2-(2-Carboxybenzoyl)imidazole (5, $R_1 = R_2 = H$). A mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29 mmol), H_2O (30 ml), MeOH (30 ml), and NaOH (2.0 g, 50 mmol) was stirred at 25 °C for 2 h. Neutralization of the resulting solution (pH 7) gave a colorless precipitate which was recrystallized (210 ml of MeOH) to give 4.31 g (20 mmol, 69%) of product as colorless needles with mp 228–229 °C dec (lit.[2] 200 °C); ν_{max} (Nujol) 3290 and 1670 cm^{-1}; λ_{max} (MeOH) 287 nm (ϵ 13 300); ^1H NMR (Me_2SO-d_6) δ 12.17 (broad) 2 H (CO_2H, NH), 8.03–7.80 (m) and 7.67–7.53 (m) 4 H (C_6H_4), and 7.27 ppm (s) 2 H (CH=CH). Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.17; H, 3.75; N, 13.23.

2-(2-Carboxybenzoyl)-4-phenylimidazole[7] (5, $R_1 = C_6H_5$, $R_2 = H$) was prepared similarly from 3 ($R_1 = C_6H_5$; $R_2 = H$) in 82% yield after recrystallization from a mixture of MeOH (20 ml), Me_2SO (10 ml), and H_2O (2 ml). The product was a colorless solid with mp 280 °C dec; ν_{max} (Nujol) 3350 and 1670 cm^{-1}; λ_{max} (MeOH) 323 nm (ϵ 16 300) and 250 (12 700); ^1H NMR (Me_2SO-d_6) δ 8.00–7.58 (m) 7 H and 7.47–7.17 ppm (m) 3 H. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.54; H, 4.23; N, 9.32.

2-(2-Carboxybenzoyl)benzimidazole (5, $R_1 + R_2 = CH{=}CHCH{=}CH$) was prepared similarly from 3 ($R_1 + R_2 = CH{=}CHCH{=}CH$) in 92% yield after recrystallization (67% MeOH). The product was a colorless solid with mp 270–271 °C (lit.[2] 250 °C); ν_{max} 3380, 3320, and 1680 cm^{-1}; λ_{max} (MeOH) 310 nm (ϵ 15 300) and 240 (10 200); ^1H NMR (Me_2SO-d_6) δ 13.40 (broad) 2 H (CO_2H, NH) and 8.12–7.17 ppm (m) 8 H (aromatic). Anal. Calcd for $C_{15}H_{10}N_2O_3$: C, 67.66; H, 3.79; N, 10.52. Found: C, 66.86; H, 3.70; N, 10.23.

Cyclization of 2-(2-Carboxybenzoyl)-4-phenylimidazole. A mixture of 5 ($R_1 = C_6H_5$; $R_2 = H$) (1.0 g, 3.43 mmol) and $SOCl_2$ (20 ml) was warmed on a steam bath for 5 min, then evaporated to leave 0.8151 g (2.98 mmol, 87%) of 2(3)-phenylimidazo[1,2-*b*]isoquinoline-5,10-dione (3, $R_1 = C_6H_5$; $R_2 = H$) as a yellow solid, mp 288–290.5 °C. Recrystallized material (DMF) was identical spectrally with material prepared from 1 and 2 ($R_1 = C_6H_5$; $R_2 = H$) above.

Treatment of 3 ($R_1 = R_2 = H$) with MeOH. A mixture of 3 ($R_1 = R_2 = H$) (1.0 g, 5.05 mmol), MeOH (20 ml), and a small chip of sodium was stirred at 25 °C for 1.5 h. The yellow color faded and the dione went into solution, but isolation by evaporation gave only starting material. Comparison of the uv spectra of 3 ($R_1 = R_2 = H$) in DMF [λ_{max} 365 nm (ϵ 2040) and 322 (3980)], where no reaction can occur, and in MeOH [λ_{max} 290 nm (ϵ 14 200)] with an authentic sample of ester 6 ($R_1 = R_2 = H$; $R = C_2H_5$) [λ_{max} (EtOH) 290 nm (ϵ 13 100)] suggests the presence of species 8 in methanol solutions of 3; 8 reverts to 3 on isolation.

2-(2-Carboethoxybenzoyl)imidazole (6, $R_1 = R_2 = H$; $R = C_2H_5$) was prepared by stirring a mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29.0 mmol), EtOH (50 ml), and H_2SO_4 (2 ml) at reflux for 2 h, during which time the solid dissolved. The mixture was diluted (H_2O) and neutralized (pH 7) to give 8 as a colorless precipitate, yield 4.97 g (20.4 mmol, 70%) after recrystallization (160 ml of 25% EtOH). Pure 6 had mp 156–158 °C (lit.[2] 170 °C); ν_{max} 1700, 1600, and 1270 cm^{-1}; λ_{max} (EtOH) 290 nm (ϵ 13 100) and 214 (13 800); ^1H NMR ($CDCl_3$) δ 11.67 (broad) 1 H (NH), 8.42–7.77 (m) 4 H (C_6H_4), 7.18 (s) 2 H (CH=CH), 4.12 (q, J = 7 Hz) 2 H (OCH_2), and 1.07 ppm (t, J = 7 Hz) 3 H (CH_3). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.81; H, 4.80; N, 11.84.

2-(2-Carbamoylbenzoyl)imidazole (7, $R_1 = R_2 = R' = H$). A mixture of 3 ($R_1 = R_2 = H$) (5.77 g, 29 mmol) and liquid NH_3 (100 ml) was stirred at −33 °C for 1 h. The solid dissolved to form a colorless solution, evaporation of which gave the crude amide. Recrystallization from a mixture of MeOH (90 ml), Me_2SO (70 ml), and H_2O (150 ml) gave 4.59 g (21.4 mmol, 74%) of colorless, crystalline product with mp 193–194 °C dec; ν_{max} (Nujol) 3290 and 1675 cm^{-1}; λ_{max} (MeOH) 275 nm (ϵ 1265); ^1H NMR (Me_2SO-d_6) δ 12.22 (broad) 1 H (NH), 9.13 and 7.12 (broad) 2 H (NH_2), 7.82–7.42 (m) 4 H (C_6H_4), and 6.92 ppm (s) 2 H (CH=CH). Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22. Found: C, 61.11; H, 4.28.

Registry No.—1, 88-95-9; 2 ($R_1 = C_6H_5$; $R_2 = H$), 670-95-1; 2 ($R_1 + R_2 = CH{=}CHCH{=}CH$), 51-17-2; 3 ($R_1 = R_2 = H$), 36142-27-5; 3 ($R_1 = C_6H_5$; $R_2 = H$), 57594-19-1; 3 ($R_1 + R_2 = CH{=}CHCH{=}CH$), 6659-72-9; 4 ($R_1 = R_2 = R_3 = H$), 57594-20-4; 4 ($R_1 = R_2 = H$; $R_3 = CH_3$), 57594-21-5; 4 ($R_1 = R_2 = H$; $R_3 = C_6H_5$), 57594-22-6; 4 ($R_1 = C_6H_5$; $R_2 = H$; $R_3 = CH_3$), 57594-23-7; 4 ($R_1 + R_2 = CH{=}CHCH{=}CH$; $R_3 = H$), 57594-24-8; 4 ($R_1 + R_2 = CH{=}CHCH{=}CH$; $R_3 = CH_3$), 57594-25-9; 5 ($R_1 = R_2 = H$), 41200-40-2; 5 ($R_1 = C_6H_5$; $R_2 = H$), 57594-26-0; 5 ($R_1 + R_2 = CH{=}CHCH{=}CH$), 41200-57-1; 6 ($R_1 = R_2 = H$; $R_2 = C_2H_5$), 41200-53-7; 7 ($R_1 = R_2 = R' = H$), 57594-27-1; 8, 57594-28-2; methylhydrazine, 60-34-4; phenylhydrazine, 100-63-0; hydrazine hydrate, 10217-52-4.

