THE FORMATION OF 1-METHYL-3-NICOTINOYLPYRROLIDINE FROM NICOTINE-1'-OXIDE

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Abstract— Several new compounds were obtained when nicotine-1'-oxide was treated with ferric nitrate in the presence of tartaric acid, the most unexpected being 1-methyl-3-nicotinoylpyrrolidine. A unified mechanism is proposed to explain the formation of this substance and other pyridine derivatives.

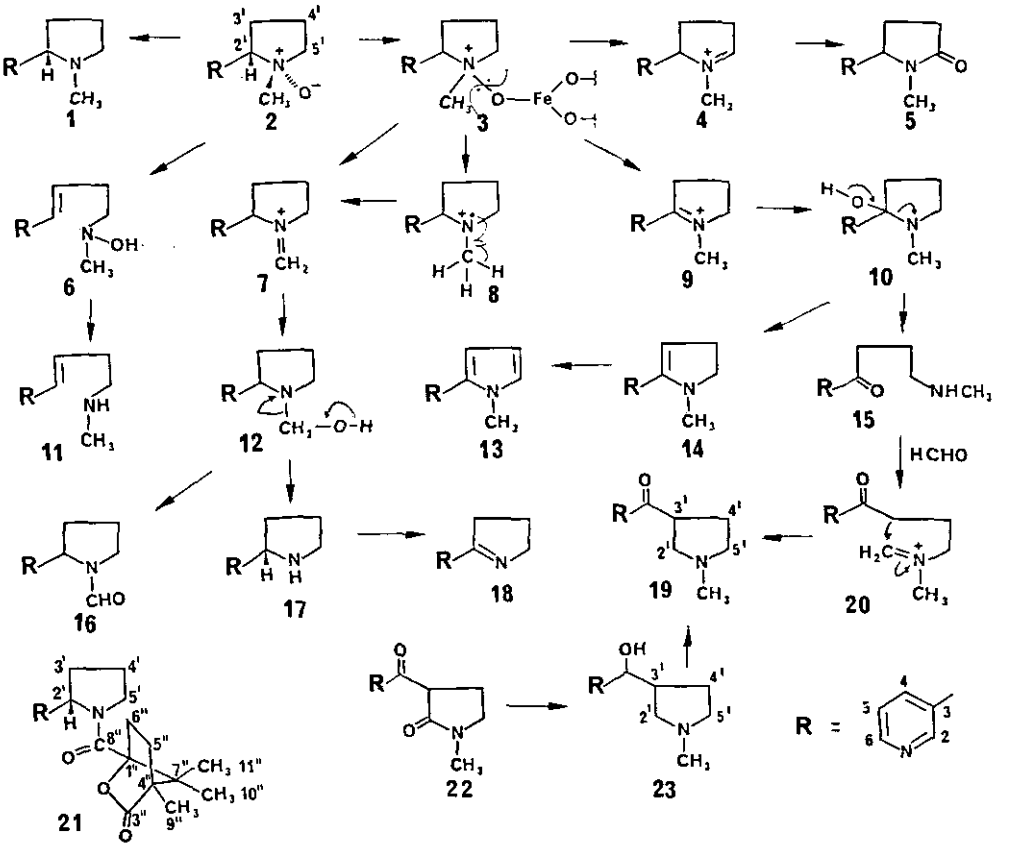
In 1964 Craig and co-workers[1] described the reaction of nicotine-1'-oxide (2) with ferric nitrate in the presence of tartaric acid at a pH of 6.8 which led to the formation of the following compounds, yields being indicated in [ ]: nicotine (1) [4.1], N-methylmyosmine (14) [2.9], nornicotine (17) [77.2], myosmine (18) [9.5], nicotyrine (13) [0.6], cotinine (5) [0.4] together with several unidentified bases. We have re-examined this reaction since we were searching for a method of obtaining (S)-nornicotine[2] from the readily available nicotine which is found in tobacco as the optically pure (S)-isomer. Acheson and co-workers[3], also looking for a good method of demethylating nicotine, reported that this method gave very poor yields of nornicotine. Jacob and co-workers[4] utilized a modification of Craig's reaction to establish the enantiomeric purity of nicotine. In the IR procedure nicotine was treated with m-chloroperbenzoic acid. The resultant 1'-oxide was then heated on a steam bath with ferrous sulfate. The basic products from this reaction were then allowed to react with (1S)-(-)-camphanic acid chloride. The diastereomeric amides of (R)- and (S)-nornicotine thus formed, were then analyzed by capillary GC. We found that Jacob's procedure, carried out on crystalline (1'S, 2'S)-nicotine-1'-oxide[4] (2) produced only about 10% nornicotine, which was however, optically pure (> 99% (S). The major product was nicotine. Following the earlier procedure of Craig[1] we were able to obtain 25-35% yields of (S)-nornicotine from 2

