the hydrogen bond is considered to play an important role for the base-catalyzed reaction of PGE and BA.

Registry No.—Benzoic acid, 65-85-0; phenyl glycidyl ether, 122-60-1; isoquinoline, 119-65-3; 3-picoline, 108-99-6; 4-picoline, 108-89-4; pyridine, 110-86-1; 2,4-lutidine, 108-47-4; 2-picoline, 109-06-8; 4-methylquinoline, 491-35-0; quinoline, 91-22-5; 2-methylquinoline, 91-63-4; 2,6-lutidine, 108-48-5.

Acknowledgment.—The author is grateful to Mr. K. Tomizuka for his help with the manuscript.

Synthesis and Chemistry of Thiazolo[3,2-a]pyridinium Compounds[1]

C. K. BRADSHER AND J. E. BOLIEK

Department of Chemistry, Duke University, Durham, North Carolina 27706

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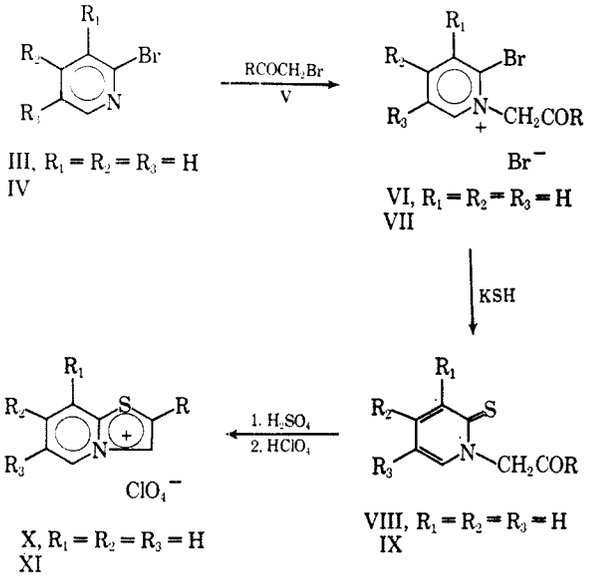
1-β-Oxoethylpyridine-2-thiones may be cyclized in sulfuric acid to yield 2-substituted thiazolo[3,2-a]pyridinium salts. The environment about position 2 appears more shielded than that about position 3 as measured either by resonance of a ring proton or of the protons of an alkyl substituent at the position. The pK_a values of the 2- and 3-carboxylic acids are the same, within experimental error.

The thiazolo[3,2-a]pyridinium cation (II) was first synthesized[2,3] by cyclization of α-(2-pyridylthio) ke-

I II

tones and -aldehyde (I). This approach to the synthesis of the thiazolopyridinium system lends itself best to the preparation of monosubstituted derivatives with substituents at position 3 (II, R = H). In connection with our study of the nmr spectrum of the thiazolopyridinium system, there was a need for a method which would afford derivatives monosubstituted at position 2 (II, R′ = H).

The new synthesis is based upon an observation by Djerassi and Pettit[4] that 2-bromo-1-phenacylpyridinium bromide (VI, R = C_6H_5) reacts with hydrosulfide ion to afford an excellent yield of 1-phenacyl-2-



