Am. Chem. Soc., **99**, 1514 (1977); A. Padwa and N. Kamigata, *ibid.*, **99**, 1871 (1977).
(39) F. D. Chattaway and G. D. Parkes, *J. Chem. Soc.*, **127**, 1307 (1925).
(40) A. Mustafa, S. Zayed, and S. Khattab, *J. Am. Chem. Soc.*, **78**, 145 (1956).
(41) P. Scheiner and W. R. Vaughan, *J. Org. Chem.*, **26**, 1923 (1961).
(42) K. Alder and G. Stein, *Ann.*, **501**, 1 (1933).
(43) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **26**, 2331 (1961).
(44) S. M. Gurvich and A. P. Terentev, *Sb. Statei, Obshch. Khim. Akad. Nank SSSR*, **1**, 409 (1953).
(45) H. W. Heine, *Angew. Chem., Int. Ed. Engl.*, **1**, 528 (1962).
(46) H. W. Whitlock and G. L. Smith, *Tetrahedron Lett.*, 1389 (1965); *ibid.*, 2711 (1966); *J. Am. Chem. Soc.*, **89**, 3600 (1967).
(47) R. V. Stevens and M. C. Ellis, *Tetrahedron Lett.*, 5185 (1967).
(48) R. S. Atkinson and C. W. Rees, *Chem. Commun.*, 1232 (1967); *J. Chem. Soc. C*, 778 (1969).
(49) S. L. Keely and F. C. Tahk, *Chem., Commun.*, 441 (1968).
(50) P. Scheiner, *J. Org. Chem.*, **32**, 2628 (1967).
(51) K. Houk, R. Duke, J. George, J. Sims, and R. Strozier, *J. Am. Chem. Soc.*, **95**, 7287 (1973).
(52) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971).
(53) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **14**, 775 (1975).
(54) J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).
(55) For a closely related reaction of 1-azido-1-pyridinylethylene, see: V. Nair and K. H. Kim, *J. Heterocycl. Chem.*, **13**, 873 (1976).
(56) S. Kwon, T. Okada, M. Ikeda, and Y. Tamura, *Heterocycles*, **6**, 33 (1977).
(57) R. Fusco, L. Garanti, and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).
(58) W. E. Truce and G. G. Brady, *J. Org. Chem.*, **31**, 3542 (1966).
(59) T. Sasaki, T. Yoshioka, and K. Shoji, *J. Chem. Soc. C*, 1086 (1969).
(60) Y. Nomura, N. Hatanaka, and Y. Takenchi, *Chem. Lett.*, 901 (1976).
(61) D. Hall, J. Ladbury, M. Lesslie, and E. Turner, *J. Chem. Soc.*, 3475 (1956).
(62) Y. Kazuaki and T. Yashiyuki, *Kobuashi Kagaku*, **26**, 317 (1969).
(63) A. O. Fitton, J. R. Frost, M. M. Zakaria, and G. Andrew, *Chem. Commun.*, 889 (1973).
(64) U. H. M. Fargerlund and D. Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1957).

Reaction of Nicotine and Sodium Nitrite: Formation of Nitrosamines and Fragmentation of the Pyrrolidine Ring[1,2]

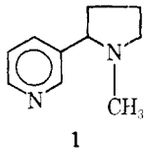
Stephen S. Hecht,* Chi-hong B. Chen, Raphael M. Ornaf, Eugenia Jacobs, John D. Adams, and Dietrich Hoffmann

Division of Environmental Carcinogenesis, Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, New York 10595

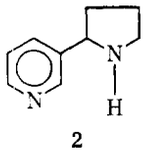
Received June 3, 1977

The reaction of nicotine and sodium nitrite was investigated in order to provide insight on the formation of potentially carcinogenic tobacco-specific nitrosamines. Reaction at 25 °C resulted in the formation of *N'*-nitrosonornicotine (**3**), 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**), and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**) in yields of 0.1–2.8%, with most of the nicotine being unreacted. When the reaction was carried out at 90 °C, with a fivefold excess of $NaNO_2$, 75–85% of the nicotine reacted. The nitrosamines **3** and **4** were formed in higher yield [up to 13.5 (**3**) and 4.3% (**4**)], but **5** was not observed. Both **4** and **5** gave secondary products under these conditions; **4** was nitrosated further to give 4-(*N*-methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (**6**), and **5** gave rise to 1-methyl-5-(3-pyridyl)pyrazole (**7**). The major products resulting from fragmentation of the pyrrolidine ring were *cis*- and *trans*-3-(3-pyridyl)acrylonitrile (**8a,b**), *N*-methylnicotinamide (**9**), and nicotinic acid (**10**). The nitrosamines **3–5** and the fragmentation products **8a**, **8b**, and **9** most probably arise via cyclic iminium salts.

