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 [$(CD_3)_2SO$] $\delta$ 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*


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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.

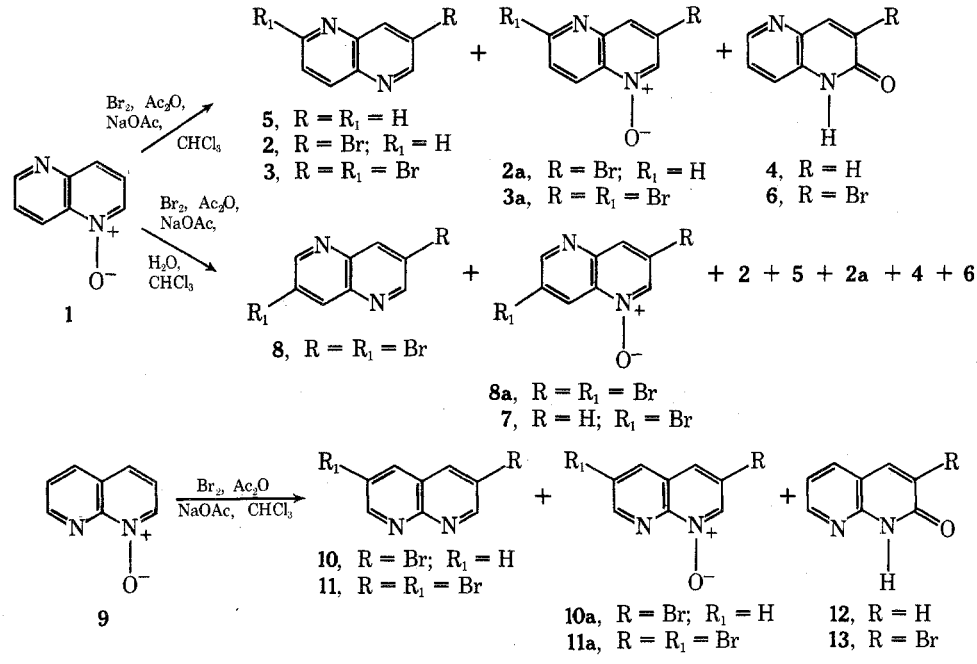

The reaction of pyridine and quinoline *N*-oxides with bromine in the presence of acetic anhydride has been reported to afford bromo derivatives resulting from substitution at positions expected to be subject to electrophilic attack. For example, quinoline *N*-oxide is reported to yield the 3,6-dibromoquinoline *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

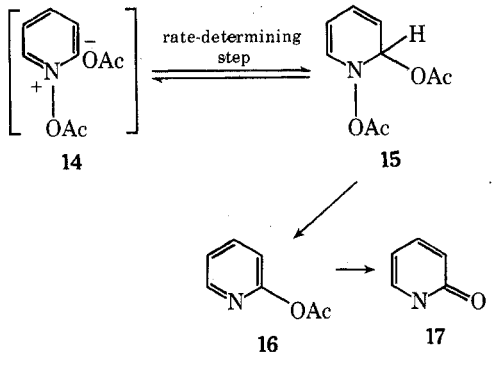
**Scheme I**




three bromine-containing products are the 3,6-dibromo-1,5-naphthyridine (**3**), its 1-oxide (**3a**), and the 3-bromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**6**), as shown by their $^1$H NMR spectra. In order to gain an understanding of this reaction variations in reaction conditions on product distributions were examined (see Table I).

In the presence of either small amounts of water (expt 4 and 5, Table I) or when 1,5-naphthyridine *N*-oxide is treated with a mixture of bromine, aqueous hydrobromic acid, and acetic acid, there are changes in some of the types of compounds formed in comparison to the "original" reaction conditions (expt 1, Table I).

**B. Formation of Brominated *N*-Oxides.** The mechanism of the reaction of pyridine *N*-oxide with acetic anhydride to yield 2-pyridone is well established.[3]




Since the reaction of 1,5-naphthyridine 1-oxide (**1**), under similar conditions, yields 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**), we suggest that the first step in the bromination involves formation of the ion pair, **18**, which slowly collapses to the 1,2-dihydro compound, **19**. The latter can react with bromine to give intermediate **20**, which may decay by two different paths. It may lose acetic acid to form the ion pair **21** or lose a hydrogen to form the dihydro compound, **22**. Structures **21** and **22** are most likely in equilibrium with one another, as are structures **18** and **19**. The ion pair **21** yields 3-bromo-1,5-naphthyridine 1-oxide (**2a**) and compound **22** affords 3-bromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**6**) upon work-up with base (see Scheme II). While structure **21** can lead only to product, compound **22** can react with another molecule of bromine to give intermediate **23**, which may give either the ion pair **24** or the dihydro compound **25**. Compound **24** will yield 3,6-dibromo-1,5-naphthyridine 1-oxide (**3a**) and compound **22** will afford 3,6-dibromo-1,2-dihydro-2-oxo-1,5-naphthyridine (**23**) during work-up with base. The latter is more than likely present in trace amounts (see Scheme III).

