A Convenient Synthesis of *N*-Aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides, *N*-Aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides and Their 1-Methyl (*O*-Methyl)-Derivatives

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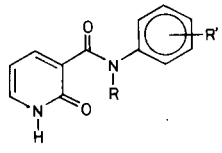
A new and versatile method for the preparation of the isonixine analogues, *N*-aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides and *N*-aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides is described *via* the selective chlorination of 2-hydroxynicotinic acid. In order to prepare these new compounds, the chemistry of the methyl-blocked forms of each tautomer is discussed.

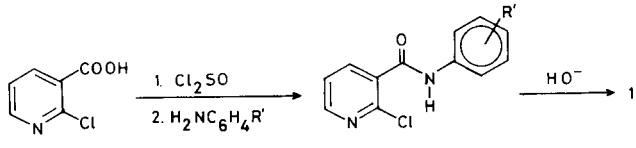
J. Heterocyclic Chem., **19**, 1093 (1982).

Recently, interest has been developed in *N*-aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **1** (1), and particularly toward isonixine, *N*-(2,6-dimethylphenyl)-1,2-dihydro-2-oxo-3-pyridinecarboxamide (2-7), because isonixine has an analgesic action similar to that of acetylsalicylic acid at doses approximately two fold greater than that of the latter (8).

To date, these compounds have been prepared *via* a controlled hydroxylation (1) of the corresponding *N*-aryl-2-chloro-3-pyridinecarboxamides (prepared from 2-chloronicotinic acid) by using potassium hydroxide in dimethylsulfoxide, thus avoiding either total or partial hydrolysis of the carboxamide group (Scheme 1).



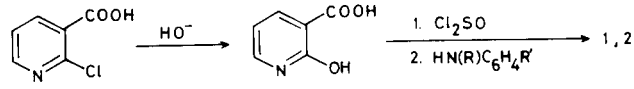
	R	R'
1a	H	4-CH_3O
1b	H	H
1c	H	3-NO_2
2a	CH_3	4-CH_3O
2b	CH_3	H
2c	CH_3	3-NO_2



SCHEME 1

We wished to prepare several *N*-aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **1** and *N*-aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **2** with different substituents on the aniline or *N*-methylaniline ring, in order to study the influence of these substituents on the tautomerism of the 2-hydroxypyridine/2-pyridone system, in the series of the 2-hydroxynicotinanilides (9). But, under the typical reaction conditions used, we could not prepare the desired *N*-methylaniline products and, when we used anilines containing electron-withdrawing groups, low yields were obtained. Although there are several other standard methods which can be used for the hydroxylation of *N*-aryl-2-chloro-3-pyridinecarboxamides with electron-donating groups on the aniline ring, for example, a 20% potassium hydroxide solution which was heated for three hours at 150-160° gives complete reaction without hydrolysis of the carboxamide group. Even the most favourable conditions give either partial or total hydrolysis of the carboxamide group for any *N*-methylanilines and anilines substituted with electron-withdrawing groups.

We now wish to report a convenient and versatile synthesis of *N*-aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **1** and *N*-aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **2** with any substituent on the aniline or *N*-methylaniline ring, from 2-hydroxynicotinic acid, which can be obtained from the commercially available 2-chloronicotinic acid in excellent yield (10) (Scheme 2).



SCHEME 2

The key to this synthesis is the accessibility of 2-hydroxynicotinic acid and the subsequent controlled chlorination which gives 2-hydroxynicotinoyl chloride. Optimal yields for 2-hydroxynicotinoyl chloride were obtained when 2-hydroxynicotinic acid in methylene chloride was refluxed for three hours employing a very slight excess of thionyl chloride (see Experimental); longer reaction times, higher temperatures or larger excesses of thionyl chloride gave predominantly 2-chloronicotinoyl chloride. Reacting 2-hydroxynicotinoyl chloride in anhydrous 1,4-dioxane

