The Deoxydative Substitution Reactions of Nicotinamide and Nicotinic Acid *N*-Oxides by 1-Adamantanethiol in Acetic Anhydride

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The reaction of nicotinamide *N*-oxide with 1-adamantanethiol in acetic anhydride yielded a mixture of 2- and 6-(1-adamantylthio)nicotinamides (49%, in the ratio of 24:1) and 2-, 5-, and 6-(1-adamantylthio)nicotinonitriles (18%, in the ratio of 79:1:20). From a reaction of nicotinic acid *N*-oxide with 1-adamantanethiol, there was isolated 2-(1-adamantylthio)nicotinic acid as the only sulfide in 23% yield. Carbon-sulfur bond cleavage took place when 2-(1-adamantylthio)nicotinic acid, or the corresponding amide or nitrile, were boiled with concentrated hydrochloric acid to furnish 2-mercaptonicotinic acid and 1-chloroadamantane, quantitatively. The reaction of nicotinamide *N*-oxide alone in acetic anhydride at 135° formed *N*-acetyl-2-hydroxynicotinamide (61%), 2-hydroxynicotinonitrile (0.5%) and *N,N*-diacetyl-2-acetoxynicotinamide (0.8%).

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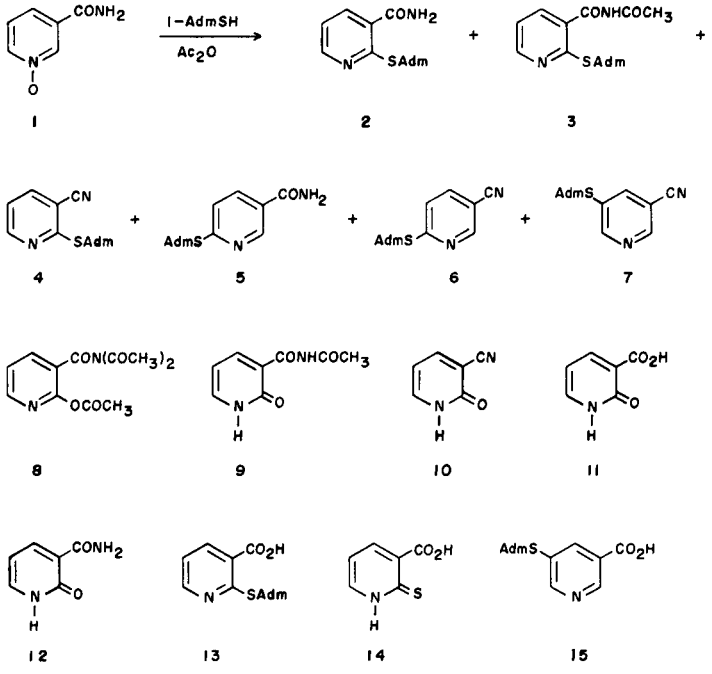
In our continuing investigation of the deoxydative substitution reactions of pyridine *N*-oxides by mercaptans in the presence of acid halides or anhydrides [2-5], we report our findings when nicotinamide and nicotinic acid *N*-oxides were used. Prior substitutions had been carried out on pyridine *N*-oxides bearing alkyl groups, in various ring positions. The most recent study utilized 3-picoline 1-oxide [6]. It interested us to discover how electron-withdrawing substituents at position 3 in the ring would effect the entry of the new sulfide. It was expected that such 3-substituted 1-oxides would produce mainly 2- and 6-sulfides together with some 5-sulfides which was the established pattern. In the past, the reaction of mercaptans with 3- and 4-alkylpyridine 1-oxides in acetic anhydride had also produced some interesting tetrahydropyridyl sulfides [4]. Although it was hoped to isolate some of these tetrahydropyridyl sulfides from these reactions of nicotinamide and nicotinic acid *N*-oxides, none could be found.

In earlier phases of the exploration of these substitution reactions in acetic anhydride, commercially available but rather noxious thiols such as methyl, propyl and *t*-butyl mercaptans were utilized. Their ready availability prompted us to use these in large excess. For this project 1-adamantanethiol (1-AdmSH) was chosen for its convenience in preparation and lack of odor. Furthermore, being a relatively large nucleophile would enable us to study some steric effects. Usually, 1-AdmSH was added generally only in equivalent amounts (or in slight excess). Therefore, the



competing acetylation of 1-AdmSH to form the thiol ester had to be examined. The acylation of 1-AdmSH in acetic anhydride was followed at 95° and 135°. It was found that relatively fast deoxydative substitution reactions could compete with the acylation. However, the acetylation of 1-AdmSH with acetic anhydride was strongly catalyzed by triethylamine and therefore only very fast deoxydative substitutions could compete for the thiol in the reaction mixture. Since the first step of these deoxydative substitution reactions consist of the conversion of the *N*-oxide to an 1-acetoxypyridinium acetate, apparently 1-AdmSCOCH$_3$ could not function as an acylating agent for these *N*-oxides. It was and that there was no reaction when the *N*-oxide was treated with 1-AdmSCOCH$_3$ in boiling acetic anhydride in the presence or absence of triethylamine. It is the 1-acetoxypyridinium cation which undergoes nucleophilic attack by the mercaptan at one of the α-positions of the pyridine ring.

