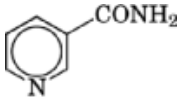
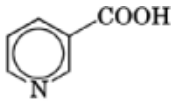
Kirk-Othmer Encyclopedia of Chemical Technology.

NIACIN, NICOTINAMIDE, AND NICOTINIC ACID

3-Pyridine carboxamide [98-92-0] (nicotinamide) (**1**) and 3-pyridine carboxylic acid [59-67-6] (nicotinic acid) (**2**) have a rich history and their early significance stems not from their importance as a vitamin but rather as products derived from the oxidation of nicotine. In 1867, Huber prepared nicotinic acid from the potassium dichromate oxidation of nicotine. Many years later, Engler prepared nicotinamide. Workers at the turn of the twentieth century isolated nicotinic acid from several natural sources. In 1894, Suzuki isolated nicotinic acid from rice bran, and in 1912 Funk isolated the same substance from yeast (1).



(**1**)



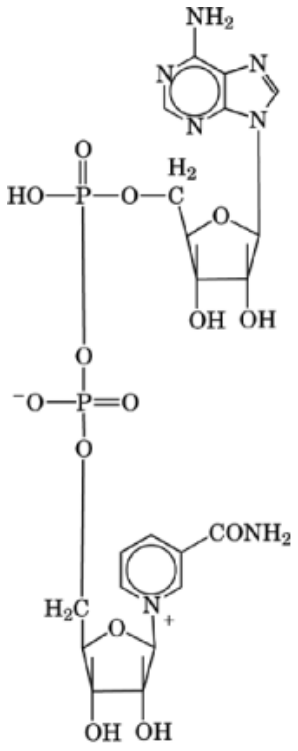
(**2**)

In 1913, Goldberger demonstrated that pellagra was due to a dietary deficiency. Pellagra had been earlier described by Thiery, who had coined the term *mal de la rosa* for this disease. Several decades later, Elvehjem and co-workers isolated nicotinamide from a liver extract and identified it as a pellagra-preventing factor (1).

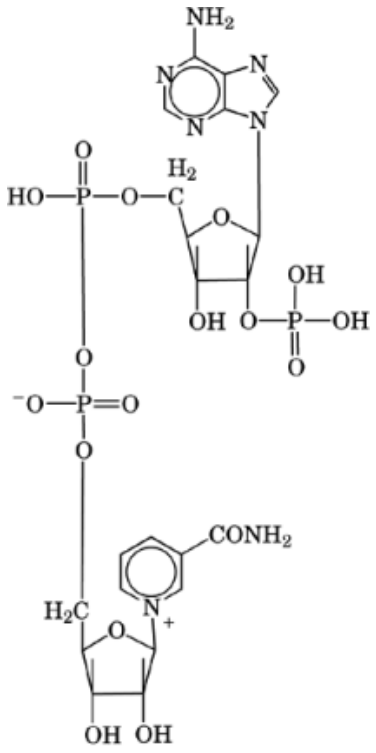
There is considerable confusion regarding the nomenclature of these simple substances. The term niacin is a generic descriptor for pyridine 3-carboxylic acid and derivatives that exhibit the biological activity of nicotinic acid (1). However, niacin and vitamin PP (pellagra preventing) are frequently used interchangeably with nicotinic acid. Vitamin B_3 is often used as a designation for nicotinamide (1). The following is a list of common names for these substances.

The biological importance of these compounds stems from their use as cofactors. Both nicotinamide and nicotinic acid are building blocks for coenzyme I (Co I), nicotinamide–adenine dinucleotide (NAD) (**3**) and coenzyme II (Co II), nicotinamide–adenine dinucleotide phosphate (NADP) (**4**) (2).

Nicotinamide	Nicotinic acid
aminicotin	akotin
benicot	apelagrin
delonin amide	daskil
NAM	efacin
niacinamide	linic
niavit PP	niacin
nicasir	nicacid
nicosan 2	nicangin
nicovit	nicolar
pelmine	pellagrin
pelonin amide	pelonin
vitamin B	SR 4390
vitamin B_3	



(3)



(**4**)

1. Chemical and Physical Properties

Nicotinamide is a colorless, crystalline solid. It is very soluble in water (1 g is soluble in 1 mL of water) and in 95% ethanol (1 g is soluble in 1.5 mL of solvent). The compound is soluble in butanol, amyl alcohol, ethylene glycol, acetone, and chloroform, but is only slightly soluble in ether or benzene. Physical properties are listed in Table 1.