(on 10-100 mmol scale). The optical purity of the nornicotine, determined by Jacob's method and by direct measurement of its optical rotation[6] was > 99%. The crude mixture of basic compounds obtained from the nicotine-1'-oxide was separated by chromatography and also analyzed by capillary GC. The major components of the reaction mixture were (S)-nicotine and (S)-nornicotine. Much smaller amounts (see Experimental) of cotinine, myosmine, nicotyrine, and ψ-oxynicotine (15)[7] were obtained. Compounds, which have been described in the literature, but were not previously reported by Craig, were metanicotine (11)[8] and N'-formylnornicotine[9] (16). This formyl derivative was synthesized in good yield by refluxing nornicotine with ethyl formate. It afforded a monopicrate and all the signals in its ^{13}C-nmr spectrum appeared as doublets due to restricted rotation at the amide bond. A new compound obtained from 2 was a colorless oil which had no optical activity. Its high resolution ms indicated a molecular formula of $C_{11}H_{14}N_2O$, having one more carbon than the starting material. Its ir and ^{13}C-nmr spectra indicated the presence of a ketone group. Its ^{1}H and ^{13}C-nmr spectra were consistent with 1-methyl-3-nicotinoylpyrrolidine (19), a compound not previously described. This structure was confirmed by synthesis. Reduction of 1-methyl-3-nicotinoyl-2-pyrrolidone (22)[10] with lithium aluminum hydride yielded the alcohol (23) as a mixture of two diastereomers. Oxidation of this mixture of alcohols with chromium trioxide in acetic acid afforded 19. It was also obtained by a Mannich reaction between ψ-oxynicotine and formaldehyde. It should be noted that this Mannich reaction, if it proceeds via the iminium ion 20 is disfavored (5-endo-Trig) according to the Baldwin Rules.[11]

The mechanism whereby N-methyl-tertiary amine-N-oxides undergo demethylation and related reactions has been discussed by Craig[1,12]. An extended version of his mechanism is illustrated in Scheme 1. It was proposed that the nicotine-1'-oxide forms a bond with ferric ion which is complexed with tartaric acid as in the partial structure 3. A homolytic fission of the N—O bond then affords the radical cation (8). Loss of a hydrogen atom then affords the iminium ion 7. An alternate route to this iminium ion would be by a proton loss from the methyl group of 3 and a heterolytic cleavage of the N—O bond. Hydration of the iminium ion 7 affords N'-hydroxymethylnornicotine (12) and this carbinolamine then decomposes to yield formaldehyde and nornicotine (17). It was proposed that nicotine (1) is formed by reduction of the 1'-oxide with this formaldehyde which is oxidized to formic acid. Scheme 1 also illustrates the possible way in which the other products are formed. N'-Formylnornicotine (16) results from oxidation of the N'-hydroxymethylnornicotine. The iminium ion 4 results from loss of a hydrogen at the C-5' position of 3. Subsequent hydration and oxidation then yields cotinine (5). Loss of a hydrogen from the C-2' position of 3 yields

the iminium ion 9 which is hydrated to 10. Ring opening of this carbinolamine yields ψ-oxynicotine (15). The 1-methyl-3-nicotinoylpyrrolidine (19) then arises by a Mannich reaction between this compound and formaldehyde derived from the decomposition of 12. Metanicotine (11) could be formed by reduction of the hydroxylamine derivative 6 which could arise by a Cope elimination on the 1'-oxide 2. Nicotyrine (13) is formed by oxidation of N-methylmyosmine (14) formed by dehydration of 10. Myosmine (18) is an oxidation product of nornicotine.

Scheme I



The Experimental Section also describes formation of the camphanate 21 on a preparative scale, previous reference[4] to this compound being on a microanalytical scale.

