Imination of *N*-Methylazinium Salts by Liquid Ammonia/Potassium Permanganate [1]

M. Woźniak, D. J. Buurman and H. C. van der Plas*

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

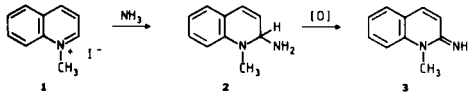
Received October 19, 1984

Treatment of 1-methylquinolinium-, 1,4-dimethylquinolinium- and 1-methyl-1,X-naphthyridinium iodides (X = 5,8) with liquid ammonia/potassium permanganate leads to introduction of the imino group at C-2 forming the 1,2-dihydro-2-imino-1-methylquinolines and 1,2-dihydro-2-imino-1-methyl-1,X-naphthyridines (X = 5,8) respectively. 1,2-Dimethylquinolinium iodide, when subjected to treatment with liquid ammonia/potassium permanganate undergoes an oxo-demethylation reaction, yielding 1-methylquinol-2-one. The nmr-measurements of solutions of the above-mentioned salts in liquid ammonia clearly show the formation of a σ-adduct, strongly suggesting that these σ-adducts are intermediates in the imination reactions.

J. Heterocyclic Chem., **22**, 765 (1985).

Very recently it has been reported [2] that 1-methylquinolinium iodide (**1**) when dissolved in liquid ammonia at -33° and subjected to treatment with potassium permanganate, is converted into 1,2-dihydro-2-imino-1-methylquinoline (**3**). 2-Amino-1,2-dihydro-1-methylquinoline (**2**) is probably intermediate in this imination reaction.

Scheme 1

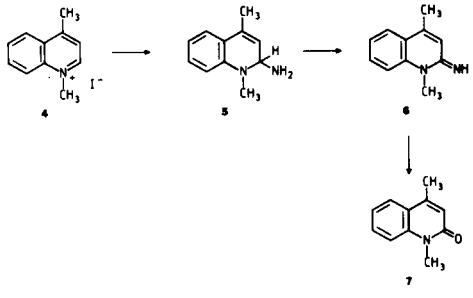


As *N*-alkyldihydroiminoazines are prepared so far by reacting aminoazines with an alkylating agent [3], we became interested in whether liquid ammonia/potassium permanganate would be a potentially useful reagent for the introduction of the imino groups into bicyclic *N*-alkylazinium salts. In this paper we present the results of our imination studies of some methyl derivatives of 1-methylquinolinium salts and of the 1-methyl-1,X-naphthyridinium salts (X = 5,8).

A. Quinolinium Salts.

On adding potassium permanganate to a solution of 1,4-dimethylquinolinium iodide (**4**) in liquid ammonia, a reaction mixture was obtained from which we were able to isolate by column chromatography and several recrystallisations the hydrogen iodide salt of 1,2-dihydro-2-imino-1,4-dimethylquinoline (**6**). The salt was identified by ^{1}H nmr spectroscopy; its free base by exact mass determination; nitrogen analysis of its picrate confirmed the presence of two nitrogen atoms. Since the work-up procedure of **6** leads to a considerable loss of product not allowing us to determine the correct yield, we heated the crude reaction mixture obtained in the imination reaction, with an aqueous solution of sodium hydroxide, allowing **6** to be converted into the more stable 1,4-dimethylquinol-2-one (**7**). The yield of **7** from **4** amounted to 80%, indicating that the conversion of **4** into **6** is about 90%. It has already

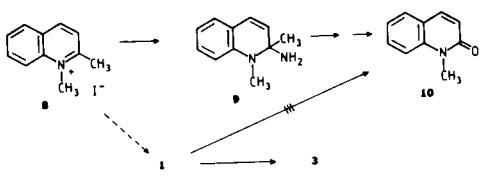
Scheme 2



been shown [4] by ^{1}H nmr spectroscopy that a solution of **4** in liquid ammonia features the presence of covalent σ-adduct **5** (see Table); it seems most likely that **5** is precursor of **6**. The high yield of **7** from **4** indicates that the imination by liquid ammonia/potasium permanganate, followed by base hydrolysis is a convenient one-pot reaction for preparing **7**; it provides us with a new method for preparing azinones.

