Attack of *S- vs N*-Nucleophiles on 2-Halomethylquinazoline 3-Oxides (1,2)

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A comparison is made of thiols with amines in their mode of reaction with different substituted 2-halomethylquinazoline 3-oxides. Whereas the reaction of some amines (particularly small primary ones), as has long been known, leads to ring-enlarging rearrangement under certain conditions, all thiol nucleophiles we have observed, ranging from small to large, lead without rearrangement to direct benzylic substitution only. Preformed aminomethylquinazoline 3-oxides are shown not to rearrange to the corresponding 1,4-benzodiazepine 4-oxides. The mechanistic implications of these and other observations are discussed. Data on over forty new compounds are presented.

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In 1961, Sternbach, *et al.*, (6) and in 1962, Childress, *et al.*, (7) first reported the ring enlargement rearrangement of 2-halomethyl-4-aryl (or alkyl) quinazoline 3-oxides into 2-alkylamino-3*H*-1,4-benzodiazepine 3-oxides which usually characterizes nucleophilic attack on the former by primary aliphatic amines. These studies led to the well-known discovery of the extremely important 1,4-benzodiazepine class of psychopharmacological agents, the first of which was chlordiazepoxide (Librium ® (8)), 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide. Concurrently, and independently, we had been studying the behavior of various benzodiazine *N*-oxides, including 2-chloromethyl-4-methylquinazoline 3-oxide toward nucleophilic attack by sulfur nucleophiles. Because of the great importance of the aforementioned rearrangement, we venture here to report our experience with the attack of both *S*- and *N*-nucleophiles on 2-halomethylquinazoline 3-oxides (I) and the light they shed on the nature of this rearrangement.

Table 1 shows the results of our work on substitution on I (fig. 1) with sulfur nucleophiles using three different methods (I→II): direct methathesis, usually at ambient temperature, with the sodium mercaptide in anhydrous ethanol (method A); reflux with an equimolar amount of

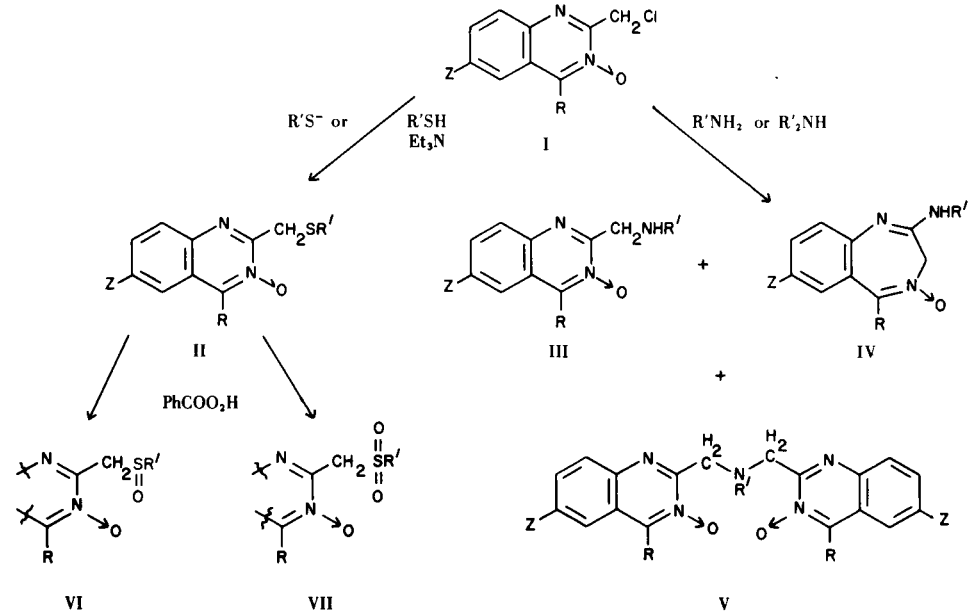


Figure 1

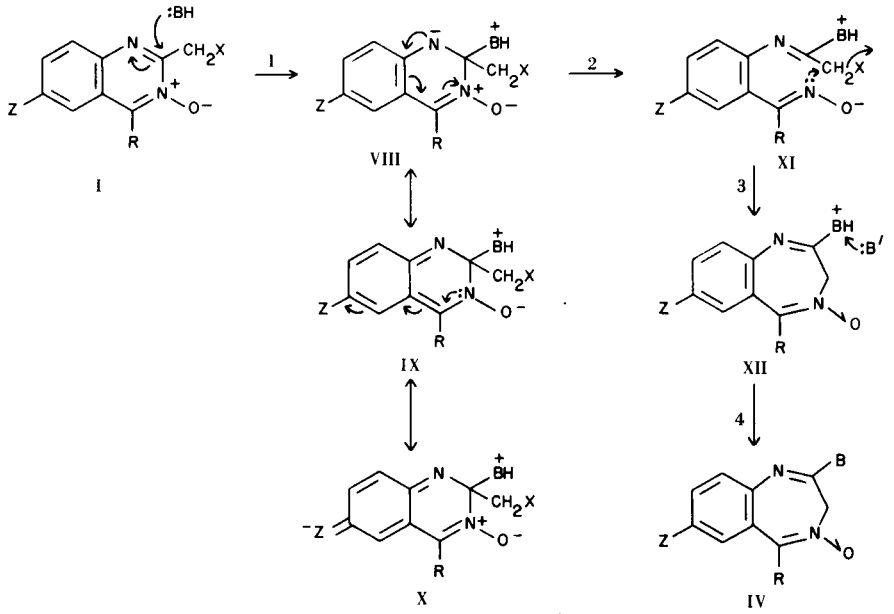


Figure 2

thiol in *p*-dioxane together with a slight excess of triethylamine (method B); and reaction in *N,N*-dimethylformamide solution with thiol and excess trimethylamine (method C). Reactions by methods A and B were accompanied by the precipitation of sodium chloride and triethylammonium chloride, respectively, which gave an immediate and direct way of monitoring the progress of reaction. Method C resulted in a rapid, vigorous exothermic reaction without precipitation of salt. Method B was more convenient than A or C and gave as good results. The products, all obtained in excellent yield, were characterized by uv, ir, nmr, and mass spectra, and by elemental analyses and deoxygenation. In contrast to the behavior of amines (6,7), in no instance was any product obtained with sulfur nucleophiles which was suggestive of ring enlargement rearrangement to 2-thio-substituted benzo-3*H*-1,4-diazepine 4-oxides.

