known[87] to react with buffer salts to produce complex brominating agents as in

$$HOBr + H_2PO_4^- \rightleftharpoons BrHPO_4^- + H_2O$$

This may account for the observed lower rate. Alternatively, in the present case, it may be due to

$$Br_2 + H_2PO_4^- \rightleftharpoons BrHPO_4^- + H^+ + Br^-$$

Table 8

Variation of the rate of bromination of 4-quinazoline (22) in buffers

KBr concentration = 0.01 M .

pH	k_2^{obs} ($M^{-1}min^{-1}$)	
3.97	25.9[a]	Acetate buffer
4.53	15.2[b]	"
4.91	12.2[b]	"
5.32	5.8[a]	"
5.76	11.7[a]	Phosphate buffer

a = An average of two determinations.

b = Single run.

Table 9

Variation of the rate of bromination of 4-quinazolone (22) with acetate ion concentration

[Substrate] = 5.0×10^{-3} M

[KBr] = 0.01 M

pH = 5.32

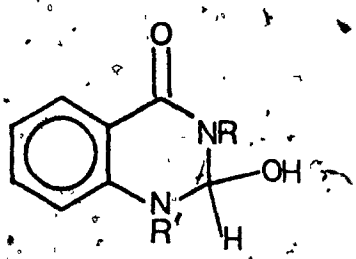
AcOH (N)	AcONa (N)	$Br_2 \times 10^4$ (M)	$k_1 \times 10^3$ (min^{-1})	k_2^{obs} ($M^{-1}min^{-1}$)	Ave. k_2^{obs} ($M^{-1}min^{-1}$)
0.03	0.17	5.34	25.4	5.70	5.76
		4.90	26.2	5.81	
0.022	0.128	5.30	36.7	8.20	8.25
		5.18	37.2	8.30	
0.015	0.085	5.23	54.4	12.2	12.5
		4.80	58.0	12.8	

since the formation of HOBr from

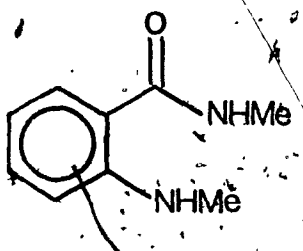
$$Br_2 + H_2O \rightleftharpoons HOBr + H^+ + Br^-$$

is not important below pH = 6 in 0.01 M Br^- solution.[88]

Model compound for pseudo base



(52, R = R' = Me).

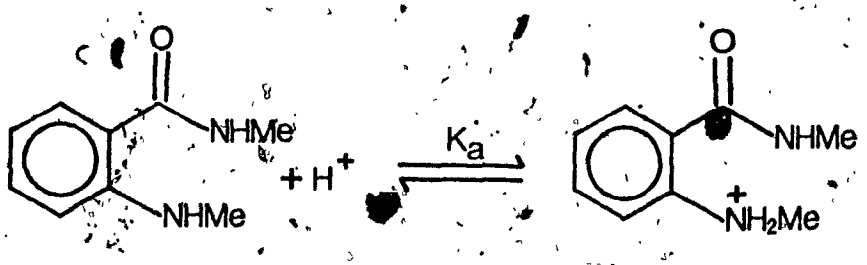


(31)

In order to obtain further support for intermediacy of the pseudo base (52 (R = R' = Me) in the bromination of the quaternary salt 37, the bromination of N-methyl-o-methylaminobenzamide (31) was studied. In the pH region, the rate of bromination of 31 was found to be too fast to be followed and therefore the rate measurements were made in 10N H_2SO_4 where 31 is predominantly protonated. (Table 10 , P. 73).

In order to interpret these results the pK_a for 31 is required. This was measured spectrophotometrically[81] and found to be 3.37 ± 0.04. This value appeared to be reasonable since it lies between the pK_a of benzamide (-2.16) and that of N-methylaniline (4.85).[81] Furthermore, since 31 almost certainly undergoes protonation on the non-amidic nitrogen, the use of the acidity function H_o is justified. The value of H_o for 10N H_2SO_4 (= -2.41) was interpolated from the curve obtained by plotting the values[81] of H_o against N H_2SO_4, in the vicinity of 10N acid.