Reaction of a solution of 1,2-dimethylquinolinium iodide (**8**) in liquid ammonia at -33° with potassium permanganate leads, unexpectedly, to 1-methylquinol-2-one (**10**, 80%). Since it was already established [4] that **8** when dissolved in liquid ammonia forms σ-adduct **9** (see Table), in which the amino group and the methyl group are attached at the same sp^3-carbon atom, it seems very likely that **9** is the intermediate in this oxo-demethylation. An alternative possibility, namely first demethylation (*via* oxidation into acid and decarboxylation into 1-methylquinolinium salt (**1**)

Scheme 3



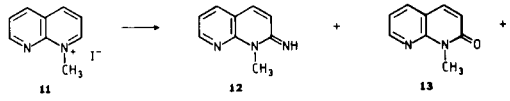
and than imination and hydrolysis), can be rejected, since it has already been established [2] that **1** under the same reaction conditions as applied for **8** leads to 1,2-dihydro-2-imino-1-methylquinoline (**3**) and not to **10**.

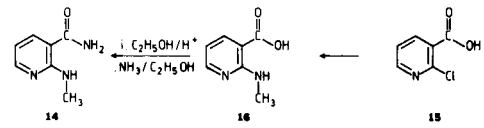
Oxo-demethylation, although under different reaction conditions, has been described [5]: treatment of 6-methyl-3,5-diphenyl-1,2,4-triazines with potassium permanganate in aqueous alkaline medium leads to the formation of the 3,5-diphenyl-1,2,4-triazin-6-one. No mechanism has been offered.

B. Naphthyridinium Salts.

A solution of 1-methyl-1,8-naphthyridinium iodide (**11**), when subjected to treatment with liquid ammonia/potassium permanganate yields 1,2-dihydro-2-imino-1-methyl-1,8-naphthyridine (**12**), isolated as its hydroiodide salt (15%), -1-methyl-1,8-naphthyrid-2-one (**13**) about 2% and 3% of a compound which structure was assigned, based on ^{1}H nmr spectroscopy and microanalysis, as 2-(methylamino)pyridine-3-carboxamide (**14**). That this structure assignment is correct, was proven by an independent synthesis. This synthesis involves the methylamino-dechlorination of 2-chloropyridine-3-carboxylic acid (**15**) into 2-(methylamino)pyridine-3-carboxylic acid (**16**), esterification of the carboxyl group in **16** and aminolysis of the ester group The structure of **12** was confirmed by base hydrolysis of**12** into **13**. It seems reasonable to suggest that the small amount of **13** is formed from **12** during the work-up procedure. When

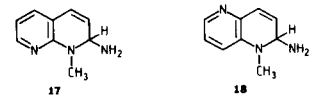
Scheme 4





the crude reaction product, being isolated after the reaction, was heated with an aqueous solution of sodium hydroxide, compound **13** was isolated in about 50-60% yield. Since this yield is much higher than that of **12** isolated after the reaction seems to indicate that during the work-up and isolation procedure of **12** a considerable part is lost, due to decomposition. Measurement of the ^{1}H nmr spectrum of a solution of **11** in liquid ammonia at -33° clearly exhibits the signals, of 2-amino-1,2-dihydro-1-methyl-1,8-naphthyridine (**17**) (see Table). This result strongly suggests that the σ-adduct **17** is intermediate in the imination reaction. The ^{1}H nmr spectrum did not change in the temperature range between -45° and +20°; adduct **17** is apparently thermodynamically the most stable one. Treatment of 1-methyl-1,5-naphthyridinium iodide (**19**) with liquid ammonia and potassium permanganate gave a deeply