References and Notes

(1) Belgian Patent 772 186 (1971) to Bayer A.G.
(2) E. Regel, K. Lürssen, and K. Büchel, West German Patent 2 145 456 (1973) to Bayer A.G.
(3) M. F. Sartori, A. Oken, and H. E. Schroeder, *J. Org. Chem.*, **31**, 1498 (1966).
(4) E. W. Bousquet, M. D. Moran, A. L. Johnson, J. Harmon, and J. W. Summers, *J. Org. Chem.*, **40**, 2208 (1975).
(5) This chemistry should be compared with that of 3-aryl-5-pyrazolylbenzoic acids: A. L. Johnson and P. B. Sweetser, *J. Org. Chem.*, **41**, 110 (1976).
(6) Melting points are uncorrected, and were determined in a Mel-Temp capillary apparatus; ir spectra were determined in KBr on a Perkin-Elmer 621 instrument; uv spectra were determined on a Cary Model 14 instrument; NMR spectra were determined vs. internal Me_4Si on a Varian Associates A-60 instrument; mass spectra were determined by direct injection into a Consolidated CEC-110 instrument.
(7) These compounds are not described in ref 1 and 2.

The Mechanism of Bromination of 4(3*H*)-Quinazolinone, Its 3-Methyl and Its 1,3-Dimethyl Derivatives in Aqueous Acidic Solutions

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The kinetics of bromination of 4(3*H*)-quinazolinone, 3-methyl-4-quinazolinone, and 1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium perchlorate have been measured in dilute aqueous acid media. The kinetic order of the reactions, the acidity dependence of the rates, the inverse dependence of the rates on bromide ion, and the relative reactivities of the substrates are all consistent with a mechanism in which the rate-determining step is attack by molecular bromine upon the covalent hydrate (or pseudobase) of the substrates.

Relatively little has been done on the mechanistics aspects of quinazoline chemistry, although many derivatives have been prepared for potential medicinal purposes.[1] It is known,[2] however, that several simple quinazolines show appreciable covalent hydration,[2,3] particularly in their protonated forms. In aqueous solution 2(1*H*)-quinazolinone[4] exists to the extent of 25% as the covalent hydrate formed by addition of water across the C_4–N_3 double bond,[5] but there is no direct evidence for the covalent hydration of 4(3*H*)-quinazoline (1, R = H). However, it is interesting to

note that the oxidation of 1 (R = H) to 2,4(1H,3H)-quinazolinedione[6] may occur via its covalent hydrate 3 (R = R′ = H).

Earlier work on 2(1H)-pyrimidinones[7] and 4(3H)-pyrimidinones[8] has pointed to the involvement of covalent hydrates in the hydrogen–deuterium exchange[7a,8a] reactions and the brominations[7b,8b,c] of these substrates in aqueous media. The object of the present work was to study the bromination of 4(3H)-quinazolinone (1, R = H) and to ascertain the involvement, or otherwise, of its covalent hydrate 3 (R = R′ = H) in this reaction.

Such studies may have ramifications with respect to oxidations catalyzed by the enzyme xanthine oxidase, e.g., aldehydes to acids, purines to hydroxypurines, and pteridines to hydroxypteridines,[9] since it is a reasonable hypothesis that covalent hydrates are involved in these oxidations. Various heterocyclic systems which are known to undergo covalent hydration are easily oxidized to hydroxy derivatives.[3]

Results and Discussion

Bogert and Geiger[10] reported that attempts to brominate 1 (R = H) with bromine in aqueous potassium bromide solution, in glacial acetic acid, or in acetic anhydride all failed. However, they did obtain a monobromo product by carrying out the bromination in sulfuric acid, but the position of the bromine in their product was not specified.

Contrary to their report[10] we find that 1 (R = H) can be synthetically brominated by bromine in aqueous potassium bromide solution and the 6-bromo product 7 (R = H) can be isolated in high yield. The product so obtained was identical with material made by cyclization of 5-bromoanthranilic acid.[11] Similarly synthetic brominations of 1 (R = Me) and 2 (R = R′ = Me) perchlorate in aqueous methanol gave good yields of 7 (R = Me) and 6 (R = R′ = Me) perchlorate, respectively.

Spectral changes occurring during a bromination of 1 (R = H) carried out in dilute acid (0.01 N H_2SO_4, pH 2.23) were completely consistent with the simple conversion of 1 (R = H) → 7 (R = H). Uv spectra traced at various times after mixing equimolar quantities (4.5×10^{-5} M) of 1 (R = H) and bromine showed a gradual diminution in absorbance due to these substrates, a clean isosbestic point at 304 nm, and a final spectrum identical with that of an authentic sample of 7 (R = H) of the appropriate concentration in the same medium. In neither the synthetic work nor in spectral studies was there any evidence of the formation of any 8-bromo-4(3H)-quinazolinone (8).[12]

Scheme I

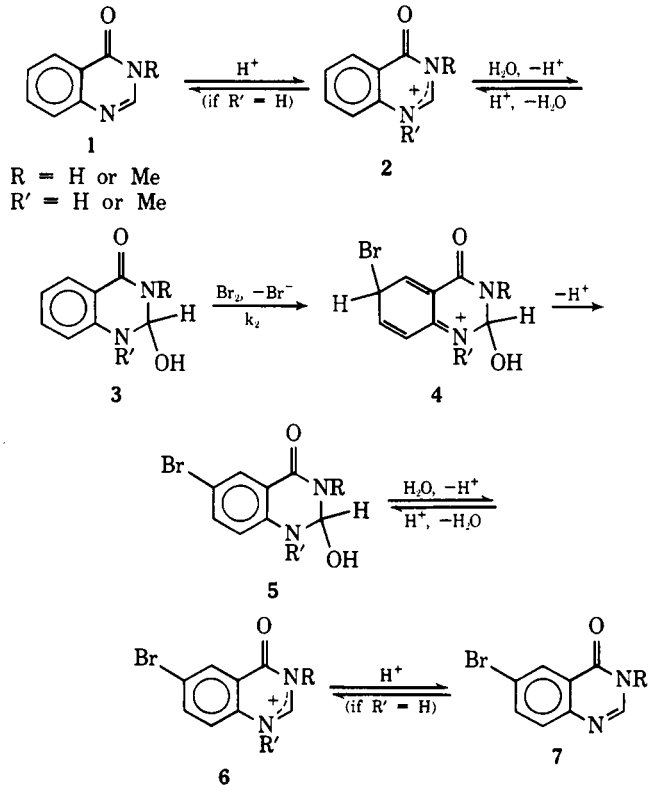
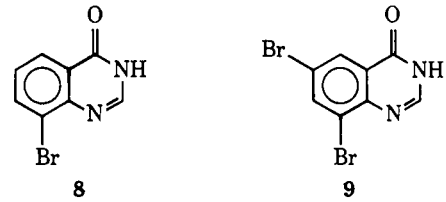


Table I. Variation of Rate of Bromination of 4(3H)-Quinazolinone (1, R = H) with Substrate Concentration[a]

[1] × 10^3, M	[Br_2] × 10^4, M	$k_1 \times 10^3$, min^{-1}	Av $k_1 \times 10^3$, min^{-1}
5.0	4.91	114	
	6.51	115	115
4.0	4.94	93.7	
	5.20	94.3	94
2.5	2.27	56.0	
	2.91	56.5	56.3
1.25	1.22	28.4	
	1.33	30.9	29.7

[a] At 30 °C, [KBr] = 0.01 M, acetate buffer pH 3.97. These data are plotted in Figure 1.



