Modification of Pyridine-3-carboxamide (Nicotinamide) by Radical Substitution

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Pyridine-3-carboxamide (**1**) was reacted with alkyl radicals to give mono-, di-, and tri-alkylated products. The *t*-butyl radical gives only 6-*t*-butylpyridine-3-carboxamide (**4a**). The reactivity decreases in the order of *t*-butyl, isopropyl, and ethyl radicals. The product **4a** reacts further with the 2-phthalimidoethyl radical to give 2- and 4-substituted products **9** and **10**, which were transformed into tetrahydronaphthyridinone derivatives **11** and **12**.

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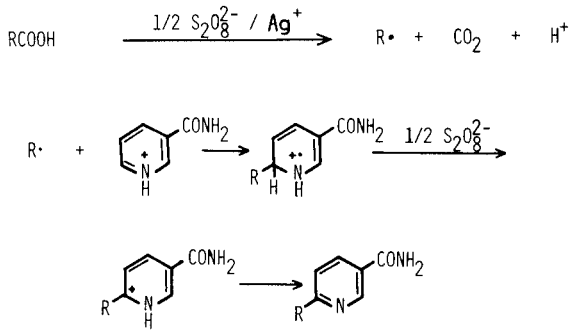
Pyridine-3-carboxamide (Nicotinamide) plays a central role in biological redox systems, and its chemistry has been well documented [1]. Structural modification of pyridine-3-carboxamide may alter its chemical properties and bring a variation in the coenzyme models of NAD(P). Chemical modification of the pyridine ring of pyridinecarboxamide, however, has been rarely reported, and we have tried simple radical alkylations after experiencing the radical substitutions of π-deficient heterocycles by Minisci *et al* [2] and ourselves [3].

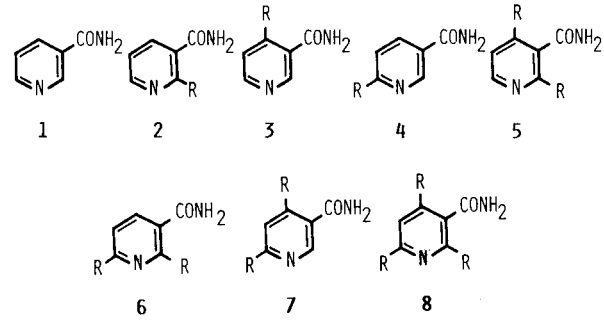
Alkyl radicals were generated by the Minisci oxidation of alkanoic acids (Scheme I) [4]. Alkyl substitution requires two equivalents of peroxodisulfate, one for the oxidation of the alkanoic acid and another for the aromatization of the intermediate radical (Scheme I). An equimolar mixture of alkanoic acid and ammonium peroxodisulfate with catalytic amount of silver nitrate was used for the following reactions.

Scheme I



The *t*-butyl radical generated from 2,2-dimethylpropanoic acid gave only 6-*t*-butylpyridine-3-carboxamide (**4a**) (Scheme II and the Table). The structure of **4a** was easily assigned by its ^{1}H-nmr spectrum, doublets at δ 8.95 (C_2-H, J = 3 Hz) and 7.39 (C_5-H, J = 9 Hz), and double doublet at 8.05 (C_4-H, J = 9 and 3). The chemical shifts of the protons of pyridine-3-carboxamide (**1**) are 9.02 for C_2-H, 8.75 for C_6-H, 8.20 for C_4-H, and 7.42 for C_5-H [5]. Evidently the proton at C_6 is missing in **4a** and the coupling pattern is in accord with the structure **4a**. The use of three equivalents of alkanoic acid or a prolongation of the reaction time reduced the yield gradually. This decrease in the yield must be due to the slow degradation of **4a** under these oxidation conditions.