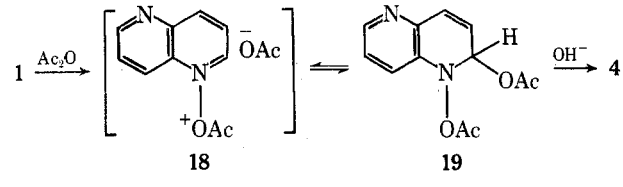
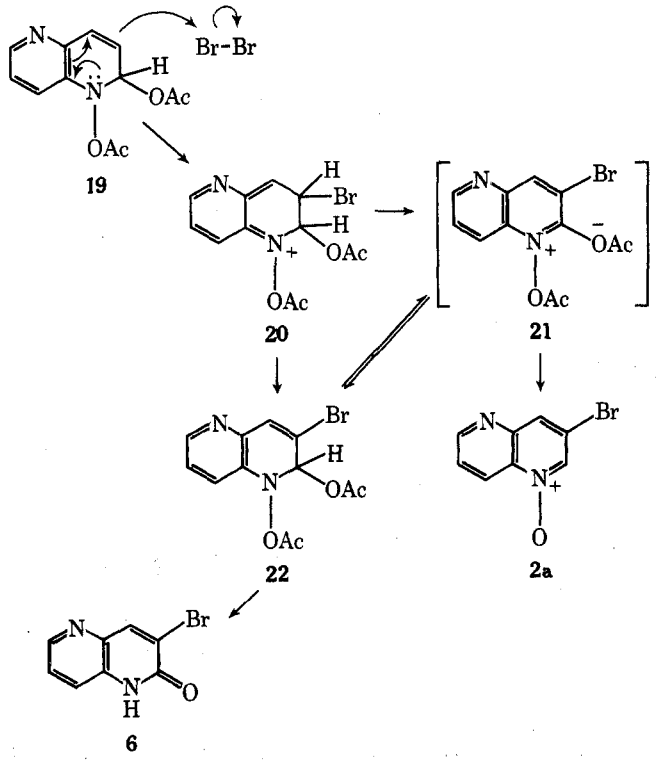



**Table I**
**Products and Percentage Yields for Various Bromination[a] Reactions of 1,5- and 1,8-Naphthyridine 1-Oxides**

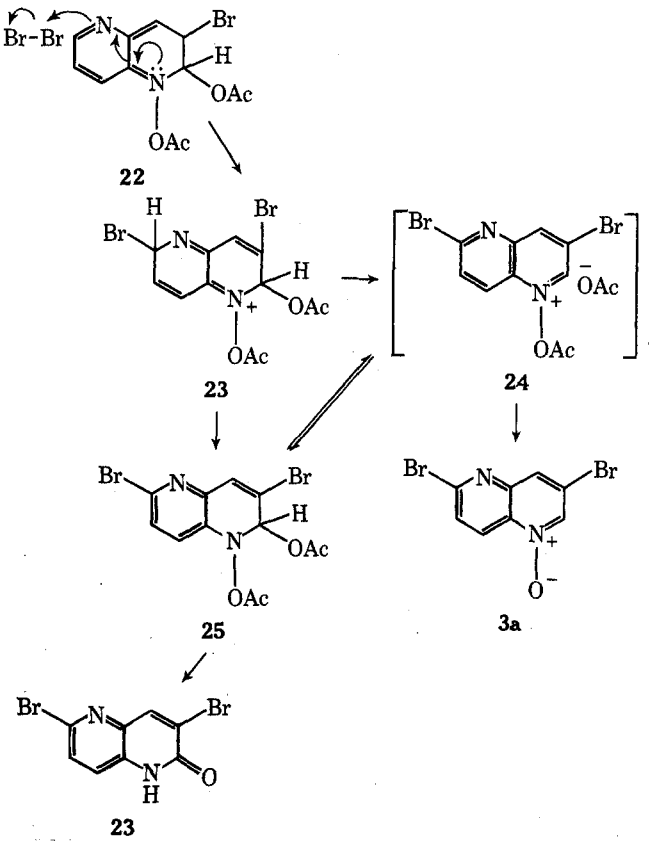
| | Compd | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Expt | 3 | 8 | 11 | 2 | 10 | 5 | 3a | 8a | 11a | 2a | 7 | 10a | 1 | 6 | 13 | 4 | 12 |
| 1 | 2.1 | | | 2.8 | | | 3.6 | | | 5.5 | | | | 6.2 | | 61.0 | |
| 2 | 1.9 | | | 21.3 | | 12.4 | 4.4 | | | 10.5 | | | | 4.7 | | 36.0 | |
| 3 | 1.0 | | | 3.8 | | 1.8 | 4.1 | | | 41.5 | | | | 3.9 | | 33.8 | |
| 4 | | 1.6 | | 4.2 | | 2.7 | | 1.0 | | 2.3 | 1.8 | | 10.4 | 10.0 | | 55.0 | |
| 5 | | 1.0 | | 2.9 | | 3.5 | | | | | 7.1 | | 61.1 | | | | |
| 6 | | | 6.6 | | 12.6 | | | | 14.8 | | | 4.1 | | | 8.4 | | 51.1 |
| 7 | | | | | | | | | 7.9 | | | 39.0 | | | 4.7 | | 37.2 |