Nicotinamide *N*-Oxide (**1**).

Because of the limited solubility of **1** in acetic anhydride, the deoxydative substitution reaction with 1-AdmSH was carried out conveniently in boiling acetic anhydride. Six new sulfides, **2-7**, were isolated from this reaction in an overall conversion of 67%. Some of the products were due to secondary reactions on the amide. For example, the acylation of the amide produced the imide **3**. Also the dehydration of the amide gave nitriles **4**, **6** and **7**. In independent experiments, boiling acetic anhydride converted **2** to a mixture of **3** and **4**. All compounds had to be separated by repeated column chromatography. Identification was by means of their proton nuclear magnetic resonance (^{1}H nmr) spectra which were characteristic for differently substituted pyridines. Whenever possible, conversions to known pyridine derivatives were also carried out to substantiate the structure of any new product.

The pattern of entry of the sulfide group was as predicted. The predominant sulfides, **2** and **4**, arose from attack of 1-AdmSH at the α-position next to the amide group. Predominant attack of a bulky nucleophile at C-2 next to an existing group (at C-3) is not unusual [7].

In prior experiments the addition of triethylamine had changed the ratio of sulfides arising from α and β substitution [2,8]. But in those experiments a large excess of mercaptan was present. In view of the facile triethylamine-catalyzed acylation of 1-AdmSH, thereby removing the thiol from the reaction, it is not surprising that **1** was only substituted in poor yield by 1-AdmSH when triethylamine was present in the reaction mixture. The starting *N*-oxide was recovered in 52% yield, along with 56% of 1-AdmSAc. There was formed about 3% of **3**. An interesting by-product was the triacetyl derivative of 2-hydroxynicotinamide (**8**) isolated in 8% yield. Apparently, with most of the 1-AdmSH out of circulation, acetate ion began to substitute **1**. Substitution by acetate ion is well recognized but is much slower than that by a thiol [9]. In an identical reaction of **1** with boiling acetic anhydride containing 3 equivalents of triethylamine the only isolable product was **8** (14%). The structure of **8** was proven by its analysis, mass spectrum and its ^{1}H nmr spectrum which showed three methyl singlets and an AMX pattern for the ring proton. Since one of the acetyl methyl signals is at 2.63 (the others were at 2.27 and 2.08) ppm, the pyridyl ester structure rather than an *N*-acetyl-2-pyridone structure was assigned to **8**. Attempts to partially hydrolyze **8**, even by hot water, led to mixtures. Complete acid-catalyzed hydrolysis produced 2-hydroxynicotinic acid (**11**). Apparently, with triethylamine present, the amide group was completely acetylated.

The reaction of **1** only in boiling acetic anhydride was also investigated. Substitution by acetate ion took place seemingly exclusively at position 2. During the workup most of the water-sensitive pyridyl acetates were hydrolyzed. There was isolated *N*-acetyl-2-hydroxynicotinamide (**9**) as well as a small amount of 2-hydroxynicotinonitrile (**10**). Another byproduct was **8** whose structure proof had been discussed above. The structure of **9** was proved by ammonolysis of the imide group to produce 2-hydroxynicotinamide (**12**). Complete hydrolysis of **9** and **10** afforded **11**.

Nicotinic Acid *N*-Oxide.

The reaction of this *N*-oxide in boiling acetic anhydride has been reported to give 2-acetylnicotinic acid 1-oxide (27%), 2-hydroxynicotinic acid (10%) and 6-hydroxynicotinic acid (3%) [10]. When 1-AdmSH was included in such a reaction mixture, the only sulfide which was isolated was 2-(1-adamantylthio)nicotinic acid (**13**). The structure of the new sulfide was proven by conversion to 2-hydroxynicotinic acid. The structure of **13** was also substantiated by its ^{1}H nmr spectrum which showed the three ring protons to be present as an AMX system.

Carbon-Sulfur Cleavage of 1-Adamantyl Sulfides.