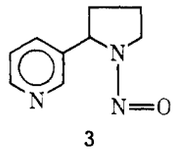
Recent studies have shown that both unburned, cured tobacco and tobacco smoke contain significant quantities of the carcinogenic compound, *N'*-nitrosonornicotine (**3**) (0.3–10 ppm in smoking tobacco, 3–90 ppm in chewing tobacco, 40–250 ng/cigarette in smoke).[3-9] This compound induces esophageal and nasal cavity tumors in rats, respiratory tract tumors in hamsters, and lung adenomas in mice, and displays carcinogenic activity and organ specificity which is typical of nitrosamines in general.[10-14] The major precursor in tobacco for **3** is the tertiary amine nicotine (**1**), which is converted to **3** during curing of tobacco.[15] Nornicotine (**2**) can also serve as



1

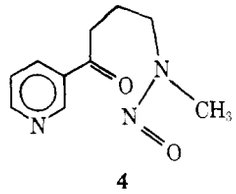


2

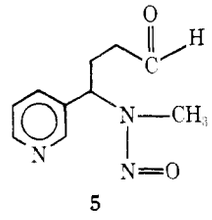


3

precursor for **3**, but its concentration in tobacco is significantly lower.[3,15] About half of **3** present in tobacco smoke is formed during smoking, and model studies have shown that **1** is more important than **2** as a precursor to **3** during cigarette smoking.[7,9] In view of these facts, studies on the reaction of **1** with nitrite were undertaken in order to provide insight on the possible formation of other nitrosamines, such as 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone (**4**) and 4-(*N*-methyl-*N*-nitrosamino)-4-(3-pyridyl)butanal (**5**), which could result from ring cleavage of the 1'–2' or 1'–5' bonds of **1** and nitrosation, respectively. In previous studies on the reaction of **1** with nitrite under various conditions, the presence of **3** was demonstrated and the possible formation of **4** and **5** discussed.[5,7,16]



4



5

Results and Discussion

When **1** was allowed to react with 1 equiv of $NaNO_2$ in aqueous solution at 20 °C for 17 h, the nitrosamines **3–5** were formed. Under these mild conditions, **1** was mostly (80–90%) unreacted. The nitrosamines were identified by comparison of GC retention times and mass spectra to those of reference standards, which were independently synthesized.[17-19] Compounds **4** and **5** are, to our knowledge, the first examples of nitrosamines which are primary products of cleavage of a ring C–N bond in the nitrosation of a cyclic tertiary amine. The yields of **3–5** under these conditions are summarized in Table I and are typical of the reaction of tertiary amines with

0022-3263/78/1943-0072$01.00/0

Table I. Formation of Nitrosamines 3–5 from Nicotine and $NaNO_2$

Conditions				% yields[a]		
$[NaNO_2]$/[Nicotine]	pH[b]	T, °C	t, h	3	4	5
1.4	2.0	20	17	0.1	ND[c]	0.2
1.4	3.4	20	17	0.5	0.1	2.8
1.4	4.5	20	17	0.5	0.5	2.3
1.4	7.0	20	17	0.2	0.1	0.1
5.0	3.4–4.2	90	0.3	8.0	0.7	ND
5.0	3.4–4.2	90	3.0	8.8	2.3	ND
5.0	3.4–4.2	90	6.0	8.0	1.5	ND
5.0	5.4–5.9	90	0.3	9.0	2.7	ND
5.0	5.4–5.9	90	3.0	13.5	4.3	ND
5.0	5.4–5.9	90	6.0	11.7	2.6	ND
5.0	7.0–7.3	90	0.3	1.3	0.1	ND
5.0	7.0–7.3	90	3.0	4.5	0.2	ND
5.0	7.0–7.3	90	6.0	5.5	0.2	ND

[a] Determined by GC and based on starting nicotine. [b] Buffer systems: pH 2, KCl/HCl; pH 3.4–7, citrate/phosphate. [c] ND = not detected.

nitrite.[20,21] Cleavage of the 1′–5′ bond to give **5** was favored in the pH range 3.4–4.5, as was the formation of all three nitrosamines.

Under more severe conditions (fivefold excess of nitrite, 90 °C), the yields of **3** and **4** increased, while **5** was no longer observed, as shown in Table I. The absence of **5** and the decreasing amounts of **4** at longer reaction times were due to secondary reactions, as discussed below. Under these conditions, nitrosamine formation was favored at pH 5.4–5.9. The optimum pH range for nitrosamine formation at both 20 and 90 °C is in agreement with previous studies on nitrosation of tertiary amines, as is the formation of nitrosamines under neutral conditions.[20,22,23] Since the yields of **3** were relatively high at 90 °C, isolation of this compound in gram quantities was feasible; unreacted **1** was steam-distilled and **3** was isolated by preparative high-performance liquid chromatography (HPLC) followed by distillation.

Examination of the mixtures formed in the reaction of **1** with $NaNO_2$ at 90 °C revealed, in addition to **3** and **4**, products arising from secondary reactions of **4** and **5** (**6** and **7**) and from fragmentation and oxidation of the pyrrolidine ring (**8–18**), as shown in Table II. Under these conditions, **1** was 15–25% unreacted. Yields of products reported in Table II were determined by GC or HPLC: approximately 65–70% of the mixture was characterized.

The structures of 4-(*N*-methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (**6**) and 1-methyl-5-(3-pyridyl)pyrazole (**7**) were deduced from spectral and analytical data, as discussed below. The other major products were the *cis*- and *trans*-3-(3-pyridyl)acrylonitrile isomers **8a** and **8b** (the formation of **8a** was also reported in ref 5), *N*-methylnicotinamide (**9**), and nicotinic acid (**10**). These products and the minor components **11–18** were identified by comparison to available reference samples.