Some representative thioethers were oxidized at ambient temperatures with anhydrous perbenzoic acid in chloroform to the corresponding sulfoxides (II→VI) and sulfones (II→VII) without concommitant oxidation of the N-1 or C-4 atoms (9). One molar-equivalent of oxidant effected smooth conversion to sulfoxides, whereas, two or more molar-equivalents gave the corresponding sulfones in good yields. Table 2 lists the 2-sulfinylmethylquinazoline 3-oxides (VI) and 2-sulfonylmethylquinazoline 3-oxides (VII).

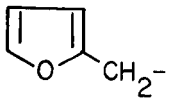
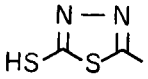
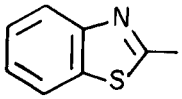
In contrast to the behavior of thiols towards I, methylamine as the attacking nucleophile led to the formation of 2-methylaminomethylquinazoline 3-oxides (III), *N,N*-bis(4-methyl-3-oxido-2-quinazolinylmethyl)methylamine (V, R = R′ = CH_3, Z = H), and 2-methylamino-3*H*-1,4-benzodiazepine 4-oxides (IV) analogous to previous reports (6,7), depending on the conditions of reaction. On the other hand, more bulky amines, whether primary or secondary, led exclusively to the unrearranged aminomethylquinazoline 3-oxides (III). These results appear in Fig. 1 and Tables 3 and 4.

Reaction of excess 40% aqueous methylamine with Ia (R = CH_3, Z = H) in *N,N*-dimethylformamide solution at 0° led to the isolation of only the unrearranged bisquinazolinylmethylamine (Va, method D), whereas anhydrous methylamine with Ia in *p*-dioxane at 25° led to a mixture of predominantly the monoquinazolinylamine (IIIa) along with the substantial amounts of the diazepine rearrangement product (IVa, method E), and pure anhydrous liquid methylamine at -70° to -7° with Ia gave predominantly the diazepine (IVa) which was isolated in good yield (method F). By comparison, Ib (R = R′ = CH_3, Z = Br) gave only the diazepine (IVb) as an isolated product (method D). Our studies on substitution by amines on Ic (R = Ph, Z = Cl) essentially paralleled those reported by Sternbach and Reeder (6) in distribution of products under varying reaction conditions.

In considering a plausible mechanism for the ring enlargement rearrangement, it seemed important to first discover whether the primary step (or one possible route) in the overall process might be direct nucleophilic substitution by the attacking amine on the halogen-bearing benzylic carbon atom to yield the 2-aminomethylquinazoline 3-oxide which subsequently rearranged to the corresponding 2-amino-3*H*-1,4-benzodiazepine 4-oxide. That such is *not* the case was established by incubating IIIa and several alkylaminomethyl-6-chloro-4-phenyl deriv-

Table 1

Thiomethylquinazoline 3-Oxides (II)

Compound	R	R′	Z	Method	Yield %	M.p., °C, (a)	Calcd. N	Calcd. S	Found N	Found S
IIa	CH_3-	CH_3	H	A	98	110-111 (a)	12.72 (i)	14.55	12.54	14.78
b	CH_3-	CH_3	Br	A	78	160-161 (e)	9.37		9.16	
c	CH_3-	C_6H_5	Cl	B	75	193-195 (g)	8.86		8.82	
d	$CH_3(CH_2)_2CH_2$-	CH_3	H	A	65	92.5-94 (b)	10.68	12.21	10.62	12.28
e	$(CH_3)_2CHCH_2CH_2$-	CH_3	H	A	63	76-77.5 (b)	10.15	11.60	10.12	11.67
f	$CH_3(CH_2)_5CH_2$-	CH_3	H	A	88	49.5-51 (c)	9.20	10.52	9.41	10.73
g	$HOCH_2CH_2$-	CH_3	H	B	90	126.5-127 (d)	11.20	(j)	11.38	
h	$HOCH_2CHOHCH_2$-	CH_3	H	A	92	122-123 (e)	10.00	(k)	9.86	
i	C_6H_5-	CH_3	H	A	65	113-118 (l)				
i	C_6H_5-	CH_3	H	C	83	119.5-121 (f)	9.92	11.34	9.65	11.25
j	$C_6H_5CH_2$-	CH_3	H	A	65	106-107.5 (b)	9.45	10.81	9.41	10.93
k	*o*-$CH_3C_6H_4$-	CH_3	H	A	70	128.5-129 (a)	9.45		9.48	
l	*m*-$CH_3C_6H_4$-	CH_3	H	A	73	106.5-107.5 (a)	9.45		9.54	
m	*p*-$CH_3C_6H_4$-	CH_3	H	A	79	124.5-125.5 (a)	9.45		9.63	
n	*o*-$H_2NC_6H_4$-	CH_3	H	A	75	164.5-165.5 (d)	14.14	10.77	14.35	10.50
o	*p*-ClC_6H_4-	CH_3	H	A	73	172.5-174 (g)	8.85		8.83	
p		CH_3	H	A	80	101-102 (d)	9.78		9.81	
q		CH_3	H	A	84	210-211 (g)	17.39		17.22	
r		CH_3	H	A	86	158.5-159.5 (h)	12.39		12.11	
s	N≡C-	CH_3	H	A	89	169.5-171 (g)	18.18		18.55	

(a) Recrystallization solvent(s) ethyl acetate-hexane. (b) 2-Propanol-water, then ethyl acetate. (c) Cyclohexane. (d) Absolute ethanol. (e) Absolute ethanol-ether. (f) Ethyl acetate. (g) Ethanol, 95%. (h) 2-Propanol. (i) Calcd: C, 59.90; H, 5.49. Found: C, 59.94; H, 5.33. (j) Calcd: C, 57.59; H, 5.64. Found: C, 57.93; H, 5.53. (k) Calcd: C, 55.71; H, 5.75. Found: C, 55.54; H, 5.67. (l) Crude.

atives (6) under a variety of time periods and temperatures while monitoring reaction by uv spectra. No spectral evidence of 1,4-3*H*-benzodiazepine 4-oxide formation was found. As evidenced by the uv spectra, but otherwise unidentified, a variety of hydrolytic and/or thermal decomposition products were formed, evidently in most cases associated with opening of the pyrimidine ring moiety. Accordingly, rearrangement must proceed only by direct attack of the nucleophile on the C-2 atom of the halomethylquinazoline 3-oxide, while the unrearranged compound must result from the attack of the nucleophile on the adjacent halogen-bearing benzylic C-atom.

