

Synthesis of Two New Nicotinamide Derivatives and of 1-Alkylthiocarbamoylpyridinium Iodides

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Some of the neurotoxic activity of 6-aminonicotinamide (6-AN) can be explained by the *in vivo* biosynthesis of 6-AN-ADP⁺ in the brain and a block in the pentose phosphate pathway resulting from this NADP⁺-analogue (1). It was of great interest to see to what extent the biochemical and toxicological effects are modified, when oxygen in the carbamoyl group of nicotinamide and 6-AN respectively is replaced by sulphur or selenium. Earlier we obtained a NADP⁺-analogue from selenonicotinamide *in vitro* using NAD(P)-glycohydrolase (2,3).

We wish to report the synthesis of selenonicotinamide (1a), 6-aminothionicotinamide (1b), 1-methyl-6-amino-3-thiocarbamoylpyridinium iodide (2c), 1-[2',6'-dichlorobenzyl]thionicotinamide iodide (2d) and some other related compounds (2a, 2b, 3a; see Table I).

The pharmacological evaluation of some of the compounds presented is under way.

Syntheses.

Nicotinic acid selenoamide and 6-aminothionicotinamide were prepared by addition of hydrogen sulfide and hydrogen selenide respectively, to the corresponding nitriles.

Thiocarbamoylpyridines cannot be *N*¹-alkylated directly. Attempts to alkylate thionicotinamide with

methyl iodide (4) or 2,6-dichlorobenzylbromide (5) did not result in homogeneous reaction products. For that reason *N*¹-alkylation had to proceed the latter formation of the thioamide moiety in 3- and 4-positions, respectively. Dependent on the nature of the substituents in 1- and 6-position we had to use two different routes.

Conversion of the amide into the thioamide by treatment with phosphorus pentasulfide was applicable only with 6-unsubstituted compounds. Halogen atoms in the *N*¹-substituent did not interfere with this method.

The second method, addition of hydrogen sulfide to the corresponding nitrile in the presence of triethylamine, worked well even with 6-amino compounds. It failed, however, with compounds bearing halogen in the *N*¹-substituent.

The attempt to prepare 1-methyl-3-selenocarbamoylpyridinium iodide by the addition of hydrogen selenide to the corresponding cyano-compound failed.

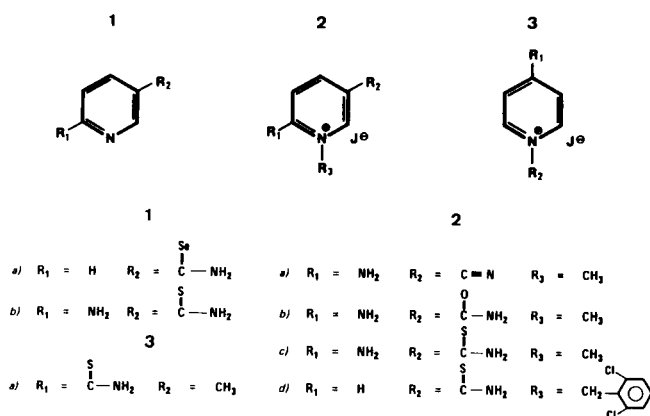
EXPERIMENTAL

Melting points were determined with a micro melting point apparatus (microscope) of Reichert Company, Vienna, Austria, and are uncorrected. Uv spectra were recorded with a Beckman DK2A spectrophotometer. The ir spectra were obtained with a Perkin-Elmer spectrometer model 621 in pressed disks of potassium bromide. Elemental analyses were performed by Dr. F. Pascher, Mikroanalytisches Laboratorium, 53 Bonn, West Germany.

Nicotinic Acid Selenoamide (1a).

Ninety ml. of absolute ethanol was saturated with ammonia gas at 0° and added to a solution of 8.3 g. (0.08 mole) of 3-cyanopyridine in 30 ml. of absolute ethanol. A constant stream of dry hydrogen selenide (generated from aluminium selenide and 5 *N* sulfuric acid) in a stream of nitrogen was lead over the surface of this solution for 60-90 minutes while being stirred (at 0°). Ochre-yellow crystals and sometimes a brown fine crystalline product respectively, precipitated from the wine red reaction mixture after having stood at room temperature (approximately 25°) for 2 days (under exclusion of daylight). The glass bottle was tightly stoppered. The product was collected by suction on a sintered glass funnel under nitrogen, washed with few mls. of absolute ethanol and dried in a desiccator (over phosphorus pentoxide). The crude product was recrystallized from approxi-