Compound **6**, isolated from the aqueous portion of the reaction mixture, had a high-resolution electron impact (EI)

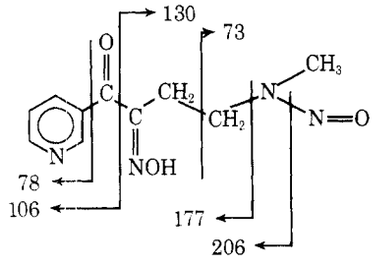
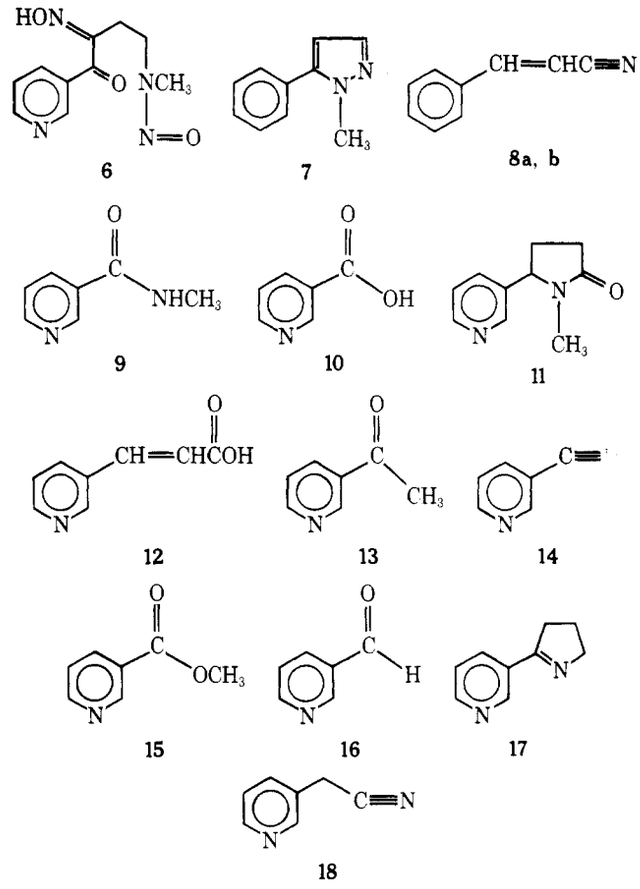


Table II. Products Formed in the Reaction of Nicotine and $NaNO_2$[a,b]

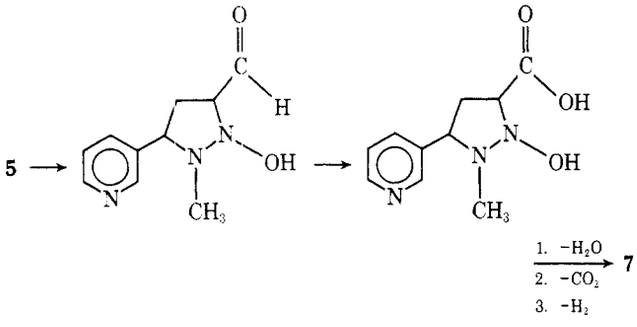
Product	% yield[c]	Method of identification[d]
3	8.8	A[e]
4	2.3	A[f]
6	4.0	C, A
7	2.1	C
8a,b	19.0	A[g]
9	6.2	B
10	4.0	B
11	0.6	A[h]
12	0.5	B
13	0.5	B
14	0.5	B
15	0.3	B
16	0.2	B
17	0.1	A[e]
18	0.1	B

[a] Reaction of 1 equiv of **1** with 5 equiv of $NaNO_2$ at 90 °C, 3 h, pH 3.4–4.2. [b] 15–25% of **1** was unreacted. [c] Based on starting **1**. [d] A, comparison of GC or HPLC retention times and mass spectra to independently synthesized standards; B, comparison to commercially available standards; C, spectral properties (see text). [e] Reference 17. [f] Reference 19. [g] Reference 24. [h] Reference 25.



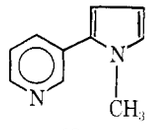
mass spectrum with fragments at 73 ($C_2H_5N_2O$), 78 (C_5H_4N), 106 (C_6H_4ON), 130 ($C_4H_8N_3O_2$), 165 ($C_8H_9O_2N_2$), 177 ($C_9H_9O_2N_2$), 206 ($C_{10}H_{12}O_2N_3$), and 219 ($C_{10}H_{11}O_2N_4$). Elemental analysis indicated an empirical formula of $C_{10}H_{12}N_4O_3$. A small (relative intensity 0.2%) peak was observed at *m/e* 237 in the low-resolution EI spectrum of **6**; the chemical ionization (CI) mass spectrum gave *m/e* 238 (100%). The fragmentation pattern can be rationalized as shown; the peaks at 237 (EI) and 238 (CI) apparently resulted from M + 1 and M + 2 ions, respectively. The structure for **6** was also

Scheme I



supported by IR and NMR data (see Experimental Section). To confirm the structural assignment, **6** was prepared in 62% yield by reaction of **4** with isopropyl nitrite. Both synthetic and isolated **6** were obtained as mixtures of *syn*- and *anti*-oxime isomers. These isomers **6a** and **6b** (mp 126–127 and 132–133 °C) could be separated after several recrystallizations. Since **6a** and **6b** each had an >NN=O group, four isomers, (*E*)-**6a**, (*Z*)-**6a**, (*E*)-**6b**, and (*Z*)-**6b**, were actually present. According to NMR, the *E* isomers predominated.