The isopropyl radical generated from 2-methylpropanoic acid gave mono- (**4b**), di- (**6b** and **7b**), and triisopropylpyridine-3-carboxamide (**8b**) (Table). The structure of **4b** was deduced in the same manner as **4a**. Structure **6b** was characterized by two doublets at 7.00 and 7.58 due to C_5-H and C_4-H respectively, and product **7b** had two singlets at δ 7.15 and 8.54 due to C_5-H and C_2-H respectively. The substitution pattern of **8b** is evident from the chemical shift of C_5-H (δ 6.89). When an equimolar amount of alkanoic acid was used, 6-isopropylpyridine-3-carboxamide (**4b**) was obtained in low yield but predominantly. The use of excess acid increased the yield of 4,6-diisopropylpyridine-3-carboxamide (**7b**) with the decrease of mono-substituted product **4b**. Another disubstitued product **6b** was obtained in lower yield and, this result indicates that the second alkylation at C_4 takes place in preference to C_2.



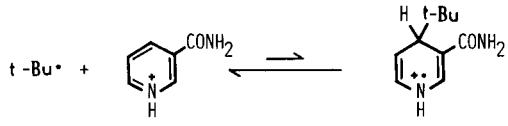
4a: R = t-Bu **4b**~ **8b**: R = i-Pr **2c** ~ **8c**: R = Et

The ethyl radical from propanoic acid gave products of diverse distribution (Table). The structures of product **4c**, **6c**, **7c**, and **8c** were assigned by the same analyses of the nmr spectra as the isopropyl derivatives. Structure **2c** was

characterized by three double-doublets at δ 7.17 (J = 8 and 5 Hz), 7.72 (J = 8 and 2 Hz), and 8.62 (J = 5 and 2 Hz) due to the *meta*, *para*, and *ortho* protons to the ring nitrogen respectively. This signal pattern indicates the existence of three neighboring protons on the ring. Structure **3c** was characterized by two doublets at δ 7.21 and 8.54 (J = 6 Hz) and a singlet at 8.63 which show the existence of two protons next to the nitrogen. Product **5c** was characterized by two doublets at δ 7.02 and 8.41 (J = 6 Hz). It is noteworthy that the mono-substituted products at C_2, **2c**, and C_4, **3c**, were obtained in a modest yield though those types of product were not obtained from the *t*-butyl or the isopropyl radical.

Alkyl radicals have a nucleophilic character in the reaction with protonated heterocycles, and the nucleophilicity decreases in the order of tertiary, secondary, and primary radical [6]. The *t*-butyl radical indeed gave the highest yield of product, but only one product **4a** was obtained. This feature is accounted for by the reversibility of the radical addition (Scheme II). The radical intermediate

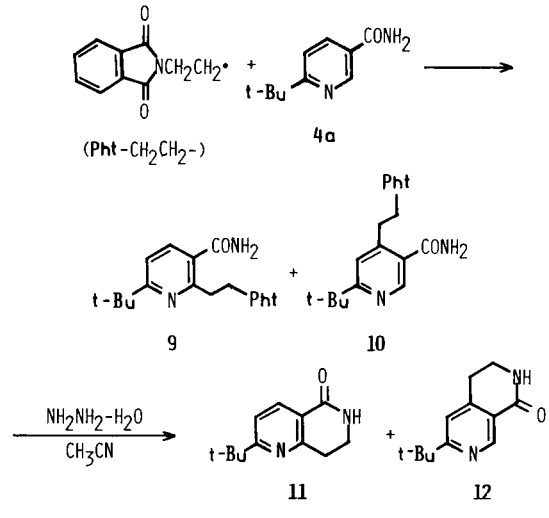
Scheme II



formed by the addition of the *t*-butyl radical at C_2 or C_4 causes oxidative aromatization unfavorably since the *t*-butyl and carboxamide groups become coplanar in a resulting aromatic system, and the intermediate eliminates the stable *t*-butyl radical exclusively. The isopropyl radical has less steric requirement and can give substitution products at C_2 and C_4. Though the yield was modest, **4b** was the major product when equimolar amount of 2-methylpropanoic acid and **1** was used whereas **7c** became the major product when three equivalents of 2-methylpropanoic acid was used (Table). The ethyl radical is weakly nucleophilic but has a modest steric requirement, and we can see no clear discrimination in reaction sites.