In such strong acid, 31 is almost completely protonated, and therefore for the scheme



(31) (47)

k_2 | Br_2

Prod.

rate = $k_2^{obs}[47][Br_2] = k_2[31][Br_2]$

and $k_2^{obs} = k_2[31]/[47]$ (15)

For the protonation of 31 in strong acid one writes

$$K_a = \frac{[31]}{[47]} \cdot \frac{a_{H^+} \cdot f_B}{f_{BH^+}} = \frac{[31]}{[47]} \cdot h_o$$

o o equation 15 may be rewritten as

$$k_2^{obs} = \frac{k_2 K_a}{h_o} \quad (16)$$

At 10% H_2SO_4 H_o = -2.41, thus $h_o = 10^{2.41}$. The measured pK_a = 3.37, thus $K_a = 10^{-3.37}$. Since, from the data in Table 10, k_2^{obs} = 40.6 $M^{-1}min^{-1}$, one can calculate

$$k_2 = 24.5 \times 10^6 \ M^{-1}min^{-1} \quad (17)$$

For the sequence (see Scheme 2, P. 62)

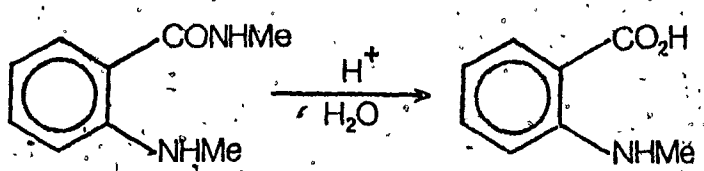
51 (R = R' = Me) $\rightleftharpoons$ 52 (R = R' = Me) $\xrightarrow[Br_2]{k_2}$ product

it was previously calculated (P. 63) that $k_2K = 0.886$. Since $K = 10^{-7.54}$, then for the pseudo base 52 (R = R' = Me)

$$k_2 = 30.7 \times 10^6 \ M^{-1}min^{-1}$$

The closeness of this number to that for 31 again supports the intermediacy of the pseudo base 52 in the bromination of 51.

The validity of this comparison is weakened by one possible complication. In the 10N acid required for studying the bromination of 31, it may also undergo acid catalysed hydrolysis to N-methyl-anthranilic acid (48). If this hydrolysis is as fast as or faster



(31) (48)

than the observed bromination, the latter may be due to the bromination of 48, not of 31.

In separate experiments (Table 11 , P. 73) it was observed that, indeed, 48 does react with bromine, and at a rate about 4 times faster than 31. Thus it is possible that the observed reaction of 31 with bromine is due primarily to 31→48 which then reacts with Br_2. Attempts to obtain a measure of the rate of 31→48 were unsuccessful.

Table 10

The rate of bromination of N-methyl-o-methylaminobenzamide in 10N H_2SO_4

Substrate x 10^3(M)	Br_2 x 10^4 (M)	k_1 (min^{-1})	k_2 ($M^{-1}min^{-1}$)	Ave k_2 ($M^{-1}min^{-1}$)
5.0	5.10	182	40.7	40.6
5.0	4.20	185	40.5	

Table 11

The rate of bromination of N-Methyl anthranilic acid in 10N H_2SO_4

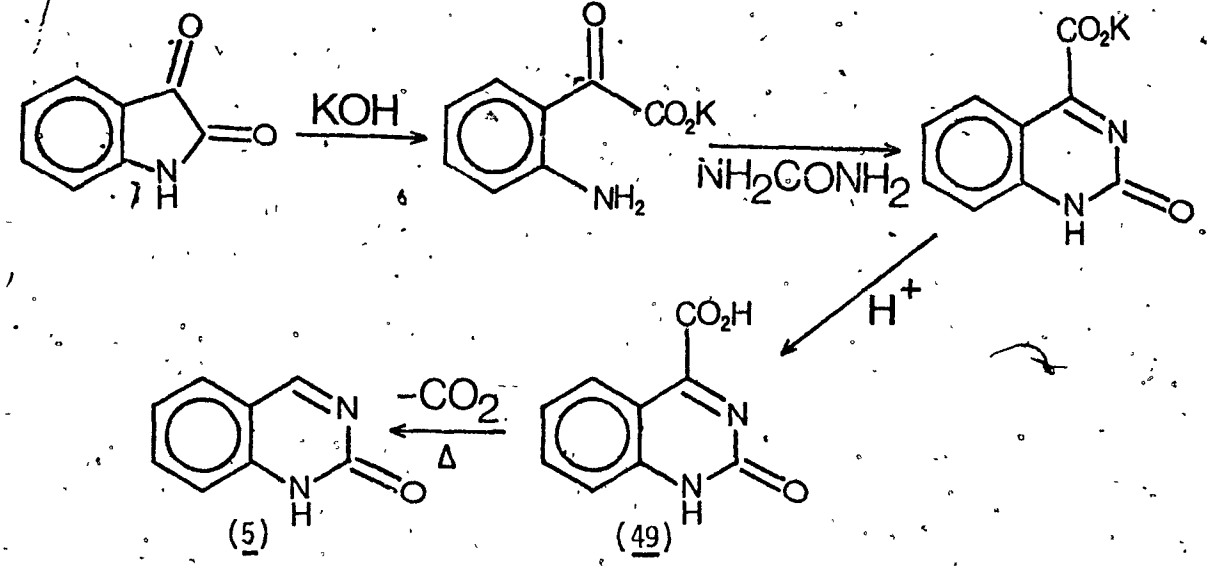
Substrate x 10^3(M)	Br_2 x 10^4 (M)	k_1 (min^{-1})	k_2 ($M^{-1}min^{-1}$)	Ave. k_2 ($M^{-1}min^{-1}$)
5.0	5.13	691	154	154
5.0	5.30	694	155	