To test the previously observed C-S cleavage of some 1-adamantyl sulfides [5,11], some of the pyridyl sulfides isolated from these reactions were subjected to this reaction. Upon boiling with concentrated hydrochloric acid, sulfides **2**, **3**, **4** and **13** each were converted almost quantitatively to 2-mercaptonicotinic acid (**14**) and 1-chloroadamantane. The structure of 2-mercaptonicotinic acid was proved by its ^{1}H nmr spectrum and its conversion by nitrous acid to 2-hydroxynicotinic acid by a literature method [12]. Similarly, **5** and **6** were cleaved by concentrated hydrochloric acid into 6-mercaptonicotinic acid and 1-chloroadamantane. Apparently, the pyridine ring nitrogen atom was too far removed from the 1-adamantly bridgehead to help promote the C-S cleavage in 5-(1-adamantylthio)nicotinonitrile (**7**) which was hydrolyzed almost quantitatively by concentrated hydrochloric acid to 5-(1-adamantylthio)nicotinic acid (**15**).

Table I

Distribution of Products from the Reaction of **1** with 1-AdmSH [a]

Structure	Yield (%) 1 hour	3 hours	3 hours (with NEt_3)
1	18.1	8.0	52.0
1-AdmSAc	3.9	15.9	55.5
2	21.6	29.7	—
3	10.0	17.3	3.1
4	12.9	13.9	—
5	1.9	2.1	—
6	1.8	3.6	—
7	0.7	0.1	—
8	—	—	7.6

[a] Based on the use of equimolar quantities of **1** and 1-AdmSH in boiling acetic anhydride; the yields are adjusted to reflect the recovery of **1**.

Conclusions.

In general, the substitution of nicotinic acid derivatives took place but in general required higher temperatures than that noted for alkylpyridine 1-oxides. Nicotinamide and nicotinic acid *N*-oxides are substituted by 1-AdmSH primarily at position 2, although some substitution took place at C-6 when the amide was used. The β-sulfide (at C-5) arises from initial attack at C-6 by the mechanism postulated previously [4]. Table I summarizes the progress and products of the reaction using **1**. No tetrahydropyridyl sulfides could be isolated (or even detected in crude mixtures).

EXPERIMENTAL

Melting points were determined on a Unimelt Thomas Hoover capillary melting point apparatus and are uncorrected. Microanalyses were carried out by Micro-Tech Labs, Skokie, IL. Infrared (ir) spectra were recorded on a FT-ir spectrometer, Model MX-1, Nicolet Instrument Corporation. Mass spectra (ms) were obtained at 70 eV by Mr. Richard Dvorak using a Hitachi-Perkin Elmer RMU-6D single focusing spectrometer or Finnigan Mass spectrometer, Model MAT 112 S. Ions with intensities of 20% or more for the base peak are reported and relative intensities are shown in parentheses. The ^{1}H nmr spectra were recorded in deuteriochloroform or DMSO-d_6 on a T60A Varian spectrometer fitted with a Nicolet TT-7 Fourier transform accessory. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are designated as singlets (s), doublets (d), triplets (t), multiplets (m). Column chromatography was carried out on silica gel (Baker Chemical Co., 60-200 mesh). Thin layer chromatograms (tlc) were run on 8 × 4 cm (0.25 mm thick) strips of silica gel mixed with an uv indicator, Brinkmann Instruments, Inc., Sil G/UV$_{254}$. Developing solvent A was petroleum ether:ether (7:3), B was ether, C was acetone:petroleum ether (7:3), and D was methanol:petroleum ether (7:3). Spots were detected by either uv light and/or iodine stains.

Removal of solvents, "*in vacuo*", implies that their distillation was by means of a rotary flash evaporator at 20-30 Torr, unless otherwise indicated. Petroleum ether refers to that fraction, bp 30-60°.

Materials.

Nicotinamide *N*-oxide was purchased from Aldrich Chemical Co., Milwaukee, WI. The generous gifts of nicotinic acid *N*-oxide from Reilly Tar and Chemical Co., Indianapolis, IN is gratefully acknowledged.

The Reaction of 1-Adamantanethiol with Acetic Anhydride.

A solution of 0.26 g of 1-AdmSH in 4.5 ml of acetic anhydride was heated in separate experiments at 95°, and under reflux. Aliquots were drawn out periodically (every 0.5 hour) and diluted with ice. The products were extracted with chloroform and the organic layer washed with water. The chloroform solution was analyzed by means of a Varian Aerograph Series 2700 (gas chromatography) equipped with a flame ionization detector and a stainless steel column (6 ft × 0.125 in) packed with 3% SE-30 on Veraport 30. Helium was used as the carrier gas and the inlet temperature was 200°. Retention times for 1-AdmSH and 1-AdmSCOCH$_3$ were 1.40 and 3.25 minutes, respectively. At 95°, the acetylation was only 5% complete after 4 hours. At reflux, the reaction was virtually complete after 4 hours. Addition of 3 equivalents of triethylamine caused complete acetylation after 0.5 hour at 95°. When 3 equivalents of 5-(1-adamantylthio)nicotinonitrile (**7**) as a "weak" basic catalyst was added to this acylation, the reaction was 60% complete after 5 hours.