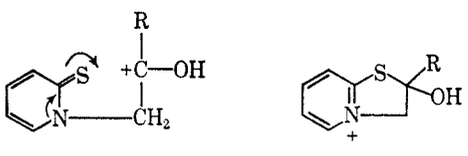
III, $R_1 = R_2 = R_3 = H$
IV

VI, $R_1 = R_2 = R_3 = H$
VII

X, $R_1 = R_2 = R_3 = H$
XI

VIII, $R_1 = R_2 = R_3 = H$
IX

pyridinethione (VIII, R = C_6H_5). From an earlier observation[5] that 1-phenacyl-2-pyridone may be cyclized in sulfuric acid to yield the 2-phenyloxazolo[3,2-a]pyridinium cation, it appeared plausible that 1-phenacyl-2-pyridinethione (VIII, R = C_6H_5) might, under the same conditions, afford the 2-phenylthiazolo[3,2-a]pyridinium (X, R = C_6H_5) cation. This prediction proved correct, for the new product had the expected composition, ultraviolet absorption, and infrared and nmr (only aromatic protons) spectra. Through use of a variety of bromomethyl ketones (V) and of bromopyridines (IV), it proved possible to prepare a variety of 2-substituted thiazolo[3,2-a]-pyridinium salts with either alkyl or aryl groups at position 2 as well as with methyl groups in the pyridine ring. In no case was there evidence that any significant portion of the thione (IX) cyclized with the loss of hydrogen sulfide to afford the related oxazolo[3,2-a]pyridinium salt. The mechanism of cyclization may be viewed as a protonation of the carbonyl oxygen atom (XII) followed by an attack of the highly nucleophilic sulfur atom on the conjugate acid. The resulting carbinol (XIII) would be expected to dehy-



XII XIII

drate readily in the concentrated acid. The results of the syntheses are summarized in Table I.

An interesting observation reported earlier[3a] was that the nmr spectrum of 2,3-dimethylthiazolo[3,2-a]-pyridinium (II, R = R′ = CH_3) perchlorate showed, in addition to aromatic resonances, a single sharp singlet (at δ 2.80 ppm) corresponding to six protons. The methyl proton resonances of the 2-methyl and 3-methyl isomers (II, R = CH_3, R′ = H, or II, R = H, R′ = CH_3) differ and occur at δ 2.84 and 2.94[6] ppm, respectively. A similar difference was shown by the methyl protons of the new 2- and 3-*t*-butyl derivatives (II, R = *t*-Bu, R′ = H, and II, R = H, R′ = *t*-Bu),

(1) This investigation was supported by Public Health Service Research Grant No. H-2170 of the National Institutes of Health.

(2) F. S. Babichev and V. N. Bubnovskaya, *Ukr. Khim. Zh.*, **30**, 848 (1964); *Chem. Abstr.*, **62**, 1766c (1965).

(3) (a) C. K. Bradsher and D. F. Lohr, Jr., *Chem. Ind.* (London), 1801 (1964); (b) C. K. Bradsher and D. F. Lohr, Jr., *J. Heterocyclic Chem.*, **3**, 27 (1966).

(4) C. Djerassi and G. R. Pettit, *J. Am. Chem. Soc.*, **76**, 4470 (1954).

(5) C. K. Bradsher and M. F. Zinn, *J. Heterocyclic Chem.*, **1**, 219 (1964).

(6) We have not been able to reproduce the value of τ 7.17 reported earlier[3b] for the 3-methyl derivative.

TABLE I

SYNTHESIS OF 2-SUBSTITUTED THIAZOLO[3,2-*a*]PYRIDINIUM PERCHLORATES

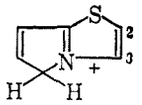
Compd	R	R_1	R_2	R_3	Yields, % Salt VII[a]	Thione IX	Product XI	λ_{max}, mμ (log ε), of XI
a	C_6H_5	...	...	...	72	93	46	318 (4.34), 250 sh (3.91), 229 sh (4.16), 214 sh (4.31), and 207 (4.37)
b	*p*-BrC_6H_4	...	...	...	36	97	53	320 (4.40), 240 sh (4.07), 221 (4.33), and 207 (4.27)
c	CH_3	...	...	...	56[b]	53	37	310 (4.27), 278 sh (3.55), 236 (3.97), and 212 (4.06)
d	*t*-C_4H_9	...	...	...	57[b]	89	28	310 (4.28), 300 sh (4.13), 277 sh (3.55), 237 (3.99), and 212 (4.02)
e	C_6H_5	CH_3	...	...	74	89	52	320 (4.35), 254 sh (3.96), 230 sh (4.14), and 207 (4.37)
f	C_6H_5	...	CH_3	...	78	79	51	318 (4.40), 250 sh (3.93), 237 sh (4.21), 217 (4.41), and 212 (4.41)
g	C_6H_5	...	...	CH_3	77	94	67	320 (4.36), 221 (4.41), and 205 (4.42)

[a] The yields are based on bromopyridine, the bromomethyl ketone being used in excess, with the exception of VIIa, where bromopyridine was used in excess. [b] Yield of material once recrystallized from methanol–ethyl acetate.

the observed resonances being at δ 1.59 and 1.69 ppm, respectively. These results show that a weaker deshielding is experienced by protons attached to an alkyl group at position 2 (adjacent to sulfur) than by protons on a group at position 3 (adjacent to nitrogen).

