

Unusual Bromination of 9-Cyano-10-methylacridan

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Acridinium cations have been widely studied due to their broad application especially in the area of chemiluminescence.^{1,2} 9-Cyano-10-methylacridinium ions (cf. **2**) are particularly important because of their chemiluminescent properties as well as their interesting chemical behavior.³ The 9-position of the cation is susceptible to nucleophilic addition. Furthermore, the cation is a good hydride acceptor and has been employed as a NAD⁺ analogue for hydride transfer reaction.^{4,5}

As a part of our studies on the mechanism of hydride transfer reaction between NAD⁺ analogues, we were interested in the preparation of 9-cyano-10-methylacridinium bromide (**2a**). One of the strategies is the oxidation of 9-cyano-10-methylacridan (**1**) with dilute nitric acid⁶ and subsequent exchange of the hydrogen dinitrate counterion with bromide ion. A polarographic study has been reported for the oxidation of **1** by LiNO₂ but its application for preparation of the acridinium salt is not certain.⁷ Direct oxidation of **1** by bromine in CCl₄ seemed to be straightforward although the yield of **2a** was low (47%).⁵ In order to improve the yield we came to examine the reaction conditions for the conversion of **1** to **2a** by bromine (Scheme 1).

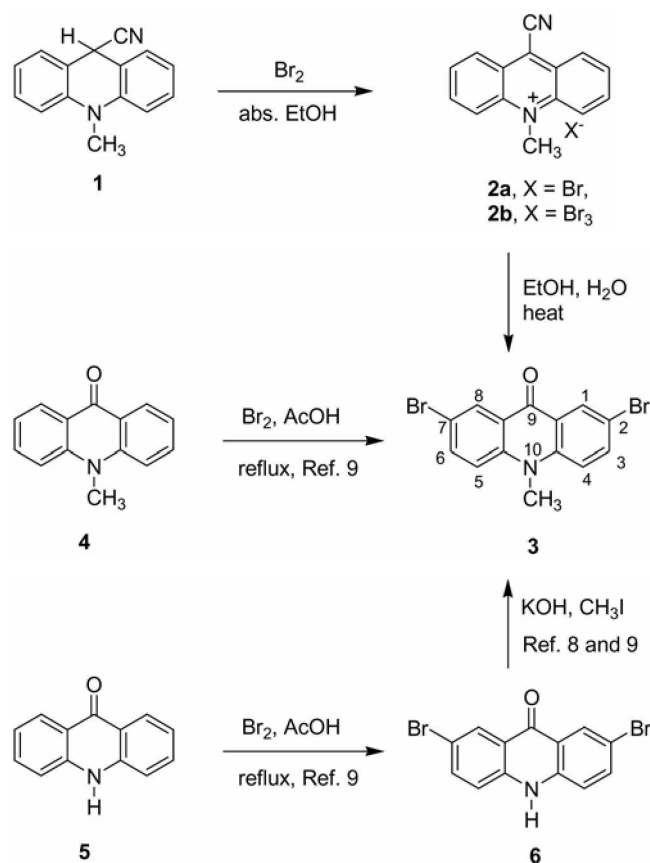
When a suspension of **1** in absolute ethanol was treated with an excess amount of bromine, a tribromide **2b**, not monobromide **2a**, was formed. However, when an attempt was made to recrystallize the crude reaction product from ethanol-water (9:1, v/v) mixture by heating to dissolve the solid, white needles were obtained within a few min. The solid was found to be 2,7-dibromo-10-methyl-9(10H)-acridone (**3**). This is quite an unusual kind of reaction because both oxidation of the acridinium cation to acridone and aromatic bromination took place in one-pot reaction. Furthermore, the source of the bromine was the tribromide ion in **2b**.

The compound **3** was reported to be prepared by methylation of the corresponding N-H compound **6**,^{8,9} which, in turn, was prepared by bromination of 9(10H)-acridone (**5**).⁹ Direct bromination of 10-methyl-9(10H)-acridone (**4**) with bromine in boiling acetic acid also gave **3**.⁹

