An Unusual Ring Contraction of 7-Methyl-1,7-naphthyridinium and 6-Methyl-1,6-naphthyridinium Salts in Reaction with Liquid Ammonia/Potassium Permanganate

M. Wozniak and H. C. van der Plas*

Laboratory of Organic Chemistry, Agricultural University, De Dreijen 5, 6703 BC Wageningen, The Netherlands

S. Harkema

Laboratory of Chemical Physics, Twente University of Technology, 7500 AE Enschede, The Netherlands

Received March 18, 1985

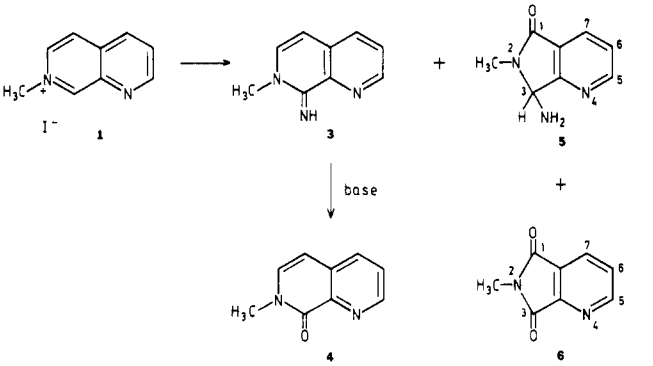
Treatment of 7-methyl-1,7-naphthyridinium iodide (1) with liquid ammonia/potassium permanganate gives the 8-imino compound 3 and two ring contraction products, which by ^{1}H NMR spectroscopy were assigned as 3-amino-1,3-dihydro-2-methyl-4-azaisoindol-1-one (5) and 1,3-dihydro-2-methyl-4-azaisoindole-1,3-dione (6). The structure of 5 was confirmed by X-ray analysis. Similarly from 6-methyl-1,6-naphthyridinium iodide (2) the 5-imino compound 7 together with 1-amino-1,3-dihydro- (8) and 1-imino-1,3-dihydro-2-methyl-4-azaisoindol-3-one (9) were formed. ^{1}H NMR spectroscopy unequivocally shows that 1 and 2 are converted with ammonia into 8-amino-7,8-dihydro-7-methyl-1,7-naphthyridine (11) and 5-amino-5,6-dihydro-6-methyl-1,6-naphthyridine (12), respectively. The mechanism of the ring contraction is discussed.

Very recently we reported[1,2] that *N*-methylpyridinium, *N*-methylquinolinium, 1-methyl-1,5-naphthyridinium, and 1-methyl-1,8-naphthyridinium salts easily undergo imination on treatment with liquid ammonia/potassium permanganate. In all these compounds the imino group is introduced on the carbon adjacent to the nitrogen, carrying the methyl group. As intermediates in these imination reactions 2-amino-1,2-dihydro-1-methylazines were proposed and their existence could be proved by ^{1}H NMR spectroscopy.[1-3] In order to explore further the general scope of this imination reaction and its potential synthetic use we extended our work to the study of the behaviour of 7-methyl-1,7-naphthyridinium iodide (1) and 6-methyl-1,6-naphthyridinium iodide (2) toward liquid ammonia/potassium permanganate.

Results

Treatment of a solution of 1 in liquid ammonia with potassium permanganate for 20 min gave a tarry reaction mixture from which we were able to isolate three compounds with TLC: (i) 7,8-dihydro-8-imino-7-methyl-1,7-naphthyridine (3, 15%) as proved by microanalysis of its pictrate and ^{1}H NMR spectroscopy; its structure was confirmed by converting 3 into 7-methyl-1,7-naphthyridone-8 (4)[4] by base treatment. (ii) 3-Amino-1,3-dihydro-2-methyl-4-azaisoindol-1-one (5, 13%). The structure assignment of 5 was based on analysis, exact mass measurements ($C_8H_9N_3O$), IR spectrum featuring the presence of a C=O group (1680 cm^{-1}) and the NH group (3380, 1620 cm^{-1}), and the ^{1}H NMR spectrum, clearly showing the chemical shifts and multiplicity pattern of a 2,3-disubstituted pyridine. The structure of 5 was firmly confirmed by X-ray analysis. (iii) 1,3-Dihydro-2-methyl-4-azaisoindole-1,3-dione (6, 2%) as proved by exact mass measurements, IR spectrum (1720 cm^{-1} (broad)), and ^{1}H NMR data, again showing the presence of a 2,3-disubstituted pyridine ring system. Similar results were obtained on treatment of II with liquid ammonia/potassium permanganate. Besides imination at position 5, leading to 5,6-dihydro-5-imino-6-methyl-1,6-naphthyridine (7, 10%),