The availability of both the 2- and 3-methylthiazolo[3,2-*a*]pyridinium systems has made it possible to make further progress in the assignment of the observed resonances of the protons attached to the unsubstituted parent system (II, R = R′ = H). The nmr spectrum of the unsubstituted system is characterized by a doublet centered at δ 9.30 ppm (J = 6 cps) assigned to proton 5, an AB quartet consisting of two doublets, one centered at δ 7.97 ppm (J = 7 cps) and the other centered at δ 8.19 ppm (J = 7 cps), assigned to the two protons at 2 and 3, and a multiplet in the region δ 8.38–8.80 ppm assigned to protons 6, 7, and 8.

The assignment of proton 5 was based upon the observation that the observed doublet collapsed to a singlet when the proton at position 6 was replaced by a chlorine atom. The assignment of the doublets centered at δ 7.97 and 8.19 ppm between positions 2 and 3 presents a problem parallel to that experienced by Molloy, Reid, and McKenzie[7] in making assignments to atoms 2 and 3 of the pyrrolo[2,1-*b*]thiazolium cation (XIV). They assigned to the proton at position

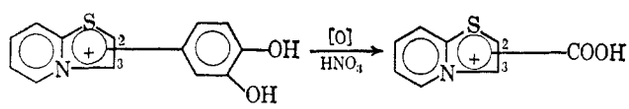


XIV

3 the doublet at the lower field because of the proximity to the more electronegative nitrogen atom. By analogy, the doublets observed by us at δ 7.97 and 8.19 ppm should be assigned to positions 2 and 3, respectively. Observation of the resonance of the ring protons of the 2-methyl- and 3-methylthiazolo[3,2-*a*]-pyridinium cation supported the correctness of this assignment. The 2-methyl (with ring proton at position 3) exhibited a broad one-proton singlet at δ 8.38 ppm, while the 3-methyl (with ring proton at position 2) showed a one-proton singlet at δ 8.04 ppm. While our results make clear that the methyl groups do have a deshielding effect on the ring protons and that this deshielding is not exactly equivalent in the 2- and 3-methyl compounds, it is felt that the data lend strong support to the assignment of the lower field resonance to the proton at position 3.

(7) B. B. Molloy, D. H. Reid, and S. M. McKenzie, *J. Chem. Soc.*, 4368 (1965).

It seemed of interest to determine whether positions 2 and 3 of the system differed greatly in electron density by synthesis of the hitherto unknown 2- and 3-carboxylic acids (XVII and XVIII) and determination of the approximate pK_a values. The acids were prepared by nitric acid oxidation of the corresponding 3,4-



XV, position 2 (not isolated)
XVI, position 3 (not isolated)

XVII, position 2
XVIII, position 3

dihydroxyphenyl derivatives XV and XVI. The pK_a determinations were carried out in aqueous solution using the bromide salts and, for purposes of comparison, it was assumed that the pK_a was approximately equal to the pH of the solution when one-half of the base needed for complete neutralization had been added. The interesting result was that both carboxylic acids had pK_a = 2.3 ± 0.2 pK units, indicating that, within the limits of the accuracy of this method, the electron densities at positions 2 and 3 are approximately the same. The high acidity of the acids must be a consequence of the partial positive charge on the adjacent heteroatoms.