Scheme 5



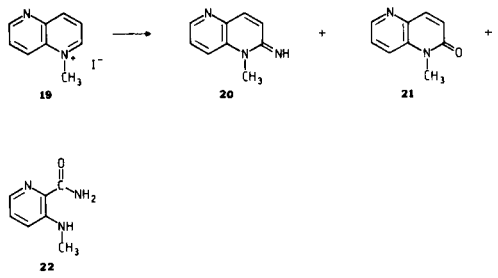
coloured reaction product, from which we could isolate 1,2-dihydro-2-imino-1-methyl-1,5-naphthyridine (**20**, 15%), 1-methyl-1,5-naphthyrid-2-one (**21**, 3%) and 3-(methylamino)pyridine-2-carboxamide (**22**, 3%). The structure of **20** was assigned by its ^{1}H nmr data and its microanalysis and confirmed by conversion of **20** into the known compound **21** by base treatment. The small amount of **21** is probably formed from **20** during the work-up procedure. The formation of **20** indicates that the initial addition of ammonia

Table

^{1}H-NMR data of the Ring Protons of the Quinolinium Salts **1**,**4**,**8**, the Naphthiridinium Salts **11**,**19** and their σ-Adducts in Liquid Ammonia

Compound	Solvent	H-2	H-3	H-4	H-5	H-6	H-7	H-8	CH_3	N-CH_3	$J_{2,3}$	$J_{3,4}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$
1-Methylquinolinium iodide (**1**)	D_2O	9.34	8.08	9.16						4.74					
2-Amino-1,2-dihydro-1-methylquinoline (**2**)	NH_3	4.65	5.82	6.54						2.89	5.4	9.6			
	$\Delta\delta$	4.69	2.26	2.62						1.85					
1,2-Dimethylquinolinium iodide (**8**)	D_2O	—	7.98	8.92					3.14	4.52					
2-Amino-1,2-dihydro-1,2-dimethylquinoline (**2**)	NH_3	—	5.62	6.43					1.69	2.89		9.6			
	$\Delta\delta$	—	2.36	2.49					1.45	1.63					
1,4-Dimethylquinolinium iodide (**4**)	D_2O	9.14	7.98	—					3.01	4.64					
2-Amino-1,2-dihydro-1,4-dimethylquinoline (**5**)	NH_3	4.55	5.65	—					1.96	2.87	5.4				
	$\Delta\delta$	4.59	2.33	—					1.05	1.77					
1-Methyl-1,5-naphthyridinium iodide (**19**)	D_2O	9.52	8.43	9.28	—	9.38	8.32	9.03		4.84	5.8	8.2	—	4.5	8.7
2-Amino-1,2-dihydro-1-methyl-1,5-naphthyridine (**18**)	NH_3	4.73	6.13	6.62	—	7.82	7.15	6.96		2.92	4.8	9.6	—	4.5	8.0
	$\Delta\delta$	4.79	2.30	2.66	—	1.56	1.17	2.07		1.92					
1-Methyl-1,8-naphthyridinium iodide (**11**)	D_2O	9.60	8.29	9.34	8.94	8.17	9.40	—		4.79	5.8	8.4	8.0	4.2	—
2-Amino-1,2-dihydro-1-methyl-1,8-naphthyridine (**17**)	NH_3	4.86	5.79	6.49	7.25	6.57	7.91	—		3.00	4.5	9.0	7.1	5.1	—
	$\Delta\delta$	4.74	2.50	2.85	1.69	1.60	1.49	—		1.79					

Scheme 6

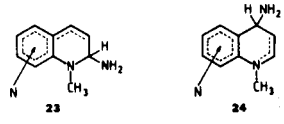


has taken place at position 2 of **19**. The presence of intermediate **18** has been confirmed by ^1H nmr studies. As shown in the table, when **19** is dissolved in liquid ammonia the hydrogen at C-2 is considerably shifted upfield ($\Delta\delta$ = 4.79) proving the formation of σ-adduct **18**. The $\Delta\delta$-value, due to the rehybridisation of C-2 (sp^2 (in **19**) to sp^3 (in **18**)) is in agreement with $\Delta\delta$-values reported in the literature [6]. The ^1H nmr spectrum did not change in the temperature range -45° to +20°.