Schematics rationalizing some important aspects of the two alternative reaction pathways are offered in Fig. 2 and 3, respectively. Sternbach, *et al.*, (10) have actually isolated a ring opened oxime intermediate similar to XI in their mechanistic investigation of the reaction of hydroxide with 6-chloro-4-phenyl-2-(dichloromethyl)quinazoline 3-oxide and shown that it reacts further under the same conditions to form the ring enlarged product, 3,7-dichloro-5-phenyl-3*H*-1,4-benzodiazepin-2(1*H*)one 4-oxide. The analogous intermediate with the 2-chloromethyl derivative could not be detected even by spectral means. Neither pathway is intended to suggest that the

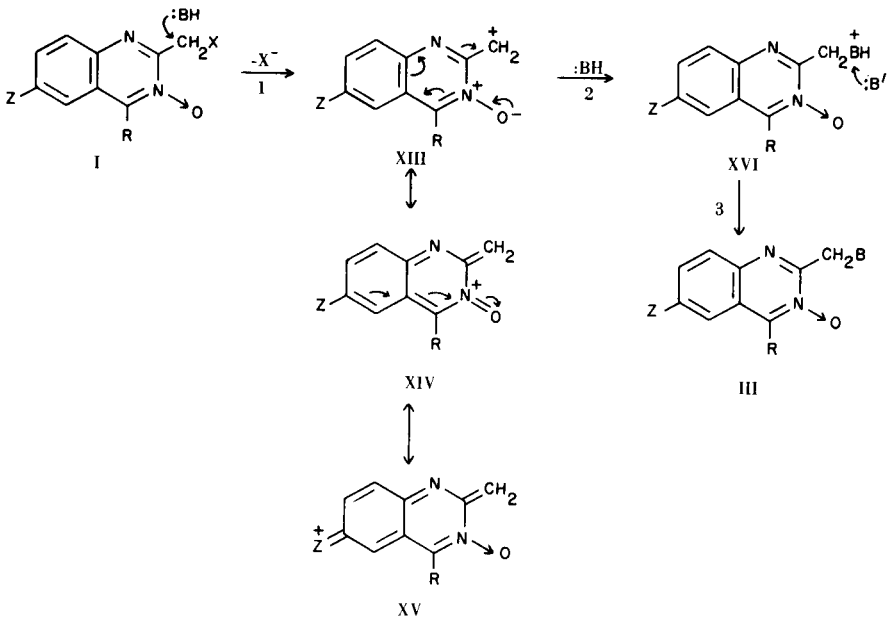


Figure 3

order and mode of protonation-deprotonation steps is exactly as indicated, but rather, they give only the likely possibility, *e.g.*, the nucleophile (:BH) is certainly already deprotonated in the case of the sodium mercaptides (:B$^-$ = RS$^-$), yet the attacking agent is probably RSH in the triethylamine-thiol reaction. In step 3, Fig. 2 internal proton transfer from B$^+$ to O$^-$ or external proton transfer to another base-site may possibly precede the displacement step.

The canonical forms, VIII, IX, X, and XIII, XIV, XV illustrate the extensive delocalization of charge possible in the transition states of either route. The known requirement (7) of the *N*-oxide function being present in order for rearrangement to occur is supported by structure IX which is likely the major component of that canonical ensemble. Note also, however, that "back-donation" by the oxido atom (structure XIV), shown to be an important factor in the chemistry of many *N*-oxides (11), demonstrates that this function *also facilitates displacement without rearrangement.*

Structure X illustrates the influence electron-withdrawing groups (Z) can have conjugatively and/or inductively in stabilizing the rearrangement transition state. Conversely, electron-releasing groups (Z) would be conjugatively stabilizing in an S_N1-like solvolysis transition state (XV) leading to substitution on the benzylic carbon atom. The tendency of the 6-bromo compound, Ib, to rearrange is greater than the non-brominated analog, Ia, probably because of the well-known fact that the inductive (-I) effect of the bromine atom is greater than its countervailing conjugative (+R) effect. The benzylic displacement may well proceed by an S_N2 process rather than by the S_N1-type formally illustrated, in which case the electronic effects of the substituent groups will be less pronounced but of the same general type, especially in the more probable instance that the mechanism is of the ρ-negative type (12). Groups, R, at C-4 are not directly conjugated to either reaction site and, hence, can affect the transition state stability only inductively--electron attraction favoring rearrangement, electron-release favoring benzylic displacement, particularyl if S_N1-like.

Prior to the intramolecular nucleophilic displacement (step 3, Fig. 2), bond making and bond breaking (steps 1 and 2, respectively) may be S_N1-like or S_N2-like; the latter is favored by the "α-effect" of the hydroxylamino function (13). Indeed, in some cases it is quite possible that the entire rearrangement process is synchronous. Also likely, however, a resonance stablized sigma-adduct is formed (VIII-IX-X) followed by synchronous rearrangement (steps 2 and 3, VIII→XI→XII). (*Cf.* (10)).

Steric hindrance must centainly be a major factor in determining which of the two pathways is dominant, whether the substrate quinazoline 3-oxide substituents at C-4 are aromatic or aliphatic, and whether substituents at C-6 are present or not. In all previously or herein reported cases, small *O*-nucleophiles such as OH$^-$ (14) and small *N*-nucleophiles such as methylamine give largely or exclusively rearrangement while even more basic but also more bulky amines, *e.g.*, piperidine or cyclohexylamine give none. Substantial amounts of even the very bulky bisquinazolinylmethylamine derivative (IV) were obtained, but none of the corresponding bis(1,4-benzodiazepinyl)-methylamine or mixed disubstituted methylamine.