We also ruled out the formation of the 6,8-dibromo derivative (9) during the bromination of 1 (R = H). It was found that the apparent rate of the bromination 7 (R = H) → 9 is very much slower than that of the parent 1 → 7 (R = H). At 30 °C, 7 (R = H) did not decolorize an equivalent amount of bromine even after 4 days. An attempted synthetic scale dibromination of 1 (R = H) (10 h at 85 °C) was unsuccessful with only the 6-bromo derivative (7, R = H) being obtained. However, 9 was obtained by prolonged heating of 7 (R = H) and bromine for 1 week at 50 °C. From these observations the possibility of significant dibromination of 1 (R = H) during the course of the kinetic studies can be safely eliminated, particularly since these were carried out with a tenfold excess of substrate over bromine.

Order of Reaction. Initial titration kinetics suggested a second-order reaction: first order in substrate, and first order in bromine. For convenience, therefore, subsequent kinetics were measured under pseudo-first-order conditions, with an approximate tenfold excess of substrate over bromine. Rate constants (k_1) thus obtained were for the pseudo-first-order disappearance of bromine due to the reaction 1 → 7 (or 2 → 6).

That this reaction is truly second order is shown by the data in Table I (plotted in Figure 1). The pseudo-first-order rate constants (k_1) diminish linearly with the substrate concentration, and within experimental error, the least-squares line in Figure 1 goes through the origin.[13]

Bromide Ion Dependence. Brominations of the type under consideration produce bromide ion, and thus complex kinetics may be observed since there is a progressive reduction in the concentration of free bromine owing to the formation of tribromide ion.[14] Moreover, there are examples known where tribromide ion acts as an electrophile and gives rise to 1–3% of the product.[15]

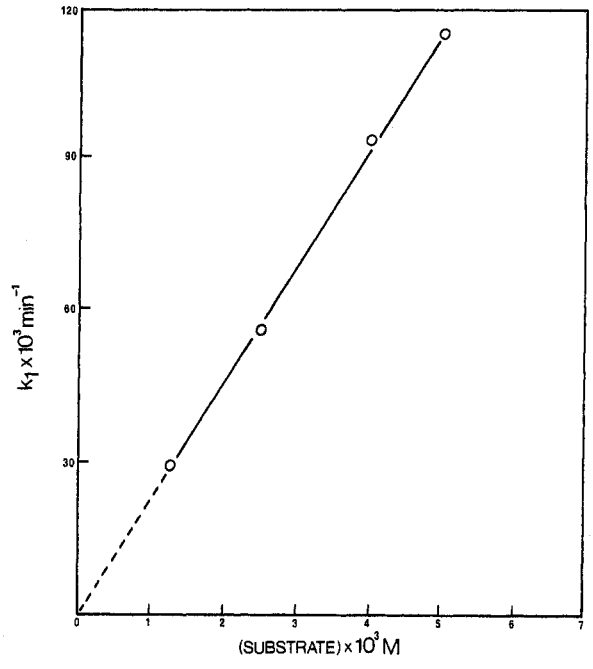


Figure 1. Variation of the rate of bromination of 4(3*H*)-quinazolinone (1, R = H) with substrate concentration.

To swamp the effect of bromide ion produced during kinetic runs all solutions used contained about a 20-fold excess of potassium bromide. In order to see if molecular bromine is the sole brominating agent, or if tribromide ion also makes a contribution,[16] the variation of rate with bromide ion concentration was studied for the bromination of 1 (R = H) (Table II).

The situation may be expressed by the equations

$$Br_3^- \overset{K}{\rightleftharpoons} Br^- + Br_2$$

$$1 + Br_2 \overset{k_2}{\rightarrow} 7$$

$$1 + Br_3^- \overset{k_2'}{\rightarrow} 7$$

where $K = [Br_2][Br^-]/[Br_3^-]$. When bromide ion is present in excess, the observed second-order rate constant should have the form

$$k_2^{obsd} = \frac{k_2K + k_2'[Br^-]}{K + [Br^-]} \quad (1)$$

However, if reaction via tribromide ion is negligible ($k_2' \simeq 0$) eq 1 reduces to

$$k_2^{obsd} = k_2K/(K + [Br^-]) \quad (2)$$

and thus k_2^{obsd} should diminish as the concentration of bromide ion is increased. This trend is evident in the observed data shown in Table II which is best analyzed in terms of the reciprocal form of eq 2

$$\frac{1}{k_2^{obsd}} = \frac{1}{k_2} + \frac{[Br^-]}{k_2K} \quad (3)$$

As shown in Figure 2 a plot of $1/k_2^{obsd}$ vs. $[Br^-]$ yields an excellent straight line[19] from whose slope and intercept[19] we calculate $k_2 = 30.3\ M^{-1}\ min^{-1}$ and $K = 0.0554$ M. This value of K, which applies to 30 °C, is very close to that obtained by Bell[20] (0.0562) for 25 °C. If reaction via tribromide ion were appreciable (>1%) the plot in Figure 2 would show significant curvature at the higher bromide ion concentrations.

Table II. Variation of the Rate of Bromination of 4(3*H*)-Quinazolinone (1, R = H) with $[Br^-]$[a]

$[Br^-]$, M	k_2^{obsd}, M^{-1} min^{-1}	$1/k_2^{obsd}$, M min	$k_2^{obsd}(K + [Br^-])$,[b] min^{-1}
0.01	25.7	0.0389	1.68
0.02	22.1	0.0453	1.67
0.03	19.6	0.0510	1.67
0.05	16.0	0.0625	1.69
0.10	10.8	0.0926	1.68
0.15	8.16	0.1226	1.68

[a] At 30 °C, [1] = 5.0×10^{-3} M, acetate buffer pH 3.55. Each k_2^{obsd} is the average of two determinations differing by 2% or less. Reciprocal data plotted in Figure 2. [b] Uses $K = 0.0554$ M derived from Figure 2.