Discussion.

The results obtained in this study clearly show that the quinolinium- and 1,X-naphthyridinium ions (X = 5,8) eas ily undergo covalent amination at position 2. Even in the 1,2-dimethylquinolinium salt **8**, which features the presence of the electron-donating methyl group at C-2, the addition of the ammonia at C-2 takes place. This result is in agreement with results of molecular orbital calculations [7] on the amination of quinoline and naphthyridines which predicted a favoured addition of nitrogen nucleophiles at C-2 in these bicyclic systems. Recently it could be established [8] that the site of attack of nitrogen nucleophiles to azines is not only determined by the electron density, but also by the temperature; addition of the amide ion to quinoline takes place at C-2 at -33°, but at C-4, when the temperature is increased to +10°; addition of ammonia to pteridines occurs at C-4 at -33°, but at C-6 and C-7 when the addition takes place at +10° [9] Apparantly the site of addition is kinetically or thermodynamically controlled. It could be expected based on kinetic as well as thermodynamic reasons that in quaternized azinium salts the carbon atom adjacent to the quaternized ring nitrogen is more favoured for nucleophilic attack than the position γ to the ring nitrogen. Moreover, in the C-2 adduct **23** the π-electrons are more delocalised than in the C-4 adduct **24**, corresponding to a transition state in the reaction pathway with the lowest activation energy.

Scheme 7



EXPERIMENTAL

Melting points are uncorrected. The ^1H nmr spectra were recorded on a Hitachi Perkin Elmer R-24 or a Varian EM 390 spectrometer with TMS or DSS as internal standard (δ = 0 ppm). In liquid ammonia the chemical shifts of the protons were measured against the ammonia signal (δ = 0.95 ppm) as standard. The mass spectra were determined using an AEI MS 902 mass spectrometer, equipped with a VG-ZAB 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.

Preparation of the Starting Materials.

1-Methylquinolinium iodide (**1**) [10], 1,4-dimethylquinolinium iodide (**4**) [11], 1,2-dimethylquinolinium iodide (**8**) [12], 1-methyl-1,5-naphthyridinium iodide (**19**) [13] and 1-methyl-1,8-naphthyridinium iodide (**11**) [14] were described according to published procedures.

Procedure of Imination of Quinolinium Salts.

To a solution of 2 mmoles of the starting material in 25-30 ml of liquid ammonia 2 mmoles of potassium permanganate were added. The reaction mixture was stirred for 4 hours at -33°. After evaporation of the ammonia the reaction product was dissolved in water, the solution was filtered and then the solvent was evaporated off to dryness. The ^1H nmr and mass spectrum were made of the crude residue. The imino compound formed was partly present as hydrogen iodide salt but attempts to isolate this salt in the pure state were not successful. To obtain good analytical data the crude imino compound was converted into the corresponding picrate. Hydrolysis of the imino compound to the corresponding oxo compound was carried out by heating with aqueous 5*N* potassium hydroxide during 4 hours. After neutralization of the solution with concentrated hydrochloric acid the oxo compound was extracted with chloroform.

Imination of 1-Methylquinolinium Iodide (**1**).

1,2-Dihydro-2-imino-1-methylquinoline (**3**) was obtained in a yield of about 90%; exact mass 158.0846. Calcd. for $C_{10}H_{10}N_2$: 158.0844; ^1H nmr (deuteriomethanol): δ 7.03 (d, H-3), 8.10 (d, H-4), 7.50-7.80 (broad, H 5-8), 3.85 (s, CH_3), $J_{3,4}$ = 8.5 Hz; mp picrate 244-246°, yellow needles (from methanol).