[a] Compounds obtained in less than 1.0% yield are not described.

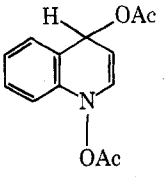
**Scheme II**



**Scheme III**



In the case of quinoline *N*-oxide the reaction is said to proceed via the 1,4-dihydro intermediate **26**.[1,4] However, since the reaction of 1,5-naphthyridine 1-oxide (**1**) with acetic anhydride yields exclusively 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**), there is no justification for invoking a 1,4-dihydro intermediate in the present instance.



**26**

**C. Formation of Deoxygenated Products.** The formation of compounds **2** and **3** were initially thought to result from nucleophilic attack of bromide ion at the 3 position, with concomitant loss of acetate ion at the 1 position, followed by elimination of acetic acid. Abramovitch and coworkers[5] have noted that pyridine *N*-oxides react with imi-

**Table II**
**$^1$H NMR Parameters and Melting Points of Some 1,5- and 1,8-Naphthyridine Derivatives[a]**

| Compd (no., mp, °C) | Chemical shifts, δ, ppm | | | | | | | Coupling constants, Hz | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_6$ | $H_7$ | $H_8$ | $J_{23}$ | $J_{24}$ | $J_{34}$ | $J_{56}$ | $J_{57}$ | $J_{58}$ | $J_{67}$ | $J_{68}$ | $J_{78}$ |
| **1,5-Naphthyridines** | | | | | | | | | | | | | | | | |
| 3-Bromo 1-oxide (**2a**, 174–175°) | 8.54 | | 8.08 | | 8.93 | 7.57 | 8.86 | | 1.5 | | | | | 4.0 | 1.5 | 9.0 |
| 3,6-Dibromo 1-oxide (**3a**, 175–176.5°) | 8.56 | | 8.02 | | | 7.74 | 8.68 | | 1.5 | | | | | | | 8.8 |
| 3,6-Dibromo (**3**, 192–193°) | 8.98 | | 8.49 | | | 7.73 | 8.21 | | 1.8 | | | | | | | 9.0 |
| 3,7-Dibromo 1-oxide (**8a**, 207–208°) | 8.60 | | 8.10 | | 9.02 | | 8.97 | | 1.8 | | | | | | 2.0 | |
| 7-Bromo 1-oxide (**7**, 161–163°) | 8.49 | 7.50 | 7.93 | | 9.16 | | 8.97 | 6.0 | 1.5 | 9.0 | | | | | 2.0 | |
| **1,8-Naphthyridines** | | | | | | | | | | | | | | | | |
| 3-Bromo 1-oxide (**10a**, 174–176°) | 8.77 | | 7.81 | 8.21 | 7.64 | 9.02 | | | 2.0 | | | 1.8 | | 5.0 | | |
| 3,6-Dibromo 1-oxide (**11a**, 273–275°)[b] | 9.39 | | 8.83 | 8.91 | | 9.29 | | | 2.0 | | 7.8 | 1.8 | | | | |
| 3-Bromo-1,2-dihydro-2-oxo (**13**, 304–306°)[b] | | | 8.09 | 8.01 | 7.25 | 8.38 | | | | | | 2.0 | | 5.8 | | |

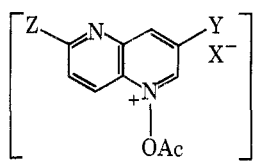
[a] Unless otherwise stated, spectra are in dilute solutions of $CDCl_3$; all compounds gave correct elemental analyses and mass spectral molecular weights. Compounds **3a** and **11a** were purified by recrystallization from methanol, compound **13** from water. The remaining compounds were purified by vacuum sublimation. [b] Deuterotrifluoroacetic acid solution.

doyl chlorides to form, among other products, 3-chloropyridines via nucleophilic attack of chloride ion at C-3.