Nicotinic acid is an amphoteric solid with needle-shaped crystals. It is less soluble than nicotinamide and its poor solubility in diethyl ether can be used as a basis to separate these compounds. Because nicotinamide has some solubility in ether, extraction of aqueous solutions of the acid and the amide with ether allows for selective extraction of the amide into the organic phase. Table 2 lists the physical properties of this vitamin.

The ring nitrogen of both the amide and the carboxylic acid can be quaternized and oxidized. *N*-methylnicotinate (trigonelline) (**5**) is an important component of green coffee beans and is converted to nicotinic acid during the roasting process. The reactivity of the 3-substituent parallels standard functional groups. Acid chlorides, esters, amides, and anhydrides have been prepared from nicotinic acid. Both the corresponding aldehyde and alcohol are available from the acid with a variety of reducing agents. Nicotinamide can be converted to nicotinic acid esters, the nitrile and acylamidines by routine methods.

Table 1. Physical Properties of Nicotinamide

Property	Value
molecular weight	122.12
melting point, °C	
stable modification	129–132
unstable modifications	
I	105
II	110
III	111
IV	113
V	116
boiling point, °C (0.067 Pa)	150–160
sublimation range, °C	80–100
true dissociation constants in water, at 20°C	
K_{b1}	2.24×10^{-11}
K_{b2}	3.16×10^{-14}
specific heat, kJ/(kgK)[a]	
solid, 55°C	1.30
65°C	1.34
75°C	1.39
liquid, 135°C	2.18
heat of solution in water, kJ/kg[a]	−148
heat of fusion, kJ/kg[a]	381
density of melt, at 150°C, g/cm^3	1.19

[a]To connvert J to cal, multiply by 4.184.

Table 2. Physical Properties of Nicotinic Acid

Property	Value
molecular weight	123.11
melting point, °C	236–237
sublimation range	≥150
density of crystals, g/cm^3	1.473
dissociation constants in water, at 25°C	
K_a	1.50×10^{-5}
K_b	1.04×10^{-12}
isoelectric point in water, at 25°C, pH	3.42
pH of saturated aqueous solution	2.7
solubility, g/L	
water	
0°C	8.6
38°C	24.7
100°C	97.6
ethanol, 96%	
0°C	5.7
78°C	76.0
methanol	
0°C	63.0
62°C	345.0

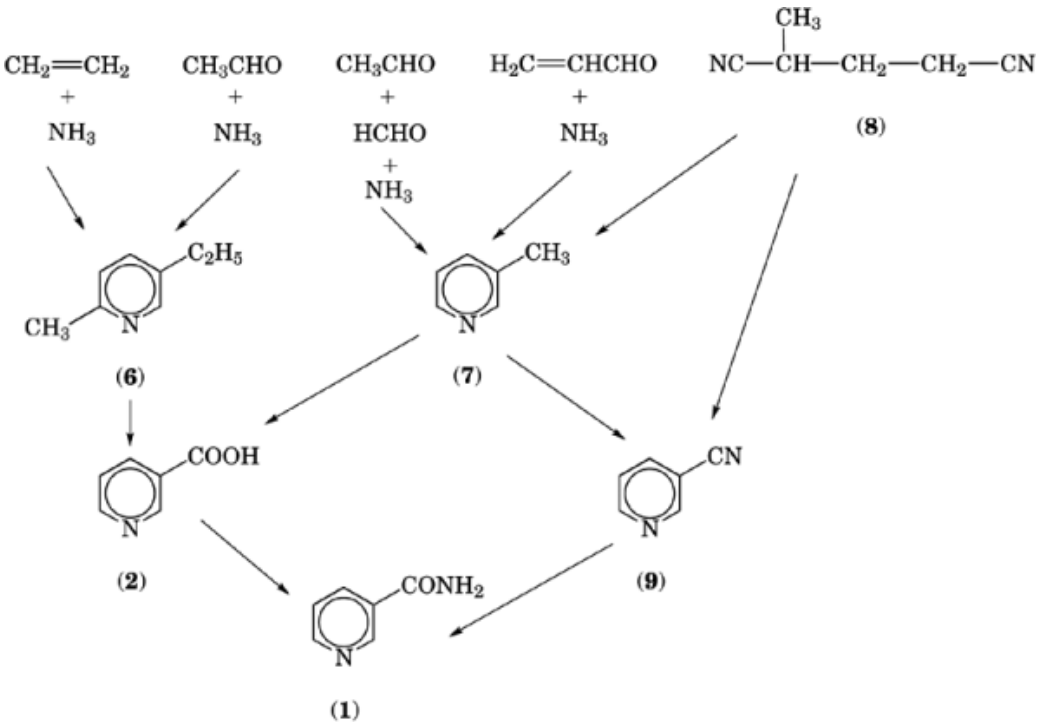
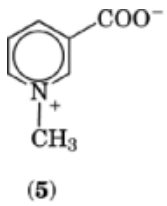