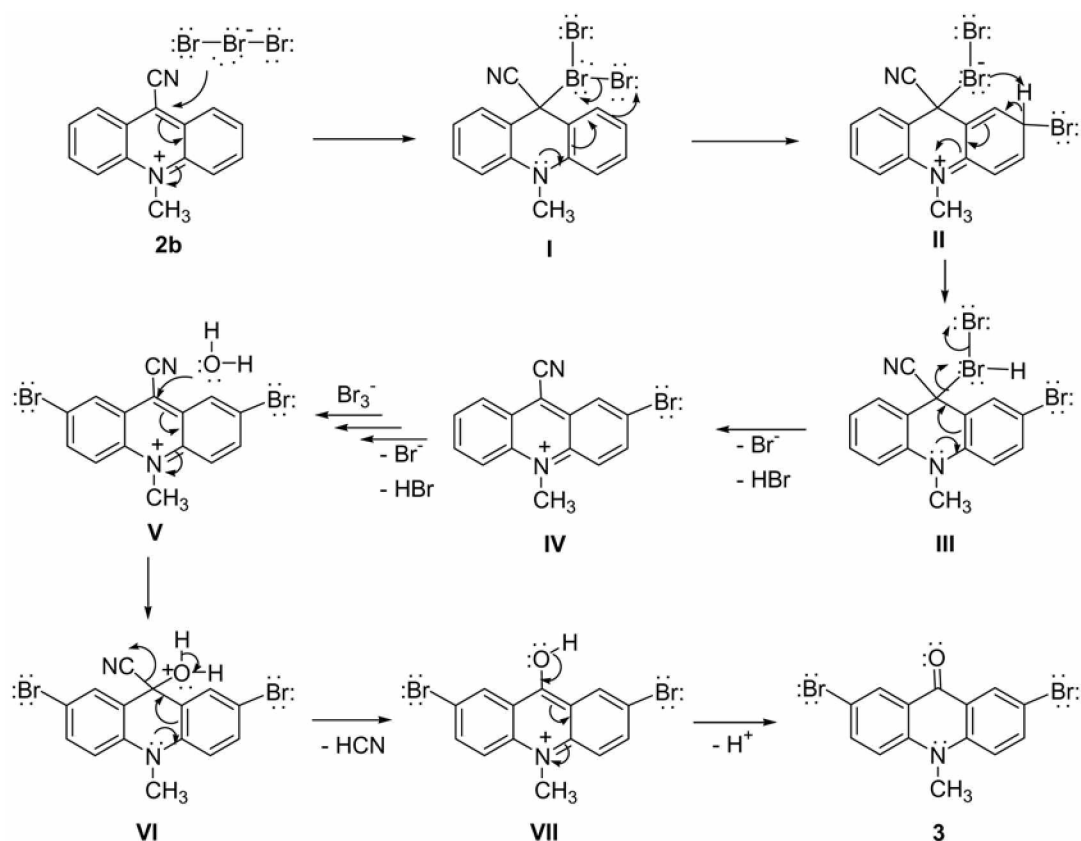
We have ruled out that 10-methyl-9(10H)-acridone (**4**) was involved as an intermediate because the compound **3** could not be obtained upon treating **4** with bromine and/or KBr in ethanol-water (9:1, v/v) solution. Furthermore, bromination is unlikely to take place in the first step from **1**,

because **2b** was successfully prepared from **1** and purified by washing with isopropyl alcohol-water (4:1, v/v) followed by CH₂Cl₂. The correct elemental analysis of **2b** with three bromine atoms was obtained. Oxidation of **1** with iodine under similar condition was unsuccessful and the starting material was recovered.

Although the mechanism for the transformation of **2b** to **3** is uncertain, we propose a mechanism in which the tribromide ion is involved in Scheme 2. Once the nucleophilic addition of the negatively-charged bromine atom at the center of Br₃⁻ to C-9 of the cation takes place to form **I** a six-membered transition state may be achieved so that the bromine atom at the side can be transferred to C-2 of the acridine ring (cf. **II**). The monobromoacridinium intermediate **IV**, once formed, may undergo similar steps introducing the second bromine atom at C-7 to give **V**. Due to the



Scheme 1



Scheme 2

presence of the two bromine atoms the intermediate **V** should be more reactive than **2b** itself, and the nucleophilic addition of H_2O should be possible to form **VI**. Loss of HCN from **VI** and subsequent loss of H^+ from **VII** should give **3**. The mechanism for the transformation of 9-cyano-10-methylacridinium cation (like **2a**) to **4** by H_2O_2 in alkaline solution or by aqueous NaOH has been reported.¹⁻³

Although the dibromoacridones **6** and **3** were reported in literature,^{8,9} the positions of the bromine atoms are ambiguous. We have established the structures of **2b** and **3** by spectroscopic methods in addition to elemental analyses. The presence of 9-acridone skeleton in **3** was confirmed by the peak at 1636 cm^{-1} in the IR spectrum, which was shifted to quite low frequency for a carbonyl stretch.¹⁰ The peak at 174.42 ppm in ^{13}C spectrum also supports the carbonyl group. The presence of two bromine atoms on the aromatic ring was readily evidenced by the typical mass spectral peaks at m/z 365 (relative intensity 53%), 367 (100%), and 369 (56%), which correspond to M^- , $M^- + 2$, and $M^- + 4$, respectively. Similar mass spectral data were reported for **3** with relative intensities of 54%, 100%, and 41%, respectively.¹¹

The positions of bromine in **3** were established by the analysis of the NMR spectra. $^1\text{H-NMR}$ spectrum showed three signals in the aromatic region, indicating that the molecule is symmetric. The peak at $\delta 8.36$ corresponding to C-1- and C-8-H should appear farthest down field because the protons are flanked by both carbonyl and bromine. It is a