When 1,5-naphthyridine 1-oxide (1) is heated with acetic anhydride either in the presence or absence of NaCl or LiCl, the naphthyridone 4 is the only product. When NaBr or LiBr are used, mixtures of the naphthyridone 4 and 1,5-naphthyridine (5) are obtained.

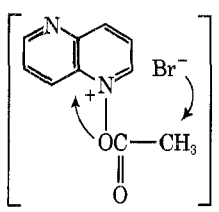
On the other hand, addition of either HI or HBr to a mixture of 1 in acetic anhydride yields only 1,5-naphthyridine (5). When either compounds **1, 2a,** or **3a** are heated with acetyl bromide alone, deoxygenation was the only reaction taking place. Acetyl chloride has no effect upon compounds **1, 2a,** or **3a.**

Since bromine reacts with the ethanol preservative present in commercial chloroform to form hydrogen bromide, an excess of bromide ion is also present in the initial experiment. When the reaction is carried out in ethanol-free chloroform and without added bromide ion, a marked decrease in the ratio of deoxygenated to N-oxidized products is observed (see Table I). These various observations can be accounted for by invoking the initial formation of an ion pair such as **27, 28,** or **29.** When X is an acetate ion,



**27**, Y = Z = H
**28**, Y = Br; Z = H
**29**, Y = Z = Br

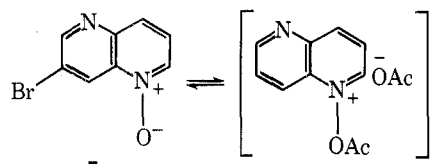
1,2-dihydro-2-oxo-1,5-naphthyridine (4) is ultimately formed. A chloride ion in the ion pair (X = Cl) inhibits this reaction and the 1,5-naphthyridine 1-oxide is recovered. On the other hand, when $X^-$ is a bromide or iodide ion, deoxygenation takes place.



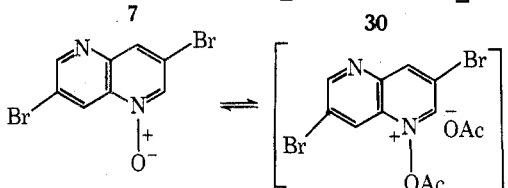
A similar nucleophilic attack has been proposed for one of the paths by which *N*-methoxypyridinium ion reacts with nucleophiles.[6] It has been shown that reaction by this path diminished with decreasing nucleophilicity of the attacking species. Since bromide and iodide ions are certainly better nucleophiles than chloride ion, this may explain the absence of deoxygenated products in the presence of the latter ion in the 1,5-naphthyridine 1-oxide reactions.

**D. Formation of 7-Brominated Products.** As mentioned earlier, the presence of water changes the site of substitution in the nonoxidized ring. This change is perhaps best explained by an examination of the results of expt 4 and 5. When 1,5-naphthyridine 1-oxide (1) is refluxed with acetic anhydride in chloroform for 12 hr, treated with water and a catalytic amount of HCl, and further refluxed for an additional 12 hr, starting material was quantitatively recovered. Therefore, under these conditions, intermediates **18** and **19** appear to revert back to 1,5-naphthyridine 1-oxide (1). When 3-bromo-1,5-naphthyridine 1-oxide (**2a**) is subjected to the same conditions, it is also recovered unchanged.

In light of these results we suggest the following explanation. On refluxing with acetic anhydride, structures **18** and **19** are formed. The simultaneous addition of bromine and water results in reaction of **19** by two different paths. Compound **19** may either revert back to the ion pair **18** or be brominated to form intermediate **20.** If collapse of **20** to **22** is slow, the conversion of **20** to **21** and subsequently to **2a** would predominate. This would explain the absence of any 3,6-dibrominated products. The acetic acid, hydrogen bromide, and bromine, a mixture known to be a more powerful brominating agent than bromine itself, will electrophilically brominate 1 and **2a** at C-7 to form 7-bromo-1,5-naphthyridine 1-oxide (**7a**) and 3,7-dibromo-1,5-naphthyridine 1-oxide (**8a**). In fact, when 1,5-naphthyridine 1-oxide (1) is treated with bromine and pyridine in chloroform, compound **7a** is obtained, albeit in low yield, as the sole product.[7] When 1,5-naphthyridine 1-oxide is treated with bromine and aqueous hydrogen bromide in acetic acid, the only products isolated are polybrominated ones. Since compounds **1** and **2a** are in equilibrium with ion pairs **18** and **21,** it is reasonable to suggest that a similar equilibrium exists between compounds **7** and **30** and compounds **8a** and **31,** and that deoxygenation occurs through these intermediates.

