2-Azacycl[3.2.2]azine. Some Electrophilic Substitutions and Addition Reactions

Omar Fuentes and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

Received June 6, 1975

Electrophilic bromination of 2-azacycl[3.2.2]azine (1), under different conditions, has afforded the 1-bromo (2), 1,4-dibromo (3), and 1,3,4-tribromo (4) derivatives. Bromination of 2-azacycl[3.2.2.]azine-4-carboxaldehyde (5) and 4-carboxylic acid (6) affords, depending upon the reaction conditions, the corresponding 1-bromo derivatives (8, 9) or the 1,4-dibromo (3) or 1,3,4-tribromo (4) compounds. Nitration of this ring system affords the 4-nitro (7) and 1,4-dinitro (10) derivatives. The 1-bromo-4-nitro-2-azacycl[3.2.3]azine (11) is obtained by bromination of the 4-nitro compound (7). Vilsmeier formylation of compound 1 affords the 1- as well as 4-formyl derivatives (12, 5). 2-Azacycl[3.2.2]azine (1) reacts with butyllithium to form the 1-butyl derivative, and with methyl iodide to give the *N*-methyl quaternary salt (14). Explanations to account for the formation of these compounds are given.

We have recently described the synthesis, CNDO/2 calculations, and ^{1}H NMR spectrum of 2-azacycl[3.2.2]azine (1).[1] As an extension of this study, we now wish to describe some of the chemical properties of this new derivative of the aromatic cycl[3.2.2.]azines.

Bromo-2-azacycl[3.2.2.]azines. The reaction of 2-azacycl[3.2.2.]azine (1) with an equimolar amount of *N*-bromosuccinimide (NBS) in the absence of peroxides, affords a monobromo (2) as well as a dibromo (3) derivative. Bromination of the monobromo compound with NBS gives the same dibromo compound. The dibromo derivative 3 becomes the only product when 2 equiv of NBS is employed. When 2-azacycl[3.2.2.]azine (1) is treated with bromine in chloroform, the dibromo derivative 3 becomes the major product, while bromine in acetic acid affords, in addition to compound 3, a small amount of a tribromo-2-azacycl[3.2.2.]azine (4). Further treatment of the dibromo derivative 3 with bromine in acetic acid under mild conditions affords the tribromo derivative 4.

The structure of the monobromo compound is readily established by an examination of its ^{1}H NMR spectrum (see Table I). The absorption of H-1 present in the parent compound (1) is absent in this derivative, while H-7 is more deshielded by 0.20 ppm. The chemical shifts of the remaining protons are essentially identical with those of the parent compound (1). Thus, bromination has afforded the 1-bromo derivative 2 (Scheme I). The structure of the dibromo compound 3 is equally easily determined as the 1,4-dibromo derivative 3 by the absence of absorptions due to H-1 and H-4 in the ^{1}H NMR spectrum. The tribromo derivative is similarly identifiable as the 1,3,4-trisubstituted compound 4 (see Table I).

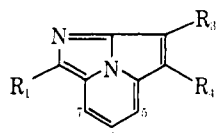
Nitro-2-azacycl[3.2.2]azines. The reaction of compound 1 at 0° with a mixture of nitric and sulfuric acids yields a mononitro derivative (7) whose ^{1}H NMR spectrum is devoid of the AB pattern due to H_3 and H_4 in the starting material while still showing the presence of H-5, H-6, and H-7 along with two singlets at τ 1.15 and 1.65, respectively. Thus, the nitro group is either substituted at C-3 or C-4, and not at C-1 as is the case in the monobromination reaction. If the nitro group is at C-4, the major deshielding effects should be on H-3 and H-5. In fact H-3 is more deshielded by 0.70 ppm and H-5 by 0.76 ppm with respect to the parent compound 1. Consequently we are dealing with the 4-nitro-2-azacycl[3.2.2.]azine (7).