Table III. Variation of Rates of Bromination of 1 (R = H), 1 (R = Me), and 2 (R = R' = Me) Perchlorate with pH[a]

Substrate	pH	k_2^{obsd}, M^{-1} min^{-1}	Log k_2^{obsd}	No. of runs
1 (R = H)	0.29	0.333	−0.476	3
	0.59	0.685	−0.164	3
	0.98	1.55	0.190	3
	1.27	2.39	0.378	3
	1.66	6.49	0.812	2
	1.94	9.32	0.969	3
	2.23	15.9	1.20	2
	2.63	21.1	1.32	3
	2.80	21.2	1.33	2
	3.07	25.4	1.40	2
	3.55	25.7	1.41	2
	3.97	25.9	1.41	2
1 (R = Me)	0.30	0.512	−0.291	2
	0.60	0.945	−0.025	2
	0.99	2.32	0.365	2
	1.27	4.39	0.642	2
	1.60	8.38	0.923	2
	1.78	12.7	1.10	2
	2.24	19.3	1.29	2
	2.40	25.6	1.41	2
	2.82	30.3	1.48	2
	3.14	36.3	1.56	2
	3.38	41.1	1.61	2
	3.61	40.0	1.61	2
2 (R = R' = Me)	0.29	1.56	0.193	4
	0.58	3.53	0.548	4
ClO_4^-	0.96	7.41	0.870	2
	1.23	15.1	1.18	2
	1.50	28.5[b]	1.46	2
	1.84	68.1[b]	1.83	4

[a] At 30 °C, [substrate] = 5.0×10^{-3} M, $[Br_2] \simeq 5.0 \times 10^{-4}$ M, [KBr] = 0.01 M. For pH 0 → 2 dilute sulfuric acid, pH 2 → 3 chloroacetate buffers, pH 3 → 4 acetate buffers. The values of k_2^{obsd} are the average of two or more determinations as indicated in column 5. [b] [Substrate] = 2.5×10^{-3} M, $[Br_2] \simeq 3.0 \times 10^{-4}$ M.

As a further check on the unimportance of reaction via tribromide ion we note that eq 2 requires that the term $k_2^{obsd}(K + [Br^-])$ remain constant over a range of bromide ion concentration. Column 4 of Table II shows that for the present data this term does indeed remain constant. If tribromide ion had $k_2' = 0.3\ M^{-1}\ min^{-1}$ (i.e., 1% of k_2) the term would rise from 1.68 to 1.72 over the range of bromide ion concentration studied.

In summary, we conclude that bromination by tribromide ion is negligible (<1%) with respect to reaction via molecular bromine.

Acidity Dependence. The rates of bromination of 1 (R

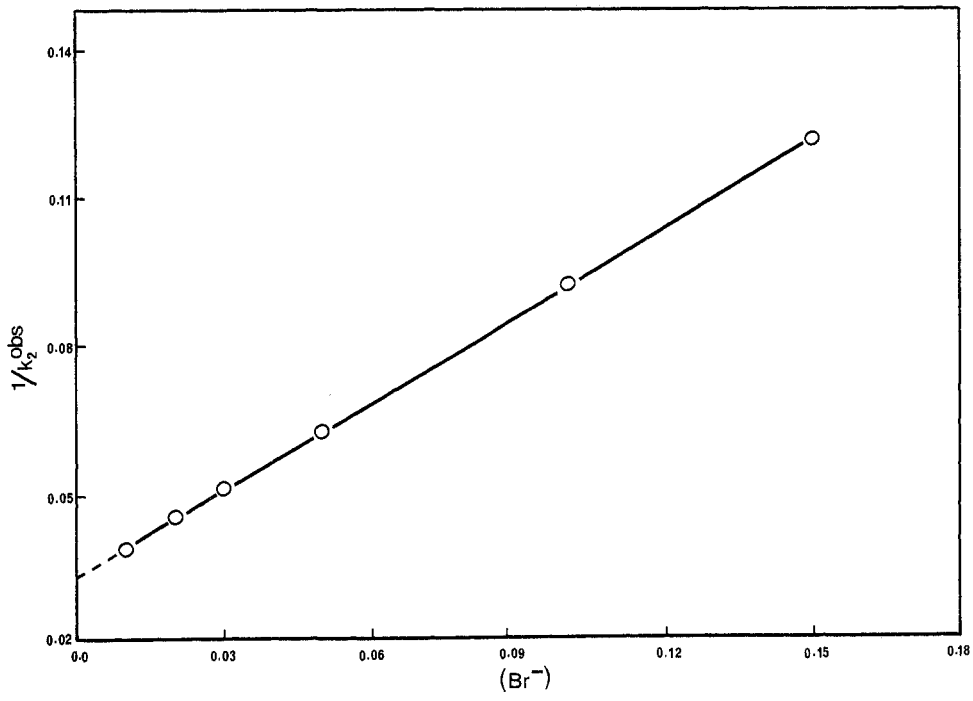


Figure 2. Variation of the rate of bromination of 4(3*H*)-quinazolinone (**1**, R = H) with $[Br^-]$.

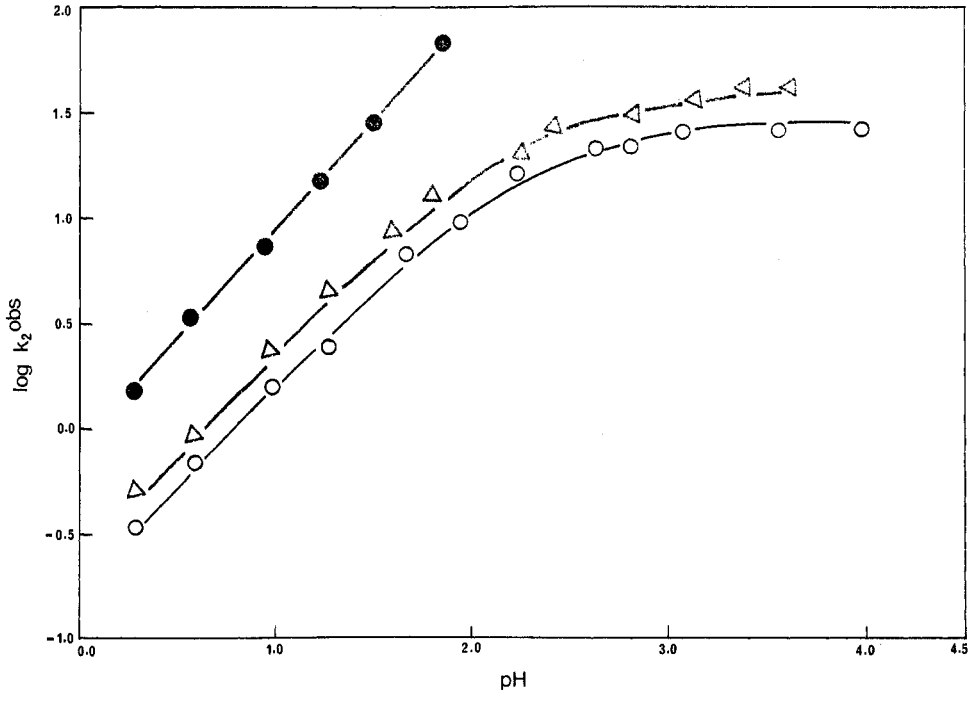


Figure 3. Acidity dependence of the rates of bromination of the substrates: ○, **1** (R = H); △, **1** (R = Me); ●, **2** (R = R′ = Me) perchlorate.

= H), **1** (R = Me), and **2** (R = R′ = Me) perchlorate were measured at various acidities in dilute sulfuric acid and in buffer solutions.[21] The data obtained are given in Table III and are plotted in Figure 3.