Table 2

Sulfinylmethyl (VI) and Sulfonylmethylquinazoline 3-Oxides (VII)

Compound	R	R'	Z	Yield %	M.p., °C. (a)	Calcd. C	Calcd. H	Calcd. N	Calcd. S	Found C	Found H	Found N	Found S
VIa	CH_3-	CH_3	H	89	168.5-169.5 (a)	55.93	5.12		13.54	56.20	5.33		13.57
VIb	CH_3-	CH_3	Br	72	194-195 (b)			8.89				8.72	
VIIa	CH_3-	CH_3	H	91	213-214 (c)	52.38	4.80		12.68	52.83	4.84		12.59
VIg	$HOCH_2CH_2$-	CH_3	H	24	145-146.5 (b)			10.52				10.52	
VIIg	$HOCH_2CH_2$-	CH_3	H	82	186-187.5 (c)			9.93				10.06	
VIi	C_6H_5	CH_3	H	93	168-169 (b)			9.39				9.45	
VIIi	C_6H_5	CH_3	H	94	182.5-184 (c)			8.91				9.13	

(a) Recrystallization solvent, ethyl acetate. (b) Absolute ethanol. (c) Ethanol, 95%.

Very disparate results were obtained with methanethiolate *vs.* methylamine. Although virtually equally basic (p*K*a 10.3 and 10.5, respectively) and the *S*-nucleophile only slightly larger, the methanethiolate gave only direct displacement to the quinazoline whereas the methylamine gave essentially only rearrangement product. It appears, therefore, that more important than either basicity or bulk in these instances is polarizability or "softness" of the displacing nucleophile (15). The amidinium-type C-2 atom is a "harder" electrophilic site than is the "softer" benzylic C-atom; hence, the "softer" *S*-nucleophiles gain an additional polarizability stabilization factor in the transition state by attacking the "softer" benzylic electrophilic site, and conversely for *N*-nucleophiles. This is particularly true if the displacement on the benzylic site is S_N2-like (*i.e.*, formal steps 1 and 2, Fig. 3, are synchronous).

EXPERIMENTAL

Melting points were taken on a Kofler Micro hotstage and are corrected. Ultraviolet spectra were run on a Beckman DK-2 spectrophotometer and infrared spectra on a Beckman IR-5 spectrophotometer. Nmr spectra were obtained on Varian A-60A and mass spectra with Perkin-Elmer Hitachi RMU-6E instruments, respectively.

2-Chloromethyl-4-methyl-6-bromoquinazoline 3-Oxide (Ib).

2-Amino-5-bromoacetophenone hydrochloride (16) (22.5 g., 0.0905 mole), 14.0 g. (0.20 mole) of hydroxylamine hydrochloride, 25 ml. of pyridine and 200 ml. of 95% ethanol were combined in a 500 ml. round-bottomed flask, and the mixture was heated at gentle reflux for 2.5 hours. The yellow-orange reaction mixture was evaporated utilizing a rotary evaporator until only a syrupy residue remained. The residue was cooled, and ice water was added in small portions with agitation until precipitation of the product appeared complete. Ice water (400 ml.) was added, and the mixture was allowed to stand overnight. The product then was collected by suction filtration, washed with three-50 ml. portions of ice water and air-dried. Yield of 2-amino-5-bromoacetophenone oxime was 20.0 g., (100%) of analytically pure product, m.p. 161-161.5°; ir (potassium bromide): 3.00 (s) 3.10(s), 3.50(s), 6.20(m), 6.35(m), 6.73(s), 7.85(m), 8.64(m), 9.10(m), 9.97(s), 12.20(s), 15.05(m), μm; nmr (deuteriochloroform): δ 2.86 (s, 3, 4-CH_3), 5.08 (s, 2, CH_2Cl), 7.88 (m, 2), 8.04 (m, 2), 8.04 (m, 1) ppm.

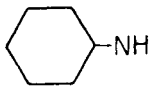
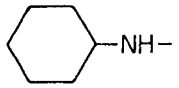
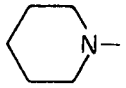
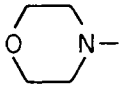
Anal. Calcd. for $C_8H_9BrN_2O$: N, 12.21. Found: N, 12.43, 12.38.

Twenty g. (0.09 mole) of the oxime was dissolved in 200 ml. of glacial acetic acid by heating the mixture to about 50°. Chloroacetyl chloride (22.6 g., 0.20 mole) was added slowly with stirring. During the addition, a heavy precipitate formed, and all of the solid material did not redissolve upon continued heating. Heating was continued for about one hour, following which the mixture was stirred for 37 hours at room temperature.

The reaction mixture was concentrated on a rotary evaporator, and the solid residue therefrom was taken up in 500 ml. of chloroform. This solution was washed with 200 ml. of ice-cold aqueous saturated sodium carbonate, dried, and evaporated. The product was left as a pale yellow crystalline residue (19.7 g.,

Table 3

Aminomethylquinazoline 3-Oxides (III and V) and Aminobenzo-1,4-diazepine 4-Oxides (IV)

Compound	RN	R′	Z	M.p., °C, (a)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	CH_3NH-	CH_3	H	96-96.5 (a)	65.00	6.45	20.68	64.76	6.41	20.77
Va	CH_3N	CH_3	H	172-174 (a)	67.18	5.64	18.66	67.26	5.53	18.65
IVa	CH_3NH-	CH_3	H	186-186.5 (a)	65.00	6.45	20.68	64.92	6.66	20.46
IVb	CH_3NH-	CH_3	Br	250-252 (a)	46.8	4.26	14.89	47.0	4.21	14.76
IIIt		CH_3	H	125-127 (b)			15.32			15.28
IIIu		CH_3	Br	120-124 (b)	54.5	5.72		54.4	5.42	
IIIv		CH_3	H	125-126.5 (c)			16.33			16.11
IIIw		CH_3	H	185-186 (d)	64.84	6.61	16.21	65.12	6.51	16.50

(a) Recrystallization solvent, ethanol, 95%. (b) Acetone, (c) Ethyl acetate-hexane. (d) EtOH-EtOAc.

Table 4

Distribution of Substitution Products
I → III + IV + V

Compound	Method	Yield, % (a) III	IV	V
a	D	--	--	54
a	E	(60) (b)	(40) (b)	--
a	F	--	(80) (b) 65	--
b	D	--	63	--
t	D	94	--	--
u	D	58	--	--
v	E	88	--	--
w	E	90	--	--

(a) Isolated yield. If no figure is given, none of that product was isolated. (b) Amount determined by nmr spectrum of crude product.