Anal. Calcd. for $C_{10}H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 49.61; H, 3.38; N, 18.08; mol wt 287.3. Found: C, 49.82; H, 3.36; N, 17.98.

On hydrolysis of the crude reaction mixture with an aqueous alkaline solution, 1-methylquinol-2-one was obtained (yield 80%); mp 68-69° (from petroleum ether, 40-60°, lit [15] mp 73-74°; exact mass 159.0681. Calcd. for $C_{10}H_9NO$ 159.0684; ^1H nmr (deuteriomethanol): δ 6.75 (d, H-3), 7.94 (d, H-4), 7.10-7.70 (broad, H 5-8), 3.78 (s, CH_3), $J_{3,4}$ = 10 Hz; mp picrate, 126-127°, yellow needles (from methanol).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H. 5.70; mol wt 159.18. Found: C, 75.65; H. 5.71.

Anal. Calcd. for $C_{10}H_9NO \cdot C_6H_3N_3O_7$: C, 49.49; H, 3.12; mol wt 388.29. Found: C, 49.13; H, 3.32.

Imination of 1,4-Dimethylquinolinium Iodide (**4**).

1,2-Dihydro-1,4-dimethyl-2-iminoquinoline (**6**) was obtained in a yield of about 60%; exact mass 172.0999. Calcd. for $C_{11}H_{12}N_2$: 172.1000; ^1H nmr (deuterium oxide): δ 6.65 (s, H-3), 7.35-7.85 (broad, H 5-8), 3.49 (s, N-CH_3), 2.38 (s, CH_3); mp picrate 273-274°, yellow needles (from methanol).

Anal. Calcd. for $C_{11}H_{12}N_2 \cdot C_6H_3N_3O_7$: C, 50.87; H, 3.77; N, 17.45; mol wt 401.33. Found: C, 50.80; H, 3.63; N, 16.98.

On hydrolysis of the reaction mixture, 1,4-dimethylquinol-2-one (**7**) was obtained in a yield of 65%, mp 129-130° (from petroleum ether 60-80°), lit [16] mp 129.5-130.5°; exact mass 173.0847. Calcd. for $C_{11}H_{11}NO$: 173.0841; ^1H nmr (deuteriomethanol): δ 6.50 (s, H-3), 7.20-7.80 (broad, H 5-8), 3.61 (s, N-CH_3), 2.40 (s, CH_3); mp picrate 159-160°, yellow needles (from methanol).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; mol wt 173.21. Found: C, 76.22; H, 6.30.

Anal. Calcd. for $C_{11}H_{11}NO{\cdot}C_6H_3N_3O_7$: C, 50.75; H, 3.51; mol wt 402.31. Found: C, 50.74; H, 3.69.

Imination of 1,2-Dimethylquinolinium Iodide (**8**).

After extraction of the reaction mixture with water 1-methylquinol-2-one was isolated in a yield of 80-85%. This compound was identical (mp, exact mass, ^{1}H nmr and microanalysis) with the product obtained by hydrolysis of **3**.

Procedure of Imination of the Naphthyridinium Iodides **11** and **19**.

To a solution of 4 mmoles of the appropriate 1-methylnaphthyridinium iodide in 40-50 ml of liquid ammonia, 8 mmoles of potassium permanganate was added and the mixture was stirred for an additional 20 minutes. The ammonia was evaporated off and 40-50 ml of water was added to the residue. After continuous extraction of the aqueous solution with chloroform and evaporating off the solvent, the residue obtained was dissolved in 50 ml of methanol, boiled with charcoal, filtered and evaporated to dryness. The yellow residue was dissolved in a small amount of a 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 using an appropriate eluent (see below). The bands, which show uv absorbance were extracted with a mixture of chloroform and methanol (1:1). Residues obtained after evaporation of the solvent were worked up as given below in each of the more detailed procedures.

Imination of 1-Methyl-1,8-naphthyridinium Iodide (**11**).