Scheme I



Scheme II

two ring contraction products were isolated: (i) 1-amino-1,3-dihydro-2-methyl-4-azaisoindol-3-one (8, 10%) and (ii) 1,3-dihydro-1-imino-2-methyl-4-azaisoindol-3-one (9, 7%). In addition a small amount of 6-methyl-1,6-naphthyridone-5 (10, 2%) was isolated. The structure of 7 was established by the usual physical means (see the Experimental Section) and by formation of 6-methyl-1,6-naphthyridone-5 (10)[4] from 7 by base treatment. The structure assignment of ring contraction product 8 was based on exact mass measurements showing that 8 is isomeric with compound 5, which structure is unequivocally established; furthermore the ^{1}H NMR spectrum of 8 is nearly identical with that of 5, and the IR spectrum shows the presence of the C=O group (1680 cm^{-1}) and NH_2 group (3350, 3280 cm^{-1}). Compound 10 is probably formed from 7 during the workup procedure and it seems very likely that 9 is formed from 8 by oxidation with the

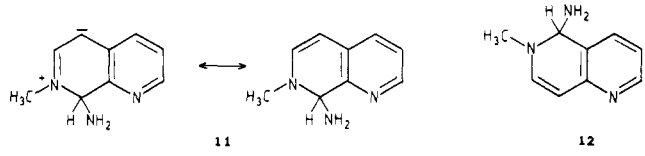
(1) Part 43 on the formation of σ adducts. For part 42 see: Wozniak, M.; Buurman, D. J.; van der Plas, H. C. *J. Heterocycl. Chem.*, in press.
(2) Van der Plas, H. C.; Buurman, D. J. *Tetrahedron Lett.* **1984**, *25*, 3763.
(3) Angelino, S. A. G. F.; van Veldhuizen, A.; Buurman, D. J.; van der Plas, H. C. *Tetrahdedron* **1984**, *40*, 433.
(4) Paudler, W. W.; Kress, F. J. *J. Heterocycl. Chem.* **1968**, *5*, 56.

0022-3263/85/1950-3435$01.50/0

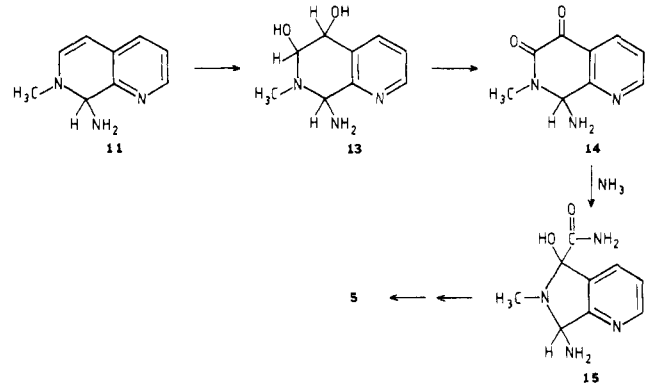
Table I. ^{1}H NMR Data of *N*-Methyl-1,*X*-naphthyridinium Iodides 1 (*X* = 7) and 2 (*X* = 6) and Their σ Adducts with Ammonia