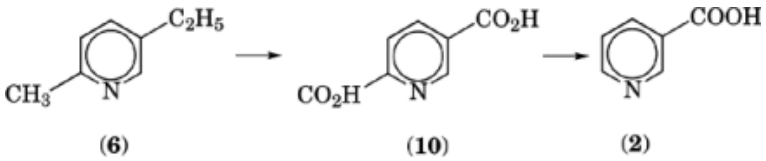
Fig. 1. Alkyl pyridines.



2. Synthesis

Key intermediates in the industrial preparation of both nicotinamide and nicotinic acid are alkyl pyridines (Fig. 1). 2-Methyl-5-ethylpyridine (**6**) is prepared in a liquid-phase process from acetaldehyde. Also, a synthesis starting from ethylene has been reported. Alternatively, 3-methylpyridine (**7**) can be used as starting material for the synthesis of nicotinamide and nicotinic acid and it is derived industrially from acetaldehyde, formaldehyde (qv), and ammonia. Pyridine is the principal product from this route and 3-methylpyridine is obtained as a by-product. Despite this and largely due to the large amount of pyridine produced by this technology, the majority of the 3-methylpyridine feedstock is prepared in this fashion.

3-Methylpyridine can also be prepared by the condensation of acrolein and ammonia. Yields of 40–50% are obtained with pyridine as a by-product. Higher yields have been claimed when both propionaldehyde and acrolein have been used. A recent U.S. patent claims better selectivity if the cyclization is carried out in the presence of zeolites (3).



(6) (10) (2)

Fig. 2. Formation of isocinchomeronic acid (**10**).

In an alternative approach, 2-methylglutaronitrile (**8**) is hydrogenated and cyclized to give high yields of 3-methylpyridine. The feedstock for this process is produced as a by-product of the production of adiponitrile. Oxidative cyclization of 2-methylglutaronitrile to nicotinonitrile (**9**) has been described (4).

The alkyl pyridines (**6**) and (**7**) can be transformed either to nicotinic acid or nicotinonitrile. In the case of nicotinic acid, these transformations can occur by either chemical or biological means. From an industrial standpoint, the majority of nicotinic acid is produced by the nitric acid oxidation of 2-methyl-5-ethylpyridine. Although not of industrial significance, the air oxidation has also been reported. Isocinchomeronic acid (**10**) (Fig. 2) is formed as an intermediate.

Although an inherently more efficient process, the direct chemical oxidation of 3-methylpyridine does not have the same commercial significance as the oxidation of 2-methyl-5-ethylpyridine. Liquid-phase oxidation procedures are typically used (5). A Japanese patent describes a procedure that uses no solvent and avoids the use of acetic acid (6). In this procedure, 3-methylpyridine is combined with cobalt acetate, manganese acetate and aqueous hydrobromic acid in an autoclave. The mixture is pressurized to 101.3 kPa (100 atm) with air and allowed to react at 210°C. At a 32% conversion of the picoline, 19% of the acid was obtained. Electrochemical methods have also been described (7).

In more recent work, several groups have reported on fermentative approaches to nicotinic acids from 3-picoline. *Rhodococcus* (8), *Acinetobactorr* (9), and *Pseudomonas* (10) have found utility in this application.

Nicotinonitrile is produced by ammoxidation of alkylpyridines (11–24). A wide variety of different catalysts have been developed for this application. For example, a recent patent describes a process in which 3-methylpyridine is reacted over a molybdenum catalyst supported on silica gel. The catalyst ($PV_4Mo_{12}O_x$) was prepared from NH_4VO_3, H_3PO_4, and $(NH_4)_5Mo_7O_{24}$. Reaction at 380°C at a residence time of 2.5 seconds gave 95% of nicotinonitrile at a 99% conversion (16).

Conversion of the nitrile to the amide has been achieved by both chemical and biological means. Several patents have described the use of modified Raney nickel catalysts in this application (25, 26). Also, alkali metal perborates have demonstrated their utility (27). Typically, the hydrolysis is conducted in the presence of sodium hydroxide (28–31). Owing to the fact that the rate of hydrolysis of the nitrile to the amide is fast as compared to the hydrolysis of the amide to the acid, good yields of the amide are obtained. Other catalysts such as magnesium oxide (32), ammonia (28, 29, 33), and manganese dioxide (34) have also been employed.