Table I



mately 170 ml. of 1-propanol. Golden yellow crystals precipitated after standing in the cold (-15°) for several hours. The product was collected by suction and dried under vacuum (25°), m.p. $228-232^{\circ}$ dec., sealed tube, 22% yield; uv (water, pH 6): with maxima at 227 nm (ϵ , 12.62×10^3), 327 nm (ϵ , 6.58×10^3); uv (in 0.01 *N* hydrochloric acid) 223 nm (ϵ , 10.21×10^3), 252 nm (ϵ , 7.16×10^3), 331 nm (ϵ , 5.59×10^3).

Anal. Calcd. for $C_6H_6N_2Se$ (mol. wt. 185.09): C, 38.9; H, 3.27; N, 15.1; Se, 42.66. Found: C, 38.7; H, 3.37; N, 14.97; Se, 43.3.

Under the exclusion of daylight the recrystallized compound has been stored in brown glass ampoules under nitrogen at -20° for three years without decomposition.

2-Amino-5-cyanopyridine.

Modification of Gregory's Method (6).

A mixture of commercially available 2-amino-5-bromopyridine (10 g., 0.0578 mole) and cuprous cyanide (5.71 g., 0.06 mole) in 12 ml. of *N,N*-dimethylformamide was heated under reflux for 4 hours. The solvent was removed under vacuum (15 mm). After cooling, the solid dark brown cake was pulverized. From 5 g. portions of this product the 2-amino-5-cyanopyridine was sublimed under vacuum (15 mm). The crude product was recrystallized from ethanol in the presence of charcoal (62% yield), m.p. 164° (Gregory reports 164°). Uv (in water, pH 6): with maximum at 263 nm (ϵ , 21.4×10^3); ir: 2214 cm^{-1} (s) ($-C\equiv N$).

6-Amino-3-thiocarbamoylpyridine (1b).

2-Amino-5-cyanopyridine (1.5 g., 0.0126 mole) was dissolved in approximately 50 ml. of anhydrous pyridine and 2.1 ml. (0.015 mole) of triethylamine are added. Through this solution (immersed in ice) was bubbled dry hydrogen sulphide for 2 hours. Thereafter the reaction mixture was kept at room temperature for 2 days in a tightly stoppered glass bottle. The solvent was removed under vacuum and the crude yellow product was recrystallized from water. Pale yellow needles (77% yield), m.p. $179-180^{\circ}$; uv (in water, pH 6): with maxima at 315.5 nm (ϵ , 15.36×10^3); uv (in 0.01 *N* hydrochloric acid): 271 nm (ϵ , 13.52×10^3), 302.5 nm (ϵ , 13.80×10^3).

Anal. Calcd. for $C_6H_7N_3S$ (mol. wt. 153.21): C, 47.04; H, 4.62; N, 27.43; S, 20.93. Found: C, 47.00; H, 4.50; N, 27.40; S, 21.10.

The following 1-alkylpyridinium derivatives were prepared according to the literature 1-methyl-3-cyanopyridinium iodide (7,8); 1-methyl-4-cyanopyridinium iodide (9); 1-methyl-3-thiocarbamoylpyridinium iodide (4); 1-[2',6'-dichlorobenzyl]nicotinamide iodide (10).

1-Methyl-2-amino-5-cyanopyridinium Iodide (2a).

2-Amino-5-cyanopyridine (500 mg., 4.2 mmoles) was dissolved in 13 ml. of ethanol and 0.8 ml. (12.8 mmoles) of methyl iodide was heated under reflux for 9 hours. The solvent was removed and the crude product recrystallized from alcohol, 30% yield, m.p. $231-233^{\circ}$; uv (in water, pH 6): with maxima at 226 nm (ϵ , 15.05×10^3), 254 nm (ϵ , 17.54×10^3), 300.5 nm (ϵ , 4.79×10^3); ir: 2236 cm^{-1} ($-C\equiv N$).

Anal. Calcd. for $C_7H_8N_3I$ (261.06): C, 32.21; H, 3.09; N, 16.1. Found: C, 32.02; H, 3.04; N, 15.94.

1-Methyl-6-amino-3-carbamoylpyridinium Iodide (2b).