The results described here show that radical substitution of pyridine-3-carboxamide is regioselective with the *t*-butyl radical, but the selectivity is rather low or poor for isopropyl and ethyl radicals. Product **4a** is substituted only at C_6 and is expected to react further at C_2 or C_4, and **4a** was treated with a ten molar equivalent of a 1:1 mixture of phthalimidopropanoic acid and peroxodisulfate. The reaction gave 6-*t*-butyl-2-phthalimidoethylpyridine-3-carboxamide (**9**) and its 4-phthalimidoethyl isomer **10** in 13% and 19% yield, respectively (Scheme III). The substitution pattern of **9** and **10** were deduced from ^{1}H-nmr analyses as in the case of alkyl derivatives **6** and **7**. Treatment of **9** or **10** with hydrazine hydrate in ethanenitrile gave 2-*t*-butyl-5,6,7,8-tetrahydro-1,6-naphthyridin-5-one (**11**) or 3-*t*-butyl-5,6,7,8-tetrahydro-2,7-naphthyridin-8-one (**12**), respectively, in nearly quantitative yield. This type of transformation of a phthalimidoalkane into an amide has been reported by Iwata and Kuzuhara [7].

Scheme III



Table

Product Yields (%) of the Reaction of Alkyl Radical with Nicotinamide (**1**)

R	[R·]/[1] [a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	total
t-Bu	1.0	–	–	49	–	–	–	–	49
t-Bu	2.0	–	–	72	–	–	–	–	72
t-Bu	3.0	–	–	67	–	–	–	–	67
i-Pr	1.0	–	–	38	–	–	5	–	43
i-Pr	2.0	–	–	24	–	3	21	1	49
i-Pr	3.0	–	–	6	–	2	36	4	48
Et	1.0	4	5	7	1	2	3	–	22
Et	2.0	–	21	–	4	17	27	2	71
Et	3.0	–	4	–	1	4	11	1	21

[a]: [R·] is assumed to be equal to the initial concentration of alkanoic acid [RCOOH].

These two derivatives, **11** and **12**, have carbonyl groups whose geometries are fixed to *syn* and *anti* with respect to the nitrogen of the pyridine ring. This feature is interesting in connection with a theoretical study by Donkersloot and Buck [8], in which the geometry of the carbonyl group in nicotinamide is correlated with the reactivity of NAD(P)H-coenzyme.

EXPERIMENTAL

The ir spectra were determined in chloroform solution and the ^{1}H-nmr spectra (a 60 MHz and a 90 MHz-FT spectrometer) were determined in deuteriochloroform using tetramethylsilane as an internal reference. Coupling constants are recorded in Hz.

The Reaction of Pyridine-3-carboxamide with Alkyl Radicals.

A mixture of pyridine-3-carboxamide (366 mg, 3 x 10^{-3} mole), alkanoic acid (15 x 10^{-3} mole), silver nitrate (3-9 x 10^{-4} mole), and 3 ml of 10%-sulfuric acid was heated to 70° and the mixture was treated with a solution of ammonium peroxodisulfate (3-9 x 10^{-3} mole) dissolved in 1.5-4.5 ml of water. Generation of carbon dioxide was observed at the beginning and the reaction mixture was kept at the same temperature for 2 hours in an argon atmosphere. After cooling, the reaction mixture was neutralized to *p*H *ca* 9 by aqueous ammonia and extracted thrice with ethyl acetate. Evaporation of the solvent after washing it with water and drying it over sodium sulfate gave white crystals or a viscous oil. To remove polar materials, the crude products were passed through a short column (2 (ϕ) x 10 cm) of silica gel using ethyl acetate as the solvent. Separation and further purification were carried out as described in the following experimental part. Minor products were difficult to purify for satisfactory elemental analyses, but those were essentially pure from tlc and spectroscopic analyses. High resolution mass spectral data are recorded for those minor products.

6-*t*-Butylpyridine-3-carboxamide (**4a**) [9].