Experimental Section

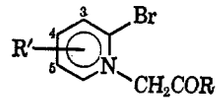
The elemental analyses were carried out by Janssen Pharmaceutica, Beerse, Belgium. All melting points were determined in capillary tubes and are corrected. Ultraviolet absorption spectra were measured in 95% ethanol using a Cary Model 14 spectrophotometer and 1-cm quartz cells. The nmr data was obtained with a Varian A-60 spectrometer using tetramethylsilane as an external standard and trifluoroacetic acid as the solvent.

Preparation of 2-Bromo-1-(β-oxoethyl)pyridinium Salts VII.—To 0.023 mole of the 2-bromopyridine (III) in 5 ml of tetramethylene sulfone, 7.18 g (excess) of the bromomethyl ketone (V) was added and the mixture was heated on the steam bath. Trituration of the cooled mixture with ether gave a crystalline precipitate which was collected, washed with ether, and dried under vacuum. This crystalline material was used directly for the preparation of the thione (IX), but for analytical purposes a small portion was converted to the perchlorate, which was recrystallized from methanol. Results of these experiments are summarized in Table II.

Preparation of 1-(β-Oxoethyl)-2-pyridinethiones (IX).—To a solution of the 2-bromo-1-(β-oxoethyl)pyridinium bromide (VII) in 100 ml of water, 3.96 g (0.020 mole) of potassium hydrosulfide was added with stirring. The product precipitated immediately, but the mixture was heated in a steam bath for 2 hr to ensure completeness of reaction. The product was collected and dried in a vacuum desiccator. The yellow product was suitable for cyclization, but was purified for analysis by re-

TABLE II

PREPARATION OF 2-BROMO-1-(β-OXOETHYL)PYRIDINIUM SALTS VII

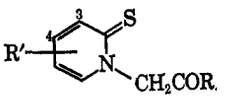


Compd	VII R	VII R′	Reaction time, hr	Mp, °C (crude bromide)	Mp, °C (perchlorate)	Crystalline form	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
b	p-BrC_6H_4	H	1	175–176	221–222	Needles	$C_{13}H_{10}Br_2ClNO_5$	34.28	2.21	3.08	34.66	2.25	3.04
c	CH_3	H	1	146–147	145–146	Needles	$C_8H_9BrClNO_5$	30.55	2.88	4.45	30.18	2.84	4.54
d	t-C_4H_9	H	6	174–176	116–118	Needles[a]	$C_{11}H_{15}BrClNO_5$	37.05	4.24	3.93	36.83	4.31	3.88
e	C_6H_5	3-CH_3	2	[b]	157–159	Plates	$C_{14}H_{13}BrClNO_5$	43.04	3.35	3.59	43.06	3.36	3.52
f	C_6H_5	4-CH_3	4	154–160	163–164.5	Needles	$C_{14}H_{13}BrClNO_5$	43.04	3.35	3.59	43.02	3.45	3.49
g	C_6H_5	5-CH_3	0.75	190–194	178–180	Prisms	$C_{14}H_{13}BrClNO_5$	43.04	3.35	3.59	43.03	3.43	3.48

[a] Crystallized from methanol–ethyl acetate. [b] Not recorded.

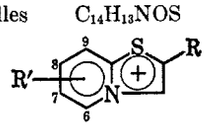
TABLE III

PREPARATION OF 1-(β-OXOETHYL)-2-PYRIDINETHIONES (IX) AND THIAZOLO[3,2-a]PYRIDINIUM PERCHLORATES (XI)



IX

Compd	R	R′	Mp, °C	Crystalline form[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
b	p-BrC_6H_4	H	177–178	Needles	$C_{13}H_{10}BrNOS$	50.66	3.27	4.55	50.73	3.30	4.76
c	CH_3	H	105–106.5	Prisms[b]	C_8H_9NOS	57.46	5.42	8.37	57.20	5.41	8.59
d	t-C_4H_9	H	119–120	Plates[c]	$C_{11}H_{15}NOS$	63.12	7.22	6.69	63.27	7.28	6.68
e	C_6H_5	3-CH_3	190–193.5	Needles	$C_{14}H_{13}NOS$	69.10	5.38	5.76	69.10	5.37	5.83
f	C_6H_5	4-CH_3	181–182	Prisms	$C_{14}H_{13}NOS$	69.10	5.38	5.76	68.97	5.48	5.65
g	C_6H_5	5-CH_3	175–176.5	Needles	$C_{14}H_{13}NOS$	69.10	5.38	5.76	69.12	5.33	6.01