EXPERIMENTAL

General Methods. All melting points were determined in open capillary tubes and are corrected. Nmr spectra were determined in a Nicolet 300 spectrometer operating at 300 and 75.5 MHz respectively for ^{1}H and ^{13}C, with the assistance of Dr. S.B. Philson. All recorded spectra are ppm from Me_4Si. Mass spectra were determined on an AE1-30 mass spectrometer by Dr. E. Larka and his assistants. Ir spectra were determined on a Beckman Acculab 1 instrument. Elemental analyses were carried out by M-H-W Laboratory, Phoenix, AZ. GC analyses were carried out in a Hewlett Packard Model 5890A GC on a 25 m glass capillary column coated with cross-linked methyl silicone (0.53 microns thick), internal diameter 0.31 mm. The following instrument parameters were used: He Flow rate 1 ml/min, injection temp 250°C, initial oven temp 50 °C, equilibration time 4 min. Program A: rate of temp increase 30°C/min to 250°C then kept at this temp for a total time of 30 min. Program B: rate of temp increase 30°C/min to 100°C, then 2°C/min to 180°C, finally 30°C/min to 250°C, and then kept at this temp for a total time of 60 min.

(RS)-N'-Formylnornicotine (16). (RS)-Nornicotine[2] (1.48 g, 10 mmol) was refluxed in ethyl formate (50 ml) for 18 h. The residue obtained on evaporation of the ethyl formate was distilled (170°C, 10^{-4} mm Hg) affording (RS)-N'-formylnornicotine as a colorless oil (1.70 g, 97%). TLC on SiO_2 PF-254, developing with $CHCl_3$/MeOH/conc NH_3 (90/10/1) R_f 0.8 (nornicotine 0.2). ^{13}C Nmr ($CDCl_3$). All signals appeared as doublets due to restricted rotation at the amide bond. The ratio of the E to the Z isomer (assigned by comparison with the ^{13}C NMR spectrum of dimethylformamide[13] was 1.5, the more abundant isomer being listed first: δ 22.6, 23.8 (4'), 35.1, 34.3 (3'), 44.5, 47.0 (5'), 59.0, 56.7 (2'), 123.7, 123.4 (5), 133.7, 133.4 (4), 137.8, 138.2 (3), 148.9, 147.6 (2 or 6), 149.1, 148.2 (2 or 6), 161.8, 161.2 (C=O). Ir (neat) 2940 (CH st. of CHO), 1670 (C=O) cm^{-1}. Ms m/z (relative intensity) 176 (M^+, 100), 147 (M-CHO, 72), 119 (54), 98 (42), 70 (46). It afforded a monopicrate, yellow needles from EtOH, mp 142-143°C. Anal. Calcd for $C_{16}H_{15}N_5O_8$: C, 47.41; H, 3.77; N, 17.28. Found: C, 47.52; H, 3.91; N, 17.14.

(2'S)-Nornicotine-(1"S)-camphanate (21). (S)-Nornicotine (148 mg, 1 mmol) in EtOAc (10 ml) was added to a solution of (1S)-(-)-camphanic acid chloride (Aldrich) (230 mg, 1.06 mmol) in EtOAc (10 ml) and the mixture was shaken with aqueous 0.2 M K_2CO_3 (10 ml) at room temp for 2 h. The organic layer was separated, dried (Na_2SO_4) and evaporated to afford a white crystalline residue. Crystallization from a mixture of EtOAc and pentane afforded (2'S)-nornicotine-(1"S)-camphanate (238 mg, 73%) as stout needles, mp 112-113°C. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.59; H, 7.39; N, 8.49. $[\alpha]_D^{25}$ - 60.5

(c 1.216 in MeOH). ^{13}C Nmr ($CDCl_3$). All signals appear as doublets due to restricted rotation at the amide bond, the more abundant isomer (30%) being listed first. δ 148.28, 148.47 (2), 138.22, 140.10 (3), 132.84, 133.19 (4), 123.29, 122.97 (5), 146.96, 147.12 (6), 60.39, 59.82 (2'), 32.83, 35.34 (3'), 24.29, 19.49 (4'), 48.62, 48.43 (5'), 92.66, 92.41 (1"), 178.50, 177.49 (3"), 54.03, 53.58 (4"), 29.00, 29.20 (5"), 31.19, 32.22 (6"), 54.73, 55.12 (7"), 165.55, 166.97 (8"), 9.52, 9.31 (9"), 17.41, 17.65 (10"), 16.85, 16.56 (11"). MS m/z (relative intensity) 328 (M^+, 28), 175 (30), 147 (100), 106 (53), 83 (48). (2'RS)-Nornicotine-(1"S)camphanate prepared similarly from (RS)-nornicotine had mp 97-98°C. The GC retention times using program A for the (2'R) and (2'S)-nornicotine-(1"S)-camphanates were 25.17 and 25.59 min respectively, their FID response being essentially identical.