The rate data for the 1,3-dimethyl cation (**2**, R = R′ = Me) increase linearly[22] with pH in the manner appropriate for the reaction taking place upon the pseudobase **3** (R = R′ = Me). As described in the Experimental Section this pseudobase may be observed, and the pK for its formation is about 7.

The rate profiles for the parent **1** (R = H) and the 3-methyl derivative **1** (R = Me) are consistent with reaction taking place upon their free base forms, since the known[23,24] pK_a's for their conjugate acids **2** (R = H, Me; R′ = H) are 2.12 and 2.18 (at 20 °C), respectively. However, the rate profiles are also consistent with the reaction taking place upon species, such as the covalent hydrates **3** (R = H, Me; R′ = H), that are in equilibrium with the free bases **1** (R = H, Me) in a manner that is independent of acidity.[7a]

In the region pH <2 where all three substrates exist predominantly as cations they react with bromine at very similar rates. For example at pH 0.29 the relative rates of **1** (R = H) to **1** (R = Me) to **2** (R = R′ = Me) are 1.00:1.54:4.68. These similarities are strongly suggestive that the three substrates react via very similar mechanisms, with the small rate differences being attributable to the normal acti-

Table IV. Uv Spectral Data and Ionization Constants of the Substrates and Their Bromination Products

Compd	pK_a	pH	λ_{max}, nm (log ϵ)	Ref
1 (R = H)		2.23	255 (3.76), 261 (3.77), 283 (3.68), 291 (3.65)	This work
	2.12	7.00	226 (4.42), 231 (4.39), 263 (3.75), 269 (3.71), 292 (3.46), 311 (3.61), 313 (3.54)	23, 44
1 (R = Me)	2.18	1.0	229 (4.34), 234 (4.39), 279 (3.78), 293 (3.74), 303 (3.59)	24
		7.0	225 (4.42), 266 (3.80), 272 (3.78), 290 (3.43), 301 (3.56), 313 (3.49)	44
2 (R = R′ = Me), ClO_4^-		2.10	273 (3.77), 283 (3.77), 294 (3.67)	This work
7 (R = H)		0.29	266 (3.97), 293 (3.72), 302 (3.56)	This work
7 (R = Me)		2.10	264 (3.85), 297.5 (3.37), 311.3 (2.23)	This work
6 (R = R′ = Me), ClO_4^-		2.10	274 (3.96), 294 (3.80), 305 (3.66)	This work

vating effect on methyl groups upon electrophilic substitution. Since the cation 2 (R = R′ = Me) almost certainly reacts via its pseudobase 3 (R = R′ = Me), this requires that 4(3*H*)-quinazolinone (1, R = H) and its 3-methyl derivative 1 (R = Me) react via their covalent hydrates 3 (R = H, Me; R′ = H).

The mechanism proposed, then, is that shown in Scheme I. In this, the covalent hydrates (or pseudobase) 3, in equilibrium with the cations 2, react with molecular bromine to give intermediates 4 in the rate-determining step.[25] Proton loss[25] from 4 gives the covalent hydrates (or pseudobase) 5 in equilibrium with the product cations 6.

The kinetically significant steps of the mechanism are

$$1 + H^+ \overset{K_a}{\rightleftharpoons} 2 \overset{K}{\rightleftharpoons} H^+ + 3 \overset{k_2, Br_2}{\longrightarrow} \text{products}$$

For this sequence

$$\text{rate} = k_2^{obsd}[2]_S[Br_2] = k_2[3][Br_2] \quad (4)$$

where $[2]_S$ is the stoichiometric concentration of the cation ($[1] + [2] + [3]$). If we define $K_a = [1][H^+]/[2]$ and $K = [3][H^+]/[2]$ then it follows from eq 4 that

$$k_2^{obsd} = \frac{k_2K}{(K_a + [H^+] + K)} \quad (5)$$

In the region of acidity studied, the observed data (Table III, Figure 3) are completely in accord with this equation.

For the dimethyl cation 2 (R = R′ = Me) the equilibrium $1 \rightleftarrows 2$ does not exist and so the term K_a disappears from eq 5. Moreover, the equilibrium constant $K \simeq 10^{-7} \ll [H^+]$ at the acidities used, and so eq 5 simplifies to

$$k_2^{absd} = k_2K/[H^+] \quad (6)$$

This equation requires that a plot of log k_2^{obsd} vs. pH should give a straight line of unit slope. The least-squares line[22] through the data in Figure 3 has a slope of 1.04.

For the substrates 1 (R = H, Me) the constant $K_a \simeq 10^{-2}$, whereas K is probably 10^{-5}–10^{-6} [since for the dimethyl cation 2 (R = R′ = Me) $K \simeq 10^{-7}$], and so eq 5 may be reduced to

$$k_2^{obsd} = k_2K/(K_a + [H^+]) \quad (7)$$

The logarithmic form of this equation

$$\log k_2^{obsd} = \log k_2K - \log (K_a + [H^+])$$

generates curves such as those shown by the observed data in Figure 3. The curve drawn through experimental points for 1 (R = H) was calculated from eq 7 using[27] $k_2K = 0.171$ min^{-1}, and $K_a = 10^{-2.21}$. The agreement between the calculated curve and the experimental points is excellent. Similarly, the curve drawn for 1 (R = Me) using[27] $k_2K = 0.256$ min^{-1} and $K_a = 10^{-2.21}$ gives an excellent fit to the observed data. The slight differences between the pK_a's used here (2.21, 2.21) and those determined experimentally (2.12, 2.18)[23,24] are probably not significant, although, of course, the former apply to 30 °C, whereas the latter apply to 20 °C.

The observed kinetic data, then, are entirely consistent with the mechanism proposed in Scheme I in which the substrates 1 (or 2) react with bromine via their covalent hydrates (or pseudobase) 3. Similar conclusions were arrived at earlier for the hydrogen–deuterium exchanges and brominations of 2(1*H*)-pyrimidinones[7] and 4(3*H*)-pyrimidinones.[8]

Relative Reactivities. As a final point we look at the relative reactivities of the three substrates in terms of the proposed mechanism. The numerator term k_2K of eq 6 and 7 is not separable except for the dimethyl cation 2 (R = R′ = Me). However, this composite term may be obtained[27,28] and compared for the three cations 2.

Cation 2	R = R′ = H	R = Me; R′ = H	R = R′ = Me
k_2K, min^{-1}	0.171	0.256	0.800
Rel	1.00	1.50	4.68

The introduction of R = Me at N_3 causes only a slight increase in rate. It should decrease the equilibrium constant K, and so there must be a compensating increase in k_2. A more substantial increase in rate is caused by the introduction of R′ = Me at N_1. Again its effect should be to decrease K, but clearly this is overshadowed by a larger increase in k_2 due to the ability of the methyl group at N_1 to help stabilize the cationic intermediate 4 (R = R′ = Me).

For the dimethyl cation 2 (R = R′ = Me) $K \simeq 10^{-7}$, and so $k_2 = 0.8 \times 10^7$ M^{-1} min^{-1} (4.6×10^5 M^{-1} sec^{-1}).[29] This value is quite reasonable since second-order rate constants for the attack of bromine upon simple alkyl anilines fall in the range 10^6–10^{10} M^{-1} sec^{-1}.[18,20]

In summary, both the relative reactivities and the absolute reactivities of the three substrates are compatible with the proposed mechanism.