2-QUINAZOLONE (5)

The existence of the covalent hydrates of 2-quinazolone (5) and its 6-chloroderivative is well established.[23,35] Therefore it was of interest to study the possibility of such intermediates in the bromination of 5 and its derivatives. However, solubility problems precluded such a study.

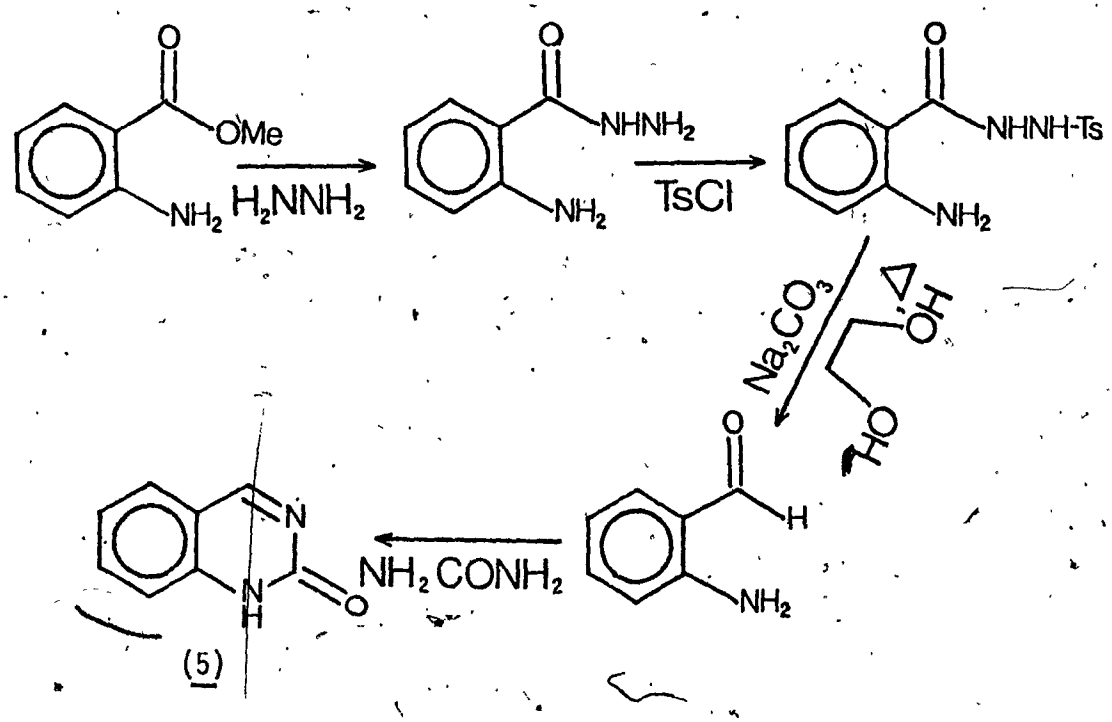
Synthesis

Route one[89]



In the last step (49→5), the decarboxylation failed on several attempts and therefore this method was abandoned.

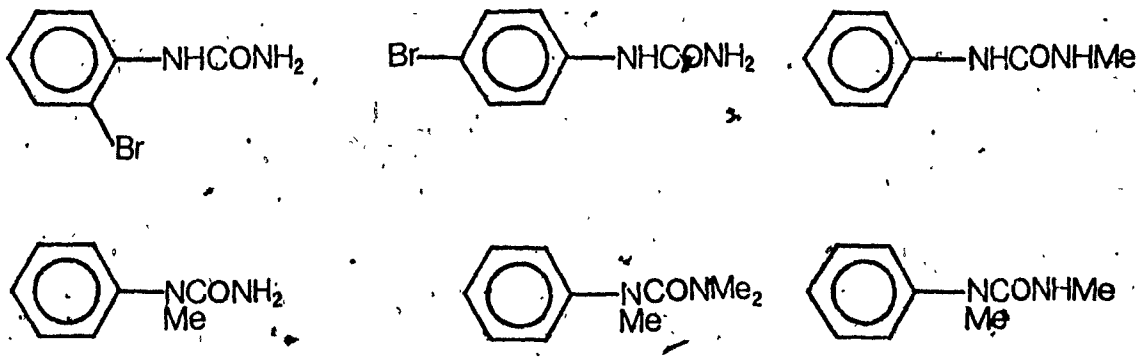
Route two[90,91]