(RS)-1-Methyl-3-nicotinoylpyrrolidine (19). (a) From ψ-Oxynicotine (15). ψ-Oxynicotine.2 HCl[7] (2.33 g, 10 mmol) was dissolved in H_2O (20 ml) and the pH adjusted to 8.3 with solid Na_2CO_3. Formaldehyde (1 ml of 37%, 12.3 mmol) was added and the mixture shaken at 25°C for 48 h. The mixture was made strongly basic with 10% NaOH and extracted with $CHCl_3$. The dried (N_2SO_4) extract was evaporated, and the residue was subjected to preparative tlc on SiO_2 PF-254, developing with $CHCl_3$/MeOH/conc NH_3 (90/10/1). Extraction of the major zone (R_f 0.8) with MeOH, afforded on evaporation and distillation (140°C, 10 mm Hg) (RS)-1-methyl-3-nicotinoylpyrrolidine as a colorless oil (1.02 g, 53%) ir (neat) 2945, 2840, 2785, 1690 (C=O), 1590 cm^{-1}. ^1H Nmr ($CDCl_3$) δ 2.17 (q, J = 7.6 Hz, 2H, 4'), 2.35 (s, 3H, NMe), 2.60 (m, 2H, 5'), 2.82 (m, 2H, 2'), 3.90 (pentet, J = 7.5 Hz, 1H, 3'), 7.40 (dd, J = 8.1, 5.5 Hz, 1H, 5), 8.21 (dt, J = 8.1, 2.1 Hz, 1H, 4), 8.75 (dd, J = 5, 1.7 Hz, 1H, 6), 9.12 (d, J = 2.2 Hz, 1H, 2). ^{13}C Nmr ($CDCl_3$) δ 27.7 (4), 41.5 (NMe), 45.5 (3'), 55.8 (5'), 57.8 (2'), 123.3 (5), 131.2 (3), 135.5 (4), 149.5 (2), 153.0 (6), 198.7 (C=O). MS m/z (relative intensity) 190 (M^+, 35), 173 (23) 134 (28), 106 (23), 84 (63), 82 (25), 57 (100), 51 (25), 42 (66). High *resolution ms: Found 190.1110, $C_{11}H_{14}N_2O$ requires 190.1106.* It afforded a dipicrate, yellow needles from EtOH, mp 200-201°C. Anal. Calcd for $C_{23}H_{20}N_8O_{15}$: C, 42.60; H, 3.11; N, 17.28. Found: C, 42.81; H, 3.29; N, 17.09.

(b) From 1-Methyl-3-nicotinoyl-2-pyrrolidone (22). Lithium aluminum hydride (1.0 g, 26 mmol) was added to a solution of the pyrrolidone **22**[10] (GC-ret. time 14.20, program A) (2.04 g, 10 mmol) in Et_2O (200 ml), and the mixture was refluxed for 18 h. Aqueous 10% NaOH (10 ml) was then added and after refluxing for 1 h the mixture was filtered. The residue obtained on evaporation of the filtrate was subjected to preparative tlc on SiO_2 PF-254, developing with $CHCl_3$/MeOH/conc NH_3 (90/10/1). The major zone (R_f 0.3) was extracted with MeOH, evaporated and the residue distilled (160°C, 10^{-4} mm Hg) to afford 1-methyl-3(hydroxy-(3-pyridyl)methyl)pyrrolidine (23) as a colorless viscous oil (1.04 g, 54%), GC-ret. time 12.91,