The chromatograms were developed using a mixture of chloroform-methanol (10:0.5). Three main bands were obtained. The residue, obtained from the first band (*i.e.* the one with the lowest Rf-value) was dissolved in 250 ml of boiling chloroform, filtered and concentrated to 10 ml. After cooling 112 mg of the hydroiodide salt of the 2-imino compound **12** was obtained, melting range 250-265°; ir (potassium bromide): 3250, 3100 cm^{-1} (NH) and 1640 cm^{-1} (C=N); ^{1}H nmr (deuteriomethanol/deuteriochloroform): δ 8.75 (dd, H-7), 8.11 (dd, H-5), 7.93 (d, H-4), 7.42 (dd, H-6), 7.40 (d, H-3), 3.37 (s, CH_3), $J_{3,4}$ = 9.0 Hz, $J_{5,6}$ = 8.0 Hz, $J_{5,7}$ = 1.8 Hz, $J_{6,7}$ = 4.5; mp picrate, 252-254°, yellow needles (from methanol).

Anal. Calcd. for $C_9H_9N_3{\cdot}C_6H_3N_3O_7$: C, 46.40; H, 3.12; mol wt 388.3. Found: C, 46.18; H, 3.23.

The solid material, obtained from the second band, was crystallized from benzene to give 18 mg (3%) of **14**, mp 182-184°; exact mass 151.0745. Calcd. for $C_7H_9N_3O$: 151.0746; ir (potassium bromide): 3370, 3270, 3170 cm^{-1} (NH); 1700 cm^{-1} (C=O), 1630 cm^{-1} (NH), ^{1}H nmr (deuteriochloroform): δ 8.29 (dd, H-6), 8.19 (broad s, NH), 7.59 (dd, H-4), 6.49 (dd, H-5), 5.63 (broad s, NH_2), 3.04 (d, CH_3), $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.8 Hz, $J_{5,6}$ = 4.8 Hz, J_{NH,CH_3} = 4.82 Hz. The compound is fully identical with 2-(methylamino)pyridine-3-carboxamide prepared independently (see further).

Anal. Calcd. for $C_7H_9N_3O$: C, 55.61; H, 6.00; mol wt 151.2. Found: C, 55.31; H, 6.07.

The oily residue, obtained after extraction of the third band (the one with the highest Rf) and evaporation of the solvent, was dried *in vacuo* at room temperature and then recrystallized from petroleum ether (60-80°) to give 8 mg (1.5%) of **13**, mp 95-96°, white needles. The compound was shown to be identical (mp, mixed mp, ir) with 1-methylnaphthyridin-2-one synthesized independently [17].

Imination of 1-Methyl-1,5-naphthyridinium Iodide (**19**).

The development of the chromatogram with the eluents, consisting of a mixture of chloroform/methanol 10:1 gave three bands. After extraction of the first band (*i.e.* the one with the lowest Rf-value) and evaporation of the solvent, a residue was obtained, which was dissolved in chloroform (200 ml). After filtration the solution was concentrated to about 10 ml and the precipitate obtained was filtered off (mother liquor A), yield, 35 mg of the hydroiodide salt of the 2-imino compound **20**, melting range 270-287° dec; ir (potassium bromide): 3230 cm^{-1} (NH), 1660 cm^{-1} (C=N), 1640 cm^{-1} (NH); ^{1}H nmr (deuteriomethanol): δ 8.81 (dd, H-6), 8.47 (dd, H-8), 8.29 (d, H-4), 7.81 (dd, H-7), 7.40 (d, H-3), 3.98 (s, CH_3), $J_{3,4}$ = 9.0 Hz, $J_{6,7}$ = 4.5 Hz, $J_{6,8}$ = 1.0 Hz, $J_{7,8}$ = 9.0 Hz; mp picrate, 244-246° (from methanol).

Anal. Calcd. for $C_9H_9N_3{\cdot}C_6H_3N_3O_7$: C, 46.40; H, 3.12; N, 21.65 mol wt 388.3. Found: C, 46.54; H, 3.22; N, 21.46.