2-proton doublet having $J = 2.2\text{ Hz}$ which is a reasonable *meta* coupling constant. The peak at $\delta 8.00$ appearing as a 2-proton doublet of doublets has *meta* (2.2 Hz) and *ortho* (9.6 Hz) coupling constants. This should be due to the C-3- and C-6-H. The 2-proton doublet at $\delta 7.84$ with $J = 9.6\text{ Hz}$ corresponds to the C-4- and C-5-H. The relative chemical shift values are in consistent with the calculated values using 2-amino-5-bromoacetophenone or similar types of compounds as a model.¹² Substitution at the 3- and 6-positions may be possible, but then the values of the chemical shift and coupling constant do not fit well.

In conclusion, we report a quite unusual bromination of an acridine derivative which leads the formation of 2,7-dibromo-10-methyl-9(10*H*)-acridone.

Experimental Section

Melting points were determined on a Fisher MEL-TEMP apparatus and were uncorrected. IR and UV-visible spectra were recorded on Perkin-Elmer 283 and Cary 14 spectrophotometers, respectively. NMR spectra were recorded on a Bruker DPX-400 FT NMR spectrometer in the Central Lab of Kangwon National University at 400 MHz for ^1H and 100 MHz for ^{13}C and were referenced to tetramethylsilane. Mass spectra were obtained on a AEI MS-30 mass spectrometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, USA.

9-Cyano-10-methylacridinium Tribromide (2b). To an

ice-cold solution of 3.00 g (13.64 mmole) of **1** which was prepared by a literature method¹³ in absolute ethanol (400 mL) was added an excess amount of bromine (*ca.* 2 mL). Soon a fine orange precipitate formed which was collected by filtration, washed with 50 mL of isopropyl alcohol-water (4:1, v/v) and subsequently with dichloromethane (2 × 50 mL). The solid was dried under vacuum to give **2b**, 3.85 g (90%), mp 210 °C; IR (KBr) 3420 w, 3010 w, 1630 m, 1610 s, 1543 s, 1458 s, 1380 s, 1295 m, 1275 m, 1190 m, 1175 m, 782 s, 760 m cm⁻¹; ¹H-NMR (DMSO-*d*₆) δ 5.02 (s, 3H, CH₃), 8.02-9.03 (m, 8H, aromatic-H); ¹³C-NMR (DMSO-*d*₆) ppm 40.30, 113.70, 117.51, 120.14, 123.10, 127.25, 130.88, 139.49, 141.47; UV (PrOH-H₂O, 4:1, v/v) λ_{max} (log ε) 481 nm (3.45), 451 (3.63), 426 (3.58), 386 (4.38), 368 (4.06), 264 (4.99). Anal. Calcd for C₁₅H₁₁Br₃N₂ (458.98): C, 39.25; H, 2.41; Br, 52.23; N, 6.10. Found: C, 39.10; H, 2.52; Br, 52.49; N, 5.95.

2,7-Dibromo-10-methyl-9(10H)-acridone (3). Compound **2b** (8.00 g) was dissolved in ethanol-water (9:1, v/v, 300 mL) by heating on a steam-bath for a few min. Once the dissolution was complete a white solid of fine needles soon formed. The mixture was cooled and filtered to collect the solid. After washing with absolute ethanol and drying under vacuum, compound **3** was obtained (3.60 g, 76%), mp 287 °C (lit.⁹ 282-283 °C); IR (KBr) 3120 w, 3080 w, 2950 w, 2845 w, 1636 m, 1595 s, 1549 m, 1480 s, 1335 s, 1288 m, 1260 m, 1180 m, 1155 m, 975 m, 920 m, 822 s, 808 m cm⁻¹; ¹H-NMR (DMSO-*d*₆) δ 3.92 (s, 3H, CH₃), 7.84 (d, 2H, 4- and 5-H, *J*_{4,3} = 9.6 Hz), 8.00 (dd, 2H, 3- and 6-H, *J*_{3,4} = 9.6 Hz, *J*_{3,1} = 2.2 Hz), 8.36 (d, 2H, 1- and 8-H, *J*_{1,3} = 2.2 Hz); ¹³C-NMR (DMSO-*d*₆) ppm 34.27, 114.16, 119.40, 122.86, 128.34, 136.72, 141.25, 174.42; UV (MeOH) λ_{max} (log ε) 415 nm (3.76), 392 (3.74), 281 (4.50), 249 (4.48); MS, *m/z*

(%) 369 (56, M⁻ + 4), 367 (100, M⁺ + 2), 365 (53, M⁻), 354 (11), 352 (21), 350 (11, M⁺ - CH₃), 164 (29). Anal. Calcd for C₁₄H₉Br₂NO (367.05): C, 45.81; H, 2.47; Br, 43.54; N, 3.82. Found: C, 45.60; H, 2.55; Br, 43.77; N, 3.80.

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