Reaction of Nicotinamide *N*-Oxide with 1-Adamantanethiol in Acetic Anhydride.

Nicotinamide *N*-oxide (5.0 g, 36.0 mmoles) was dried azeotropically by distillation with toluene (2 × 20 ml) at 30 Torr. The *N*-oxide was dissolved in hot acetic anhydride (75 ml, 120°) and treated dropwise (20 minutes) with a solution of 1-adamantanethiol [11] (6.05 g, 36.0 mmoles) in acetic anhydride (25 ml). The mixture was refluxed (3 hours) and then solvents were distilled *in vacuo* (5 Torr). To remove residual acetic acid and anhydride by azeotropic distillation, the residue was boiled down several times with xylene *in vacuo* (3 × 60 ml). The residue (13.0 g) was now neutral to wet *p*H paper and its ^{1}H nmr spectrum was devoid of CH_3 resonances attributable at either acetic acid or anhydride. Upon trituration with a mixture of petroleum ether and ether, nicotinamide *N*-oxide (0.4 g, 8.0%) crystallized out and was filtered. The mother liquor was concentrated *in vacuo* and placed onto a column of silica gel (400 g) prepared in petroleum ether. Elution with 2.5 ℓ of petroleum ether:toluene (4:1) yielded 1-adamantyl thiolacetate (1.2 g, 16%) mp 61-62°, lit [14] mp 61-64°; tlc R_f 0.76 (solvent A). Further elution (1 ℓ) of petroleum ether:toluene (1:1) furnished 6-(1-adamantylthio)nicotinonitrile (**6**) (0.32 g, 3.6%), which was recrystallized from ether (80% recovery), mp 142-144°; tlc, R_f 0.67 or 0.90 (solvent A or B); ^{1}H nmr (deuteriochloroform): δ 8.63 (d, H-6), 7.63 (dd, H-4, 7.17 (d, H-3), ($J_{3,4}$ = 8.7, $J_{4,6}$ = 1.8 Hz), 2.24-1.75 (m, 1-Adm); ms: 270 (M$^+$, 50), 135 (100), 93 (33), 79 (40).

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.70; N, 10.36. Found: C, 71.09; H, 6.77; N, 10.26.

Elution with toluene (2 ℓ) gave 2-(1-adamantylthio)nicotinonitrile (**4**) (1.25 g, 14%) which was recrystallized from ether (85% recovery), mp 150-151°; tlc, R_f 0.39 or 0.83 (solvent A or B); ir (Nujol): 2224 (CN) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.59 (dd, H-6), 7.79 (dd, H-4), 7.08 (dd, H-5), ($J_{4,5}$ = 7.2, $J_{5,6}$ = 4.7, $J_{4,6}$ = 1.8 Hz), 2.25-1.74 (m, Adm); ms: 270 (M$^+$, 92), 135 (100), 107 (22), 93 (52), 79 (55).

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.70; N, 10.36. Found: C, 71.19; H, 6.86; N, 10.37.

5-(1-Admantylthio)nicotinonitrile (**7**), (0.01 g, 0.1%) was eluted by 2.5 ℓ of toluene:chloroform (1:1) and was recrystallized from ether (~ 50% recovery); mp 96-97°; tlc, R_f 0.48 or 0.91, (solvent A or B); ^{1}H nmr (deuteriochloroform): δ 8.84 (d, H-2, H-6), 8.06 (t, H-4) ($J_{2,4}$ = $J_{4,6}$ = 1.8 Hz), 2.05-1.64 (m, 1-Adm); ms: 270 (M$^+$, 2), 135 (100), 93 (23), 79 (27).

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.70; N, 10.36. Found: C, 71.22; H, 6.59; N, 10.31.

Further elution with chloroform (1 ℓ) gave **3** (2.5 g). Recrystallization from ether furnished pure **3** (1.9 g, 17%); mp 136-137°; tlc , R_f 0.63 (solvent B); ir (Nujol): 3282 (NH), 1713, 1692 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 9.63 (br, NH), 8.6 (dd, H-6), 8.02 (dd, H-4), 7.2 (dd, H-5), ($J_{4,5}$ = 7.2, $J_{5,6}$ = 4.7, $J_{4,6}$ = 1.8 Hz), 2.55 (s, NCOCH$_3$), 2.16-1.70 (m, 1-Adm); ms: 330 (M$^+$, 26), 329 (27), 244 (38), 243 (47), 135 (100), 73 (33), 79 (34).

Anal. Calcd. for $C_{18}H_{22}N_2O_2S$: C, 65.42; H, 6.70; N, 8.47. Found:

C, 65.19; H, 6.79; N, 8.29.