By further evaporation of the mother liquor A an additional amount of the hydroiodide salt of **20** (65 mg) was obtained, picrate (mp 244-246°), mixed mp with the picrate mentioned above gave no depression. The residue obtained after extraction of the second band was sublimed at 100°/0.2 mm, yielding 18 mg (3%) of **21**, mp 104-106°, (lit [13] mp 104-105°. The compound is identical (ir and ^{1}H nmr spectra) with the product obtained in the base hydrolysis of **19** (see later). After extraction of the third band and evaporation of the solvent a residue was obtained, which was dissolved in boiling petroleum ether (40-60°). Filtration and evaporation of the solvent till about 5 ml gave 16 mg (3%) of the pyridine derivative **22** mp 140-142°, light-yellow needles; exact mass 151.0744. Calcd. for $C_7H_9N_3O$ 151.0740; ir (potassium bromide): 3420, 3340, 3250, 3180 (NH); 1670 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 8.17 (broad s, NH_2), 7.78 (dd, H-6), 7.24 (dd, H-5), 7.00 (dd, H-4), 5.53 (broad s, NH), 2.89 (d, CH_3), $J_{4,5}$ = 8.5 Hz, $J_{4,6}$ = 1.5 Hz, $J_{5,6}$ = 4.5 Hz, J_{NH,CH_3} = 6.0 Hz.

Hydrolysis of the 1,2-Dihydro-2-imino-1-methyl-1,X-naphthyridinium HydroIodides (X = 5,8).

The hydroiodide of **12** or **20** (30 mg) was dissolved in 10 ml of 10% aqueous sodium hydroxide solution and this solution was heated for 4 hours on a boiling water bath. After cooling, the solution was extracted with chloroform. The residue, obtained after stripping of the solvent, was recrystallized from petroleum ether (60-80°) yielding 10-15 mg of the appropriate naphthyridin-2-one 1-Methyl-1,5-naphthyridin-2-one, mp 104-106° (lit [13] mp 104-105°); 1-methyl-1,8-naphthyridin-2-one, mp 95-96°, (lit [14] mp 94-95°). There is complete ir identity with the authentic specimen.

Conversion of the naphthyridinium salts **11** and **19** into the corresponding naphthyridin-2-ones **13** and **21** by treatment with ammonia/potassium permanganate and subsequent alkaline hydrolysis.

To a solution of 0.42 g (2.6 mmoles) of potassium permanganate in 20 ml of liquid ammonia, 0.345 g (1.3 mmoles) of 1-methyl-1,5- or -1,8-naphthyridinium iodide was added. After stirring this mixture for 25 minutes the ammonia was evaporated. The residue obtained was heated with 20 ml of 10% aqueous sodium hydroxide solution under reflux for 4 hours. The solution was extracted with chloroform. After drying the chloroform solution and evaporating off the solvent the residue was crystallized from petroleum ether (60-80°). From **11** 0.12 g (54%) of **13** was obtained and from **19** 0.046 g (35%) of **21**. The compounds are identical with reference samples.

2-(Methylamino)pyridine-3-carboxylic Acid (**16**).

A mixture of 2.1 g (13.3 mmoles) of 2-chloropyridine-3-carboxylic acid (**15**) [18] and 15 ml of 40% aqueous solution of methylamine was heated in a sealed tube at 120° for 15 hours. After having removed the water and excess of methylamine *in vacuo*, the residue obtained was shaken with 30 ml of 2% of aqueous sodium hydroxide solution for 5 minutes. After removing the solvent *in vacuo* and dissolving the residue in water (30 ml), the solution was acidified with acetic acid to *p*H 5 and subsequently extracted with chloroform for 20 hours. The residue obtained after stripping off the solvent gave 1.13 g (56%) of **16**, mp 264-266° (from ethanol and sublimation); ir (potassium bromide): 3340 cm^{-1} (NH), 1660, 1680 (CO); ^{1}H nmr (DMSO-d_6): δ 8.30 (dd, H-6), 8.09 (dd, H-4), 6.60 (dd, H-5), 2.99 (s, CH_3), $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.0 Hz, $J_{5,6}$ = 5.0 Hz.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; mol wt (152.14). Found: C, 55.48; H, 5.62.