(5)

Model compounds

The following phenyl urea derivatives were made as model compounds for 5 by literature procedures



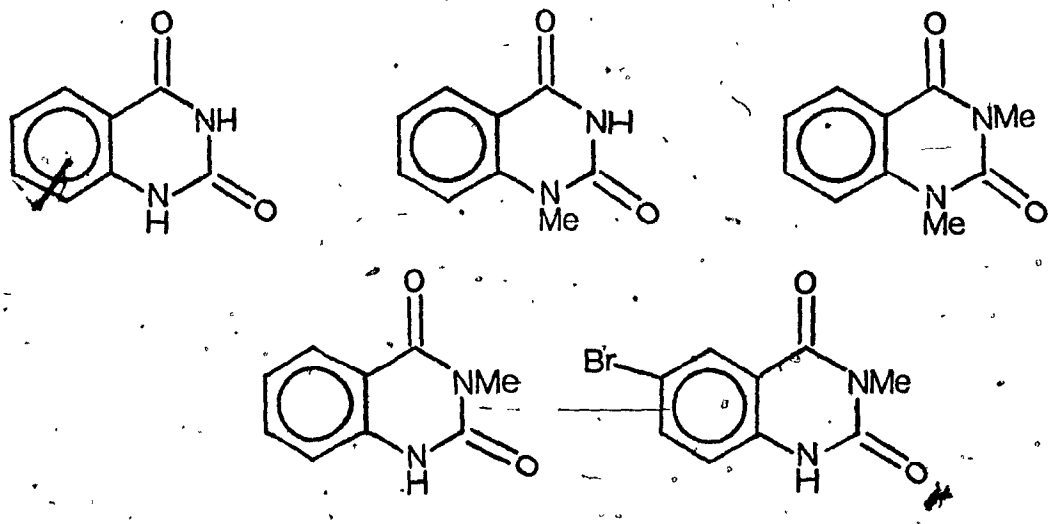
Solubility

2-quinazolone (5) is very poorly soluble in water, and even in 4N H_2SO_4 its maximum solubility is 1.0×10^{-4}M. The rate of its

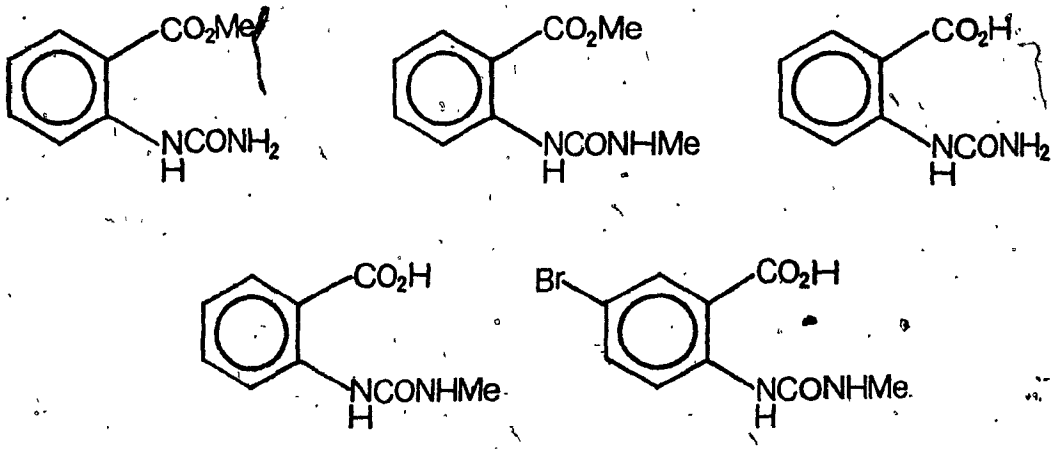
bromination in this medium is extremely slow and, the bromination product (presumably the 6-bromo derivative) precipitates out from the solution. Because of such complexities the study of the bromination of 5 was not pursued.

2,4-QUINAZOLINEDIONES

These compounds were also of interest since the mechanism of bromination of their non-benzenoid analogues (uracils) have been extensively studied in this laboratory.[16] The following 2,4-quinazolinediones were prepared by modifications of literature procedures.



The following ureido compounds were prepared either as models or as intermediates for the synthesis of a particular 2,4-quinazolinedione.



The bromination study of 2,4-quinazolinedione was not pursued because of its very poor solubility in aqueous and acidic media.

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