Continued nitration of compound 1 yields a small amount of dinitro derivative 10, identified as the 1,4-disubstituted derivative by its mass spectral fragmentation pattern, which is very similar to that of the 1,4-dibromo compound (3) (vide infra).

The 4-nitro-2-azacycl[3.2.2]azine (7) when brominated with NBS affords a monobromomononitro compound

Table I

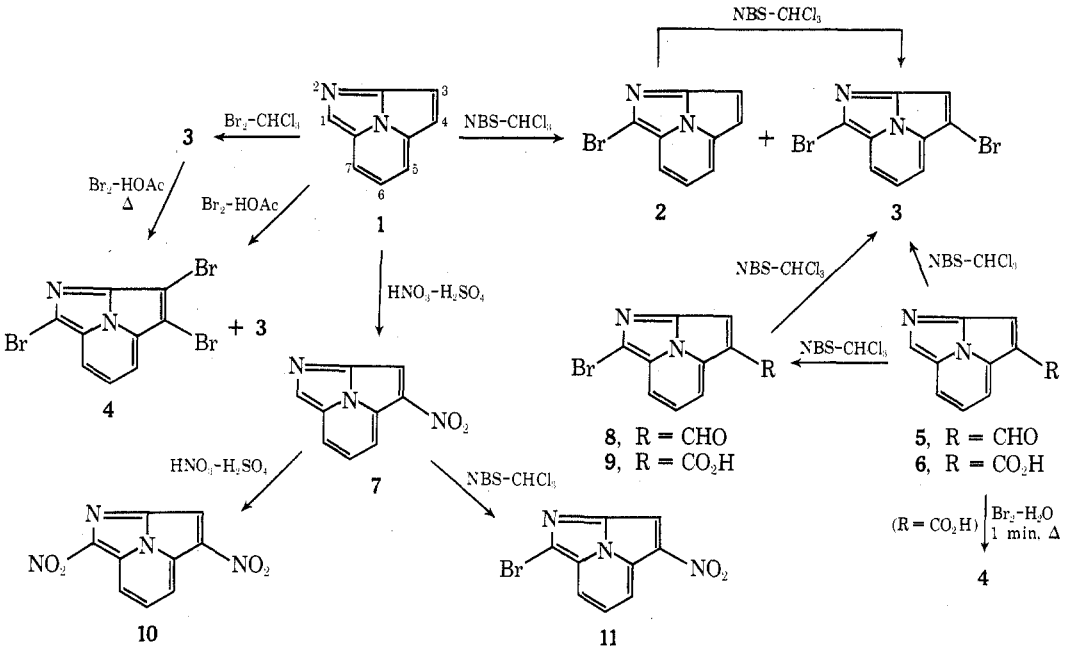
^{1}H NMR Spectral Data of Some 2-Azacycl[3.2.2]azines[a]



Compd[b]	Chemical shifts, τ						Substituents
	H_1	H_3	H_4	H_5	H_6	H_7	
1 ($R_1 = R_3 = R_4 = H$)[c]	1.55	2.35	2.70	2.04	2.49	2.18	
2 ($R_1 = Br$; $R_3 = R_4 = H$)		2.37	2.64	2.02	2.33	1.98	
3 ($R_1 = R_4 = Br$; $R_3 = H$)		2.31		1.89	2.23	1.97	
4 ($R_1 = R_3 = R_4 = Br$)				1.91	2.22	1.99	
5 ($R_4 = CHO$; $R_1 = R_3 = H$)	1.28	1.86		1.45	2.02	1.74	−0.26 (R_4)
7 ($R_4 = NO_2$; $R_1 = R_3 = H$)	1.15	1.65		1.28	1.86	1.66	
8 ($R_4 = CHO$; $R_1 = Br$; $R_3 = H$)		2.02		1.57	2.10	1.94	−0.21 (R_4)
11 ($R_1 = Br$; $R_4 = NO_2$; $R_3 = H$)		1.73		1.25	1.78	1.73	
13 ($R_1 = n$-C_4H_9; $R_3 = R_4 = H$)		2.33	2.65	1.88	2.32	2.00	0.65 (t), 9.2–7.6 (m) (R_1)
12 ($R_1 = CHO$; $R_3 = R_4 = H$)		2.24	2.42	1.45	2.06	1.45	−0.37 (R_1)