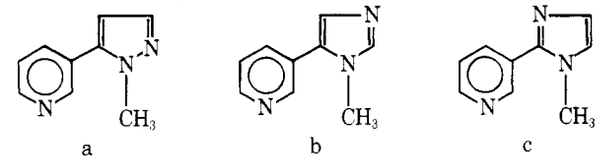
Compound **7** was isolated from the distillable portion of the reaction mixture; its volatility was similar to **8a**, **8b**, and **17**. High-resolution mass spectral data (EI) indicated a molecular ion of $C_9H_9N_3$ (rel intensity, 100%) with fragments corresponding to $C_8H_7N_2$ (50%), C_7H_6N (15%), and C_5H_4N (8%). This spectrum is similar to that of nicotyrine (**19**).[26] The CI



19

spectrum showed an M + 1 peak at *m/e* 160. The IR spectrum was similar to that of myosmine (**17**). The proton NMR spectrum of **7** showed a methyl singlet at 3.94 ppm and doublets (1 H each, J = 4 Hz) at 6.40 and 7.59 ppm, in addition to resonances for four pyridyl protons. The fully decoupled ^{13}C NMR spectrum showed resonances at 37.9 (1 C), 107.8 (2 C), 124.4 (1 C), 137.0 (1 C), 140.0 (2 C), and 150.8 (2 C) ppm.

These MS, IR, and NMR data required a pyridine ring attached to an *N*-methylated five-membered ring containing two nitrogens. Such a heterocyclic compound could be either a pyrazole or an imidazole; assuming that the *N*-methyl group remained in the same relative position as in **1**, three structures (a, b, and c) were possible. Based on the proton NMR spec-



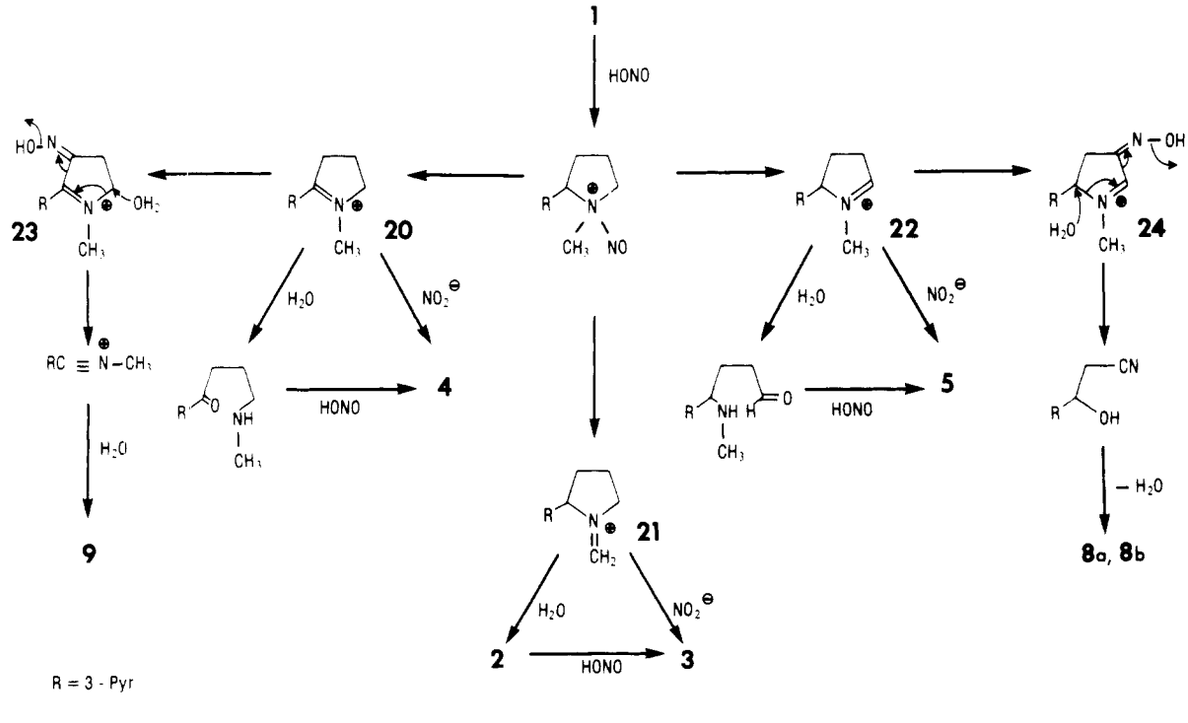
a b c

trum, the pyrazole structure a was assigned; the ring protons on C-4 and C-5 of 3-methylpyrazole resonate at 6.10 and 7.52 ppm, compared to 6.40 and 7.59 ppm in **7**; in 1-methylimidazole the ring protons are observed at 6.96, 7.10, and 7.49 ppm and in 1,2-dimethylimidazole at 6.70 and 6.80 ppm.[27]

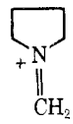
The origin of **7** in the reaction mixture from **1** and $NaNO_2$ may be attributed, at least partially, to secondary reactions of nitrosaminoaldehyde **5**. When **5** was treated under the reaction conditions (pH 3.4, 90 °C, 3 h, fivefold excess nitrite), **7** was formed in 10% yield. Disappearance of **5** was complete under these conditions. When $NaNO_2$ was omitted from the mixture, **5** was recovered unchanged. The mechanism of this conversion is not yet known, but could proceed as shown in Scheme I. In the acidic medium, **5** could cyclize by reaction of its enol with the nitroso group. Oxidation followed by loss of H_2O, CO_2, and H_2 would give **7**. A related reaction has been observed in the HNO_3 oxidation of nicotine to nicotinic acid.[28] In this oxidation, a minor product (5%) was 3-nitro-5-(3-pyridyl)pyrazole, which may be formed by a mechanism similar to that shown in Scheme I.