This compound was recrystallized from water-ethanol (3:1) and melted at 167-168°; ir: 3500, 3400, 1680, 1600, 1390 cm^{-1}; ^{1}H-nmr: δ 1.40 (s, 9H), 6.03-6.60 (broad, 2H, -NH$_2$), 7.39 (d, J = 9, 1H), 8.05 (dd, J = 9 and 3, 1H), 8.95 (d, J = 3, 1H).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.13; H, 7.85; N, 15.42.

A mixture of isopropyl-substituted pyridine-3-carboxamides were separated by preparative tlc on three plates (20 x 20 cm) of alumina using THF-chloroform-ethyl acetate (2:2:1) as the solvent.

6-Isopropylpyridine-3-carboxamide (**4b**) [10].

This compound was recrystallized from water-ethanol (3:1) and melted at 161-162°; ir: 3510, 3400, 1678, 1600, 1380 cm^{-1}; ^{1}H-nmnr: δ 1.32 (d, J = 7, 6H), 3.13 (sept, J = 7, 1H), 5.60-6.25 (broad, 2H, -NH$_2$), 7.27 (d, J = 8, 1H), 8.07 (dd, J = 8 and 3, 1H), 8.92 (d, J = 3, 1H).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.66; H, 7.40; N, 16.74.

2,6-Diisopropylpyridiene-3-carboxamide (**6b**).

This compound was recrystallized from benzene and melted at 137-138°; ir: 3510, 3400, 1675, 1589, 1380 cm^{-1}; ^{1}H-nmr: δ 1.28 (d, J = 7, 6H), 1.29 (d, J = 7, 6H), 3.04 (sept, J = 7, 1H), 3.51 (sept, J = 7, 1H), 5.67-5.90 (broad, 2H, -NH$_2$), 7.00 (d, J = 8, 1H), 7.58 (d, J = 8, 1H).

Mass Calcd. for $C_{12}H_{18}N_2O$: m/z = 206.1420. Found: m/z = 206.1416.

4,6-Diisopropylpyridine-3-carboxamide (**7b**).

This compound was recrystallized from water-ethanol (3:1) and melted at 131-133°; ir: 3510, 3400, 1675, 1600, 1390 cm^{-1}; ^{1}H-nmr: δ 1.26 (d, J = 7, 6H), 1.30 (d, J = 7, 6H), 3.05 (sept, J = 7, 1H), 3.52 (sept, J = 7, 1H), 5.87-6.16 (broad, 2H, -NH$_2$), 7.15 (s, 1H), 8.54 (s, 1H).

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.43; H, 9.00; N, 13.24.

2,4,6-Triisopropylpyridine-3-carboxamide (**8b**).

This compound was recrystallized from (benzene/hexane 1:2) and melted at 195-196°; ir: 3520, 3400, 1675, 1591, 1370 cm^{-1}; ^{1}H-nmr: δ 1.25, 1.27, 1.29 (d, J = 7, each 3H), 2.83-3.26 (m, 3H), 5.48-5.88 (broad, 2H, -NH$_2$), 6.89 (s, 1H).

Mass Calcd. for $C_{15}H_{24}N_2O$: m/z = 248.1890. Found: m/z = 248.1902.

A mixture of ethyl-substituted pyridine-3-carboxamide was separated in the same manner as in the case of the isopropyl derivatives.

2-Ethylpyridine-3-carboxamide (**2c**).

This compound was recrystallized from benzene and melted at 153-154°; ir: 3495, 3375, 1670, 1580, 1355 cm^{-1}; ^{1}H-nmr: δ 1.34 (t, J = 8, 3H), 3.03 (q, J = 8, 2H), 5.72-5.83 (broad, 2H, -NH$_2$), 7.14 (double d, J = 8 and 5), 7.72 (double d, J = 8 and 2), 8.62 (double d, J = 5 and 2).

Mass Calcd. for $C_8H_{10}N_2O$: m/z = 150.0794. Found: m/z = 150.0785.

4-Ethylpyridine-3-carboxamide (**3c**).