2-(Methylamino)pyridine-3-carboxamide (**14**).

A solution of 1.33 g (8.7 mmoles) of **16** in 40 ml of absolute ethanol, which contains 3 ml of concentrated sulphuric acid, was refluxed for 20

hours. After evaporation of the solvent, 50 ml of water was added to the residue. The solution was neutralized with sodium carbonate, and extracted with chloroform. After drying and removing of the solvent a residue was obtained which was recrystallized from pentane (by cooling in solid carbon dioxide/acetone), yield 450 mg (29%) of ethyl 2(methylamino)pyridine-3-carboxylate mp 49-50°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; mol wt 180.20. Found: C, 60.21; H, 6.97.

Heating of above-mentioned ester with ethanol, saturated at 0° with ammonia in a sealed tube at 120° for 20 hours gave after the usual work-up in 40% yield compound **14**, mp 182-184° (benzene). This compound has ir and ^1H nmr identity with the compound obtained in the imination reaction of **11**.

Acknowledgement.

We are indebted to Drs. C. A. Landheer and Mr. C. J. Teunis for mass spectrometric data, to Mr. A. van Veldhuizen for measuring nmr spectra and to Mr. H. Jongejan for determination of the micro-analytical data.

REFERENCES AND NOTES

[1] Part **42** on σ-adduct formation. For part **41** see H. Tondys, H. C. van der Plas and M. Wozniak, *J. Heterocyclic Chem.*, **22**, 353 (1985).

[2] H. C. van der Plas and D. J. Buurman, *Tetrahedron Letters*, 3763 (1984).

[3] A. E. Tschitschibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54**, 814 (1921).

[4] S. A. G. F. Angelino, B. H. van Valkengoed, D. J. Buurman, H. C. van der Plas and F. Müller, *J. Heterocyclic Chem.*, **21**, 107 (1984).

[5] R. Metze and S. Meyer, *Chem. Ber.*, **90**, 481 (1957).

[6] See H. C. van der Plas, M. Wozniak and H. J. W. van den Haak, *Adv. Heterocyclic Chem.*, **33**, 96-146 (1983).

[7] M. Hirota, K. Abe, H. Endo and H. Masuda, *Rep. Asaki Glass Found. Ind. Technol.*, **35**, 109 (1979); M. Hirota, H. Masuda, Y. Hamada and I. Takeuchi, *Bull. Chem. Soc. Japan*, **52**, 1498 (1979).

[8] See reference 1; J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King and P. E. Kandetzki, *J. Org. Chem.*, **38**, 1947 (1973).

[9] A. Nagel. H. C. van der Plas and A. van Veldhuizen, *Rec. Trav. Chim.*, **94**, 45 (1975).

[10] W. Marchwald and E. Meijer, *Ber.*, **33**, 1884 (1900).

[11] D. Sutherland and C. Compton, *J. Org. Chem.*, **17**, 1257 (1952).

[12] O. Doebner and W. v. Miller, *Ber.*, **16**, 2464 (1883).

[13] H. Rapoport and A. D. Batcho, *J. Org. Chem.*, **28**, 1753 (1963).

[14] W. W. Paudler and F. J. Kress, *J. Heterocyclic Chem.*, **5**, 561 (1968).

[15] E. Späth and F. Galinoosky, *Ber.*, **69**, 2059 (1936).

[16] C. E. Kaslow and D. J. Cook, *J. Am. Chem. Soc.*, **67**, 1969 (1945).

[17] E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. (C)*, 1564 (1967).

[18] L. R. Fibel and P. E. Spoerri, *J. Am. Chem. Soc.*, **70**, 3908 (1948).