The formation of nitrosamines **3–5** and the fragmentation products **8a**, **8b**, and **9** can be explained via the intermediacy of cyclic iminium salts, as shown in Scheme II. Previous studies on nitrosation of tertiary amines support an initial addition of NO^+ to the amine, followed by loss of HNO.[22] In the case of nicotine, this would give rise to three iminium species, **20–22**. Reaction of **20–22** to give nitrosamines **3–5** could proceed in either of two ways. The iminium salts could be hydrolyzed to the corresponding secondary amines, which are then nitrosated. Alternatively, **20–22** could react directly

Scheme II

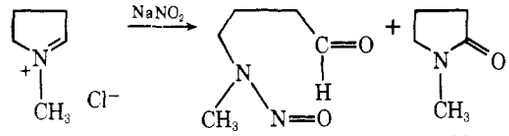


with NO_2^- to give **3–5**. This pathway, which would be more important at neutral pH, has been demonstrated for the exocyclic iminium salt **25**, which gives nitrosopyrrolidine upon nitrosation.[29] To examine the formation of nitrosamines by



25

interaction of an endocyclic pyrrolinium salt with nitrite, the reaction of **26** with nitrite was investigated. When **26**, obtained by reduction of *N*-methylpyrrolidone (**28**),[30] was allowed to react with $NaNO_2$ under neutral conditions in either H_2O or 95% EtOH, the nitrosaminoaldehyde **27** was isolated in 5–10% yield.[18] The major product was *N*-methylpyrrolidone (**28**). Thus, both exocyclic and endocyclic pyrrolinium salts, such as **20–22**, **25**, and **26**, can serve as precursors for nitrosamines.



26 **27** **28**

The intermediates **20** and **22** offer the simplest rationale for formation of products **8a**, **8b**, and **9**. Under the reaction conditions, these salts should be in equilibrium with the corresponding enamines, which can undergo C-nitrosation to give isonitrosoiminium ions **23** and **24**. Beckmann type fragmentation reactions of **23** and **24** would then lead to **8a**, **8b**, **12**, and **9**. Compounds **10**, **11**, **13**, and **15–17** are typical oxidation products of nicotine, which have been observed under similar conditions.[31]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 267 grating infrared spectrophotometer in Nujol mull or as liquid films. NMR spectra were determined with a Hitachi Perkin-Elmer Model R-24 spectrometer in $CDCl_3$ solution and are reported as parts per million downfield from Me_4Si as internal reference. ^{13}C NMR spectra were obtained on a Varian Associates XL-100A spectrometer. Mass spectra and combined GC–MS were run with a Hewlett Packard Model 5982A dual source instrument using a membrane separator. Chemical ionization mass spectra were determined with methane as ionizing gas. High-resolution mass spectra were determined by Shrader Analytical and Consulting Laboratories, Detroit, Mich. GC analysis was done on a Hewlett Packard Model 5711 instrument equipped with a flame ionization detector and columns: A, 6 ft × ⅛ in. 10% Carbowax 20M–TPA on Gas Chrom Q; B, 6 ft × ⅛ in. 10% UCW-98 on Gas Chrom Q; C, 6 ft × ⅛ in. 10% Carbowax 20 M-2% KOH on Chromosorb W, with helium as carrier gas. HPLC was performed with a Waters Associates Model ALC/GPC–202 high-speed liquid chromatograph equipped with a Model 6000A solvent delivery system, a Model 660 solvent programmer, a Model U6K septumless injector, a Model 440 UV detector, and a 6 mm × 30 cm Microbondapak/C18 column. Preparative HPLC was done with a Waters Associates Prep LC/System 500 using Prep-Pak-500/Silica cartridges. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reaction of Nicotine and $NaNO_2$. (A) Analytical Scale. Redistilled nicotine (Aldrich Chemical Co., Milwaukee, Wisc.) which contained <0.01% nornicotine according to GC analysis (column C, 165 °C) and was free of other impurities (1.0 g, 6.2 mmol) was added to 10 mL of the appropriate buffer and $NaNO_2$ (2.1 g, 30.4 mmol in 5 mL of H_2O) was added in one portion. The resulting solution was heated at 90 °C for the appropriate time interval, and then basified to pH 10–12 by addition of aqueous NaOH. The solution was saturated with NaCl and extracted with 3 × 40 mL of $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated to give an oily residue, 0.4–0.5 g. Reactions under mild conditions (entries 1–4, Table I) were done similarly, except that the molar ratio of $NaNO_2$ to nicotine was 1.4 and the solutions were stirred at 20 °C for 17 h before basification.