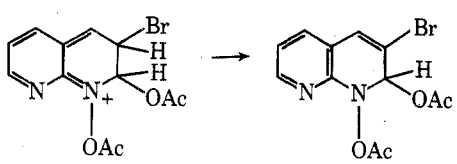


**7** **30**



**8a** **31**

**1,8-Naphthyridine 1-Oxide.** Bromination of 1,8-naphthyridine 1-oxide (**9**) with bromine in chloroform in the presence of acetic anhydride follows essentially the same paths as those for 1,5-naphthyridine 1-oxide (1). A few differences in product ratios do, however, merit comment. It is interesting to note that the ratio of monobrominated to dibrominated product decreases in the 1,8-naphthyridine 1-oxide (**9**) instance. If, as suggested earlier, the collapse of **20** to **22** is slow relative to bromination, one would expect to see this effect on going from 1,5- to 1,8-naphthyridine 1-oxide. The collapse of **32** to **33** should be faster than the



**32** **33**

collapse of **20** to **22** because of removal of the lone pair–N-acetoxy repulsion. This should lead to the formation of increased amounts of dibrominated products relative to monobrominated products and a corresponding decrease in the ratio (**10** + **10a**/**11** + **11a**).

## Summary

One of the nonmechanistic goals of this study was to attempt to prepare the 3-bromo-1,5- and -1,8-naphthyridine 1-oxides, which were needed for another study.

A comparison of the yields of these compounds, 5 and 4.1%, respectively, obtained under the "original" experimental conditions, with those obtained, 41.5 and 39.0%, by the reaction conditions modified on the basis of this mech-

Table III
Reaction Conditions for Bromination Reactions

| Expt | 1,5-Naphthyridine 1-oxide, g | 1,8-Naphthyridine 1-oxide, g | Commercial chloroform, ml | Ethanol-free chloroform, ml | Acetic anhydride, g | Bromine, g | Sodium acetate, g | Sodium acetate trihydrate, g | Sodium bromide, g | Water, g | Acetic acid, g |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.0 | | 50 | | 1.4 | 3.3 | 1.65 | | | | |
| 2 | 1.0 | | 50 | | 1.4 | 3.3 | 1.65 | | 2.12 | | |
| 3 | 1.0 | | | 50 | 1.4 | 3.3 | 1.65 | | | | |
| 4 | 2.0 | | 100 | | 2.8 | 6.6 | | 3.7 | | | |
| 5 | 1.0 | | 50 | | | 3.3 | 1.65 | | | 0.86 | 1.64 |
| 6 | | 1.0 | 50 | | 1.4 | 3.3 | 1.65 | | | | |
| 7 | | 1.0 | | | 1.4 | 3.3 | 1.65 | | | | |

anistic study (expt 3 and 7) shows that this goal has been achieved.

## Experimental Section

Melting points are uncorrected. Mass spectral analyses were performed on a Hitachi Perkin-Elmer RMU-6M spectrometer, ionizing voltage of 80 eV. $^1H$ NMR data were obtained with a Varian Associates HA-100 spectrometer.

**Reagents.** The "commercial" chloroform used was obtained from Fischer Scientific Co. and contained 0.75% ethanol. Ethanol-free chloroform was prepared by washing "commercial" chloroform with sulfuric acid and water, drying over $K_2CO_3$, and distillation. Unless stated otherwise, "commercial" chloroform was used. All other reagents were used as supplied by the manufactures.

**Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride.** A solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in $CHCl_3$ (50 ml) was refluxed for 16 hr, and cooled, and the $CHCl_3$ was removed in vacuo. The residue was dissolved in 10% aqueous NaOH (50 ml) and the aqueous solution was extracted continuously (24 hr) with $CHCl_3$. Evaporation of the dried ($MgSO_4$) $CHCl_3$ extracts and sublimation (110°, 0.1 mm) of the residue gave 1,2-dihydro-2-oxo-1,5-naphthyridine (4, 622 mg, 62.2%), mp 254–255° (lit.[9] mp 256°). Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.11; N, 19.18. Found: C, 66.18; H, 4.18; N, 19.12.

**General Bromination Procedure.** The following general procedure was used in expt 1–7. Reagents employed and their amounts are listed in Table III.