compound	solvent	chemical shift δ H-2	H-3	H-4	H-5	H-6	H-7	H-8	CH_3
7-methyl-1,7-naphthyridinium iodide (1)	D_2O	9.39	8.20	8.78	8.62	8.78		9.86	4.80
8-amino-7,8-dihydro-7-methyl-1,7-naphthyridine (11)	NH_3	8.18	7.14	7.34	5.25	6.35		5.05	3.05
	$\Delta\delta$	1.21	1.06	1.44	3.37	2.43		4.81	1.75
6-methyl-1,6-naphthyridinium iodide (2)	D_2O	9.50	8.13	9.00	10.02		8.91	8.57	4.72
5-amino-5,6-dihydro-6-methyl-1,6-naphthyridine (12)	NH_3	8.27	7.03	7.53	5.19		6.62	5.41	3.09
	$\Delta\delta$	1.23	1.10	1.47	4.83		2.29	3.16	1.63

Scheme III



Scheme IV



permanganate present in the solution.

^{1}H NMR Spectroscopy of Solutions of 1 and 2 in Liquid Ammonia. In order to obtain insight in the mechanism of these reactions we measured the ^{1}H NMR spectrum of a solution of 1 and 2 in liquid ammonia without the presence of potassium permanganate. As seen in Table I both compounds when dissolved in liquid ammonia (at −33 °C) easily undergo addition of the nucleophile. Based on the upfield shift ($\Delta\delta$) for the various hydrogen atoms, when comparing the chemical shifts in D_2O and in NH_3 (liquid), it is evident that in 1 the addition takes place at position 8, i.e., formation of 11, and that in 2 the addition occurs at position 5, i.e., formation of 12. The upfield shifts are caused by the $sp^2 \rightarrow sp^3$ hybridization due to ammonia addition; the $\Delta\delta$ values of about 4.8 are in agreement with those observed before in similar heterocyclic systems.[5,6] The considerable upfield shift of $\Delta\delta$ 3.37, observed for H-5 in the formation of 11, and of $\Delta\delta$ 3.16 for H-8 in the formation of 12 can be explained on the basis of azaallylic stabilization in these neutral species.[7] These stabilization contributions are observed before in the σ-adducts formed between quinoline and naphthyridines with potassium amide.[7,8] The vulnerability of position 8 in 1 for nucleophilic attack is in agreement with the results of a ^{1}H NMR study on the addition of liquid ammonia to the parent system 1,7-naphthyridine, although in 1,7-naphthyridine besides C-8 also C-2 is attacked by the liquid ammonia at −50 °C.[7] Due to quaternization of N-7, position 8 in 1 is now highly favored for nucleophilic attack. In contrast in 1,6-naphthyridine position C-2 is the favored position for nucleophilic addition with ammonia, but due to quaternization of N-6 the electron density at C-5 in 2 is lower than at C-2. It seems reasonable to suppose that the formation of the imino compounds 3 and 7 occurs by oxidation of the dihydroaminonaphthyridines 11 and 12, respectively.

Mechanistic Pathway for the Ring Contraction of 1 into 5 and 2 into 8. The mechanism of the ring contraction is not very clear. ^{14}C studies on the ring contraction of six-membered heterocycles into five-membered heterocycles by action of hydrogen peroxide in acidic medium (for example 8-nitroquinoline into 7-nitrooxindole,[10] 5-nitrocinnoline into 4-nitroindazole[11]) have shown[12] that the carbon atom adjacent to the nitrogen is expelled during the ring contraction (the C–C bond is weaker than the C–N bond). We assume that also in the ring contraction of 1 into 5 and of 2 into 8 the non-isoquinolinic carbon atom, located adjacent to the *N*-methyl group is "lost" during the ring contraction. Since the amino group in both σ adducts 11 and 12 occupys the same carbon atom as in the respective ring contraction products 5 and 8 we suggest that 11 and 12 are the precursors of 5 and 8, respectively. It is proposed that the styrene-type C=C bond in these adducts is converted via an intermediary dihydroxy compound (see for example the formation of 13 from 11) into the diketo compound. In the presence of the base a benzilic acid type rearrangement of 14 into the hydroxy acid 15 occurs, which undergoes a decarboxylative oxidation process yielding 5.[13]