76.5%) melting at 176-181° dec. An analytical sample melting at 182-185° dec. was prepared by four additional recrystallizations from acetone; ir (potassium bromide): 3.24(m), 6.24(m), 6.73(s), 7.75(vs), 8.40(vs), 11.86(vs), 13.57(vs), 14.54(s), μm; nmr (deuteriochloroform): δ 2.86 (s, 3, 4-CH_3), 5.07 (s, 2, CH_2Cl), 7.86 (m, 2, 7,8-H_2), 8.05 (m, 1, 5-H) ppm.

Anal. Calcd. for $C_{10}H_8BrClN_2O$: N, 9.74. Found: N, 9.67.

2-Chloromethyl-4-methylquinazoline 3-Oxide (Ia).

This compound was prepared in essentially the same way as the now-published procedure (14) in 94% yield, m.p. 168-171.5°. Recrystallization from either ethanol or acetone gave the product as yellow needles, m.p. 172-175° (Lit. m.p. 169-170° (14)); ir (potassium bromide): 3.27(w), 6.21(w), 6.41(m), 6.67(m), 7.72(vs), 8.24(vs), 8.71(s), 13.07(s), 14.12(s), 14.65(w) μm; uv λ max (95% ethanol): 263 nm (ε = 22,800), 301 (6,850), and 353 (2,790); nmr (deuteriochloroform): δ 2.87 (s, 3, CH_3), 5.03 (s, CH_2), 7.7 (broad multiplet, 4, aromatic) ppm; Mass Spectrum: m/e (relative intensity) 210 (20), 208 (parent, 60), 191 (100), 173 (18), 143 (25), 128 (55), 116 (20), 102 (25), 93 (67), 77 (42), 63 (20), 51 (28), 39 (23), 28 (38).

Anal. Calcd. for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.34; N, 13.41. Found: C, 57.48; H, 4.29; N, 13.43.

2-(α-Bromoethyl)-4-methylquinazoline 3-Oxide.

This compound was prepared essentially as above except that α-bromopropionyl bromide was used instead of chloroacetyl chloride, m.p. 173-174° dec. The compound slowly discolors upon exposure to light; ir (potassium bromide): 6.22(w), 6.41(m), 6.67(m), 7.75(vs), 8.25(vs), 13.20(s) μm.

Anal. Calcd. for $C_{11}H_{11}BrN_2O$: N, 10.49. Found: N, 10.46.

2-α-Bromoethyl)-4-methyl-6-bromoquinazoline 3-Oxide.

Prepared in the same manner as Ib above (m.p. 189-190°, 37%).

2-Ethoxycarbonyl-4-methylquinazoline 3-Oxide.

Prepared essentially as was Ia except that ethyl oxalyl chloride was used as the acid chloride (86%, m.p. 151-153°); ir (potassium bromide): 3.25(w), 3.35(w), 3.44(w), 5.74(vs), 6.21(w), 6.41(w), 6.65(w), 6.77(m), 7.70(vs), 7.99(s), 8.25(s), 8.53(s), 9.86(s), 12.83(s), 13.21(vs), 14.56(m) μm.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.34; H, 5.36; N, 12.05.

2,4-Dimethylquinazoline 1-Oxide.

A mixture of 5.0 g. of 2,4-dimethylquinazoline and 0.032 mole of perbenzoic acid in 60 ml. of chloroform was refluxed for 7 hours, then additional 0.016 mole portions of perbenzoic acid were added after 1.5 hours and 4.5 hours of refluxing. After evaporating the solvent, the residue was stirred with cold, saturated, aqueous sodium carbonate, and extracted with chloroform. Evaporation of the extract left an oily residue which was taken up in 15 ml. of acetone. After addition of 200 ml. of cyclohexane and digestion on a steam bath, the mixture was filtered. On chilling, the filtrate yielded 1.3 g. (24%) of pale-yellow crystals melting at 134-136°; ir (potassium bromide): 6.17(m), 6.49(s), 6.65(m), 6.94(m), 7.30(s), 7.57(vs), 7.70(s), 8.23(m), 8.34(m), 8.70(m), 8.99(m), 13.01(s), 13.10(vs), 13.84(s) μm.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.65; N, 16.1. Found: C, 68.7; H, 5.97; N, 16.06.

2-Methyl-4-phenylquinazoline 1-Oxide.

A solution of 4.4 g. (0.02 mole) of IV, 2.4 ml. (0.02 mole) of 30% hydrogen peroxide and 30 ml. of glacial acetic acid was heated on a steam bath for 16 hours, additional 1.2 ml. portions of hydrogen bromide being added at 2-3 hours intervals. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane, washed with ice-cold sodium carbonate solution, dried, and evaporated. The dark red-brown residue was triturated with acetone and crystallized from cyclohexane to give 1.2 g. (26%) of yellow-brown crystals melting at 154-159°. Vacuum sublimation gave yellow prisms, m.p. 165-167°; ir (potassium bromide): 3.29(w), 6.20(m), 6.55(s), 6.93(m), 7.20(s), 7.62(vs), 12.60(m), 13.04(s), 13.83(m), 14.20(s), 14.96(m), 15.50(m) μm.

Anal. Calcd. for $C_{15}H_{12}N_2O$: N, 11.85. Found: N, 11.66.

Preparation of Thioethers.

The following three procedures are representative.

Method A: 4-Methyl-2-methylthiomethylqunazoline 3-Oxide (IIa).

Sodium methoxide (2.70 g., 0.050 mole) was stirred in 75 ml. of dry ethanol until dissolution was complete. Twenty-five ml. (0.050 mole) of a solution containing 0.1 g./ml. of methanethiol in absolute ethanol was added, and the mixture was stirred until most of the precipitated solid had redissolved. Compound Ia (10.0 g.) was added, and the mixture was allowed to stand with intermittent shaking for 48 hours. The sodium chloride which had formed during the course of the reaction was removed by suction filtration, and the filtrate was evaporated to dryness leaving an orange-red oil which solidified on standing. It was dissolved in 50 ml. of chloroform, filtered, and evaporated to dryness yielding an orange-yellow solid. Recrystallization from ethyl acetate-Skellysolve B gave 10.3 g. (97.5%) of product, m.p. 102-104°. An analytical sample melting at 110-111° was prepared by five recrystallizations from ethyl acetate-Skellyslove B; ir (Nujol): 6.20(w), 6.40(w), 6.66(m), 7.70(s), 8.24(s), 8.74(s), 12.79(m), 13.10(s), 14.16(w) μm.