[a] Dilute solutions in $CDCl_3$. [b] $J_{14} = 1.0$; $J_{34} = 4.7$; $J_{56} = 7.8$–8.0; $J_{67} = 7.0$–7.5 Hz. [c] Taken from ref 1. In this reference, chemical shifts are given in τ and not as parts per million as printed. The Table heading ^{3}H should read ^{1}H NMR.

Scheme I



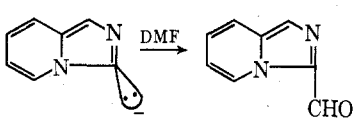
whose structure (11) (Scheme I) is readily deduced by a comparison of its ^1H NMR spectrum with that of **7**.

Bromination of 2-Azacycl[3.2.2]azine-4-carboxaldehyde (5) and -carboxylic Acid (6). Bromination of compound **5** with NBS in chloroform yields a monobromo derivative whose structure is established as 1-bromo-2-azacycl[3.2.2.]azine-4-carboxaldehyde (**8**) by its ^1H NMR and mass spectra. This compound upon continued bromination is converted to the 1,4-dibromo derivative **3**, presumable via oxidation of the carboxaldehyde to the carboxylic acid, followed by decarboxylation and bromination at C-4.

Bromination of the carboxylic acid **6** affords the 1,4-dibromo compound **3** and only traces of 1-bromo-2-azacycl[3.2.2.]azine-4-carboxylic acid (**9**) and its ethyl ester. The carboxylic acid **6**, when treated with bromine water, yields the tribromo derivative **4** as the major product.

Formylation of 2-Azacycl[3.2.2.]azine. The treatment of the parent compound **1** under Vilsmeier formylation conditions affords two monoformyl derivatives $C_{10}H_6N_2O$ (**12** and **5**) in essentially equal amounts (Scheme II). One of these monoformyl derivatives (**5**) was identified as the 4-substituted compound by comparison with an authentic sample.[1] The other compound was shown to be the 1-formyl derivative **12** by an analysis of its ^1H NMR spectrum (see Table I).

Alkylation of 2-Azacycl[3.2.2.]azine. Earlier work[2,3] has shown that formylation of polyazaindenes and related compounds can be effected by initial formation of carbanions such as **15**, generated by means of butyllithium, followed by treatment with dimethylformamide (DMF).

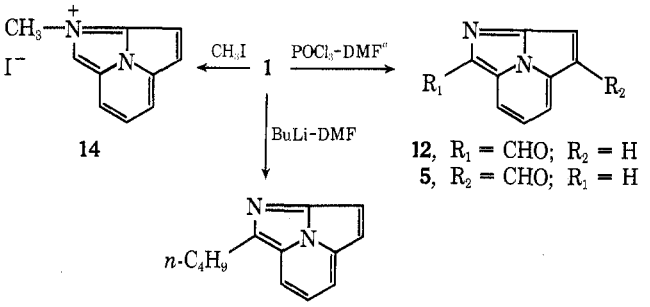


15 16

When this reaction was attempted on the cyclazine **1**, a compound corresponding to a monobutyl derivative was obtained rather than the expected formyl compound. The structure of this material was established as the 1-*n*-butyl compound by comparison with an authentic sample.[6]

We have already shown that protonation of compound **1** occurs on the peripheral nitrogen atom. When the azacyclazine **1** is treated with methyl iodide, a monomethyl derivative is obtained whose ^1H NMR spectrum is essentially identical with that of the protonated species. Thus, not surprisingly, methylation has occurred on the peripheral nitrogen to form the quaternary salt **14**.