The $CHCl_3$ extracted products were examined by GC using column A with a temperature program of 100 °C for 4 min, then 4°/min to 240 °C. The flow rate was 60 mL/min and injector and detector temperatures were 250 °C. The relative retention times of the volatile components of the mixture were as follows: **16**, 0.67; **13**, 0.72; **14**, 0.73; **15**, 0.84; **1**, 1.00; **17**, 2.05; **18**, 2.20; **8a** and/or **8b**, 2.26 and/or 2.78; **7**, 2.52; **9**, 3.70; **11**, 3.70; **3**, 4.23; **5**, 4.82; and **4**, 5.20. The absolute retention time of **1** was 12.8 min. Identity was confirmed by comparison of retention times and mass spectra to standards.

Compounds **6**, **10**, and **12** were isolated from the aqueous portion of the reaction mixture. The aqueous extract was readjusted to pH 7 and freeze-dried to give a residue which was triturated with methanol. Aliquots were concentrated and silylated with bis(trimethylsilyl)trifluoroacetamide and then examined by GC using column B (flow rate 60 mL/min) and a temperature program of 100–240 °C at 4°/min. Compounds **10** and **12** were identified by comparison of mass spectra and retention times to those of silylated standards.

An aliquot of the above methanol solution was examined by HPLC for identification and quantification of **6**, using program 8 with elution by 15% CH_3OH in H_2O to 100% CH_3OH in 45 min at a flow rate of 1.5 mL/min. The retention volume of **6** was 37.5 mL. When the reaction was done on a larger scale, **6** could be isolated by column chromatography on silica gel with elution by chloroform/methanol followed by recrystallization from EtOAc.

(B) Preparative Scale. Isolation of 3. Nicotine (250 g, 1.54 mol) was brought to pH 3 by cautious addition of concentrated HCl. The resulting salt was added to 3 L of pH 3 citrate/phosphate buffer in a 12-L round bottom flask. The mixture was heated with stirring to 90 °C. The heating mantel was removed and a solution of $NaNO_2$ (525 g, 7.61 mol) in 1 L of H_2O was added dropwise over a period of 1.5 h at a rate which maintained the temperature at 90 °C. The mixture was then stirred for 5 h at 90 °C, cooled to room temperature, saturated with NaCl, cooled to 0 °C, and brought to pH 12 by cautious addition of NaOH pellets. The resulting mixture was extracted with 4 × 3 L of $CHCl_3$ and the combined $CHCl_3$ layers were dried (Na_2SO_4) and concentrated to give a residue of 115 g. This material was steam-distilled to remove unreacted nicotine (53 g). The pH of the distillation pot was maintained at 10 by addition of NaOH. After distillation was complete, the residue was extracted with $CHCl_3$ and the $CHCl_3$ solution was dried and concentrated to give 45 g of material. This was chromatographed by preparative HPLC using two cartridges with elution by $CHCl_3$/cyclohexane/CH_3CN/MeOH (44:48:7:1) at a flow rate of 250 mL/min. Fractions containing **3**, as determined by TLC on silica gel [$CHCl_3$/MeOH (20:1)], were combined and concentrated to give a residue of 20 g. This was distilled to give 10 g (3.7%) of **3**, bp 150–160 °C (0.2 mm), identical with **3** prepared from **2**.[17] The forerun from this distillation was enriched in **7**.

4-(*N*-Methyl-*N*-nitrosamino)-2-oximino-1-(3-pyridyl)-1-butanone (6). The nitrosamino ketone **4** (100 mg, 0.48 mmol) was dissolved in dry methanol (10 mL) which had been saturated with dry HCl. Isopropyl nitrite (225 mg, 2.6 mmol) was added at 0 °C and the solution was stirred for 2 h at 0 °C and an additional 3 h at room temperature. The mixture was brought to pH 7 and extracted with 4 × 25 mL of $CHCl_3$. Drying (Na_2SO_4) and concentration gave a solid residue, which was recrystallized from EtOAc to give 80 mg (62%) of **6**, mp 127–129 °C, as a mixture of isomers. Further recrystallization from EtOAc gave the *syn*- *anti*-oxime isomers **6a**, mp 126–127 °C, and **6b**, mp 132–133 °C. Spectral properties: IR (**6a**) 3200–2100, 1642, 1590, 1131, 1030, 1010, 732, 712, 692, 673, 630 cm^{-1}; IR (**6b**) 3200–2100, 1659, 1590, 1510, 1418, 1340, 1265, 1131, 1027, 1008, 758, 738, 714, 691, 675, 630 cm^{-1}; MS *m/e* (rel intensity) 237 (0.2), 219 (6), 206 (29), 177 (8), 165 (7), 130 (10), 114 (4), 106 (100), 78 (97), 73 (49), 51 (40), 42 (45), identical for **6a** and **6b**; NMR (mixture of **6a** and **6b**) ($CDCl_3$) 9.42–7.25 (4 H, m, pyridyl CH), 4.48 (1.8 H, t, $CH_2NN{=}O$, **6a** + **6b** *E* isomers), 3.81 (0.5 H, m, $-CH_2N(N{=}O)CH_3$, **6a** + **6b** *Z* isomers), 3.21 (2 H, t, $HON{=}CCH_2-$), 3.15 ppm (2.7 H, s, $CH_3NN{=}O$, **6a** + **6b** *E* isomers). Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.85; H, 5.12; N, 23.72. Found: C, 50.75; H, 5.19; N, 23.66.