Method B: 2-β-Hydroxyethylthiomethyl-4-methylquinazoline 3-Oxide (IIg).

A mixture of 10.0 g. (0.048 mole) of Ia, 3.75 g. (0.048 mole) of 2-hydroxyethanethiol, 8 ml. of triethylamine and 80 ml. of triethylamine and 80 ml. of anhyd *p*-dioxane was refluxed gently for 5 hours. The cooled reaction mixture was filtered to remove the triethylamine hydrochloride (6.0 g., *ca.* quantitative), and the filtrate was evaporated to dryness leaving 12.0 g. of crude product as a viscous orange oil which solidified upon standing. Recrystallization from absolute ethanol gave 10.8 g. (90%) of product as pale yellow needles, m.p. 126-127.5°. An analytical sample melting at 126.5-127.5° was prepared by three additional recrystallizations from absolute ethanol; ir (potassium bromide): 2.96(s), 3.21(w), 3.41(w), 6.20(w), 6.39(m), 6.65(s), 7.70(vs), 8.22(vs), 9.70(s), 9.55(vs), 9.67(vs), 12.79(vs), 13.09(vs), 14.02(s) μm.

Method C: 4-Methyl-2-phenylthiomethylquinazoline 3-Oxide (IIi).

Ten g. (0.048 mole) of Ia, 6.0 g. of triethylamine and 5.3 g. (0.048 mole) of benzenethiol were combined in 30 ml. of *N,N*-dimethylformamide, and the mixture was shaken vigorously. An exothermic reaction ensued, and it was necessary to cool the reaction mixture in a cold water bath. After about three minutes, the reaction mixture subsided. After standing for 30 minutes, the reaction mixture was washed with ice water and filtered. The crude product thus obtained was recrystallized from ethyl acetate to give 11.3 g. (83%) of product as pale yellow needles, m.p. 119-120.5°. An analytical sample melting at 119.4-121° was prepared by three additional recrystallizations from acetone and one recrystallization from ethyl acetate; ir (Nujol): 6.20(vs), 6.30(w), 6.40(m), 6.68(msh), 6.74(ssh), 7.77(vs), 8.31(vs), 8.84(s), 12.82(m), 13.73(vs), 13.99(m), 14.58(m) μm; nmr (deuteriochloroform): δ 2.83 (s, 3, 4-CH_3), 4.67 (s, 2, CH_2S), 7.5 (complex multiplet, 9, aromatic) ppm.

Compound IIb.

This compound had uv (95% ethanol): λ max 234 (ε = 27,200), 262 (42,100); λ min 241 (25,400), 332 (2,990); (0.1 *N* aqueous hydrochloric acid): λ max 261 (44,500); λ min 330 (32,400) nm; ir (potassium bromide): 3.28(w), 3.45(w), 6.27(m), 6.48(m), 6.75(m), 7.03(w), 7.25(m), 7.38(s), 7.60(m), 7.70(s), 7.81(s), 8.10(w), 8.42(vs), 9.36(m), 11.95(s), 12.91(w), 13.51(2), 14.72(2) μM; nmr (deuteriochloroform): δ 2.27 (s, 3, CH_3S), 2.85 (s, 3, 4-CH_3), 4.20 (s, 2, CH_2S), 7.82 (m, 2, 7,8-H_2), 8.02 (m, 1, 5-H) ppm.

Compound IIc.

This compound had uv (95% ethanol): λ max 233 (25,600), 267 (31,300); λ min 246 (19,300), 310 (6650); (0.1 *N* aqueous hydrochloric acid): λ max 232 (22,400), 263 (32,100); λ min 224 (19,800) nm; ir (potassium bromide): 3.29(m), 3.45(w), 6.26(m), 6.48(m), 6.80(s), 7.27(m), 7.38(vs), 7.53(s), 7.63(s), 7.74(vs), 8.42(s), 8.68(s), 8.97(m), 9.27(m), 10.15(m), 11.46(m), 11.68(m), 11.95(s), 12.05(vs), 13.35(vs), 14.17(s), 14.91(w) μm.

Deoxygenation of IIa to 2-Methylthiomethyl-4-methylquinazoline.

Two g. (0.009 mole) of IIa was cautiously added to 4 ml. of phosphorus trichloride in 30 ml. of chloroform. A vigorous reaction ensued. The mixture was then refluxed for one hour, cooled, washed with a mixture of 20 g. of crushed ice, and 20 ml. of 40% aqueous sodium sulfate. Evaporation left a gummy orange-red residue, which was dissolved in boiling hexane leaving behind some insoluble gummy material. Upon cooling the solution, beautiful, canary-yellow crystals were obtained, m.p. 65-67° after a second crystallizaiton. These were identical in appearance, melting point, and spectra with an authentic sample made by direct displacement of sodium methanethiolate on 2-chloromethyl-4-methylquinazoline; ir (Nujol): 6.19(w), 6.40(m), 6.66(m), 13.15(s) μm.

Anal. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71. Found: C, 64.81; H, 6.05; N, 13.92.

Preparation of Sulfoxides.

The following procedure is typical.

4-Methyl-2-methylsulfinylmethylquinazoline 3-Oxide (VIa).

One g. (0.0045 mole) of IIa was dissolved in 25 ml. of chloroform and 8.3 ml. of solution of peroxybenzoic acid in chloroform (0.00055 mole/ml.) was added dropwise with stirring. The mixture was allowed to stand at room temperature for 34.5 hours, then the cloudy suspension which resulted was filtered. The filtrate was washed with cold, saturated sodium carbonate solution, dried, and evaporated leaving 0.95 g. (89%) of a pale yellow residue, m.p. 159-161.5°. Recrystallization from ethyl acetate gave a pure material melting at 168.5-169.5°; ir (potassium bromide): 3.30(w), 3.45(w), 6.40(w), 6.60(m), 7.35(m), 7.73(vs), 8.27(vs), 9.70(vs), 12.82(s), 13.12(s), 14.340(m) μm; nmr (deuteriochloroform): δ 2.90(6), 3.73(2), 7.8(4) ppm.