XI

a	C_6H_5	H	161–162[d]	Plates	$C_{13}H_{10}ClNO_4S$	50.08	3.23	4.49	49.71	3.29	4.46
b	p-BrC_6H_4	H	269–271[e]	Needles	$C_{13}H_9NrClNO_4S$	39.97	2.32	3.59	39.68	2.28	3.44
c	CH_3	H	98–98.5[f]	Needles	$C_8H_8ClNO_4S$	38.48	3.23	5.61	38.33	3.19	5.62
d	t-C_4H_9	H	144–144.5[g]	Needles	$C_{11}H_{14}ClNO_4S$	45.28	4.84	4.80	45.36	4.94	4.75
e	C_6H_5	9-CH_3	189–190	Needles	$C_{14}H_{12}ClNO_4S$	51.61	3.71	4.30	51.49	3.74	4.22
f	C_6H_5	8-CH_3	176.5–177	Prisms	$C_{14}H_{12}ClNO_4S$	51.61	3.71	4.30	51.49	3.70	4.29
g	C_6H_5	7-CH_3	202–203	Needles	$C_{14}H_{12}ClNO_4S$	51.61	3.71	4.30	51.42	3.67	4.22

[a] All the thiones (IX) were yellow. [b] From ethanol. [c] From methanol–water. [d] The thione (IXa) used in this experiment was prepared essentially as described in ref 4. The yields of thione given in Table I are those obtained by us. [e] The reaction time was 0.5 hr. [f] The reaction time was 1 hr. [g] The reaction time was 24 hr. The nmr spectra in trifluoroacetic acid showed a singlet at δ 1.59 ppm (nine protons) attributable to the t-butyl group and a series of peaks δ 7.75–9.25 ppm (five protons) assigned to ring protons.

crystallization from ethyl acetate. The results of these experiments are summarized in Table III.

2-Substituted Thiazolo[3,2-a]pyridinium Perchlorates (XI).—Thione IX (1 g) was dissolved in 10 ml of concentrated sulfuric acid and the mixture allowed to stand for 8 hr at room temperature. At the end of the reaction period, the mixture was cooled in ice and poured into 100 ml of cold anhydrous ether. The bisulfate salt usually separated immediately, but the mixture was allowed to stand for several hours at −15° to effect more complete precipitation. The ethereal solution of sulfuric acid was decanted and the residual salt, either a solid or a viscous oil, was dissolved in about 50 ml of water and the mixture warmed to expell dissolved ether. To the aqueous solution, an excess of 35% perchloric acid was added to precipitate the perchlorate salt. The precipitate was usually crystallized from methanol giving a colorless product. Results of these cyclization experiments are summarized in Table III.

3,3-Dimethyl-2-oxo-1-(2-pyridylthio)butane (I, R = H, R′ = t-Bu) Hydrobromide.—A mixture of 1.11 g of 2-mercaptopyridine and 1.79 g of 1-bromopinacolone in 20 ml of dry acetone was refluxed for 12 hr. The resulting precipitate was collected, washed with acetone and ether, and dried in a vacuum desiccator: yield 2.20 g (76%), mp 139–144° from methanol–acetone.

Anal. Calcd for $C_{11}H_{16}BrNOS$: C, 45.52; H, 5.56; N, 4.83; Found: C, 45.83; H, 5.54; N, 4.74.