A solution of the naphthyridine *N*-oxide and acetic anhydride in 50 ml of $CHCl_3$ was refluxed for 12 hr and cooled, and sodium acetate, bromine, and any additional reagents (see Table III) were added. The resulting suspension was stirred at reflux for an additional 48 hr, cooled, and shaken with 10% aqueous $K_2CO_3$–$Na_2SO_3$. The aqueous layer was then adjusted to pH 7 and continuously extracted with chloroform for 24 hr. The combined $CHCl_3$ solutions were dried over $MgSO_4$ and filtered and the filtrate was evaporated to dryness. The residue was then chromatographed on neutral alumina (Brockman grade III).

In the 1,5-naphthyridine *N*-oxide experiments, the following sequence of eluents was used: 100 ml of benzene, 100 ml of 1:3 chloroform–benzene, 100 ml of 1:1 chloroform–benzene, 100 ml of 3:1 chloroform–benzene, 100 ml of chloroform, 100 ml of ethanol, 100 ml of 1:19 acetic acid–ethanol.

In the 1,8-naphthyridine *N*-oxide experiments, the sequence of eluents was 100 ml of carbon tetrachloride, 100 ml of 1:4 chloroform–carbon tetrachloride, 100 ml of 3:7 chloroform–carbon tetrachloride, 100 ml of 1:1 chloroform–carbon tetrachloride, 100 ml of chloroform, 100 ml of 1:9 methanol–chloroform, 100 ml of ethanol, 100 ml of 1:9 acetic acid–ethanol.

In each case 10-ml fractions were collected and their contents ascertained by TLC. The products and amounts of each experiment are listed in Table I and the analytical data in Table II.

**Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride and Inorganic Halides.** The reactions of 1,5-naphthyridine 1-oxide with sodium, lithium, or hydrogen bromide and also with acidified potassium iodide were carried out according to the following general procedure.

A solution of 1,5-naphthyridine 1-oxide (1, 1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in 50 ml of $CHCl_3$ was refluxed for 12 hr and cooled, and any additional reagents were added. The stirred suspension was refluxed for a further 12 hr, cooled, and shaken with 10% aqueous NaOH (50 ml). The aqueous layer was extracted with $CHCl_3$ (5 × 25 ml). The $CHCl_3$ extracts were combined and evaporated to dryness and the residue was chromatographed on neutral alumina (Brockman Grade III). Elution with ether (300 ml) afforded any 1,5-naphthyridine present. Subsequent elution with $CHCl_3$ (300 ml) afforded any 1,5-naphthyridine 1-oxide present. Neutralization of the aqueous solution followed by continuous extraction with $CHCl_3$ and evaporation of the $CHCl_3$ extracts to dryness afforded any 1,2-dihydro-2-oxo-1,5-naphthyridine present. The identities of all products were established by comparisons with authentic samples.

(a) The reaction of 1 with acetic anhydride and NaBr (1.4 g, 13.6 mmol) afforded 1,5-naphthyridine (**5**, 0.06 g, 7%), 1,5-naphthyridine 1-oxide (1, 0.44 g, 44%), and 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**, 0.3 g, 30%).

(b) The reaction of 1 with acetic anhydride and LiBr (1.2 g, 13.6 mmol) afforded 1,5-naphthyridine (**5**, 0.08 g, 9%), 1,5-naphthyridine 1-oxide (1, 0.418 g, 41%), and 1,2-dihydro-2-oxo-1,5-naphthyridine (**4**, 0.29 g, 29%).

(c) The reaction of 1 with acetic anhydride and excess anhydrous HBr afforded 1,5-naphthyridine (**5**, 0.19 g, 21.2%) and 1,5-naphthyridine 1-oxide (1, 0.73 g, 73%).

(d) The reaction of 1 with acetic anhydride, KI (2.28 g, 13.7 mmol), and 98% $H_2SO_4$ (0.2 ml) afforded 1,5-naphthyridine (**5**, 0.23 g, 26.0%) and 1,5-naphthyridine 1-oxide (1, 0.64 g, 64.0%).

**Reaction of 1,5-Naphthyridine 1-Oxide (1) with Hydrogen Bromide.** Anhydrous HBr was bubbled into a solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) in $CHCl_3$ (50 ml) until the solution was saturated. The resulting suspension was stirred at reflux for 48 hr, cooled, and shaken with 10% aqueous NaOH (100 ml). The aqueous layer was extracted with $CHCl_3$ (5 × 25 ml) and the combined $CHCl_3$ solutions dried over $MgSO_4$. The $CHCl_3$ was removed to afford a quantitative recovery of starting material (1).

**Reactions with Acetyl Halides.** Compounds **1, 2a,** and **3a** were treated with acetyl bromide or acetyl chloride according to the following procedure.