Three g. (0.022 mole) of 6-aminonicotinamide and 4 ml. (0.064 mole) of methyl iodide in 140 ml. of methanol gave 66% yield of product, m.p. $263-267^{\circ}$; uv (in water, pH 6):

with maxima at 226 nm (ϵ , 16.25×10^3), 257 nm (ϵ , 12.9×10^3), 296 nm (ϵ , 5.15×10^3).

Anal. Calcd. for $C_7H_{10}N_3OI$ (mol. wt. 279.08): C, 30.13; H, 3.61; N, 15.06; O, 5.73; I, 45.47. Found: C, 30.01; H, 3.57; N, 14.25; O, 5.88; I, 45.50.

Preparation of 1-Methylthiocarbamoylpyridinium Iodides from the Corresponding Cyanopyridinium Derivatives by the Addition of Hydrogen Sulphide.

General Technique.

The cyanopyridinium iodides were dissolved in dry pyridine and triethylamine was added in molar proportions. A constant stream of dry hydrogen sulphide was bubbled through the reaction mixture for 1-2 hours, while being stirred (at 0°). Thereafter the green-yellow reaction mixture stands tightly stoppered at room temperature (approximately 25°) for 2-3 hours. The solvent was removed under vacuum (15 mm). The crude product was recrystallized from methanol and precipitated with diethyl ether from methanol, respectively.

1-Methyl-3-thiocarbamoylpyridinium Iodide.

One g. (4 mmoles) of 1-methyl-3-cyanopyridinium iodide and 0.6 ml. (4.2 mmoles) of triethylamine in approximately 100 ml. of pyridine, yield 70.5%, m.p. $196-197^{\circ}$. The m.p. and uv spectra are in good agreement with the product obtained by Shiffrin's method (4).

Reduction with Sodium Borohydride.

To 2.5 ml. of a solution of 1-methylthionicotinamide iodide in water, 0.5 ml. of an aqueous sodium borohydride solution (2 g. of sodium borohydride/100 ml. kept at 0°) were added. After rapid stirring, the uv spectra were recorded instantaneously. The resulting mixture of 1,2-, 1,4-, and 1,6-dihydro compounds shows a pronounced absorption band with λ max at 508 nm, presumably due to the occurrence of the 1,2-dihydro compound.

1-Methyl-4-thiocarbamoylpyridinium Iodide (3a).

One g. (4 mmoles) of 1-methyl-4-cyanopyridinium iodide and the other components as mentioned above gave the product in 64% yield, m.p. $197-200^{\circ}$; uv (in water, pH 6): with maxima at 227 nm (ϵ , 24.19×10^3), 327 nm (ϵ , 3.15×10^3). P. Böger *et al.*, (8) reported the synthesis of this compound but they did not give any analytical data.

Anal. Calcd. for $C_7H_9IN_2S$ (mol. wt. 280.15): C, 30.01; H, 3.24; N, 10.0. Found: C, 30.59; H, 3.01; N, 10.13.

1-Methyl-6-amino-3-thiocarbamoylpyridinium Iodide (2c).

One hundred mg. (0.383 mmole) (2a) and 0.06 ml. (0.42 mmole) of triethylamine in approximately 10 ml. of dry pyridine gave the compound in 88% yield, m.p. $216-218^{\circ}$; uv (in water, pH 6): with maxima at 301 nm (ϵ , 12.05×10^3), 264 nm (ϵ , 12.31×10^3).

Anal. Calcd. for $C_7H_{10}IN_3S$ (mol. wt. 295.14): C, 28.49; H, 3.42; N, 14.24; S, 10.86. Found: C, 28.58; H, 3.42; N, 14.24; S, 10.98.

1-[2',6'-Dichlorobenzyl]-3-thiocarbamoylpyridinium Iodide (2d).

One g. of 1-[2',6'-dichlorobenzyl]nicotinamide iodide and 2 g. of phosphorus pentasulfide were melted according to Shiffrin (4). After 15 minutes, a dark brown tarry mass was formed and exhaustively extracted with methanol, yield 56%, m.p. $153-154^{\circ}$; uv (in methanol): with maxima at 257 nm (ϵ , 5.7×10^3), 284 nm (ϵ , 3.9×10^3), 315 nm (ϵ , 3.87×10^3).

Anal. Calcd. for $C_{13}H_{11}IN_2Cl_2S$ (mol. wt. 425.116): C, 36.73; H, 2.60; N, 6.59; Cl, 16.68; I, 29.85; S, 7.54. Found: C, 36.23; H, 2.72; N, 6.13; Cl, 16.55; I, 29.88; S, 8.27.

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