The major fraction was eluted next by chloroform (2.5 ℓ) and consisted of pure **2** (2.85 g, 30%) which could be recrystallized from ether, mp 177-178°; tlc, R_f 0.22 (solvent B); ir (Nujol): 3501, 3365 (NH_2), 1685 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 8.54 (dd, H-6), 8.18 (dd, H-4), 7.2 (dd, H-5), ($J_{4,5}$ = 7.2, $J_{5,6}$ = 4.7, $J_{4,6}$ = 1.8 Hz), 6.62 (br, $CONH_2$ complete deuterium oxide exchange after a month at 25°), 2.13-1.69 (m, 1-Adm); ms: 288 (M^+, 57), 135 (100), 93 (23), 79 (24), 32 (80), 31 (84), 29 (60).

Anal. Calcd. for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.46; H, 6.96; N, 9.68.

Continued elution with chloroform (7.5 ℓ) furnished a crude mixture of **5** (1.0 g) which was rechromatographed on silica gel (30 g). Elution with chloroform (2 ℓ) gave pure **5** (0.2 g, 2.1%) which was recrystallized from ether, mp 198-199°; tlc: R_f 0.18 (solvent B); ir (Nujol): 3361, 3175 (NH_2) 1684 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 8.85 (dd, H-6), 7.91 (dd, H-4), 7.28 (dd, H-3), ($J_{3,4}$ = 8.4, $J_{4,6}$ = 2.4, $J_{3,6}$ = 0.6 Hz), 6.03 (br, $CONH_2$), 2.18-1.71 (m, 1-Adm); ms: 288 (M^+, 10), 135 (100), 93 (28), 79 (41), 67 (21).

Anal. Calcd. for $C_{16}H_{20}N_2OS$: C, 66.63; H, 6.99; N, 9.71. Found: C, 66.38; H, 7.18; N, 9.77.

This column was not eluted further with more polar solvents.

Reaction of **1** with 1-Adamantanethiol in Acetic Anhydride Containing Triethylamine.

A solution of 1-adamantanethiol (6.05 g, 36.0 mmoles) in acetic anhydride (25 ml) was added to the hot solution of **1** (5.0 g, 36.0 mmoles) in acetic anhydride (80 ml) containing triethylamine (14.2 ml, 0.1 mole). The reaction mixture was heated at reflux for 3 hours. Upon cooling, nicotinamide *N*-oxide (2.6 g, 52% recovery) was filtered off and washed with cold petroleum ether. The filtrate was evaporated *in vacuo* (~5 Torr) to yield 10.0 g of residue which was worked up as for the last experiment. Chromatography on a column of silica gel (300 g, prepared in petroleum ether). Initial elution using 1 ℓ of petroleum ether: toluene (1:1) gave 1-adamantylthiolacetate (4.20 g, 56%). Further elution with chloroform (1 ℓ) furnished *N*-acetyl-2-(1-adamantylthio)nicotinamide (**3**) (0.18 g, 3.1%), identical (mp, ir, ^1H nmr, ms) to the sample described above. The next fraction (with 5 ℓ) of choroform produced *N,N*-diacetyl-2-acetoxynicotinamide (**8**) (0.35 g, 7.6%). The latter was recrystallized from ether (~75% recovery), mp 189-190°; tlc, R_f 0.36 (solvent C); ir (Nujol): 1768, 1762, 1749, 1706, 1700 cm^{-1} (C=O); ^1H nmr (deuteriochloroform, 200 MHz): δ 8.3 (dd, H-6), 7.72 (dd, H-4),7.46 (dd, H-5), $J_{4,5}$ = 7.6, $J_{5,6}$ = 6.5, $J_{4,6}$ = 0.8 Hz), 2.63, 2.27, 2.08 (s, 3 CH_3's); ms: 264 (M^+, 2), 163 (100), 162 (29), 146 (25).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.57; N, 10.60. Found: C, 54.35; H, 4.75; N, 10.63.

Reaction of **1** with Acetic Anhydride.

A solution of **1** (13.8 g, 0.1 mole) in acetic anhydride (200 ml) was refluxed (3 hours) and worked up as described in the first experiment. Chromatography on silica gel (600 g) with 1% methanol in chloroform (1.5 ℓ) first gave **8** (0.2 g, 0.8%); then 3% methanol in chloroform (2.3 ℓ) gave 13.0 g solid. Recrystallization from chloroform gave pure *N*-acetyl-2-hydroxynicotinamide (**9**) (7.9 g, 44%), mp 220-221°; tlc, R_f 0.47 (solvent C); ir (Nujol): 3182, 3120 (NH), 1712, 1694 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 12.33 (br s, NH), 8.45 (dd, H-4), 7.87 (dd, H-6), 6.57 (dd, H-5), ($J_{4,5}$ = 7.2, $J_{5,6}$ = 6.0, $J_{4,6}$ = 2.4 Hz); ms: 120 (M^+, 100), 93 (23), 76 (25), 66 (20), 65 (72), 64 (69), 51 (23), 50 (27).