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra are recorded on a Hitachi-Perkin Elmer R-24 or a Varian EM 390 spectrometer with Me_4Si or DSS as internal standard (δ 0). In liquid ammonia the chemical shifts of the protons were measured against the ammonia signal (δ 0.95) as standard. The mass spectra were determined with an AEI MS 902 mass spectrometer equipped with a VG-2AB console. Preparative thin-layer chromatography was carried out on standard plates (20 × 40 cm) covered with a 2-mm layer of Merck Silica gel 60 PF 254. IR spectra were measured on a Jasco A-100.

General Procedure for the Reaction of the Naphthyridinium Salts 1 and 2 with Liquid Ammonia/Potassium Permanganate. To a yellow colored solution of 1.08 g (4 mmol) of 1 and 2 in 40–50 mL of liquid ammonia at −33 °C was added 1.3 g (8 mmol) of potassium permanganate in portions over a

(5) Van der Plas, H. C.; Wozniak, M.; van den Haak, H. J. W. *Adv. Heterocycl. Chem.* **1983**, *33*, 96. See also: Wozniak, M.; van der Plas, H. C. *Heterocycles* **1982**, *19*, 363.
(6) Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462.
(7) Van den Haak, H. J. W.; van der Plas, H. C.; van Veldhuizen, A. *J. Org. Chem.* **1981**, *46*, 2134.
(8) Zoltewicz, J. A.; Helmick, L. S.; Oestreich, T. M.; King, R. W.; Kandetzky, P. E. *J. Org. Chem.* **1973**, *38*, 1947.
(9) Van der Plas, H. C.; van Veldhuizen, A.; Wozniak, M.; Smit, P. *J. Org. Chem.* **1978**, *43*, 1673.
(10) Nakashima, T.; Suzuki, I. *Chem. Pharm. Bull.* **1969**, *17*, 2293. Coutts, R. T.; Hindmarsh, K. W.; Mah, E. *Can. J. Chem.* **1970**, *48*, 3747.
(11) Suzuki, I.; Nakashima, T.; Nagasawa, N. *Chem. Pharm. Bull.* **1965**, *13*, 713.
(12) Van der Plas, H. C.; Buurman, D. J. *Chem. Pharm. Bull.* **1975**, *23*, 2682.
(13) A somewhat similar mechanism has been proposed for the ring contraction of 3-hydroxy-1-mercaptoisoquinoline into phthalimide.[14]
(14) Smith, P. A. S.; Kan, R. O. *J. Am. Chem. Soc.* **1961**, *83*, 2580.

period of 5 min. This mixture was stirred for an additional 20 min. After evaporation of the liquid amonia, 40–50 mL of water were added and the solution was continuously extracted with chloroform. Evaporation of the chloroform gave a residue which was dissolved in 50 mL of methanol. The solution was treated with charcoal, filtered, and evaporated till dryness. The residue was dissolved in a small amount of chloroform–methanol mixture (1:1) and applied by an automatic autoliner (Desaga) on two plates (20 × 40 cm) covered with a 2-mm layer of silica gel. PF 254 chromatograms were developed with an appropriate solvent (see below for description of the more detailed procedure). The bands having an UV absorbance were extracted with a mixture of chloroform and methanol (1:1). Residue obtained after evaporation of the solvent was worked up as given below in each of the procedures.