Experimental Section

The melting points given below are uncorrected. Uv measurements were made on a Cary 14 instrument, ^{1}H NMR spectra were obtained from a Varian A-60 spectrometer, and ir spectra were run on a Perkin-Elmer 425 spectrophotometer as KBr disks. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Ultraviolet spectral data for the substrates and their 6-bromo derivatives are presented in Table IV.

4(3*H*)-Quinazoline (1, R = H), which was prepared by the reaction of anthranilic acid and formamide,[30] was methylated to produce **3-methyl-4-quinazolinone (1, R = Me).**[10]

6-Bromo-4(3*H*)-quinazolinone (7, R = H) was prepared by cyclization,[11] and by direct bromination.

1 (R = H) (1.46 g, 0.01 mol) was stirred overnight in 30 ml of water containing bromine (1.6 g, 0.01 mol) and KBr (1.19 g, 0.01 mol). The resulting orange-white slurry was warmed until the orange color due to bromine disappeared, cooled, filtered off, washed with a little acetone, and dried at 75 °C. Recrystallization from methanol–DMF gave fine white crystals (2.1 g, 94%), mp 260–264 °C (lit.[11] 261–273 °C). The ir spectrum was identical with that of material made from the cyclization[11] of 5-bromoanthranilic acid.

5-Bromoanthranilic acid was prepared by a modification of the method of Wheeler and Oates.[31]

Anthranilic acid (13.7 g, 0.1 mol) in 120 ml of glacial acetic acid was stirred until all the solid dissolved (0.5 h). Bromine (16.0 g, 0.1 mol) in 50 ml of acetic acid was added dropwise over a period of 1.25 h. The resulting light yellow slurry was filtered off and washed with water and then with benzene. Recrystallization from 95% ethanol gave 15.4 g (71.4%) of the desired compound, mp 210–213 °C (lit.[32] 213 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 39347).

6,8-Dibromo-4(3H)-quinazolinone (9). 3,5-Dibromoanthranilic acid (14.7 g, 0.05 mol) and formamide (6.75 g, 0.15 mol) were heated together at 210 °C for 30 min. After cooling the crystalline slurry was filtered off, washed with water and then with ethanol, and recrystallized from methanol–DMF to give 16.0 g (86.3%) of **9**, mp 340 °C dec (lit.[32] 337 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 45518).

3,5-Dibromoanthranilic acid required for the above was prepared as follows.

A solution of bromine (32 g, 0.2 mol) in 50 ml of glacial acetic acid was added dropwise to anthranilic acid (13.7 g, 0.1 mol) in 200 ml of the same solvent. The resultant slurry was stirred for 40 h, and then heated on a water bath for 2 h. The yellow precipitate was filtered off, washed with benzene, and dried at 75 °C. Recrystallization from 90% aqueous ethanol gave 21.9 g (74.9%) of product, mp 229–231 °C (lit.[32] 230–232 °C). The ir spectrum was identical with that in the Sadtler Index[32] (No. 43810).

6-Bromo-3-methyl-4-quinazolinone (7, R = Me) (as HBr salt). Bromine (0.8 , 5 mmol) in 10 ml of 80% aqueous methanol was added to 1 (R = Me) (0.8 g, 5 mmol) in 10 ml of the same solvent. The yellow solution was stirred for 5 h at room temperature and then the white precipitate was filtered off and washed with water. Recrystallization from 95% aqueous ethanol gave 1.1 g (68.8%) of **6** (R = Me; R′ = H) bromide: mp 338–340 °C; ir (KBr) 1700 (C=O), 1610 (C=N), 1360 cm^{-1} (N–Me); uv, see Table IV; ^1H NMR (Me_2SO-d_6, Me_4Si) δ 3.52 (s, N_3 CH_3), 7.63–8.35 (m, aromatic), 8.63 (s, C_2 H).

Anal. Calcd for $C_9H_8N_2OBr_2$: C, 33.78; H, 2.52; N, 8.75. Found: C, 33.79; H, 2.67; N, 8.76.

Attempts to prepare this compound (**7**, R = Me) by methylation or by cyclization failure, but it was successfully converted to **6** (R = R′ = Me) iodide and thence to **6** (R = R′ = Me) perchlorate which was identical with the material obtained by direction bromination of **2** (R = R′ = Me) perchlorate.

1,4-Dihydro-1,3-dimethyl-4-oxoquinazolinium (2, R = R′ = Me) iodide was prepared by the method of Bogert and Geiger.[33] The corresponding **2** (R = R′ = Me) perchlorate[34] was prepared as follows.

A solution of silver perchlorate (4.15 g, 0.02 mol) in 10 ml of methanol was added to **2** (R = R′ = Me) iodide (6.04 g, 0.02 mol) in 200 ml of warm methanol, and was stirred at 40 °C for 0.5 h. The mixture was cooled, the silver iodide was filtered off, and the filtrate was evaporated. Recrystallization of the residue from ethanol–water gave 4.67 g (85%) of **2** (R = R′ = Me) perchlorate: mp 254–257 °C; ir (KBr) 1715 (C=O), 1654 (C=N), 1386 (N–Me), 1110–1060 cm^{-1} (ClO_4^-); uv in Table IV.

Anal. Calcd for $C_{10}H_{11}N_2O_5Cl$: C, 43.73; H, 4.04; N, 10.20. Found: C, 43.90; H, 3.91; N, 10.20.

6-Bromo-1,4-dihydro-1,3-dimethyl-4-oxoquinazolinium (6, R = R′ = Me) Iodide. Methyl iodide (1.0 g, 7 mmol) and **7** (R = Me) (1.2 g, 5 mmol) were heated together at 120 °C in a sealed tube for 12 h. The crystalline mass was washed with methanol and recrystallized from ethanol–water to give 1.64 g (86%) of the desired compound: mp 287–288 °C; ir (KBr) 1700 (C=O), 1645 (C=N), 1375 cm^{-1} (N–Me); ^1H NMR (Me_2SO-d_6, Me_4Si) δ 3.66 (s, N_3 CH_3), 4.08 (s, N_1 CH_3), 7.96–8.49 (m, aromatic), 9.99 (s, C_2 H).

Anal. Calcd for $C_{10}H_{10}N_2OBrI$: C, 31.52; H, 2.65; N, 7.35. Found: C, 31.58; H, 2.62; N, 7.32.

The corresponding **6** (R = R′ = Me) perchlorate[34] was made in two ways.

A. From the Iodide. Silver perchlorate (0.207 g, 1 mmol) in 10 ml of ethanol was added to the above **6** (R = R′ = Me) iodide (0.381 g, 1 mmol) in hot aqueous ethanol, and the silver iodide precipitate was filtered off. Cooling the filtrate gave crystals of the perchlorate, which were recrystallized from aqueous ethanol to yield 0.332 g (94%) of **6** (R = R′ = Me) perchlorate: mp 395–397 °C; ir (KBr) 1708 (C=O), 1650 (C=N), 1381 (N–Me), 1100–1050 cm^{-1} (ClO_4^-); uv in Table IV; ^1H NMR identical with that of the iodide.

Anal. Calcd for $C_{10}H_{10}N_2O_5BrCl$: C, 33.97; H, 2.85; N, 7.92. Found: C, 34.23; H, 2.71; N, 7.94.