Table 1

Physical Data for 2-Hydroxynicotinanilides

Compound No.	R	R'	Yield (%)	Mp (°C) (Recrystallization Solvent)	Formula	Analyses (%) Calcd./(Found) C	H	N
1a	H	4-CH_3O	75	218-219 (1-butanol)	$C_{13}H_{12}N_2O_3$	63.93 (63.87)	4.92 (4.95)	11.47 (11.35)
1b	H	H	74	264-265 (1-butanol)	$C_{12}H_{10}N_2O_2$	67.29 (67.42)	4.67 (4.71)	13.08 (12.95)
1c	H	3-NO_2	83	302-304 (a)	$C_{12}H_9N_3O_4$	55.60 (55.43)	3.47 (3.50)	16.21 (16.33)
2a	CH_3	4-CH_3O	40	93-94 (b) (hexane-ethyl acetate)	$C_{14}H_{14}N_2O_3$	65.11 (65.34)	5.42 (5.47)	10.85 (11.02)
2b	CH_3	H	55	116-117 (hexane-ethyl acetate)	$C_{13}H_{12}N_2O_2$	68.42 (68.20)	5.26 (5.10)	12.28 (12.22)
2c	CH_3	3-NO_2	65	225-226 (1-butanol)	$C_{13}H_{11}N_3O_4$	57.14 (57.36)	4.03 (3.99)	15.38 (15.45)

(a) This compound could not be recrystallized. It was washed with hot methanol and gave a product of satisfactory purity. (b) This product, after recrystallization was purified by chromatography on a silica gel column with methylene chloride and ethyl acetate as eluents.

Table 2

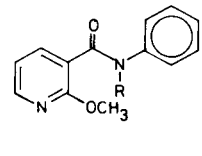
Spectral Data for 2-Hydroxynicotinanilides

Compound No.	R	R'	IR λ max cm^{-1} (C=O)	NMR, δ (dimethyl sulfoxide-d_6)	Fragment (Relative Abundance)
1a	H	4-CH_3O	1670	3.67 (s, 3H), 6.4-6.6 (m, 1H), 6.83 (d, J9, 2H), 7.53 (d, J9, 2H), 7.65-7.8 (m, 1H), 11.95 (s, 1H), 12.6 (s, 1H)	244 (36.8), 123 (100.0), 122 (66.3)
1b	H	H	1675	6.3-6.55 (m, 1H), 6.9-7.7 (m, 6H), 8.25-8.45 (m, 1H), 12.05 (s, 1H), 12.55 (s 1H)	214 (28.9), 122 (72.2), 93 (100.0)
1c	H	3-NO_2	1690	6.4-6.55 (m, 1H), 7.1-7.75 (m, 4H), 7.8-7.95 (m, 1H), 8.6-8.7 (m, 1H), 12.5 (s, 1H), 12.75 (s, 1H)	259 (10.7), 138 (5.0), 122 (100.0)
2a	CH_3	4-CH_3O	1635	3.47 (s, 3H), 3.8 (s, 3H), 6.15-6.4 (m, 1H), 6.6-7.6 (m, 6H), 11.70 (s, 1H)	258 (5.6), 137 (27.8), 122 (55.5), 39 (100.0)
2b	CH_3	H	1640	3.25 (s, 3H), 5.9-6.1 (m, 1H), 6.5-6.75 (m, 7H), 11.9 (s, 1H)	228 (9.3), 122 (66.6), 107 (93.3), 39 (100.0)
2c	CH_3	3-NO_2	1660	3.26 (s, 3H), 5.95-6.15 (m, 1H), 7.3-7.45 (m, 1H), 7.5-7.7 (m, 3H), 7.85-7.95 (m, 1H), 8.0-8.1 (m, 1H), 11.85 (s, 1H)	273 (4.0), 152 (8.2), 122 (100.0), 39 (72.3)

with any aniline or any *N*-methylaniline gave very good yields of the corresponding products **1** or **2**.

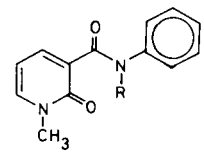
Structural assignments for the *N*-aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **1** and *N*-aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides **2** have been made on the basis of the ir, ms and nmr spectral data; all compounds gave satisfactory elemental analyses (Tables 1 and 2).