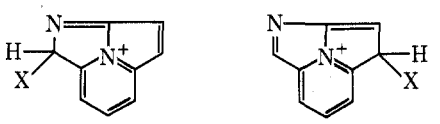
Scheme II



14 13

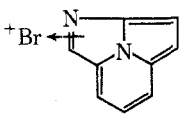
Discussion

If one assumes that the stabilities of the intermediates in the electrophilic substitutions are similar to those of the transition states involved, one finds that structures **17**, and **18** are stabilized by the presence of a central pyridinium

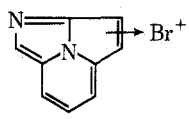


17 18

ring. Thus, one would predict that electrophilic substitution should preferentially occur at positions 1 and 4. The stabilities of intermediates **17** and **18** should be essentially the same. A comparison of these predictions with the results of the bromination reactions seems, at first glance, to contradict them. However, if one considers that the first step in the bromination reactions involves the formation of a π complex, it becomes necessary to compare the stabilities of structures **19** and **20**. Clearly, because of the π-electron densities at the C_1–N_2 bond vs. the C_3–C_4 bond,[1] the π complex **19** would be more stable than **20**. Thus, we can readily account for the preferential bromination at C_1 followed by introduction of the second bromine at C-4.

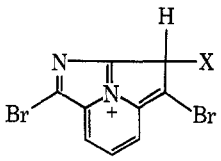


19



20

The introduction of the third bromine at C-3 can be rationalized in terms of the intermediate **21**. This intermedi-

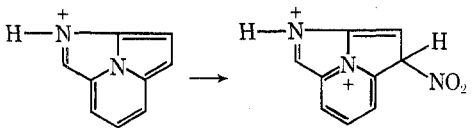


21

ate certainly would be less stable than the pyridinium ring containing ones **17** and **18**. Thus, the sequential order of the brominations is readily accounted for.

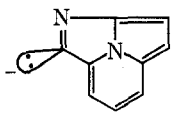
The suggested intermediacy of the π complexes **19** and **20** finds support in the observation that the Vilsmeier formylation affords the two monoformyl derivatives **12** and **5** rather than the monoformyl compound **12** and a 1,4-diformyl compound. It is of interest to note that 1,4-diacetylation occurs in cycl[3.2.2.]azine.[4]

The selective formation of the 4-nitro derivative **7** can be rationalized on the basis that under the highly acidic reaction conditions, nitration occurs on the protonated compound **22** via the intermediate **23**.



22 23

Since the reaction of butyllithium in dimethylformamide did not afford the expected formyl derivative, and when the reaction was quenched with D_2O, no deuterium was incorporated, one must conclude that anion **24** is not generat-



24

ed by butyllithium. Consequently, the *n*-butyl derivative is probably formed by a simple 1,2-addition reaction followed by oxidation of the resulting dihydro compound in a manner typical of many heterocyclic ring systems.[5]

Experimental Section

General. All melting points are uncorrected. ^{1}H NMR spectra were obtained on a Varian Associates HA-100 with Me_4Si internal standard. Mass spectra were measured with a Hitachi Perkin-Elmer RMU-6M at 80 eV. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Ga., and by the Analytical Services Division, Chemistry Department, The University of Alabama.

Bromination of 2-Azacycl[3.2.2]azine (1) with *N*-Bromosuccinimide (NBS). A. With 1 Equiv of *N*-Bromosuccinimide. To a solution of **1** (160 mg, 1.12 mmol) in 10 ml of $CHCl_3$ was added, in portions, solid NBS (214 mg, 1.2 mmol) and the reaction mixture was stirred at room temperature for 3 hr. The solvent was evaporated in vacuo and the solid residue was chromatographed on neutral Al_2O_3 (grade III), using *n*-hexane as eluent. The first fraction afforded 45 mg (13.6%) of compound **3**. The second fraction afforded 60 mg (24.1%) of compound **2** and the third fraction 90 mg (56.3%) of compound **1**. The analytical sample of **2** was prepared by sublimation (60°, 0.02 Torr): mp 72–73°; ^{1}H NMR (see Table I); mass spectrum *m/e* 222 (M^+ + 2), 220 (M^+), 141 (M^+ − 79). Anal. Calcd for $C_9H_5N_2Br$: C, 48.86; H, 2.28; N, 12.67; Br, 36.19. Found: C, 48.77; H, 2.30; N, 12.62; Br, 36.25.