Reaction of 1. Chromatograms were developed with a mixture of chloroform/ethyl acetate/methanol (ratio 8:2:1). Three bands were obtained. The residue, obtained from the band with the lowest R_f value, was dissolved in 50 mL of methylene chloride, filtered, and concentrated to give 32 mg of the hydroiodide salt of the 2-imino compound **3**: mp 235–270 °C (dec); ^{1}H NMR (deuteriomethanol) δ 8.78 (dd, H-2), 8.06 (dd, H-4), 7.68 (dd, H-3), 7.40 (d, H-6), 6.65 (d, H-5), 3.75 (s, CH_3), $J_{2,4}$ = 1.5 Hz, $J_{3,4}$ = 8.2 Hz, $J_{5,6}$ = 7.5 Hz; mp picrate 231–233 °C; yellow needles (from methanol). Anal. Calcd for $C_9H_3N_3{\cdot}C_6H_3N_3O_7$: C, 46.39; H, 3.12. Found: C, 46.60; H, 3.25. Residue obtained after extraction of the second band was crystallized from benzene to give 85 mg (13%) of **5**: white needles; mp 173–175 °C; exact mass 163.0743, calcd for $C_8H_9N_3O$ 163.0746; IR (potassium bromide) 3380 and 3330 (shoulder) (NH), 1680 (C=O) and 1620 cm^{-1} (NH); ^{1}H NMR (deuteriochloroform) δ 8.74 (dd, H-5), 8.06 (dd, H-7), 7.40 (dd, H-6), 5.21 (s, CH), 3.21 (s, CH_3), 2.08 (broad s, NH_2), $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz). Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56. Found: C, 58.97; H, 5.41. The solid obtained after extraction of the band with the highest R_f value gave after renewed separation on silica gel a product that was sublimed at 100 °C (0.2 mm) yielding 8 mg (2%) of **6**: white needles; mp 120–122 °C (lit.[15] mp 121–123 °C); exact mass 162.0434, calcd for $C_8H_6N_2O_2$ 162.0424; IR (potassium bromide) 1720 cm^{-1} (C=O); ^{1}H NMR (in deuteriochloroform) δ 8.97 (dd, H-5), 8.20 (dd, H-7), 7.62 (dd, H-6), 3.28 (s, CH_3), $J_{5,7}$ = 1.5 Hz, $J_{5,6}$ = 4.5 Hz, $J_{6,7}$ = 7.5 Hz.

Reaction of 2. For development of the chromatogram a mixture of chloroform/methanol (10:1.5) was used. Four main bands were obtained. The residue of the first band (lowest R_f value) was dissolved in boiling methylene chloride, filtered, and concentrated to about 10 mL. The hydroiodide salt of **7** (28 mg) was obtained: white crystals; mp 270–282 °C (dec); ^{1}H NMR (deuteriochloroform/deuteriomethanol) δ 8.92 (dd, H-2), 8.85 (dd, H-4), 7.53 (dd, H-3), 7.46 (d, H-7), 6.86 (dd, H-8), 3.81 (s, CH_3), $J_{2,3}$ = 4,5 Hz, $J_{2,4}$ = 1.5 Hz, $J_{3,4}$ = 8.1 Hz, $J_{7,8}$ = 7.8 Hz, $J_{4,8}$ = 0.5 Hz); mp picrate 224–225 °C; yellow needles (methanol). Anal. Calcd for $C_9H_3N_3{\cdot}C_6H_3N_3O_7$: C, 46.39; H, 3.12; M_r 388.29. Found: C, 46.69; H, 3.24.

The solid residue, obtained after extraction of the second band was crystallized from absolute ethanol (charcoal) to give 102 mg (16%) of **8**: mp 210–212 °C (white needles); exact mass 163.0749, calcd for $C_8H_9N_3O$ 163.0746; IR (potassium bromide) 3350 and 3280 (NH), 1680 cm^{-1} (C=O); ^{1}H NMR (deuteriochloroform) δ 8.86 (dd, H-5), 7.93 (dd, H-7), 7.42 (dd, H-6), 5.20 (s, CH), 3.17 (s, CH_3), 1.85 (broad s, NH_2), $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz. Anal. Calcd for $C_8H_9N_3O$: C, 58.88; H, 5.56. Found: C, 59.18; H, 5.42.

(15) Hemmerich, P.; Fallab, S. *Helv. Chim. Acta* **1958**, *41*, 498.