Since the late 1980s, there has been considerable activity in the development of fermentative approaches for the preparation of the amide from the nitrile. Organisms such as *Achromobacter* (35), *Agrobacterium* (36), *Streptomyces* (37), *Rhodococcus* (38, 39), and *Cornebacterium* (40) have been described. Purified enzymes in either free (41) or immobilized form (42, 43) have also been used in this application.

Nicotinic acid has also been produced by microbial means from the nitrile. *Rhodococcus* (44, 45) has frequently been used in this regard. Interestingly, irradiation of a *Corynebacterium* suspension during the fermentation led to higher yields of nicotinic acid (46).

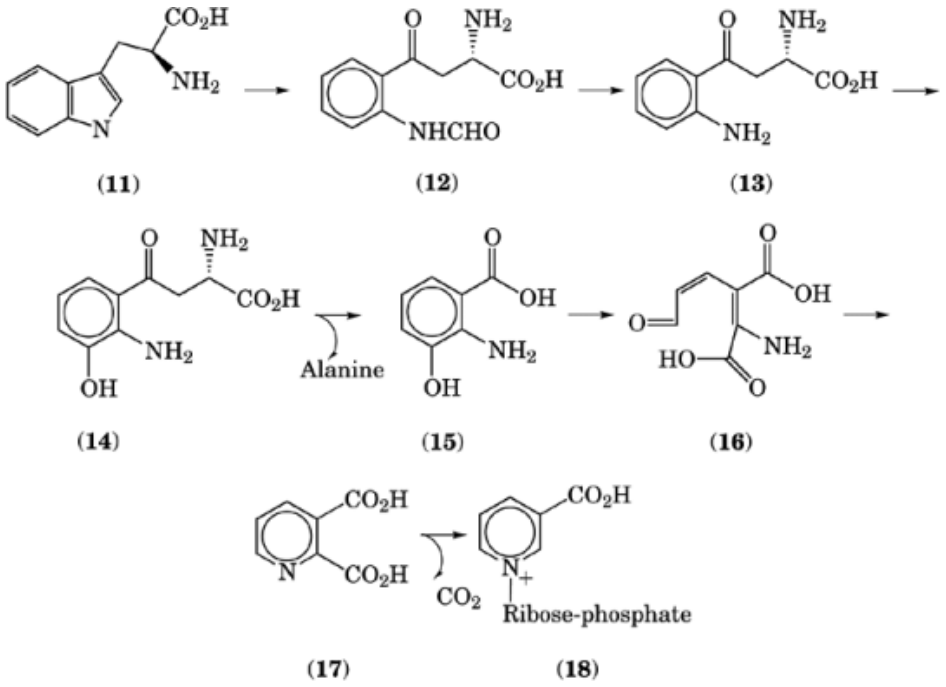


Fig. 3. Formation of nicotinic acid mononucleotides.

3. Biosynthesis

A significant pathway for the formation of nicotinic acid mononucleotides begins with tryptophan (**11**). In the first step, cleavage of the indole ring is catalyzed by the enzyme L-tryptophan-2,3-dioxygenase. This step is rate determining unless it is hormonally induced by glucocortocoids and even tryptophan itself. The resulting *N*′-formylkynurenine (**12**) is deformylated to the free aniline derivative, kynurenine (**13**). Hydroxylation to yield (**14**) is followed by oxidative removal of alanine to form 3-hydroxyanthranilic acid (**15**). Oxidative cleavage of the aromatic ring to the semialdehyde (**16**) is followed by dehydration to the important metabolite, quinolinic acid (**17**). Quinolinic acid is decarboxylated with concomitant alkylation at nitrogen to yield nicotinic acid mononucleotide (**18**) (Fig. 3).

The result of this biosynthesis is that the product is nicotinic acid mononucleotide rather than free nicotinic acid. Ingested nicotinic acid is converted to nicotinic acid mononucleotide which, in turn, is converted to nicotinic acid adenine dinucleotide. Nicotinic acid adenine dinucleotide is then converted to nicotinamide adenine dinucleotide. If excess nicotinic acid is ingested, it is metabolized into a series of detoxification products (Fig. 4). Physiological metabolites include *N*-methylnicotinamide (**19**) and *N*-methyl-6-pyridone-2-carboxamide (**24**) (1).

Nicotinamide is incorporated into NAD and nicotinamide is the primary circulating form of the vitamin. NAD has two degradative routes: by pyrophosphatase to form AMP and nicotinamide mononucleotide and by hydrolysis to yield nicotinamide adenosine diphosphate ribose.