To a solution of the *N*-oxide (3.4 mmol) in alcohol-free $CHCl_3$ (50 ml) was added the acetyl halide (3.6 mmol) and the resulting suspension was stirred at reflux for 48 hr. The cooled reaction mixture was washed with 10% aqueous $Na_2CO_3$ (25 ml) and dried over $MgSO_4$. After evaporation of the $CHCl_3$, the residue was chromatographed on neutral alumina (Brockman Grade III). Elution with ether (300 ml) afforded any deoxygenated product and subsequent elution with $CHCl_3$ afforded any unreacted *N*-oxide.

(a) The reaction of **1** (0.5 g), **2a** (0.76 g), or **3a** (1.04 g) with acetyl chloride (0.28 g) afforded only starting material, **1, 2a,** and **3a,** respectively.

(b) The reaction of **1** (0.5 g) with acetyl bromide (0.45 g) afforded 1,5-naphthyridine (**5**, 0.093 g, 21%) and starting material, **1**.

(c) The reaction of **2a** (0.76 g) with acetyl bromide (0.45 g) afforded 3-bromo-1,5-naphthyridine (**2**, 0.42 g, 59%) and starting material, **2a**.

(d) The reaction of **3a** (1.04 g) with acetyl bromide (0.45 g) afforded 3,6-dibromo-1,5-naphthyridine (**3**, 0.71 g, 72%) and starting material, **3a**.

**Bromination of 1,5-Naphthyridine 1-Oxide (1) in Aqueous Acetic Acid.** A solution of 1,5-naphthyridine 1-oxide (1, 1.0 g, 6.85 mmol), $Br_2$ (3.3 g, 22.55 mmol), and 48% aqueous HBr (0.1 ml) in 60% aqueous acetic acid (50 ml) was stirred at reflux for 24 hr and cooled, and the solvent was removed under an aspirator vacuum. The residue was suspended in 5% aqueous NaOAc (150 ml) and continuously extracted with $CHCl_3$ (24 hr). The precipitate formed in the $CHCl_3$ extract was filtered and the $CHCl_3$ filtrate was passed over neutral alumina (Brockman Grade III). The alumina was then washed with methanol (300 ml). The $CHCl_3$ eluate was evaporated to dryness. Mass spectrometric analysis of the residue (274 mg) gave a molecular weight of 415, indicating the presence of

three bromine atoms. The precipitate (520 mg) from the $CHCl_3$ extracts and the residue (90 mg) from the methanol eluate were shown, by TLC, to be identical. Mass spectrometric analysis gave a molecular weight of 386 indicating the presence of three bromine atoms. $^1H$ NMR analysis was not possible because of insufficient solubility of the two compounds in any of the common NMR solvents.

**Reaction of 1,5-Naphthyridine 1-Oxide (1) with Acetic Anhydride and Dilute HCl.** A solution of 1,5-naphthyridine 1-oxide (1.0 g, 6.85 mmol) and acetic anhydride (1.4 g, 13.7 mmol) in alcohol-free $CHCl_3$ (50 ml) was refluxed for 12 hr and cooled, and dilute HCl (1 ml of a 3.37% solution) was added. The solution was stirred at reflux for an additional 12 hr, cooled, and dried over $Na_2CO_3$. Removal of the $CHCl_3$ gave only starting material (0.98 g, 98%).

**Registry No.**—1, 27305-48-2; **2a**, 56247-21-3; **3**, 56247-22-4; **3a**, 56247-23-5; **4**, 10261-82-2; **7**, 56247-24-6; **8a**, 56247-25-7; **9**, 27284-59-9; **10a**, 56247-26-8; **11a**, 56247-27-9; **13**, 56247-28-0; acetic anhydride, 108-24-7; NaBr, 7647-15-6; LiBr, 7550-35-8; HBr, 10035-10-6; KI, 7681-11-0; acetyl bromide, 506-96-7; acetyl chloride, 75-36-5; $Br_2$, 7726-95-6; HCl, 7647-01-0.

### References and Notes


(1) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, **9**, 414 (1961); M. Yamazaki, Y. Chono, K. Noda, and M. Hamana, *Yakugaku Zasshi*, **85**, 62 (1965).
(2) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **33**, 1384 (1968).
(3) M. Katada, *J. Pharm. Soc. Jpn.*, **67**, 51 (1947); *Chem. Abstr.*, 9536 (1951); J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Am. Chem. Soc.*, **85**, 958 (1963).
(4) For a discussion of these mechanisms see A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N.Y., 1971, pp 231–251.
(5) R. A. Abramovitch and G. M. Singer, *J. Am. Chem. Soc.*, **91**, 5672 (1969).
(6) A. R. Katritzky and E. Lunt, *Tetrahedron*, **25**, 4291 (1969).
(7) We have already shown that Eisch bromination of 1,5-naphthyridine 1-oxide affords only, not unexpectedly, 7-bromo-1,5-naphthyridine 1-oxide (D. Pokorny, Ph.D. Thesis, Ohio University, Athens, Ohio, 1972).