B. By Bromination. Bromine (0.8 g, 5 mmol) in methanol was added to **2** (R = R′ = Me) perchlorate (1.37 g, 5 mmol) dissolved in warm 80% aqueous methanol. The mixture was stirred for 2 h until the yellow color disappeared. The crystalline precipitate was filtered off, washed with methanol, and recrystallized from 80% aqueous ethanol to give 1.62 g (91.5%) of **6** (R = R′ = Me) perchlorate, mp 394–397 °C, spectral properties as in A above.

***o*-(Methylamino)-*N*-methylbenzamide (10)** was made by two different routes which gave identical materials, even though our melting points differ considerably from those in the literature.

A. From 2 (R = R′ = Me) Iodide.[35,36] Twenty milliliters of 2 N NaOH solution was added to **2** (R = R′ = Me) iodide (1.51 g, 5 mmol) in 20 ml of water, and the mixture was stirred at 40 °C for 1 h. After cooling, the white slurry precipitate was filtered off, washed with water, and recrystallized from cyclohexane to give 0.80 g (98%) of **10**: mp 83–85 °C (lit.[36,37] 43–45, 70–72 °C); ir (KBr) 3280 (amide NH), 2870 (N–Me), 2800 (N–Me), 1610 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6, Me_4Si) δ 2.87 (s, –NHMe), 2.78 (s, –CONHMe), 7.60 (–NHMe), 6.17 (s, –CONHMe), 6.27–7.32 (m, aromatic).

B. From *N*-Methylisatoic Anhydride.[37] To *N*-methylisatoic anhydride (11.7 g, 0.066 mol) in 30 ml of water was added 15 ml of 30% aqueous methylamine, and the mixture was stirred and heated for 30 min. The clear top layer was decanted off, and upon cooling it gave white needles which were filtered off and recrystallized from cyclohexane to give 10.25 g (95%) of **10**, mp 84–86 °C (lit.[37] (43–45 °C), spectral properties identical with those given in A above.

Kinetic Procedures. All inorganic reagents were of analytical grade. Sulfuric acid, sodium thiosulfate, and starch solutions were prepared from commercial standard volumetric concentrates. Buffer solutions (0.2 M) were prepared after Vogel[38] and Perrin.[39] The acidities of all substrate solutions were measured using a Beckman Expandomatic pH meter. The pH values thus obtained for sulfuric acid solutions were, within experimental error, the same as those calculated[40] on the basis of the known pK_a's of 1 (R = H) and 1 (R = Me) where applicable.

Initial experiments suggested a second-order reaction between the substrates and bromine, and so subsequently all kinetic runs were carried out under pseudo-first-order conditions with an approximate tenfold excess of substrate. The reaction was most conveniently[40] followed by monitoring the disappearance of bromine titrimetrically as follows.

A stock solution containing potassium bromide (0.01 M) in the desired acid or buffer solution made up. Using this medium separate 50-ml solutions of bromine ($1.0–1.6 \times 10^{-3}$ M) and of substrate (1.0×10^{-2} M) were then prepared. The pH of the substrate solution was recorded. The flasks containing the bromine and the substrate solutions were wrapped in foil to prevent deterioration due to light, and were then equilibrated in a constant-temperature bath at 30.0 ± 0.2 °C for at least 15 min. At the start of a timer the substrate solution was added to the bromine solution, and the mixture was thoroughly shaken[41] and returned to the bath.

At appropriate time intervals 5-ml aliquots of the reaction mixture were withdrawn and quenched in 20 ml of 5% potassium iodide solution. The liberated iodine was titrated immediately against a standard 0.01 M sodium thiosulfate solution contained in a Metrohm E274 semiautomatic microburet (5-ml capacity, graduated in 0.005 ml) using 1% starch indicator.

Depending upon the rate of the reaction between 7 and 17 aliquots were drawn over a period extending well beyond 1 half-life. For the fast runs, the aliquots were quenched in the potassium iodide solution, and stored in the dark until time permitted their titration in rapid succession.

From the titration data [Br_2] was calculated for various times t, and linear least-squares analysis in terms of the equation $\ln [Br_2] = \ln [Br_2]_0 - k_1 t$ was used to obtain a pseudo-first-order rate constant k_1. All kinetic runs were carried out at least twice, and only those were accepted which gave correlation coefficients >0.9998 in the least-squares analysis.

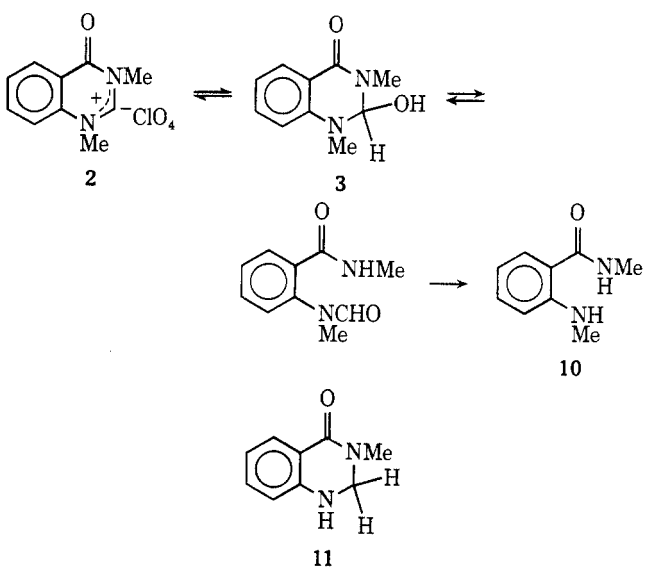
Strictly speaking the second-order rate constant k_2 should be

obtainable from the pseudo-first-order rate constant by $k_2 = k_1/[S]$. However, following Bell,[20] we used $k_2 = k_1/([S] - [Br_2]_0)$ to give a better estimate of k_2, since the excess of substrate over bromine is not particularly large.

The best curves to fit the data for 1 (R = H or Me) in Figure 3 were obtained by an iterative technique. Equation 7 requires that the term $k_2^{obsd}(K_a + [H^+]) = k_2K$ = a constant. A computer program was written which, given a value of pK_a, calculates values of this constant for the observed data set of k_2^{obsd} and pH, and then computes the average value of this constant. Using this averaged value of k_2K in eq 7 the program then calculates a value of k_2^{obsd} (k_2^{calcd}, say) for each pH and the standard deviation of log k_2^{obsd} with respect to log k_2^{calcd}. This process is repeated for various values of pK_a, and the best value is chosen such that the standard deviation of log k_2^{obsd} from log k_2^{calcd} is a minimum. In the present instances this also coincides with the lowest standard deviation of $k_2^{obsd}(K_a + [H^+])$ values from their average.

Pseudobase Formation. Since it is postulated that bromination of the cation 2 (R = R′ = Me) proceeds via the pseudobase 3 (R = R′ = Me), attempts were made to observe the equilibrium between these two species.

The solubility of 2 (R = R′ = Me) perchlorate in D_2O is too low to obtain decent NMR spectra. The salt can be dissolved in dilute NaOD solution, but in this medium it underwent ring opening and irreversible hydrolysis to *o*-(methylamino)-*N*-methylbenzamide (**10**) (cf. ref 35, 37).