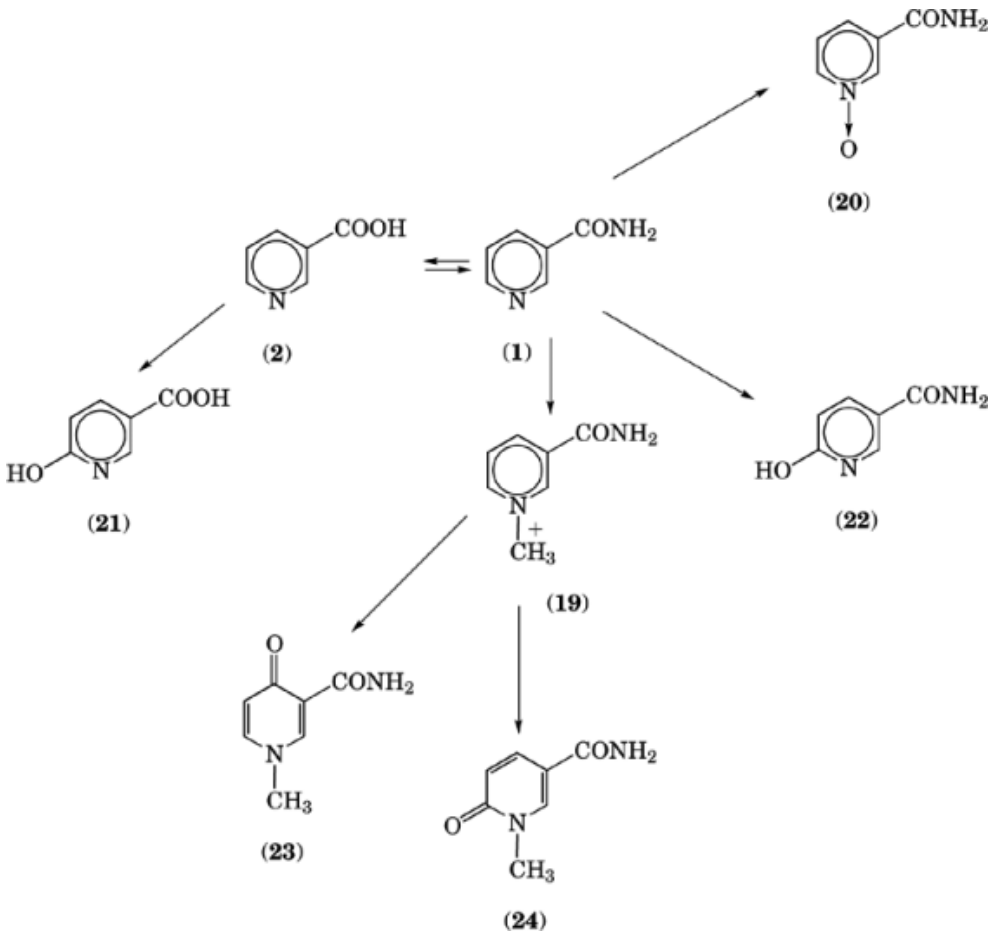


Fig. 4. Detoxification products as the result of digestion of excess nicotinic acid.

4. Analytical Methods

Both nicotinic acid and nicotinamide have been assayed by chemical and biological methods. Owing to the fact that niacin is found in many different forms in nature, it is important to indicate the specific analyte in question. For example, if biological assay procedures are used, it is necessary to indicate whether the analysis is to determine the quantity of nicotinic acid or if niacin activity is the desired result of the analysis. If nicotinic acid is desired, then a method specific for nicotinic acid should be used. If quantitation of niacin activity is the desired outcome, then all compounds (bound and unbound) which behave like niacin will assay biologically for this substance (1).

The König reaction (Fig. 5) has been used to determine the amount of nicotinic acid and niacinamide. In this procedure, quaternization of the pyridine nucleus by cyanogen bromide is followed by ring opening to generate the putative dialdehyde intermediate. Reaction of this compound with an appropriate base, such as *p*-methylaminophenol sulfate (47) or sulfanilic acid (48), generates a dye. The concentration of this dye is determined colorimetrically.