B. With 2 Equiv of *N*-Bromosuccinimide: To a solution of **1** (142 mg, 1 mmol) in 10 ml of $CHCl_3$ was added solid NBS (400 mg, 2.25 mmol) and the mixture was stirred at room temperature[7] for 1 hr. The solution was filtered and the filtrate evaporated to dryness. Recrystallization of the resulting solid from ethanol–water afforded **3** as yellow crystals (280 mg, 93%): mp 121–122°; ^{1}H NMR (see Table I); mass spectrum *m/e* 302 (M^+ + 4), 300 (M^+ + 2), 298 (M^+), 219 (M^+ − 79), 140 (M^+ − 2 × 79). Anal. Calcd for $C_9H_4N_2Br_2$: C, 36.00; H, 1.33; N, 9.33; Br, 53.33. Found: C, 35.87; H, 1.34; N, 9.34; Br, 53.42.

C. With Bromine in Chloroform. To **1** (142 mg, 1 mmol) dissolved in 10 ml of $CHCl_3$ was added Br_2 (170 mg, 1.06 mmol) and the mixture was stirred at room temperature for 15 min. The reaction mixture was poured into 20 ml of water and made basic with solid Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was removed under vacuum. Recrystallization of the solid from ethanol–water gave 282 mg (94%) of 1,4-dibromo derivative **3**.

D. With Bromine in Acetic Acid. To **1** (100 mg, 0.701 mmol) dissolved in 10 ml of glacial acetic acid, Br_2 (200 mg, 1.15 mmol) was added dropwise and the reaction mixture was stirred for 15 min. The solution was diluted with H_2O, made basic with solid Na_2CO_3, and extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was chromatographed on neutral Al_2O_3 (grade III) and eluted with *n*-hexane. Compound **3** was obtained as the major product[8] (200 mg, 75%).

Nitration of 2-Azacycl[3.2.2]azine (1). To a cold solution (0°) of 1.1 ml of concentrated H_2SO_4 and 0.45 ml of concentrated HNO_3 was added **1** (180 mg, 1.27 mmol) and the mixture was allowed to warm to room temperature with stirring. After 1 hr the mixture was poured into ice–water. The abundant yellow precipitate which formed was separated by filtration, treated with an aqueous Na_2CO_3 solution, and extracted with $CHCl_3$ (2 × 100 ml). The filtrate was also made basic with Na_2CO_3 and extracted with $CHCl_3$ (100 ml). The two $CHCl_3$ extracts were combined and dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was recrystallized from 95% ethanol to afford **7** as burnt-yellow crystals (170 mg, 72%): mp 200–201; ^{1}H NMR (see Table I); mass spectrum *m/e* 189 (M^+), 157 (M^+ − 30), 141 (M^+ − 46). Anal. Calcd for $C_9H_5N_2O_2$: C, 57.75; H, 2.67; N, 22.46. Found: C, 57.57; H, 2.78; N, 22.35. A dinitro compound (**10**, 15 mg, 5.1%) was also formed when the reaction mixture was stirred for more than 5 hr: mp 225–226°; mass spectrum *m/e* 232 (M^+), 202 (M^+ − 30), 186 (M^+ − 46), 174 (M^+ − 58), 140 (M^+ − 90). Anal. Calcd for $C_9H_4N_4O_4$: C, 46.55; H, 1.72; N, 24.13. Found: C, 46.48; H, 1.79; N, 24.46.