Anal. Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.24; H, 4.58; N, 15.56.

Further elution with an increasing amount of methanol (up to 15%) in chloroform gave 4.27 g of solid which was rechromatographed on silica gel (200 g, prepared in chloroform). Elution with chloroform (5 ℓ) produced 2-hydroxynicotinonitrile (**10**) (0.065 g, 0.54%) mp 170-171° which was recrystallized from aqueous methanol, mp 174-175°; tlc, R_f 0.18 (solvent C); ir (Nujol): 3102 (NH), 2245 cm^{-1} (CN); ^1H nmr (DMSO-d_6): δ 8.85 (NH), 8.48 (d, H-6), 7.70 (m, H-4, H-5), ($J_{5,6}$ = 6.0 Hz); ms: 180 (M^+, 11), 122 (100), 95 (27), 94 (28), 43 (45), 39 (32).

Anal. Calcd. for $C_6H_4N_2O$: C, 59.99; H, 3.36; N, 23.32. Found: C, 59.98; H, 3.45; N, 23.43.

Continued elution with 1-5% methanol in chloroform (3 ℓ) afforded *N*-acetyl-2-hydroxynicotinamide (2.98 g, 17%).

Reaction of Nicotinamide *N*-Oxide with Acetic Anhydride and Triethylamine.

Nicotinamide *N*-oxide (13.8 g, 0.1 mole) was refluxed with acetic anhydride (200 ml) and triethylamine (42.6 ml, 0.3 mole) for 3 hours. Upon cooling 7.5 g of *N*-oxide was filtered off, (56%) the work up procedure is similar to the previous reaction. The dark oil (23 g) was placed on silica gel (300 g) and eluted with chloroform (4.5 ℓ) to give **8** (2.3 g, 19%) which was recrystallized from acetone (1.7 g, 14%). Further elution with more polar solvents gave small quantities of intractable materials.

Reaction of Nicotinic Acid *N*-Oxide with 1-Adamantanethiol in Acetic Anhydride.

A solution of 1-AdmSH (16.8 g, 0.1 mole) in acetic anhydride (25 ml) was added to a solution of nicotinic acid *N*-oxide (13.9 g, 0.1 mole) in acetic anhydride (75 ml). The solution was refluxed (3 hours). Upon cooling, the starting *N*-oxide was recovered (2.3 g, 16.5%). The mother liquor was concentrated *in vacuo* (5 Torr) to yield 36.0 g of an oil which was chromatographed on silica gel (400 g, in toluene). Elution first with 0.5 ℓ of toluene gave 1-AdmSAc (2.3 g, 11%) then with chloroform (1 ℓ) furnished an additional 2.0 g of this ester (9.5%). Finally, elution with chloroform (8 ℓ) produced a solid (8.2 g) which was recrystallized from methanol to give pure 2-(1-adamantylthio)nicotinic acid (**13**) (6.74 g, 23%), mp 223-224°; tlc, R_f 0.74 (solvent D); ir (Nujol): 3200-2200 (br, OH), 1709 cm^{-1} (C=O); ^1H nmr (DMSO-d_6): δ 8.55 (d, H-6), 8.05 (d, H-4), 7.16 (dd, H-5), ($J_{4,5}$ = 7.8, $J_{5,6}$ = 4.8 Hz), 2.24-1.73 (m, 1-Adm); ms: 289 (M^+, 3), 135 (100), 93 (27), 79 (34).

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.45; H, 6.43; N, 4.59.

Cleavage of 1-Adamantyl Sulfides with Concentrated Hydrochloric Acid.

Examples of this cleavage are provided. 2-(1-Adamantylthio)nicotinamide (**2**) (0.2 g, 0.69 mmole) was boiled with concentrated hydrochloric acid (10 ml) for 1 hour. Upon cooling, yellow needles of 2-mercaptonicotinic acid (**14**) (0.095 g, 88%) were filtered off and were recrystallized from hot water (~90% recovery) mp 259-262°, lit [13] mp 265-266°; tlc, R_f 0.37 (solvent D); ir (Nujol): 3100-2000 (broad OH), 1684 cm^{-1} (acid C=O); ^1H nmr (DMSO-d_6): δ 14.57 (br, H-bonding), 8.54 (dd, H-4), 8.15 (dd, H-6), 7.13 (dd, H-5), ($J_{4,5}$ = 7.8; $J_{5,6}$ = 6.0, $J_{4,6}$ = 1.8 Hz); ms: 155 (M^+, 3), 110 (51), 108 (27), 83 (23), 82 (21), 67 (100), 51 (57).