# The Effect of Ring Size on Hydrogenation of Cyclic Allylic Alcohols


Raj K. Sehgal,*[1] Renate U. Koenigsberger, and Terence J. Howard

*Department of Organic Chemistry, University of Surrey, Guildford, Surrey, England*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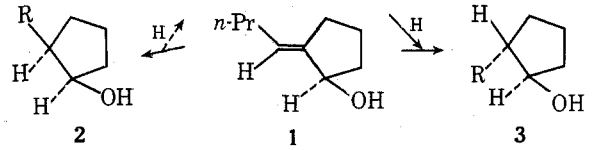
2-Butylidenecyclopentanone, 2-butylidenecyclohexanone, and 2-butylidenecycloheptanone were prepared by the Reformatsky reaction of *n*-butyraldehyde with 2-bromocyclopentanone, 2-bromocyclohexanone enol acetate, and 2-bromocycloheptanone, respectively. Reduction of 2-butylidenecyclanones with lithium aluminum hydride gave the corresponding allylic cyclanols which were characterized by their mass spectra. On catalytic hydrogenation over a variety of catalysts, the products were *cis*- and *trans*-2-butylcyclanols as well as 2-butylcyclanones. The stereochemistry of the epimeric 2-butylcyclanols was assigned by hydroxyl proton splitting in $Me_2SO$ as observed by NMR. Alternatively, 2-butylidenecyclanones could be hydrogenated with Pd/C to 2-butylcyclanones, and reduced by lithium aluminum hydride or Raney Ni hydrogenation to *cis*- and *trans*-2-butylcyclanols.


Although product stereochemistry resulting from catalytic hydrogenation of organic compounds has been attributed to direct transfer of hydrogen,[2] compounds containing polar substituents, notably hydroxyl group, near a reducible double bond are known to exert special directing effects[3-5] in contrast with the well-known case in which the bulk of the nearby substituents is the controlling factor and imposes trans stereochemistry by sterically blocking cis approach to the catalyst surface.[6] In such instances presumably some type of attractive interaction has bound the hydroxyl group to the catalyst surface during reduction so as to enforce addition of hydrogen from the same side in spite of group's hindrance.

From their results Mitsui et al. concluded that in the case of Raney Ni the directive effect of the hydroxyl group was very efficient, but that it was small over Pd.[4d] They suggested that the difference in the affinity of nickel and palladium for the oxygen atom controlled not only the stereochemistry of the hydrogenolysis of benzyl-type alcohols, but also that of the hydrogenation of the double bond of allyl-type alcohols. To clarify the effects of hydroxyl group and also the effect of change in ring size on the stereochemistry of hydrogenation of cyclic allylic alcohols over a number of catalysts, prompted an investigation of five-, six-, and seven-membered 2-alkylidenecyclanols.

## Results and Discussion

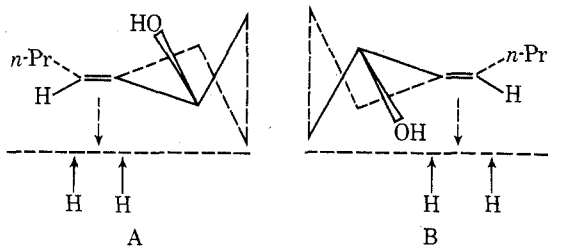
**2-Butylidenecyclopentanol (1).** Calculations on cyclopentane derivatives containing $sp^2$ hybridized atoms such as methylenecyclopentane and cyclopentanone suggest that such molecules exist in the half-chair form with the maximum puckering occurring at carbon atoms 3 and 4, i.e., away from the $sp^2$ hybridized atom.[7] In the hydrogenation of 1 over Raney nickel, a catalyst of low isomerizing ability,[8] 96% **3**, is obtained.




2 1 3

R = *n*-Bu

From models of 1 it is found that either side of the double bond can be presented in an equally planar conformation to the catalyst. Thus steric factors cannot be responsible for this overwhelmingly one-sided addition of hydrogen. The two possible adsorption conformations of the unsaturated alcohol (A and B) differ only in that in one the




A B

OH is directed away from the catalyst surface (A), while in the other it is directed toward it (B). It is suggested that the latter is the preferred adsorption conformation, since the molecule may be adsorbed by interaction of the lone