1-Bromo-4-nitro-2-azacycl[3.2.2]azine (11). To a solution of **7** (33 mg, 0.178 mmol) in 10 ml of $CHCl_3$ was added solid NBS (63.0 mg, 0.356 mmol) and the mixture was refluxed for 3 days. The solution was evaporated to dryness, and the residue was recrystallized from 95% ethanol. Purification by sublimation gave a burnt-yellow solid (34 mg, 81%): mp 237–238°; ^{1}H NMR (see Table I); mass spectrum *m/e* 267 (M^+ + 2), 265 (M^+), 235 (M^+ − 30), 219 (M^+ − 46), 140 (M^+ − 46 − 79). Anal. Calcd for $C_9H_4H_3O_2Br$: C, 40.60; H, 1.50; N, 15.78; Br 30.00. Found: C, 40.85; H, 1.65; N, 15.68; Br, 30.14.

1,3,4-Tribromo-2-azacycl[3.2.2]azine (4) from Compound 3. To compound **3** (80 mg, 0.267 mmol) dissolved in 10 ml of acetic acid was added Br_2 (100 mg, 0.556 mmol) and the mixture was stirred at room temperature for 10 min and then heated on a steam bath for 5 min. After cooling, the mixture was treated with aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 100 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated in vacuo. The residue was recrystallized from methanol–benzene to give **4** as a yellow solid (86 mg, 85%): mp 199–200°; ^{1}H NMR (see Table I); mass spectrum *m/e* 382 (M^+ + 6), 380 (M^+ + 4), 378 (M^+ + 2), 376 (M^+), 297 (M^+ − 79), 218 (M^+ − 2 × 79), 139 (M^+ − 3 × 79). Anal. Calcd for $C_9H_3N_2Br_3$: C, 28.49; H, 0.79; N, 7.38. Found: C, 28.53; H, 0.81; N, 7.44.

Bromination of Compound 5. To a solution of **5** (20 mg, 0.116 mmol) in 10 ml of $CHCl_3$ was added solid NBS (50 mg, 0.281 mmol) and the reaction mixture was stirred for 36 hr. The solvent was evaporated under vacuum and the residue was chromatographed on neutral Al_2O_3 (grade III) and eluted with *n*-hexane. The first fraction afforded compound **3** (20 mg, 59%). The second fraction gave a mixture of 1-bromo-2-azacycl[3.2.2]azine-4-carboxylic acid (**9**) and its ethyl ester[9] (3 mg) as evidenced by their mass spectra: *m/e* 266 (M^+ + 2), 264 (M^+), 247 (M^+ − 17, 219 (M^+ −

45) and 294 ($M^+ + 2$), 292 (M^+), 247 ($M^+ - 45$), 219 ($M^+ - 73$), respectively.

In another separate experiment, when the reaction was run for a short period of time, the intermediate **8** was detected by ^1H NMR and mass spectrometry: ^1H NMR (see Table I); mass spectrum *m/e* 250 ($M^+ + 2$), 249 ($M^+ + 1$), 248 (M^+), 247 ($M^+ - 1$), 219 ($M^+ - 29$), 140 ($M^+ - 108$).

Bromination of Compound 6. A. With NBS in $CHCl_3$. To a solution of NBS (93 mg, 0.523 mmol) in 15 ml of $CHCl_3$, compound **6** was added in portions (50 mg, 0.269 mmol) and the mixture was stirred for 2 hr. The solution was filtered and evaporated to dryness in vacuo. Column chromatography on neutral Al_2O_3 (grade III) using *n*-hexane as the eluent gave 50 mg (62%) of compound **3**.