Anal. Calcd. for $C_6H_5NO_2S$; C, 46.45; H, 3.25; N, 9.03. Found: C, 46.26; H, 3.29; N, 9.09.

1-Chloroadamantane (0.12 g, 100% sublimed into the condenser during this hydrolysis, mp 158-160°, lit [5] mp 165° sublimes.

Similarly, 2-(1-adamantylthio)nicotinonitrile (**4**) (0.1 g, 0.37 mmole) was cleaved and hydrolyzed by refluxing concentrated hydrochloric acid (5 ml, 1 hours) to produce 2-mercaptonicotinic acid (0.055 g, 96%) and 1-chloroadamantane (0.063 g, 100%).

6-(1-Adamantylthio)nicotinonitrile (**6**) (0.133 g, 0.49 mmole) was refluxed with concentrated hydrochloric acid (7 ml) for 1 hour. Upon cooling, 0.044 g of yellow needles were filtered. The mother liquor was evaporated to dryness *in vacuo* and the residue was washed with petroleum ether to give additional 0.044 g of 6-mercaptonicotinic acid (quantitative yield), mp 278-280° (lit [15] mp 273-275°); tlc, R_f 0.74 (solvent D); ir (Nujol): 1698 cm^{-1} (CO); ^1H nmr (DMSO-d_6): δ 13.8 (OH), 8.02 (d, H-2), 7.71 (dd, H-4), 7.30 (d, H-5), ($J_{4,5}$ = 9.0, $J_{2,4}$ = 2.4 Hz); ms: 155 (M^+ 100), 111 (71), 94 (24), 28 (37), 18 (80).

1-Adamantyl chloride (0.068 g, 81%) was collected from the condensor.

Similarly, 6-(1-adamantylthio)nicotinamide (**5**) (0.057 g, 0.20 mmole) was cleaved in concentrated hydrochloric acid (5 ml) for 1.5 hours. During this time 1-adamantyl chloride (0.031 g, 91%) sublimed into the condenser and was collected. The aqueous phase was evaporated to dryness

(*in vacuo*). The residue consisted of 6-mercaptonicotinic acid (0.027 g, 90%).

Cleavage was accomplished by refluxing 2-(1-adamantylthio)nicotinic acid (0.1 g, 0.35 mole) with concentrated hydrochloric acid (5 ml) for 1 hour. Work up was as described above furnished 2-mercaptonicotinic acid (0.05 g, 92%) and 1-chloroadamantane (0.05 g, 88%).

Also, *N*-acetyl-2-(1-adamantylthio)nicotinamide (**3**) (0.07 g, 0.2 mmole) was treated with boiling concentrated hydrochloric acid (5 ml, 1 hour) to yield 2-mercaptonicotinic acid (0.03 g, 91%) and 1-chloroadamantane (0.035 g, 97%).

Milder hydrolysis of *N*-acetyl-2-(1-adamantylthio)nicotinamide (0.01 g, 0.03 mmole) was carried out with 3.7% boiling hydrochloric acid (1 ml) for 10 minutes. In order to maintain a solution, ethanol (5 ml) was added to this hot mixture and heating was continued (20 minutes) at 95°. The solution was then cooled and neutralized with 5% sodium hydroxide. The white solid (100%) which was filtered off was identical to 2-(1-adamantylthio)nicotinamide (tlc, ^{1}H nmr) so described above.

Conversion of 2-Mercaptonicotinic Acid to 2-Hydroxynicotinic Acid.

The thione (0.2 g, 1.30 mmoles), concentrated hydrochloric acid (10 ml) and methanol (10 ml) was stirred vigorously (25°). We added at once a solution of sodium nitrite (0.18 g, 2.60 mmoles) in water (4 ml) and the reaction mixture was stirred (25°) for 2 days. After evaporation of methanol, a white solid (0.11 g) was filtered. The mother liquor was concentrated to dryness and gave a crude yellow solid which was extracted with several portions of 2-propanol (150 ml). Evaporation of this extract yielded 0.158 g of the corresponding pyridone as a yellow semisolid. Recrystallization from water gave yellow needles (0.065 g, 36%) mp 256-260° dec (lit [10] mp 260-262°); tlc, R_f 0.08 (solvent C); ir (Nujol): 2094-3300 (br, OH), 1700 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 14.8, 13.38 (OH, NH), 8.40 (dd, H-6), 7.96 (dd, H-4), 6.68 (t, H-5), ($J_{4,5} = J_{5,6} = 6.0$, $J_{4,6} = 1.2$ Hz); ms: 139 (M$^+$, 27), 95 (100), 94 (34), 93 (42), 67 (32), 66 (33).