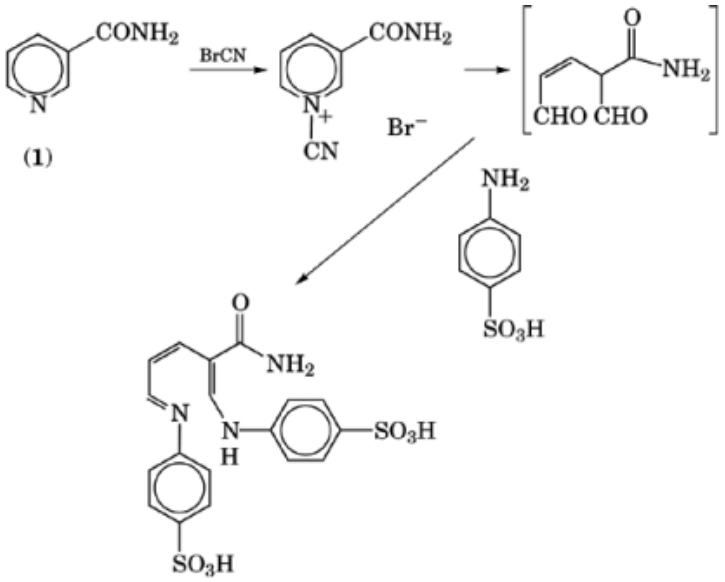


Fig. 5. The König reaction.

In the case of nicotinamide, the color yield is often low. This problem can be circumvented by either hydrolysis to nicotinic acid or by conversion of the amide to a fluorescent compound. Treatment of nicotinamide with methyl iodide yields the quaternary ammonium salt, *N*-methyl nicotinamide (**5**). Reaction of this compound with acetophenone yields a fluorescent adduct (49). Other carbonyl compounds have also been used (50–54).

For more specific analysis, chromatographic methods have been developed. Using reverse-phase columns and uv detection, hplc methods have been applied to the analysis of nicotinic acid and nicotinamide in biological fluids such as blood and urine and in foods such as coffee and meat. Derivatization techniques have also been employed to improve sensitivity (55). For example, the reaction of nicotinic amide with DCCI (*N′*-dicyclohexyl-*O*-methoxycoumarin-4-yl)methyl isourea to yield the fluorescent coumarin ester has been reported (56). After separation on a reversed-phase column, detection limits of 10 pmol for nicotinic acid have been reported (57).

Owing to poor volatility, derivatization of nicotinic acid and nicotinamide are important techniques in the gc analysis of these substances. For example, a gc procedure has been reported for nicotinamide using a flame ionization detector at detection limits of ∼0.2 μg (58). The nonvolatile amide was converted to the nitrile by reaction with heptafluorobutryic anhydride (56). For a related molecule, quinolinic acid, fmol detection limits were claimed for a gc procedure using either packed or capillary columns after derivatization to its hexafluoroisopropyl ester (58).

As with many of the vitamins, biological assays have an important historical role and are widely used. For example, microbiological assays use *Lactobacillus plantarum* ATCC No. 8014 (57, 59) or *Lactobacillus arabinosus* (60). These methods are appropriate for both nicotinamide and nicotinic acid. Selective detection of nictonic acid is possible if *Leuconostoc mesenteroides* ATCC No. 9135 is used as the test organism (61). The use of microbiological assays have been reviewed (62).

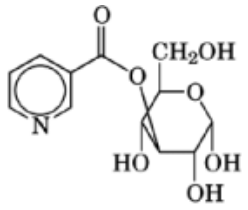
Bioassays procedures have been developed in species such as chicks which have been fed a niacin-deficient diet. Due to the fact that, for example, tryptophan is a biological precursor of niacin, niacin can be produced from other sources (55). As a result, the tryptophan content of the diet has to be monitored carefully for accurate results.

Specifications for niacin and niacinamide for food use are given in the *Food Chemicals Codex* (63) and for pharmaceutical use in the *United States Pharmacopeia* (64). The *Codex* also gives specifications for niacinamide ascorbate.

5. Occurrence

Nicotinamide and nicotinic acid occur in nature almost exclusively in the bound form. In plants, nicotinic acid is prevalent whereas in animals nicotinamide is the predominant form. This nicotinamide is exclusively in the form of NAD and NADP.

Nicotinic acid is found in plants associated with both peptides and polysaccharides. For example in wheat bran, two forms are described: a peptide with a molecular weight of approximately 12,000 and a carbohydrate complex that is called niacytin. Polysaccharides isolated from wheat bran have been found to contain 1.05% nicotinic acid in bound form. Hydrolysis yielded a fragment identified as β-3-*O*-nicotinoyl-D-glucose (**25**).



(25)

From a bioavailability standpoint, the fact that a significant amount of nicotinic acid is in a bound form has important biological consequences. Poor bioavailability stems from the fact that the ester linkage is resistance to digestive enzymes. In the case of corn, this condition can be alleviated if corn is pretreated with alkali. This food preparation method is frequently practiced in Mexico for the preparation of tortillas.