Formation of 1-Methyl-5-(3-pyridyl)pyrazole (7) from 5. Nitrosaminoaldehyde **5** (12.8 mg, 0.06 mmol) was dissolved in 1 mL of pH 3 buffer and $NaNO_2$ (200 mg, 2.9 mmol) was added. The solution was heated at 90 °C for 3 h, cooled, adjusted to pH 10, and extracted with 3 × 5 mL of $CHCl_3$. After drying and concentration, the residue was examined by GC using column A, programmed from 100 to 240 °C at 4°/min. The predominant volatile product (10% yield from **5**) was **7**, which was identified by comparison of its retention time and mass spectrum to **7** isolated from the reaction of **1** with $NaNO_2$. An unknown component, with a molecular ion of 192, eluted at 23.8 min.

Nitrosaminoaldehyde **5** was not detected. Spectral data for **7** are given in the text.

Reaction of *N*-Methyl-Δ^1-pyrrolinium Chloride (26) with $NaNO_2$. *N*-Methyl-Δ^1-pyrrolinium chloride (**26**) was prepared by the lithium aluminum hydride reduction of *N*-methyl-2-pyrrolidone (**28**), followed by dehydration as previously reported.[30] The NMR spectrum ($CDCl_3$) showed the following absorptions: 12.91 (br s, 1 H, $CH{=}N^+$), 3.78 (t, 2 H, CH_2N^+), 3.14 (s, 3 H, N^+CH_3), 3.02 (m, 2 H, $CH_2C{=}N^+$), and 2.31 ppm (m, 2 H, ring CCH_2C), indicating the absence of **28**. The pyrrolinium salt **26** (1.6 g, 0.023 mol) thus obtained was dissolved in 20 mL of H_2O and allowed to react with $NaNO_2$ (1.6 g, 0.023 mol) in 20 mL of H_2O at reflux for 10 min. The aqueous solution was extracted with $CHCl_3$ (3 × 20 mL), and the $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed on silica gel with elution by hexane/Et_2O/CH_2Cl_2 (1:2:2); 4-(*N*-methyl-*N*-nitrosamino)butanal (**27**) was obtained pure in 5% yield. The nitrosamine **27** showed spectral characteristics which were identical with those of a reference sample synthesized independently.[18] The major product (50%) was eluted from the column with acetone and identified as *N*-methyl-2-pyrrolidone (**28**). The nitrosation of pyrrolinium salt **26** was also done in refluxing 95% EtOH, in pH 6 buffer under reflux, and at 20 °C, under N_2, in 95% EtOH. Similar results were obtained.

Acknowledgments. We thank Dr. Curt R. Enzell and Dr. T. Nishida of the Swedish Tobacco Company, Stockholm, Sweden, for providing ^{13}C NMR and high-resolution data on 1-methyl-5-(3-pyridyl)pyrazole and for correctly suggesting the structure of this compound. We also thank Dr. Edward Leete of the School of Chemistry, University of Minnesota, for calling our attention to the formation of 3-nitro-5-(3-pyridyl)pyrazole from nicotine.

Registry No.—**3**, 16543-55-8; **4**, 64091-91-4; **5**, 64091-90-3; *anti*-**6**, 64091-89-0; *syn*-**6**, 64091-88-9; **7**, 64091-87-8; **26**, 18028-53-0; isopropyl nitrite, 541-42-4; nicotine, 54-11-5; $NaNO_2$, 7632-00-0.