We wished to prepare the methyl blocked forms of each tautomer, specifically, *N*-phenyl-2-methoxy-3-pyridinecarboxamide **(3)**, *N*-methyl-*N*-phenyl-2-methoxy-3-pyridinecarboxamide **(4)**, *N*-phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide **(5)** and *N*-methyl-*N*-phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide **(6)** in order to study the tautomerism between 2-hydroxypyridine and 2-pyridone in the series of 2-hydroxynicotin-



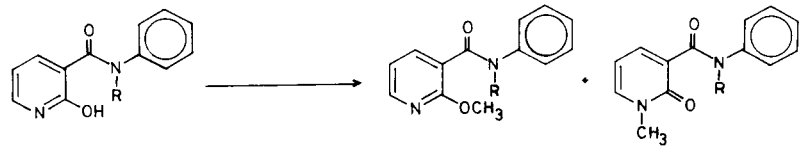
3, R=H

4, R=CH_3



5, R=H

6, R=CH_3



1, R=H

2, R=CH_3

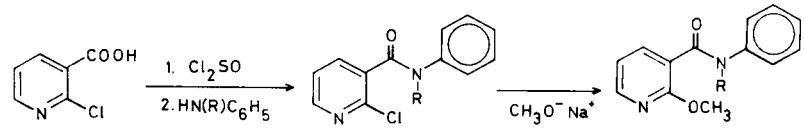
3

4

5

6

SCHEME 3



7, R=H

8, R=CH_3

3

4

SCHEME 4

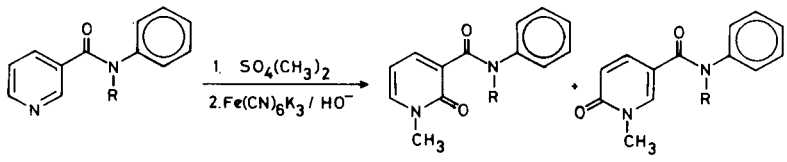
anilides.

Apparently, the compounds **3-6** could be obtained by either the corrseponding selective methylations of compounds **1** and **2** or *via* a conventional methylation and suitable separation procedures (Scheme 3).

Although treating 2-hydroxypyridine with methyl iodide gives 1-methyl-2-pyridone, while, with diazomethane 2-methoxypyridine is formed, the alkylation of 2-hydroxypyridine derivatives by reaction of the anion with an alkyl halide, may give either *N*- or *O*-alkyl derivatives, or mixtures of the two, depending on the nature of the metal salt, the structure of the halide, the solvent and the ring substituents (11). Thus all attempts for selective methylation of compounds **1** and **2** were unsuccessful and the separations of the mixtures were very tedious and resulted in very low yields.

However, the products **3** and **4** could be obtained by an alternative sequence shown above (Scheme 4) by nucleophilic substitution of the corresponding *N*-phenyl-2-chloro-3-pyridinecarboxamide (**7**) and *N*-methyl-*N*-phenyl-2-chloro-3-pyridinecarboxamide (**8**), which were easily obtained from the commercially available 2-chloronicotinic acid. Nucleophilic substitution of compound **7** occurs in excellent yield to give **3** when we used sodium methoxide and methanol, however, nucleophilic substitution of **8** requires three hours and it occurs with partial hydrolysis of the carboxamide group under the same conditions. A mixture of 1,4-dioxane:methanol (50:50) was employed in order to carry out the substitution more rapidly without cleavage of the carboxamide group.

The products **5** and **6** could be obtained by methylation with dimethyl sulfate followed by oxidation with potassium ferricyanide and sodium hydroxide from the corresponding *N*-phenyl-3-pyridinecarboxamide **9** and *N*-methyl-*N*-phenyl-3-pyridinecarboxamide (**10**) (Scheme 5), which can be easily obtained from the commercially available nicotinic acid (12). The same reaction with **9** was very successful, resulting in a mixture of **5** and **11** which was easily separated by column chromatography on silica gel using methylene chloride and ethyl acetate as eluents. However,



9, R = H 5 11, R = H

10, R = CH_3 6 12, R = CH_3

SCHEME 5

Table 3

Physical Data for Methyl Blocked Tautomers

Compound No.	R	Yield (%)	Mp (°C)	Formula	Analyses (%) Calcd./(Found) C	H	N
3	H	70	63-64	$C_{13}H_{12}N_2O_2$	68.42 (68.57)	5.26 (5.25)	12.28 (12.35)
4	CH_3	42	94-95	$C_{14}H_{14}N_2O_2$	69.42 (69.56)	5.78 (5.70)	11.57 (11.60)
5	H	40	167-168	$C_{13}H_{12}N_2O_2$	68.42 (68.46)	5.26 (5.19)	12.28 (12.08)
6	CH_3	52	142-143	$C_{14}H_{14}N_2O_2$	69.42 (69.31)	5.78 (5.76)	11.57 (11.49)
11	H	45	174-176	$C_{13}H_{12}N_2O_2$	68.42 (68.31)	5.26 (5.29)	12.28 (12.40)

in the case of **10**, hydrolysis of the carboxamide group occurs because of the presence of sodium hydroxide in the rection mixture.