Nicotinamide and nicotinic acid are prevalent in many common foodstuffs and are especially concentrated in brewer's yeast, wheat germ and liver. In this regard, tryptophan is considered a provitamin and is assigned a niacin equivalent of 1/60. The following lists the vitamin B_3 content of many common foodstuffs and in Table 3, values of vitamin B_3 content are compared to niacin potential from tryptophan.

corn, yellow
corn, glutten feed
rye
oats
milo
barley
wheat
wheat bran
tapioca flour
potatoes
soybean meal
rapeseed-extract meal

Table 3. Nicotinic Acid and Nicotinamide (Vitamin B_3) Content of Foodstuffs, mg / kg[a]

Foodstuff	Vitamin B_3	Potential from tryptophan
cow milk, fresh whole summer	0.8	7.8
cheese, cream cheese	0.8	7.4
eggs, whole, raw	0.7	36.1
butter, salted	trace	trace
beef, lean, average, raw	52	43
beef liver, fresh	178	
pork, lean, average, raw	62	38
pork liver, fresh	118	
corn, whole	12	
corn, flour	trace	1
breakfast cereals, all-bran	490	32
cornflakes		
fortified	210	9
unfortified	6	
wheat flour		
whole meal	56	25
white, 72% for bread		
fortified	20	23
unfortified	7	
brown, 85%		
fortified	42	26
unfortified	12	
bread, white	14	16
macaroni, boiled	3	9
rice, polished, boiled	3	5
rice, bran	366–437	
soybean flour, full fat	20	86
spaghetti, boiled	3	9
potatoes, raw	12	5
yeast, Baker's dry	257	

[a]Ref. 2.

cottonseed cake
palm kernel meal
groundnut cake
sunflower cake
blood meal
meat and bone meal
fish meal
skim milk, dried
torula yeast

Coffee represents a fertile source of nictonic acid and the average cup of coffee contains between 1–2 mg. The amount of nicotinic acid depends on the roasting conditions (Table 4). During the roasting process, trigonelline (**5**), a plentiful component in green beans is demethylated to nictonic acid (65). The ratio of trigonelline (**5**) to nicotinic acid and nicotinamide is defined as the roasting number.

Table 4. Vitamin B_3 Content in Roasting Coffee[a]

Coffee beans	Vitamin B_3, mg/kg
green	20
medium roasted	80–150
dark roasted	≤500

[a]Ref. 2.

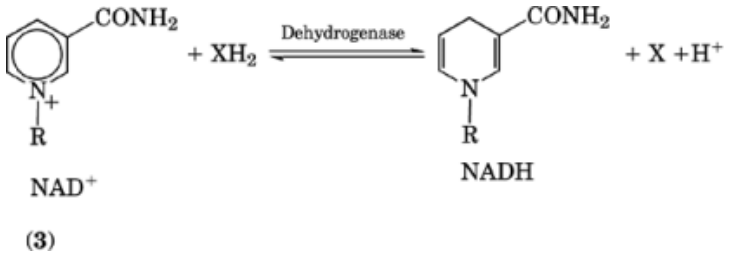


Fig. 6. Coenzymes required for dehydrogenase.

6. Biochemical Function

NAD and NADP are required as redox coenzymes by a large number of enzymes and in particular dehydrogenases (Fig. 6). NAD^+ is utilized in the catabolic oxidations of carbohydrates, proteins, and fats, whereas $NADPH_2$ is the coenzyme for anabolic reactions and is used in fats and steroid biosynthesis. $NADP^+$ is also used in the catabolism of carbohydrates (2).

In addition to their *in vivo* function, these cofactors have important *in vitro* functions as co-factors in enzymatic synthesis. Because these co-factors are too expensive to be used in equimolar amounts, many methods have been developed for their regeneration. These include chemical (66), biological (67) and electrochemical (68) methods. Enzymatic regeneration has found particular utility in this application (69).

7. Deficiency

A deficiency of niacin manifests itself in the disease pellagra. The symptoms of pellagra include dermatosis, dementia, and diarrhea. The dermatosis is expressed as lesions. These lesions are most frequently found on the hands, wrists, elbows, face and neck, knees, and the feet. At the onset of the disease, the affected areas resemble sunburn, progressing to keratosis and scaling of pigmented skin. Other symptoms include insomnia, loss of appetite, weight and strength loss, soreness of the tongue and mouth, indigestion, diarrhea, abdominal pain, burning sensations, vertigo, headache, numbness, nervousness, distractability, apprehension, mental confusion, and forgetfulness (1).

A deficiency of niacin also affects the nervous system. Numbness is initially observed and later, paralysis, particularly in the extremities is common. Severe cases are characterized by tremor and a spastic or ataxic gait and are frequently associated with peripheral neuritis. Left untreated, severe thought disorders can ensue (1).