References and Notes

(1) No. 52. Chemical Studies on Tobacco Smoke.
(2) Supported by Public Health Service Contract N01-CP55666 from the Division of Cancer Cause and Prevention, National Cancer Institute, and NCI Grant CA12376-05. S.S.H. is recipient of NCI Research Career Development Award No. 5K04CA00124.
(3) S. S. Hecht, R. M. Ornaf, and D. Hoffmann, *J. Natl. Cancer Inst.*, **59**, 1237 (1974).
(4) V. P. Bharadwaj, S. Takayama, T. Yamada, and A. Tanimura, *Gann*, **66**, 585 (1975).
(5) H. Klus and H. Kuhn, *Fachliche Mitt. Oesterr. Tabakregie*, **16**, 307 (1975).
(6) S. S. Hecht, R. M. Ornaf, and D. Hoffmann, *Anal. Chem.*, **47**, 2046 (1975).
(7) D. Hoffmann, G. Rathkamp, and Y. Y. Liu, *Int. Agency Res. Cancer Sci. Publ.*, **No. 9**, 159 (1974).
(8) H. Klus and H. Kuhn, *Fachliche Mitt. Oesterr. Tabakregie*, **14**, 251 (1973).
(9) D. Hoffmann, M. Dong, and S. S. Hecht, *J. Natl. Cancer Inst.*, **58**, 1841 (1977).
(10) D. Hoffmann, R. Raineri, S. S. Hecht, R. Maronpot, and E. L. Wynder, *J. Natl. Cancer Inst.*, **55**, 977 (1975).
(11) G. M. Singer and H. W. Taylor, *J. Natl. Cancer Inst.*, **57**, 1275 (1976).
(12) J. Hilfrich, S. S. Hecht, and D. Hoffmann, *Cancer Lett.*, **2**, 169 (1977).
(13) E. Boyland, F. J. Roe, and J. W. Gorrod, *Nature (London)*, **202** 1126 (1964).
(14) D. Hoffmann, S. S. Hecht, R. M. Ornaf, T. C. Tso, and E. L. Wynder, *Int. Agency Res. Cancer Sci. Publ.*, **14**, 307 (1976).
(15) S. S. Hecht, C. B. Chen, N. Hirota, R. M. Ornaf, T. C. Tso, and D. Hoffmann, *J. Natl. Cancer Inst.*, in press (1978).
(16) G. B. Neurath, M. Dünger, and F. G. Pein, *Int. Agency Res. Cancer Sci. Publ.*, **14**, 227 (1976).
(17) M. W. Hu, W. E. Bondinell, and D. Hoffmann, *J. Labelled Compd.*, **10**, 79 (1974).
(18) S. S. Hecht, C. B. Chen, and D. Hoffmann, *Tetrahedron Lett.*, 593 (1976).
(19) S. S. Hecht, C. B. Chen, M. Dong, R. M. Ornaf, D. Hoffmann, and T. C. Tso, *Beitr. Tabakforsch.*, **9**, 1 (1977).
(20) W. Lijinsky, L. Keefer, E. Conrad, and R. van de Bogart, *J. Natl. Cancer Inst.*, **49**, 1239 (1972).
(21) W. Lijinsky, *Cancer Res.*, **34**, 255 (1974).
(22) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89**, 1147 (1967).
(23) P. A. S. Smith and H. G. Pars, *J. Org. Chem.*, **24**, 1325 (1959).
(24) M. Strell and E. Kopp, *Chem. Ber.*, **91**, 1621 (1958).
(25) E. R. Bowman and H. McKennis, Jr., *Biochem. Prep.*, **10**, 36 (1963).
(26) A. Pilotti, C. R. Enzell, J. McKennis, Jr., and E. R. Bowman, *Beitr. Tabakforsch.*, **8**, 339 (1976).
(27) C. J. Pouchert and J. R. Campbell, "The Aldrich Library of NMR Spectra", Vol. 8, Aldrich Chemical Co., Milwaukee, Wisc., 1974, pp 22–35.
(28) H. Lund, *J. Chem. Soc.*, 686 (1933).
(29) L. K. Keefer and P. P. Roller, *Science*, **181**, 1245 (1973).
(30) E. Leete, *J. Am. Chem. Soc.*, **89**, 7081 (1967).
(31) W. G. Frankenburg, A. M. Gottscho, and A. A. Vaitekumas, *Tobacco Sci.*, **2**, 9 (1958).

Thermal Decomposition of 2-Azidoquinoxaline *N*-Oxides

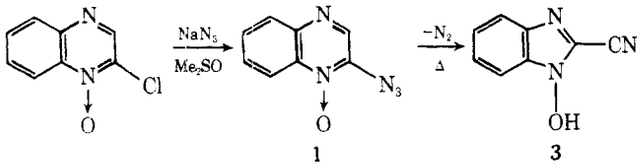
John P. Dirlam,* Berkeley W. Cue, Jr.,* and Kerry J. Gombatz

Department of Agricultural Organic Chemistry, Pfizer Central Research, Groton, Connecticut 06340

Received July 5, 1977

The thermolysis of some 2-azidoquinoxaline 1-oxides and 1,4-dioxides has been studied. When these are unsubstituted in the 3 position, 2-cyano-1-hydroxy-1*H*-benzimidazoles are obtained in high yield. The thermolysis of 2-azido-3-methylquinoxaline 1,4-dioxide, on the other hand, resulted in the formation of 2-cyano-2-methyl-2*H*-benzimidazole 1,3-dioxide, which underwent further intramolecular rearrangement to afford a novel 3*H*-2,1,4-benzoxadiazine 4-oxide. A mechanistic interpretation of these observations, as well as a discussion of ^{13}C NMR spectra of the thermolysis products, is presented.

In the course of work on the chemistry of quinoxalines, 2-azidoquinoxaline 1-oxide (**1**) and 2-azidoquinoxaline 1,4-dioxide (**2**) were synthesized and their thermal chemistry was studied. The thermolysis of **1** to give 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**) has been described.[1] We now wish to report our observations concerning the modes of reaction of several such azides.



1 **3**

2-Azidoquinoxaline 1-oxide (**1**) was prepared by sodium azide displacement of 2-chloroquinoxaline 1-oxide[2] in Me_2SO at room temperature. Prolonging the reaction time resulted in loss of nitrogen from **1** and formation of 2-cyano-1-hydroxy-1*H*-benzimidazole (**3**). The benzimidazole **3** was more efficiently prepared by the thermolysis of **1** at 90 °C in benzene solution. The structural assignment of **3** was based on its spectral properties (NMR, IR, UV, mass spectrum), combustion analysis, and an unambiguous synthesis from 2-nitroanilinoacetonitrile according to a literature procedure.[3]

Extension of this reaction to 2-azidoquinoxaline 1,4-dioxide (**2**) was accomplished in the following manner. 2-Methylsulfonylquinoxaline 1,4-dioxide[4] (**4**) was allowed to react with

0022-3263/78/1943-0076$01.00/0