program A. The ^{13}C Nmr ($CDCl_3$) spectrum indicated that this product is a mixture of diastereomers, the more abundant (64%) being listed first. δ 28.5, 24.4 (4'), 41.6, 41.4 (NMe), 44.6, 44.3 (3'), 55.8, 55.5 (5'), 57.8, 60.9 (2'), 75.4, 74.9 (benzylic C), 123.3, 123.5 (5), 133.9, 133.8 (4), 140.1, 139.3 (3), 148.0, 147.8 (6), 148.2, 148.1 (2). MS m/z (relative intensity) 192 (M^+ 100), 134 (37), 83 (47). Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.83; H, 8.38; N, 14.47. Only oily material was obtained on attempts to prepare a picrate. The alcohol **23** (60 mg) dissolved in a mixture of acetic acid (5 ml) and H_2O (1 ml) was stirred with CrO_3 (60 mg) for 4 h. The solution was then evaporated, the residue was made basic with 10% NaOH and extracted with $CHCl_3$. The residue obtained on evaporation of this extract was subjected to preparative tlc as described in part (a) yielding 1-methyl-3-nicotinoylpyrrolidine (40 mg) identical (GC, nmr, ir, dipicrate) with the previously described material.

(1'S, 2'S)-Nicotine-1'-oxide (2). This was prepared by reaction of (S)-nicotine (Aldrich, freshly distilled) with m-chloroperbenzoic acid.[5] It was obtained as colorless delequescent

Table I. Products Obtained from (1'S, 2'S)-Nicotine-1'-oxide

Compound	% Yield[a] (isolated)	Retention Time (min) Capillary GC Program A	Program B
(S)-Nicotine (1)[b]	37	10.87	22.82
(S)-Nornicotine (17)	30	11.32	25.54
Myosmine (18)	0.8	11.36	25.79
ψ-Oxynicotine (15)	2.0	11.47	25.84
Nicotyrine (13)	1.5	11.76	29.09
Metanicotine (11)	0.7	11.82	31.52
1-Methyl-3-nicotinoyl-pyrrolidine (19)	3.5	12.61	38.61
Cotinine (5)	2.5	12.82	40.31
N'-Formylnornicotine (16)[c]	1.4	13.32	44.13

[a]Average of multiple experiments carried out with 10-100 mmol of nicotine-1'-oxide. [b]This nicotine was > 98% of the (S)-isomer, determined from its optical activity and by Jacob's method.[4] [c]This N'-formylnornicotine had $[\alpha]_D^{25}$ - 136° (c 5.02 in EtOH). Hydrolysis of this material with NaOEt in EtOH afforded (S)-nornicotine (> 95% ee).

needles from EtOAc, mp 165°C, $[\alpha]_D^{22}$ + 66° (c 4.7 in MeOH), lit.[14] mp 168°C, $[\alpha]_D^{22}$ + 65.1°. ^{1}H-Nmr ($CDCl_3$) δ 2.00-2.35 (m, 4H), 3.00 (s, NMe, 3H), 3.40-3.95 (m, 2H), 4.00-4.40 (m, 1H), 7.50-7.75 (m, 1H), 8.10-8.45 (m, 1H), 8.50-8.85 (m, 2H), ^{13}C Nmr ($CDCl_3$) δ 19.9 (4′), 28.8 (3′), 54.1 (NMe), 70.5 (5′), 76.9 (2′), 123.0 (5), 127.9 (3), 138.6 (4), 150.4 (6), 151.3 (2). Examination of the crude reaction product, before crystallization, by Nmr showed no evidence of the (1′R, 2′S)-isomer.

Reaction of (1′S, 2′S)-Nicotine-1′-oxide with Ferric Nitrate. (1′S, 2′S)-Nicotine-1′-oxide (1.78 g, 10 mmol) in H_2O (10 ml) was added to a stirred solution of L-tartaric acid (45 g) and ferric nitrate • 9 H_2O (13 g) in H_2O (200 ml) at 60 °C, the pH having been adjusted to 6.8 by the addition of solid Na_2CO_3. The temperature was raised to 95°C and maintained at this temperature for 1 h. The cooled mixture was made strongly basic with 10% NaOH and extracted with $CHCl_3$ (5 x 100 ml). The residue obtained on evaporation of this dried (Na_2SO_4) extract was distilled (140°C, 10^{-4} mm Hg). The resultant pale yellow oil was analyzed by capillary GC using the programs described in the General Methods. The components of the distilled oil were separated by preparative tlc either on rectangular plates or with a Chromatotron® (Harrison) with 4 mm thick SiO_2 PF-254, developing with CH_2Cl_2/MeOH/conc NH_3 (90/10/1). Average yields and their GC retention times are recorded in Table I. The various compounds obtained were characterized by their nmr (^{1}H, ^{13}C), ms, and ir spectra, and by the preparation of their picrates.

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