Compound VIb had uv (95% ethanol): λ max 240s (22,400), 255 (33,700), 305 (6300); λ min 332 (2200); (0.1 *N* aqueous hydrochloric acid λ max 263 (39,700), 305 (4,900); λ min 332 (2500) nm; ir (potassium bromide): 3.22(w), 3.42(w), 6.20(m), 6.68(s), 7.31(s), 7.55(s), 7.70(vs), 8.41(vs), 8.63(s), 9.69(vs), 10.12(m), 11.95(s), 13.72(s), 14.56(m) μm.

Preparation of Sulfones.

The following procedure is typical.

4-Methyl-2-methylsulfonylmethylquinazoline 3-Oxide (VIIa).

To 1.0 g. (0.0045 mole) of IIa, 24.9 ml. of a solution of peroxybenzoic acid in chloroform (0.00055 mole/ml.) was added very slowly with stirring and cooling. After standing for 23 hours, the cloudy solution was filtered, washed with cold sodium carbonate solution, dried and evaporated. The residue (1.05 g., 91%) was a pale, yellow solid melting at 205.5-208.5°. An analytical sample, m.p. 213-214°, was prepared by five recrystallizations from 95% ethanol; ir (potassium bromide): 3.33(m), 3.41(m), 6.21(w), 6.41(m), 6.69(m), 7.70-7.78(vs), 8.31(vs), 8.88(vs), 8.88(vs), 14.27(s) μm: nmr (deuteriochloroform): δ 2.92 (s, 3), 3.36 (s, 3), 5.15 (s, 2), 7.9 (m, 4) ppm.

Reaction of Amines with α-Halomethylquinazoline 3-Oxides.

Method D:

A solution of 5.0 g. (0.024 mole) of Ia in 7 ml. of DMF was cooled in an ice bath and 5.0 ml. (0.05 mole) of 40% aqueous methylamine was added. The mixture was maintained at 0° for 1 hour, and it was then allowed to warm up to ambient temperature and stand several hours. Cold water (100 ml.) was added to the mixture, and the crude product, which precipitated as a yellow-brown solid, was removed by filtration and washed with two 40 ml. portions of ice water. Recrystallization of the crude product gave 2.45 g. (54%) of yellow solid, m.p. 172-174°, *N,N*-bis(4-methyl-3-oxide-2-quinazolinylmethyl)methylamine (Va). The same product was obtained by the action of aqueous methylamine on the substrate in *p*-dioxane solution; uv (95% ethanol): λ max 218 (ε = 28,800), 256 (21,500), 298 (7,650) nm; ir (potassium bromide): 3040(w), 2910(w), 1600(w), 1550(m), 1490(m), 1350(m), 1290(s), 1200(s), 1135(s), 760(s) cm^{-1}; Mass spectrum: m/e (relative intensity) 375 (mol ion) (49), 358 (41), 343 (4), 341 (4), 198 (75), 186 (100), 184 (45), 172 (16), 149 (30), 148 (95), 144 (28), 143 (41), 128 (20), 116 (44), 102 (25), 89 (20), 77 (21), 76 (19), 75 (15).

Method E:

To a saturated anhydrous solution of methylamine in 50 ml. of *p*-dioxane at 25° was added a solution of 2.0 g. (0.01 mole) of Ia in 100 ml. of *p*-dioxane dropwise with stirring over a 3 hour period. Additional anhydrous methylamine gas was passed through the reaction mixture throughout the addition. The mixture was stirred at room temperature for 12 hours, and the solvent then removed under vacuum. The residue was treated with 30 ml. of saturated aqueous sodium carbonate, and the resulting mixture was extracted with five 50 ml. portions of benzene. The dried extract was evaporated leaving a yellow-brown oil which was shown by thin-layer chromatography (silica gel, 10:1 benzene-methanol) to be a mixture containing two major constituents. Separation could not be effected by fractional crystallization, but preparative thin-layer chromatography led to isolation. One constituent (~60% of the crude mixture, basis nmr analysis) was characterized as 2-methylaminomethyl-4-methylquinazoline 3-oxide (IIIa), m.p. 96-96.5°; uv (95% ethanol): λ max 220 (ε = 27,500), 255 (24,600), 298 (7,350) nm; ir (potassium bromide): 3400(m), 2910(2), 1600(2), 1550(m), 1470(m), 1350(m), 1290(s), 1210(s), 1130(m), 760(s); nmr (deuteriochloroform): δ 2.57 (3, N-CH_3), 2.86 (3, 4-CH_3), 2.94 (1, NH), 4.58 (2, N-CH_2), 7.75 (4, aromatic); Mass spectrum: m/e (relative intensity) 203 (parent) (0.2), 186 (100), 149 (37), 148 (20), 147 (6), 145 (19), 144 (8), 143 (9), 129 (6), 128 (14), 118 (6), 117 (8), 116 (12), 103 (7), 102 (14), 89 (9), 77 (12), 76 (11).

The other constituent (~40% of the mixture) was characterized as 2-methylamino-5-methyl-3*H*-1,4-benzodiazepine 4-oxide (IVa), m.p. 186-186.5°; uv (95% ethanol): λ max 252 (25,400), 333 (1240) nm; ir (potassium bromide): 3250(m), 3080(m), 2910(2), 1625(s), 1585(s), 1570(s), 1470(m), 1435(s), 1280(s), 1220(m), 1150(m), 760(s) cm^{-1}; nmr (deuteriochloroform): δ 2.48 (3), 2.90 (3, broad singlet), 4.50 (2, very broad), 7.3 (4, complex multiplet); Mass spectrum: m/e (relative intensity) 203 (parent) (85), 187 (100), 159 (24), 158 (27), 157 (42), 145 (56), 131 (24), 130 (44), 117 (25), 116 (38), 103 (22), 102 (20), 91 (22), 90 (22), 89 (26), 77 (40).

Method F:

Compound Ia (2.0 g., 0.01 mole) was added to 20 ml. of liquid anhydrous methylamine at -70°. The mixture was stirred and allowed to warm to the boiling point of methylamine (-7°), and the methylamine was allowed to escape from the boiling reaction flask. The residue was then worked up as per Method E, above, to yield a crude product which was shown by nmr analyses to contain *ca.* 80% of IVa and 20% of IIIa. Fractional crystallization from cyclohexane yielded IVa in 65% yield, m.p. 186-186.5°.

Compound IIIu.