B. With Br_2–Water. To a solution of **6** (50 mg, 0.269 mmol) in 40 ml of H_2O, Br_2 (87 mg, 0.541 mmol) was added and the mixture was stirred at room temperature for 10 min and then heated on a steam bath for 1 min. The solution was made basic with Na_2CO_3 and extracted with $CHCl_3$ (2 × 50 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was evaporated under reduced pressure. The crude product was purified by sublimation (160°, 0.2 Torr) to give **4** (82.0 mg, 80%).[10]

Formylation of 2-Azacycl[3.2.2]azine (1). A. With $POCl_3$ and DMF. To **1** (71 mg, 0.5 mmol) dissolved in 10 ml of dry DMF was added Vilsmeier reagent (0.17 g of $POCl_3$ in 1 ml of DMF) and the mixture was stirred at room temperature for 1 hr. The solution was treated with 20 ml of cold H_2O and made basic with solid Na_2CO_3. The solvent and excess DMF were removed in vacuo to give a dark solid which was chromatographed on neutral Al_2O_3 (grade III) by using *n*-hexane–chloroform (90:10) as eluent. The first fraction gave 18 mg of starting material. The second fraction afforded 1-formyl-2-azacycl[3.2.2]azine (**12**), a yellow solid: 30 mg (37.6%); mp 100–101°; ^1H NMR (see Table I); mass spectrum *m/e* 170 (M^+), 169 ($M^+ - 1$), 142 ($M^+ - 28$), 141 ($M^+ - 29$), 115 ($M^+ - 55$), 114 ($M^+ - 56$). Anal. Calcd for $C_{10}H_6N_2O$: C, 20.58; H, 3.52; N, 16.47; Found: C, 70.55, H, 3.46, N, 15.49.

The third fraction gave 4-formyl-2-azacycl[3.2.2]azine (**5**, 20 mg, 25%) as compared with an authentic sample.[1]

B. With *n*-C_4H_9Li and DMF. To a solution of 2-azacycl[3.2.2]-azine (**1**,70 mg, 0.49 mmol) in 15 ml of dry THF was added 0.245 ml of 2 *M* *n*-BuLi (in hexane) under a N_2 atmosphere and at 0°C. Dry DMF (36.0 mg, 0.49 mmol) was then added at once and the mixture was stirred for 1 hr, during which time the solution warmed to room temperature. The reaction mixture was treated with H_2O (20 ml) and extracted with $CHCl_3$ (2 × 50 ml). The combined $CHCl_3$ extracts were dried over anhydrous Na_2CO_3 and the solvent was removed under reduced pressure. The residue was chromatographed on neutral Al_2O_3 (grade III), using *n*-hexane as eluent. The first fraction afforded 1-butyl-2-azacycl[3.2.2]azine (**13**, 50 mg, 55%) as a pale fluorescing yellow liquid, identified by comparison with an authentic sample.[6] The second fraction gave starting material.

***N*-Methyl-2-azacycl[3.2.2]azinium Iodide (14).** A mixture of 2-azacycl[3.2.2]azine (**1**, 20 mg, 0.141 mmol) and methyl iodide (1 ml) was heated in a sealed tube on a steam bath for 15 min. The yellow solid was washed with anhydrous ethyl ether and collected by filtration. Recrystallization of the solid from ethanol gave 38 mg (95%) of burnt-yellow crystals: mp 158–159°; ^1H NMR [$(CD_3)_2SO$] δ 9.36 (s, 1 H), 8.18 (d, 1 H, J = 4.5 Hz), 8.30 (d, 1 H, J = 4.5 Hz), 8.98 (d, 1 H, J = 8.0 Hz), 8.36 (t, 3 H, J = 7.5 Hz), 8.75 (d, 1 H, J = 7.5 Hz), 4.68 (s, CH_3^-); mass spectrum *m/e* 142 ($M^+ - CH_3I$), 127 (Br^+), 115 ($M^+ - CH_3I - 27$). Anal. Calcd for $C_{10}H_9N_2I$: C, 42.24; H, 3.17, N, 9.86. Found: C, 42.13; H, 3.17; N, 9.85.