The material, obtained after extraction of the third band, was crystallized from benzene to give 42 mg (7%) of **9**: mp 189–191 °C; white needles; exact mass 161.0584, calcd for $C_8H_7N_3O$ 161.0584; IR (potassium bromide) 3280, 3250 (NH), 1730 (C=O), 1660 cm^{-1} (C=N); ^{1}H NMR (deuteriochloroform) δ 8.91 (dd, H-5), 8.26 (dd, H-7), 7.63 (dd, H-6), 3.40 (s, CH_3), 3.13 (broad s, NH), $J_{5,6}$ = 4.5 Hz, $J_{5,7}$ = 1.5 Hz, $J_{6,7}$ = 7.5 Hz. Anal. Calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38. Found: C, 59.54; H, 4.17.

The residue obtained after extraction of the band with the highest R_f value was sublimed at 100 °C (0.2 mm) to give 12 mg (2%) of **10** (white needles): mp 96–98 (lit.[4] mp 97–98 °C). The ^{1}H NMR data are in agreement with those reported. The IR and ^{1}H NMR spectra are fully identical with those of the product obtained by basic hydrolysis of **7**.

Hydrolysis of the Imino Compounds 3 and 7. A solution of 15 mg of the imino compound in 10 mL of 10% sodium hydroxide solution was heated under reflux for a few hours. After cooling, the reaction mixture was extracted with chloroform and the chloroform solution dried with anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was crystallized from petroleum ether (60–80 °C) to give about 10 mg of the naphthyridone. 6-Methyl-1,6-naphthyridone-5 (**10**): mp 96–98 °C (lit.[4] mp 97–98 °C); the ^{1}H NMR data are also in agreement with those reported.[4] 7-Methyl-1,7-naphthyridone-8 (**4**): mp 119–121 °C (lit.[4] oil). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03. Found: C, 67.79; H, 5.01. The ^{1}H NMR data are in agreement with those reported.[4]

X-ray Crystal Structure of 5. Crystals of **5** ($C_8H_9N_3O$) belong to the triclinic space group $P\bar{1}$: a = 9.984 (1) Å, b = 9.710 (1) Å, c = 9.590 (2) Å, α = 112.51 (1)°, β = 112.76 (2)°, γ = 73.99 (1)°, Z = 4, d_c = 1.38 g cm^{-3}. Intensities were measured with a Philips PW1100 diffractometer with Mo K_α radiation. Experimental data: w – 2θ scan mode, scan speed (ω) 0.02° s^{-1}, scan width (ω) 2.0°, $4 < \omega < 22.5°$. Structure solution[16] and refinement by a local block-diagonal modification of ORFLS[17] were based on 1757 reflections with $I > \sigma(I)$ (from counting statistics). The structure has two independent molecules in the asymmetric unit. After refinement with anisotropic thermal parameters for the heavy atoms disorder in one of the two molecules was observed. This disorder in the amino group could be described by assuming two positions for the nitrogen atom. Hydrogen atoms were located in difference Fourier maps. Due to the disorder three hydrogen atoms (two amino hydrogens and one bonded to the adjacent carbon atom) could not be located. Refinement of positional and thermal (isotropic for hydrogen atoms, anisotropic for others) parameters gave a final R factor of 5.9%. Figure 1[18] (supplementary material) shows the structure of the molecule not affected by disorder.

Acknowledgment. We are indebted to Dr. C. A. Landheer and C. J. Teunis for mass spectrometric data, to A. van Veldhuizen for measuring NMR spectra, and to H. Jongejan for the microanalytical data.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, bond distances, and bond angles (6 pages). Ordering information is given on any current masthead page.

(16) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274. Main, P. In "Computing in Crystallography"; Schenk, H., Ed.; Delft University Press: Delft, 1978; p 93.

(17) Busing, W. R.; Martin, K. O.; Levy, H. A. "ORFLS"; Oak Ridge National Laboratory, Report ORNL-TM-305, 1962.

(18) Johnson, C. K. "ORTEP"; Oak Ridge National Laboratory, Report ORNL-3794, 1965.