3-t-Butylthiazolo[3.2-a]pyridinium (II, R = H, R′ = t-Bu) Perchlorate.—The hydrobromide of the sulfide (I, R = H, R′ = t-Bu) (1 g) was dissolved in 10 ml of concentrated sulfuric acid and allowed to stand for 6 hr. Isolated as in the case of the isomer XId, 0.52 g (52%) of colorless needles, mp 224–225°, were obtained by recrystallization from methanol. The nmr spectrum in trifluoroacetic acid exhibited a singlet at 1.69 ppm (nine protons) attributable to the t-butyl group and a series of peats at δ 7.87–9.53 ppm assigned to the ring protons; the ultraviolet spectrum showed λ_{max}, mμ (log ε), 315 (4.17), 305 (4.07), 234 (4.00), and 208 (3.88).

Anal. Calcd for $C_{11}H_{14}ClNO_4S$: C, 45.28; H, 4.84; N, 4.80. Found: C, 45.31; H, 4.86; N, 4.86.

3′,4′-Dihydroxy-2-(2-pyridylthio)acetophenone (I, R = H, R′ = 3,4-$(OH)_2C_6H_3$).—A solution of the sodium salt of 2-mercaptopyridine was prepared by dissolving 1.15 g of sodium in 50 ml of anhydrous methanol and adding 5.55 g of 2-mercaptopyridine. To this solution, a methanolic solution containing 3.30 g of 3,4-dihydroxyphenacyl chloride was added and the mixture allowed to stand for 12 hr. The precipitate was collected and washed with water to remove sodium chloride and the remaining

solid recrystallized from methanol. The product, 5.4 g (47%), mp 156–158°, crystallized from methanol as colorless needles (analytical sample, mp 158–159°).

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.75; H, 4.24; N, 5.36. Found: C, 59.67; H, 4.33; N, 5.39.

3-Carboxylthiazolo[3,2-*a*]pyridinium Bromide (XVIII).—Keto sulfide (I, R = H, R′ = 3,4-$(OH)_2C_6H_3$) (1 g) was heated on a steam bath for 9 hr with 10 g of polyphosphoric acid. The mixture which contained XV was diluted with ice water, 20 ml of 8 *M* nitric acid was added, and the solution was heated for 12 hr on a steam bath. After the mixture was cooled, the product was precipitated as the tribromide salt by addition of a solution of bromine in 48% hydrobromic acid. The orange-brown precipitate was collected and dissolved in dry acetone. After 15 min, the bromide precipitated as a cream powder, mp 285° dec, yield 0.55 g (55%). The analytical sample was crystallized from methanol–ethyl acetate: mp 287° dec; λ_{max}, mμ (log ϵ), 311 (4.17), 304 (4.06), and 229 (4.16).

Anal. Calcd for $C_8H_6NSO_2Br$: C, 36.94; H, 2.33; N, 5.39. Found: C, 36.94; H, 2.39; N, 5.46.

2-Carboxylthiazolo[3,2-*a*]pyridinium Bromide (XVII).—The reaction of 5.58 g of 3′,4′-dihydroxyphenacyl chloride with an excess of 2-bromopyridine in 10 ml of tetramethylene sulfone afforded 12.0 g of a light gray powder which was allowed to react in water solution with 2.2 g of potassium hydrogen sulfide. The gummy precipitate solidified when triturated with acetone affording a tan powder, mp 188° dec, yield 4.0 g (40% based on the phenacyl halide). The tan powder (0.5 g) was heated on a steam bath for 13 hr with 10 ml of polyphosphoric acid and, after dilution of the polyphosphoric acid with ice water, the crude XV present was oxidized with 8 *M* nitric acid and the bromide salt of the acid XVII was isolated as in the case of the isomer XVIII. The product was obtained from methanol–ethyl acetate as a buff powder: mp 270–274° (darkens at 200°); yield 0.05 g (4% over-all from the dihydroxyphenacyl chloride); λ_{max}, mμ (log ϵ), 310 (3.86), 277 sh (3.62), 260 sh (3.60), 228 (3.93), and 201 (4.08).