Registry No.—**1**, 54384-90-6; **2**, 56363-23-6; **3**, 56363-24-7; **4**, 56363-25-8; **5**, 54446-41-2; **6**, 54384-89-3; **7**, 56363-26-9; **8**, 56363-27-0; **9**, 56363-28-1; **9** Et ester, 56363-29-2; **10**, 56363-30-5; **11**, 56363-31-6; **12**, 56363-32-7; **13**, 56363-33-8; **14**, 56363-34-9; NBS, 128-08-5; bromine, 7726-95-6; HNO_3, 7697-37-2; $POCl_3$, 10025-87-3; DMF, 68-12-2; *n*-C_4H_9Li, 109-72-8; methyl iodide, 74-88-4.

References and Notes

(1) O. Fuentes and W. W. Paudler, *J. Org. Chem.*, **40**, 1210 (1975).
(2) W. W. Paudler and H. G. Shin, *J. Org. Chem.*, **33**, 1638 (1968); O. Fuentes, *J. Heterocycl. Chem.*, **12**, 379 (1975).
(3) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).
(4) V. Boekelheide and R. J. Windgassen, *J. Am. Chem. Soc.*, **81**, 1459 (1959).
(5) R. A. Abramovitch and B. Vig, *Can. J. Chem.*, **41**, 1961 (1963), and earlier papers.
(6) O. Fuentes and W. W. Paudler, *J. Heterocycl. Chem.*, in press.
(7) The same product is obtained under reflux conditions.
(8) Some traces of the tribromo compound **4** were also detected.
(9) The ethyl ester is believed to be formed by an esterification reaction of the carboxylic acid and the ethanol used as stabilizing agent for $CHCl_3$.
(10) Some traces of a tetrabromo compound are formed.

Bromination Reactions of 1,5- and 1,8-Naphthyridine 1-Oxides

Richard A. VanDahm and William W. Paudler*

Department of Chemistry, The University of Alabama, University, Alabama 35486

Received May 27, 1975

The reactions of 1,5- and 1,8-naphthyridine 1-oxides with acetic anhydride in the presence of bromine have been studied in detail. The compounds formed, depending upon the reaction conditions, are the 3-bromo-, 3,6-dibromo-, and 3,7-dibromo-1,5-naphthyridines and their *N*-oxides (**2, 3, 8, 2a, 3a,** and **8a**) as well as some 7-bromo-1,5-naphthyridine 1-oxide (**7**). The 3-bromo-, 3,6-dibromo-, and their *N*-oxides (**10, 11, 10a, 11a**) are obtained from 1,8-naphthyridine 1-oxide. Along with these compounds the 1,2-dihydro-2-oxonaphthyridines as well as their 3-bromo derivatives (**4, 6, 12, 13**) along with 1,5-naphthyridine are generated. Possible mechanisms for the formation of these various reaction products are discussed.

The reaction of pyridine and quinoline *N*-oxides with bromine in the presence of acetic anhydride has been reported to afford bromo derivatives resulting from substitution at positions expected to be subject to electrophilic attack. For example, quinoline *N*-oxide is reported to yield the 3,6-dibromoquinoline *N*-oxide.[1] We thought it of some interest to examine the behavior of some 1,X-naphthyridine 1-oxides under these reaction conditions and now wish to describe the results of these studies.

Results and Discussion

1,5-Naphthyridine 1-Oxide. A. Experimental Results. The reaction of 1,5-naphthyridine 1-oxide with bromine, in chloroform, and in the presence of acetic anhydride affords at least six different products. The mass spectrometrically determined molecular weights in conjunction with elemental analyses identify the compounds as a monobromo- and a dibromo-1,5-naphthyridine, a monobromo- and a dibromo-1,5-naphthyridine 1-oxide, 1,2-dihydro-2-oxo-1,5-naphthyridine, as well as its 3-bromo derivative. In addition, traces of 1,5-naphthyridine (**5**) are occasionally obtained.

The monobromo-1,5-naphthyridine is identified as the 3-bromo derivative **2** by a comparison with an authentic sample.[2] The ^1H NMR spectrum of the monobromo *N*-oxide identifies it as the 3-bromo derivative **2a**. The other