This compound had uv (95% ethanol): λ max 232 (29,400), 302 (6450); λ min 240 (21,000), 288 (6050), 332 (2800); (0.1 *N* aqueous hydrochloric acid): λ max 249 (53,200), 298 (5,600), 336 (3,150); λ min 298 (5,430), 330 (2,950); ir (potassium bromide): 3.05(w), 3.30(w), 3.46 (vs), 3.54(s), 3.62(w), 6.75(s), 7.40(s), 7.70(s), 7.84(s), 8.45(vs), 8.59(s), 12.16(vs), 12.41(s), 13.38(m), 14.00(s) μm.

Compound IVb.

This compound had uv (95% ethanol): λ max 248 (22,000); λ min 315 (2400); (0.1 *N* aqueous hydrochloric acid): λ max 251 (21,100); ir (potassium bromide): 3.10(s), 3.25(m), 3.44(2), 6.19(vs), 6.38(s), 6.83(s), 7.90(s), 8.62(s), 11.85(m), 12.25(m), 13.66(m), 14.65(m) μm; nmr (deuteriochloroform): δ 2.16 (s, 1, NH), 2.50 (s, 3, NCH_3), 2.90 (s, 2, CH_2), 2.98 (s, 3, 5-CH_3), ~7.4 (complex m, 3, aromatic); Mass spectrum: m/e (relative intensity) 283 (8), 281 (M^+, 8), 264 (12), 235 (5), 223 (7), 208 (5), 196 (4), 185 (8), 170 (5), 156 (8), 142 (5), 129 (12), 115

(18), 102 (13), 89 (23), 75 (22), 63 (25), 56 (63), 41 (75), 28 (100), 15 (40).

Attempts to Rearrange 2-Aminomethylquinazoline 3-Oxides into 1-Amino-3*H*-1,4-benzodiazepine 4-Oxides.

Twenty-four trials were made on IIIa and 2-allylamino-, 2-β-hydroxyethylamino-, and 2-β-methoxyethylaminomethyl-4-phenyl-6-chloroquinazoline 3-oxides incubating them variously in methanol, ethanol, *p*-dioxane, diglyme, acetone, *N,N*-dimethylformamide, and dimethyl sulfoxide, either alone or in the presence of hydrogen chloride at various concentrations for time periods ranging from 3 hours to 13 days and at temperatures ranging from ambient to reflux while monitoring the system by uv spectra. In some cases, no change at all was observed. In others, change occurred, evidently associated with opening of the pyrimidine ring moiety, but at no time was a spectrum or other evidence obtained associated with rearrangement to the corresponding 3*H*-1,4-benzodiazepine 4-oxide. The following three examples are representative.

Example 1.

One hundred mg. of IIIa dissolved in 5 ml. of DMF was refluxed at 148° for 13 hours. The solvent was removed at reduced pressure. Both uv and ir spectra were essentially identical with the starting material.

Example 2.

2-Allylaminomethyl-4-phenyl-5-chloroquinazoline 3-oxide (6) (150 mg.) dissolved in a mixture of 9 ml. of DMF and 0.5 ml. of 6*N* hydrochloric acid and allowed to stand for 13 days. It was then diluted with water, neutralized, and filtered to yield 140 mg. of unchanged quinazoline m.p. 137-139°.

Example 3.

Five mg. of the allylamino compound above dissolved in 50 ml. of *p*-dioxane was allowed to stand. At intervals, 1 ml. aliquots were taken, evaporated to dryness and taken up in 0.1*N* hydrochloric acid and their uv spectra obtained. At the onset, the uv spectrum (0.1*N* aqueous hydrochlorid acid) gave λ max 232 (30,800), 262 (54,000), 320 (7,500), and λ min 243 (28,400) and 293 (6,180) nm. The corresponding diazepine in the same solvent gives λ max 247 (32,900), 310 (880), and λ min 293 (8,300) nm. After 12 days, the spectrum of the sample gave λ max 235 (25,600) and no other band. While its identity has not been established, it cannot be the diazepine or a mixture of it alone with the starting quinazoline.

Deoxygenation of Ia to 2-Chloromethyl-4-methylquinazoline.

Five g. (0.024 mole) of **Ia** was refluxed with 15 ml. of phosphorus trichloride in 100 ml. of chloroform for 1 hour. After cooling, washing with ice-cold sodium carbonate, drying, and evaporation, the mixture yielded 1.1 g. (24%) of crude 2-chloromethyl-4-methylquinazoline melting at 53-57°. Vacuum sublimation gave colorless prisms, m.p. 58-60°; ir (potassium bromide): 3.26(m), 3.33(m), 6.16(m), 6.35(s), 6.65(m), 6.95(m), 7.15(s), 13.20(s), 14.50(m), 15,58(m) μm.

Anal. Calcd. for $C_{10}H_9ClN_2$: C, 62.35; H, 4.71; H, 14.54; Cl, 18.40. Found: C, 62.42; H, 4.68; N, 14.49; Cl, 18.59.

REFERENCES AND NOTES

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(6) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961) and following papers reviewed by G. A. Archer and L. J. Sternbach, *Chem. Revs.*, **68**, 747 (1968) and L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).

(7) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962) and following papers. Review: S. J. Childress and M. I. Bluckman, *J. Pharm. Sci.*, **53**, 577 (1964).

(8) Trademark of Hoffmann-LaRoche.

(9) Quinazolines, *e.g.*, 4-methylquinazoline are oxidized to the corresponding 1-oxides by the action of peroxybenzoic acid in chloroform at reflux temperatures [I. Higashino, *Chem. Pharm. Bull.*, **9**, 635 (1961)] or, often with side-chain attack, to the corresponding 4-quinazolinones by 30% peracetic acid at 50° (K. Adachi, *Yakugaku Zasshi*, **77**, 507 (1957) [*Chem. Abstr.*, **51**, 14744i (1957)].

(10) A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **30**, 4267 (1965).

(11) *Cf.* A. R. Katritzky and M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides," Academic Press, 1971.

(12) C. D. Johnson, "The Hammett Equation", Cambridge, 1973, Chapter 2.

(13) J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.*, **84**, 16 (1962).

(14) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

(15) R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963); R. G. Pearson and J. Songstad; *ibid.*, **89**, 1827 (1967); T. L. Ho, *Chem. Revs.*, **75**, 1 (1975).

(16) Prepared by a modification of the method of C. S. Gibson and B. Levin, *J. Chem. Soc.*, 2394 (1931).