In order to obtain **6**, it was necessary to eliminate the strongly basic reaction conditions. This was accomplished by using potassium carbonate and dimethyl sulfate in DMF while heating and stirring for two hours. Under these conditions, **6** was the predominant product.

Structural assignments for all compounds have been made on the basis of the ir, ms and nmr spectral data.

All compounds gave satisfactory elemental analyses (see Experimental and Table 3).

EXPERIMENTAL

Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Infrared Spectrophotometer Model 283. The nmr spectra were measured on a Perkin-Elmer R-12 B spectrometer, the solvents used were: deuteriochloroform for **3**, **4**, **5** and **6** and DMSO-d_6 for **1** and **2** with tetramethylsilane as the internal standard. Mass spectra were recorded on a Hewlett-Packard 5943A mass spectrophotometer at 70 eV ionising beam using a direct insertion probe. Microanalyses were in satisfactory agreement with the calculated values and were measured on a Perkin-Elmer 240-B analyzer.

General Procedure for Preparaton of *N*-Aryl-1,2-dihydro-2-oxo-3-pyridinecarboxamides (**1a,b,c**) and *N*-Aryl-*N*-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxamides (**2a,b,c**).

2-Hydroxynicotinic acid (1.39 g 10 mmoles), 1.5 ml of thionyl chloride and 60 ml of methylene chloride were refluxed for 3 hours. Excess thionyl chloride and methylene chloride were evaporated under reduced pressure and the resulting product in 20 ml of anhydrous 1,4-dioxane was added dropwise to a solution of 10 mmoles of the corresponding aniline or *N*-methylaniline in 10 ml of anhydrous 1,4-dioxane. After 1 hour at reflux, the solvent was removed under reduced pressure and the crude product was recrystallized from a suitable solvent to afford the pure product (Tables 1 and 2).

N-Phenyl-2-methoxy-3-pyridinecarboxamide (**3**).

2-Chloronicotinic acid (1.89 g, 12 mmoles) and 10 ml of thionyl chloride were heated until solution was completed. Excess thionyl chloride was evaporated under reduced pressure. The resulting 2-chloronicotinoyl chloride in 30 ml of anhydrous 1,4-dioxane was added dropwise to 1.12 g (12 mmoles) of aniline in 10 ml of anhydrous 1,4-dioxane and the mixture was refluxed for 1 hour. At the end of this time the solvent was removed under reduced pressure and the crude product was recrystallized from ethanol to give 2.18 g (78%) of *N*-phenyl-2-chloro-3-pyridinecarboxamide (**7**), mp 119-120°.

Compound **7** (0.93 g, 4 mmoles) and a solution of 0.138 g (6 mmoles) of sodium in 30 ml of methanol were refluxed for two hours. The solvent was removed under reduced pressure and the residue was poured into 30 ml of water. The solution was neutralized with dilute hydrochloric acid and extracted with ether. The ethereal layer was separated, washed with

water and dried over anhydrous sodium sulfate. After removal of the ether the crude product was recrystallized from hexane-ethyl actate to afford 0.82 g (90%) of *N*-phenyl-2-methoxy-3-pyridinecarboxamide (**3**), mp 63-64°; ir: 1670 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.85 (s, 3H), 6.7-7.7 (m, 6H), 7.8-7.95 (m, 1H), 8.05-8.2 (m, 1H), 10.1 (s, 1H); ms: 228 (M^+, 15), 136 (M − 92, 100).

N-Methyl-*N*-phenyl-2-methoxy-3-pyridinecarboxamide (**4**).