Hydrolysis of 5-(1-Adamantylthio)nicotinonitrile.

5-(1-Adamantanethio)nicotinonitrile (**7**) (0.1 g, 0.37 mmole) was refluxed with concentrated hydrochloric acid (5 ml) for 2 hours. White shiny crystals were deposited during this period. Upon cooling, 0.067 g of the solid (0.067 g) was filtered off, and the mother liquor was evaporated to dryness to give an additional 0.031 g of acid (**15**) (overall yield 92%), mp 258-259° (unchanged after crystallization from aqueous ethanol); tlc, R_f 0.74 (solvent D); ir (Nujol): 3000-2000 (broad OH), 1730 cm^{-1} (C=O); ^{1}H nmr (DMSO-d_6): δ 9.05 (d, H-2), 8.79 (d, H-6), 8.25 (t, H-4), $J_{2,4} = J_{4,6} = 1.8$ Hz), 1.98-1.59 (m, 1-Adm); ms: 289 (M$^+$, 8), 135 (100).

Anal. Calcd. for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84. Found: C, 66.30; H, 6.51; N, 4.93.

Reaction of 2-(1-Adamantylthio)nicotinamide with Acetic Anhydride.

A solution of the amide (0.1 g, 0.35 mmole) was boiled in acetic anhydride (5 ml) for 3 hours. The residue (0.12 g, after evaporation of the solvent, *in vacuo*) was recrystallized from 95% ethanol to give 2-(1-adamantylthio)-3-cyanopyridine (0.042 g, 45%) which was filtered off. The nitrile was identical to a sample isolated above. The mother liquor (after concentration) was placed onto a column of silica gel (10 g, chloroform). Elution with chloroform (250 ml) provided *N*-acetyl-2-(1-adamantylthio)nicotinamide (0.065 g, 59%).

The startng amide (0.20 g, 0.7 mmole) was refluxed with acetic anhydride (10 ml) containing triethylamine (4 ml) for 2 hours. Solvents were removed *in vacuo* (5-10 Torr). The oil (0.48 g) so produced solidified at room temperature. The mixture was separated by silica gel (10 g), prepared in petroleum ether. Elution with 100 ml of petroleum ether:ether (7:3) gave pure 2-(1-adamantylthio)-3-cyanopyridine (0.007 g, 3.7%). The next fraction from ether (100 ml), furnished *N*-acetyl-2-(1-adamantylthio)nicotinamide (**3**) (0.175 g, 76%).

Hydrolysis of **8** and **9**.

N,N-Diacetyl-2-acetoxynicotinamide (**8**) (0.1 g, 0.38 mmole) was heated at 95° (steam bath) with 2 ml of concentrated hydrochloric acid for 0.5 hour. Starting material had disappeared (tlc) and upon evaporation of the solution 2-hydroxynicotinic acid (quantitative yield) was obtained. Recrystallization from methanol:water (3:2) gave pure acid (0.032 g, 60%).

Similarly, *N*-acetyl-2-hydroxynicotinamide (**9**) (0.1 g, 0.55 mmole) was heated on a steam bath with 5 ml of hydrochloric acid (3.7%) for 3 hours. After removing solvents, 2-hydroxynicotinic acid was isolated (100%).

N-Acetyl-2-hydroxynicotinamide (**9**) (0.1 g, 0.55 mmole) was boiled with concentrated ammonium hydroxide (5 ml) for 2 hours. Upon cooling at room temperature, 2-hydroxynicotinamide (0.068 g, 88%) was filtered and was recrystallized from water, mp 269-271° (lit [16] mp 263-266°); tlc, R_f 0.18 (solvent C); ir (Nujol): 3341, 3167 (NH_2), 3087 (NH), 1680 cm^{-1} (CO); ^{1}H nmr (DMSO-d_6): δ 9.05 (br s, NH), 7.52 (br s, NH_2), 8.32 (dd, H-4), 7.68 (dd, H-6), 6.45 (dd, H-5), ($J_{4,5} = 7.2$, $J_{5,6} = 6.0$, $J_{4,6} = 2.4$ Hz); ms: m/e 138 (M$^+$, 100), 122 (51), 95 (39), 94 (29), 39 (21).

Similarly, *N*-acetyl-(2-hydroxy)nicotinamide (**9**) (0.05 g, 0.27 mmole) was dissolved in methanol (5 ml), and hydrazine (0.5 ml) was added. The solution was stirred at room temperature for 10 minutes after which starting material had disappeared (tlc). After solvents were removed *in vacuo*, the residue was triturated with petroleum ether and ether to yield 2-hydroxynicotinamide (0.035 g, 100%).

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