This compound was recrystallized from ethyl acetate and melted at 133-134°; ir: 3520, 3400, 1681, 1595, 1375 cm^{-1}; ^{1}H-nmr: δ 1.26 (t, J = 8, 3H), 2.88 (q, J = 8, 2H), 6.02-6.13 (broad, 2H, -NH$_2$), 7.21 (d, J = 6, 1H), 8.54 (d, J = 6, 1H), 8.63 (s, 1H).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.03; H, 6.63; N, 18.82.

6-Ethylpyridine-3-carboxamide (**4c**) [10].

This compound was recrystallized from benzene and melted at 159-160°; ir: 3530, 3410, 1683, 1602, 1390 cm^{-1}; ^{1}H-nmr: δ 1.31 (t, J = 7, 3H), 2.88 (q, J = 7, 2H), 6.00-6.65 (broad, 2H, -NH$_2$), 7.26 (d, J = 8, 1H), 8.07 (dd, J = 8 and 2, 1H), 8.94 (d, J = 2, 1H).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.21; H, 6.59; N, 18.98.

2,4-Diethylpyridine-3-carboxamide (**5c**).

This compound was recrystallized from benzene melted at 133-135°; ir: 3520, 3390, 1680, 1588, 1365 cm^{-1}; ^{1}H-nmr: δ 1.27 (t, J = 7, 3H), 1.31 (t, J = 7, 3H), 2.69 (q, J = 7, 2H), 2.72 (q, J = 7, 2H), 5.82-6.68 (broad, 2H, -NH$_2$), 7.02 (d, J = 6, 1H), 8.41 (d, J = 6, 1H).

Mass Calcd. for $C_{10}H_{14}N_2O$: m/z = 178.1107. Found: m/z = 178.1101.

2,6-Diethylpyridine-3-carboxamide (**6c**).

This compound was recrystallized from benzene and melted at 122-122.5°; ir: 3520, 3400, 1675, 1590, 1360 cm^{-1}; ^{1}H-nmr: δ 1.30 and 1.32 (t, J = 8, each 3H), 2.85 (q, J = 8, 2H), 3.02 (q, J = 8, 2H), 5.60-6.10 (broad, 2H, -NH$_2$), 7.02 (d, J = 8, 1H), 7.65 (d, J = 8, 1H).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.65; H, 8.00; N, 15.76.

4,6-Diethylpyridine-3-carboxamide (**7c**).

This compound was recrystallized from ethyl acetate and melted at 107-108°; ir: 3510, 3400, 1680, 1600, 1380 cm^{-1}; ^{1}H-nmr: δ 1.25 (t, J = 7, 3H), 1.30 (t, J = 7, 3H), 2.50-3.20 (m, 4H), 5.78-6.35 (braod, 2H, -NH$_2$), 7.05 (s, 1H), 8.54 (s, 1H).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.07; H, 7.81; N, 15.57.

2,4,6-Triethylpyridine-3-carboxamide (**8c**).

This compound was recrystallized from benzene and melted at 133-136°; ir: 3510, 3390, 1675, 1590, 1360 cm^{-1}; ^{1}H-nmr: δ 1.23 (t, J = 7, 3H), 1.26 (t, J = 7, 3H), 1.28 (t, J = 7, 3H), 2.42-3.12 (m, 6H), 5.62-6.54 (braod, 2H, -NH$_2$), 6.87 (s, 1H).

Mass Calcd. for $C_{12}H_{18}N_2O$: m/z = 206.1420. Found: m/z = 206.1407.

The Reaction of 6-*t*-Butylpyridine-3-carboxamide (**4a**) with the 2-Phthalimidoethyl Radical.