Pseudobase formation was observed, however, by uv spectroscopy. The uv spectrum of 2 (R = R′ = Me) perchlorate in water (1.0×10^{-3} M) was recorded. Upon addition of some dilute NaOH solution, a new band at 330 nm appeared. When an equivalent amount of dilute HCl was added, this band disappeared, and the original spectrum was retraced. Since the uv spectrum of 2,3-dihydro-3-methyl-4-quinazolinone (**11**)[42] in MeOH has a band at 338 nm, the 330-nm band is ascribed to the pseudobase 3 (R = R′ = Me). Note, however, that addition of an excess of dilute NaOH solution again resulted in irreversible formation of **10**.

Potentiometric titration[43] of the salt 2 (R = R′ = Me) perchlorate with dilute NaOH solution suggested that the equilibrium constant $K = [3][H^+]/[2] \simeq 10^{-7}$. Three separate titrations gave values of $pK \simeq 7.1, 7.2, 7.5$. Back titration with acid *did not* give pH values corresponding to these values, but rather to a pK value about 3.5. In a separate experiment the protonation pK value of **10** was determined spectrophotometrically[43] to be 3.77. During the titration experiments on 2 (R = R′ = Me) perchlorate the pH values after the addition of several aliquots of base were not steady. Immediately following a further addition, the pH rose as expected, but subsequently peaked and then fell. It appears, therefore, that during the latter parts of the titrations there was significant irreversible opening of the pseudobase 3 (R = R′ = Me) to **10**.

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Registry No.—1 (R = H), 491-36-1; 1 (R = Me), 2436-66-0; 2 (R = R′ = Me) perchlorate, 57573-55-4; 2 (R = R′ = Me) iodide, 2453-94-3; 6 (R = R′ = Me) perchlorate, 57573-56-5; 6 (R = R′ = Me) iodide, 57573-58-7; 7 (R = H), 32084-59-6; 7 (R = Me), 57573-59-8; 7 (R = Me) HBR, 57573-60-1; **10**, 32212-33-2; *N*-methylisatoic anhydride, 10328-92-4.

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(27) The values of k_2K and K_a were arrived at as described in the Experimental Section.
(28) The k_2K term for the dimethyl cation is derived from the intercept (log k_2K) of the straight line[22] in Figure 3.
(29) If we take into account the reduction (15.3%) in free bromine concentration due to tribromide formation, this value is raised to 5.4×10^5 M^{-1} sec^{-1}.
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Electrochemistry of Natural Products. IV. Electrochemical and Chemical Oxidative Dimerization of 1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline[1]

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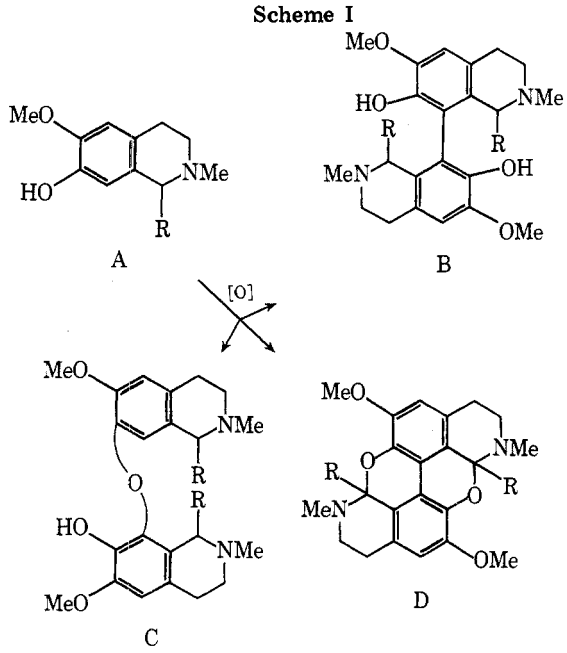
Racemic 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (1) has been oxidatively coupled by controlled-potential electrolysis in excess base to yield one (3) of three possible isomers of the carbon–carbon dimer. The reaction was carried out at +0.16 V (vs. SCE) in wet acetonitrile at a graphite felt anode with tetraethylammonium perchlorate as an electrolyte. Other reaction conditions gave the same stereochemical results in poor yields. During the oxidation, only molecules of 1 having the same configuration at C-1 coupled with each other to form product (*R* with *R* and *S* with *S*). Furthermore, only one of two possible rotational isomers was formed. The structure of the single product was established by the chemical [$K_3Fe(CN)_6$] and electrochemical oxidation of racemic 1 and its enantiomers. Additional products of the chemical oxidation are described.

In a previous paper of this series,[2] we studied the electrochemical and catalytic oxygenation of 1-alkyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolines (A) and established the general structures of the products as B, C, and D (Scheme I). All three products were formed as

Scheme I



mixtures of stereoisomers, but only B could be resolved into its components. The centers of chirality at C-1 of B (when R = CH_3) and the newly formed center caused by restricted biphenyl rotation lead to the possible formation of three sets of enantiomers: **2, 3,** and **4,** designated as *RS, SS* rotamer A, *SS* rotamer B, and their enantiomers, respectively (Scheme II). All three isomers of B (R = CH_3) were obtained from the catalytic oxygenation of A (R = CH_3) although specific stereochemical structures were not established. When the electrooxidation of **1** was carried out in acetonitrile solution,[3] only one of the three possible isomers of B was obtained. In this paper, we would like to describe the structure elucidation of the single stereochemical product and to discuss the implications of its formation.

Structures of the Three Carbon–Carbon Dimers 2, 3, and 4. Three dimers were isolated from the catalytic oxygenation of racemic 1 over a Pt catalyst: two crystalline compounds melting at 132–134 and 222–224° and one noncrystalline glass, all of which had characteristic spectral properties.[2] The general structures of the three dimers were confirmed in the present work by equilibrating them via oxygenation over platinum on carbon[2] of **3** to give a mixture of bis-3,4-dihydroisoquinolinium salts[5a] (the open form of a type D compound). The mixture was reduced with $NaBH_4$ to give a mixture of compounds **2, 3,** and **4,** shown by direct chromatographic comparison.

Electrooxidation of racemic **1** under a variety of conditions yielded only the isomer melting at 226–227°.[4] Of the three dimers, only **3** and **4** have the same configuration at C-1 of both isoquinoline rings. Since oxidation of the separated enantiomers of **1** (both *R* and *S*) yielded the enantiomers of the same products as obtained from racemic **1**, the single electrochemical product must be **3** or **4**, and must result from the coupling of identical stereoisomers of **1**. Oxidation of the separated enantiomers of **1** with $K_3Fe(CN)_6$ (which is not stereospecific)[5] yielded the appropriate enantiomers of **3** and **4** having the melting points of the two crystalline isomers (132–134[6] and 224–226°). Since both of these products must have identical configurations in the isoquinoline rings, the third noncrystalline dimer from the catalytic oxygenation of racemic **1** must have structure **2**. When the NMR spectra of the two crystalline dimers were measured in deuterated dimethyl sulfoxide, the C–CH_3 protons appeared at δ 0.71 for the compound melting at 226–227° and at δ 1.17 for the one melting at 132–134° (as compared with δ 1.22 in **1**). Molecular models of the two possibilities show that the CH_3 in **3** is located on top of the benzene ring whether the methyl group is axial or equatorial. In **4**, the methyl group is well away from the benzene ring when in the axial position but fairly close to it when