Anal. Calcd for $C_8H_6NSO_2Br$: C, 36.94; H, 2.33; N, 5.39. Found: C, 36.95; H, 2.40; N, 5.63.

pK_a Determinations on Acids XVII and XVIII.—The determination of the pK_a for the 2- and 3-carboxylic acids (XVII and XVIII) was carried out by titrating aqueous solutions of the bromides with standard sodium hydroxide solution and measuring the hydrogen ion concentration with a pH meter. Since only relative pK_a values were required for our purpose, it was assumed that the pK_a was approximately equal to the pH when one-half of the volume of hydroxide needed for complete neutralization had been added. By this method both acids XVII and XVIII were shown to have pK_a values of 2.3 ± 0.2.

Registry No.—I [R = H, R′ = 3,4-$(OH)_2C_6H_3$] 13134-60-6; I (R = H, R′ = *t*-Bu) hydrobromide, 13134-61-7; II (R = H, R′ = *t*-Bu) perchlorate, 13169-24-9: VIIb bromide, 13134-62-8; VIIb perchlorate, 13134-63-9; VIIc bromide, 13127-29-2; VIIc perchlorate, 13134-64-0; VIId bromide, 13134-65-1; VIId perchlorate, 13134-662-; VIIe perchlorate, 13134-67-3; VIIf bromide, 13134-68-4; VIIf perchlorate, 13434-69-5; VIIg bromide, 13221-14-2; VIIg perchlorate, 13434-70-8; IXb, 13134-71-9; IXc, 13134-80-0; IXd, 13134-81-1; IXe, 13134-82-2; IXf, 13134-83-3; IXg, 13134-84-4; XIa, 13134-85-5; XIb, 13134-86-6; XIc, 13127-33-8; XId, 13127-34-9; XIe, 13134-87-7; XIf, 13134-88-8; XIg, 13134-89-9; XVII, 13169-29-4; VXIII, 13134-90-2.

Pyrazines. V. The Amination of Chloropyrazines and Chloropyrazine N-Oxides[1a]

BERNARD KLEIN,[1b] EILEEN O'DONNELL, AND JOSEPH AUERBACH

Laboratory Service, Veterans Administration Hospital, Bronx, New York 10468

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Marked activation of the chloro group to nucleophilic replacement by ammonia and amines by the N-oxide function was demonstrated when the reactivities of chloropyrazine and 3-chloropyrazine-1-oxide were compared. Similarly enhanced activation by the $N^+ \rightarrow O^-$ was observed when 2-chloro-3,6-dimethylpyrazine and 3-chloro-2,5-dimethylpyrazine 1-oxide were compared, although dialkyl substitution further retarded over-all aminolysis. 3-Chloropyrazine 1-oxide heated 2.5 hr (120°) with aqueous ammonia gave a good yield of the 3-amino derivative. However, when the reactants were heated 16 hr at 140°, aminopyrazine and 2,3-diaminopyrazine were formed also. A reaction sequence accounting for these products is suggested. Heating chloropyrazine with benzylamine produced benzaldehyde and aminopyrazine in addition to the expected benzylamino derivative. 2-Benzylamino-3,6-dimethylpyrazine underwent similar cleavage and benzaldehyde and 2-amino-3,6-dimethylpyrazine were isolated.

In connection with another investigation, information was required on the reactivity of chloropyrazine, the alkyl chloropyrazines, and their N-oxides toward ammonia and amines. Aminolysis of chloropyrazine and alkylchloropyrazines has usually been conducted under fairly severe conditions, *e.g.*, heating in a sealed vessel for 16–24 hr or longer at elevated temperatures.[2–7] Arylaminopyrazines have been prepared by boiling the chloro compound with excess amine at temperatures over 200°.[8]

In the previous paper in this series,[9] N-oxide activation was demonstrated in nucleophilic displacement of the chloro group by hydroxyl, although this effect was not as apparent when alkoxide was the reagent. Recent descriptions of the preparation of 3-aminopyrazine 1-oxide[10] and the amination of 3-chloro-2-methylpyrazine 1-oxide[11] suggested similar halogen activation by the N → O since milder conditions were used to effect the amination. This report presents the results of an extended examination of the comparative N-oxide activation and the influence of alkyl heterocyclic ring substitution on the nucleophilic reaction.

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