Table 5. RDA and U.S. RDA for Niacin

Category	Niacin, mg NE
RDA	
infants	
0.0–0.5 yr	5
0.5–1.0 yr	6
children	
1–3 yr	9
4–6 yr	12
7–10 yr	13
males	
11–14 yr	17
15–18 yr	20
19–50 yr	19
>51 yr	15
females	
11–50 yr	15
>51 yr	13
pregnant	17
lactating	20
U.S. RDA	
infants and children <4 yr	9
adults and children >4 yr	20
pregnant or lactating women	20

8. Requirements

The RDA for niacin is based on the concept that niacin coenzymes participate in respiratory enzyme function and 6.6 niacin equivalents (NE) are needed per intake of 239 kJ (1000 kcal). One NE is equivalent to 1 mg of niacin. Signs of niacin deficiency have been observed when less than 4.9 NE/239 kJ or less than 8.8 NE per day were consumed. Dietary tryptophan is a rich source of niacin and the average diet in the United States contains 500–1000 mg of tryptophan. In addition, the average diet contains approximately 8–17 mg of niacin. In total, these two quantities total 16–34 NE daily. Table 5 lists the RDA and U.S. RDA for niacin (69).

9. Safety

Despite structural similarities, the pharmacological consequences of excesses of these substances are quite different. Due to the interest in the effects of nicotinic acid on atherosclerosis, and in particular its use based on its ability to lower serum cholesterol, the toxicity of large doses of nicotinic acid has been evaluated. For example, in a study designed to assess its ability to lower serum cholesterol, only 28% of the patients remained in the study after receiving a large initial dose of 4 g of nicotinic acid due to intolerance at these large doses (70).

Nicotinamide can also be toxic to cells at concentrations that increase the NAD levels above normal. Individuals consuming nicotinamide at levels of 3 g/d for extended periods (3–36 months) have experienced various side effects such as heartburn, nausea, headaches, hives, fatigue, sore throat, dry hair, and tautness of the face (1).

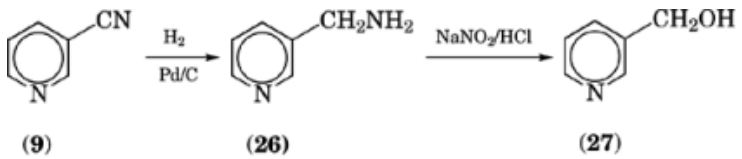


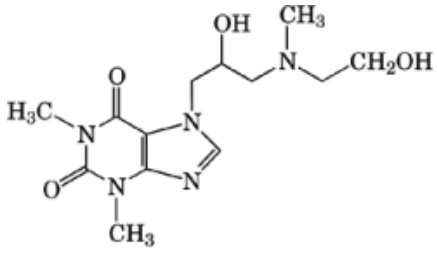
Fig. 7. Formation of nicotinyl alcohol (**27**).

10. Uses

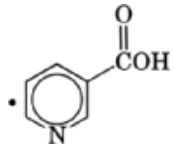
Both nicotinic acid and nicotinamide have been used in the enrichment of bread, flour, and other grain-derived products. Animal feed is routinely supplemented with nicotinic acid and nicotinamide. Nicotinic acid is rarely used in this application. The amide and carboxylic acid have been used as a brightener in electroplating baths and as stabilizer for pigmentation in cured meats.

11. Derivatives

Nicotinyl alcohol (3-pyridinylcarbinol, 3-pyridinemethanol) (**27**) has use as an antilipemic and peripheral vasodilator. It is available from either the reductions of nicotinic acid esters or preferably, the reduction of the nitrile to the amine followed by diazotation and nucleophilic displacement. It is frequently administered in the form of the tartrate (Fig. 7). Nicotinic acid is frequently used as a salt in conjunction with basic drugs such as the peripheral vasodilator xanthinol niacinate (**28**). Nicotinic acid and its derivatives have widespread use as antihyperlipidemic agents and peripheral vasodilators (1).



(**28**)



12. Economic Aspects

U.S. manufacturers of niacin and niacinamide include Nepera, Inc. and Reilly Industries, Inc. U.S. suppliers include BASF Corporation, Hoffmann-La Roche Inc., and Rhône-Poulenc. Western European producers and

suppliers include Degussa, Rhône-Poulenc, BASF, Hoffmann-La Roche, and Lonza (71). In 1995, the prices for niacin and nicotinamide were $9.75/kg and $9.25/kg, respectively (72, 73).

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