A mixture of **4a** (178 mg, 1 x 10^{-3} mole), 3-phthalimidopropanoic acid (2.19 g, 1 x 10^{-2} mole), ammonium peroxodisulfate (1.14 g, 5 x 10^{-3} mole),

silver nitrate (170 mg, 1 x 10^{-3} mole), and cetyltrimethylammonium bromide (160 mg) dissolved in 8 ml of 10%-sulfuric acid was heated to 70° and then treated with ammonium peroxodisulfate (1.14 g, 5 x 10^{-3} mole) dissolved in 12 ml of ethanenitrile-water (3:7). The mixture was kept at the same temperature for 2 hours, and the cooled mixture was neutralized by aqueous ammonia. Extraction of the products with dichloromethane and condensation of the extract after washing it with water and drying it over sodium sulfate gave viscous oil. The oily products were passed through a short column (2 (ϕ) x 5 cm) of silica gel using ethyl acetate as the solvent to remove polar materials. The products were separated into 6-*t*-butyl-2-(2-phthalimidoethyl)pyridine-3-carboxamide (**9**) and 6-*t*-butyl-4-(2-phthalimidoethyl)pyridine-3-carboxamide (**10**) by preparative tlc on four 20 x 20 cm plates of alumina using THF-chloroform-ethyl acetate (2:2:1) as the solvent.

Product **9** recrystallized from hexane-benzene and melted at 153-154°. Purification of **9** for satisfactory elemental analysis was difficult though the spectroscopic data showed it to be highly pure; ir: 3460, 3408, 1710, 1675, 1595, 1395 cm^{-1}; ^{1}H-nmr: δ 1.12 (s, 9H), 3.38 (t, J = 7, 2H), 4.19 (t, J = 7, 2H), 6.30-6.80 (broad, 2H, -NH_2), 7.12 (d, J = 8, 1H), 7.64 (d, J = 8, 1H), 7.50-7.92 (m, 4H).

Mass Calcd. for $C_{20}H_{21}N_3O_3$: m/z = 351.1584. Found: m/z = 351.1559.

Product **10** recrystallized from benzene and melted at 198-199°; ir: 3530, 3400, 1720, 1680, 1595, 1400 cm^{-1}; ^{1}H-nmr: δ 1.11 (s, 9H), 3.29 (t, J = 6, 2H), 4.08 (t, J = 6, 2H), 6.15-6.62 (broad, 2H, -NH_2), 7.00 (s, 1H), 7.60-7.90 (m, 4H), 8.65 (s, 1H).

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.14; H, 5.87; N, 11.72.

Tetrahydronaphthyridinones **11** and **12**.

A mixture of **9** (35.1 mg, 1 x 10^{-4} mole), hydrazine monohydrate (2 x 10^{-4} mole), and 2 ml of ethanenitrile was refluxed for 1 hour. The cooled mixture was filtered to remove the precipitate of phthalazinedione, and the filtrate was condensed to give a viscous oil. 6-*t*-Butyl-1,2,3,4-tetrahydro-2,5-naphthyridin-1-one (**11**) was recrystallized from benzene and melted at 178-179°. Purification of product **11** for satisfactory elemental analysis was difficult though tlc and spectral analyses showed it to be essentially pure; ir: 3415, 1665, 1595, 1340 cm^{-1}; ^{1}H-nmr: δ 1.47 (s, 9H), 3.12 (s, J = 7, 2H), 3.63 (double t, J = 7 and 3, 2H), 7.31 (d, J = 7, 1H), 7.50-7.90 (broad, 1H, -NH), 8.20 (d, J = 7, 1H).

Mass Calcd. for $C_{12}H_{16}N_2O$: m/z = 204.1264. Found: m/z = 204.1246.

6-*t*-Butyl-1,2,3,4-tetrahydro-2,7-naphthyridin-1-one (**12**).

The compound was obtained in the same manner and recrystallized from benzene. It melted at 158-161°; ir: 3410, 1665, 1602, 1340 cm^{-1}; ^{1}H-nmr: δ 1.36 (s, 9H), 2.95 (t, J = 6, 2H), 3.60 (double t, J = 6 and 3, 2H), 7.14 (s, 1H), 7.28-7.70 (broad, 1H, -NH), 9.04 (s, 1H).

Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.06; H, 7.86; N, 13.95.

Acknowledgment.

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