2-Chloronicotinic acid (1.89 g, 12 mmoles) and 10 ml of thionyl chloride were heated until solution was completed. Excess thionyl chloride was evaporated under reduced pressure. The resulting 2-chloronicotinoyl chloride in 30 ml of anhydrous 1,4-dioxane was added dropwise to 1.28 g (12 mmoles) of *N*-methylaniline in 10 ml of anhydrous 1,4-dioxane and the mixture was refluxed for 1 hour. At the end of this time the solvent was removed under reduced pressure and the crude product was recrystallized from ethanol to give 2.04 g (69%) of *N*-methyl-*N*-phenyl-2-chloro-3-pyridinecarboxamide (**8**), mp 114-115°.

Compound **8** (0.986 g, 4 mmoles) and a solution of 0.138 g (6 g-atom) of sodium in 15 ml of methanol and 15 ml of 1,4-dioxane were refluxed for 1 hour. The solvent was removed under reduced pressure and the residue was poured into 30 ml of water, the solution was neutralized with dilute hydrochloric acid and extracted with ether. The ethereal layer was separated, washed with water and dried over anhydrous sodium sulfate. After removal of the ether the crude product was recrystallized from hexane-ethyl acetate to afford 0.58 g (60%) of *N*-methyl-*N*-phenyl-2-methoxy-3-pyridinecarboxamide (**4**), mp 94-95°; ir: 1635 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.49 (s, 3H), 3.82 (s, 3H), 6.65-6.9 (m, 1H), 7.0-7.25 (s, 5H), 7.4-7.6 (m, 1H), 7.85-8.05 (m, 1H); ms: 242 (M^+, 9), 136 (M − 106, 100).

N-Phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide (**5**).

To a solution of 0.99 g (5 mmoles) of *N*-phenyl-3-pyridinecarboxamide in 5 ml of dimethyl sulfoxide, 0.95 g (7.5 mmoles) of dimethylsulfate were added dropwise. After addition, the solution heated on a boiling water bath for four hours to complete the reaction. At the end of this time the solution was allowed to cool to room temperature. Separate solutions of 3.5 g (10 mmoles) of potassium ferricyanide in 10 ml of water and of 1 g (25 mmoles) of sodium hydroxide in 5 ml of water were added dropwise to the stirred solution of the pyridinium salt at such a rate that the temperature of the reaction mixture did not rise above 10°. This usually requires two hours. The solution was poured into 20 ml of ice water and the precipitate was filtered, washed with cold water and dried. The resulting mixture was separated by chromatography on a silica gel column with methylene chloride and ethyl acetate as eluents affording 0.456 g (40%) of *N*-phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide (**5**), mp 167-168°; ir: 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.73 (s, 3H), 6.4-6.6 (m, 1H), 7.2-8.0 (m, 6H), 8.1-8.3 (m, 1H), 10.2 (s, 1H); ms: 228 (M^+, 8), 136 (M − 92, 100) and 0.513 g (45%) of *N*-phenyl-1,2-dihydro-1-methyl-2-oxo-5-pyridinecarboxamide (**11**), mp 174-176°; ir: 1680 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.8 (s, 3H), 6.6-6.8 (m, 1H), 7.3-8.3 (m, 6H), 8.4-8.6 (m, 1H), 10.25 (s, 1H); ms: 228 (M^+, 11), 136 (M − 92, 100).

N-Methyl-*N*-phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide (**6**).

A mixture of 0.848 g (4 mmoles) of *N*-methyl-*N*-phenyl-1,2-dihydro-2-oxo-3-pyridinecarboxamide (**2**), 1.26 g (10 mmoles) of dimethylsulfate and 30 g (216 mmoles) of potassium carbonate in 35 ml of dimethylformamide was heated on a boiling water bath for two hours. Excess potassium carbonate was filtered and the solvent was removed under reduced pressure giving a product which tlc indicated to be a 1:2 mixture of **4** and **6**, respectively. A single recrystallization of the mixture from ethyl acetate gave 0.5 g (52%) of pure *N*-methyl-*N*-phenyl-1,2-dihydro-1-methyl-2-oxo-3-pyridinecarboxamide (**6**), mp 142-143°; ir: 1640 cm^{-1} (C=O); nmr (deuteriochloroform): δ 3.3 (s, 3H), 3.35 (s, 3H), 5.95-6.15 (m, 1H), 7.1-7.25 (s, 5H), 7.25-7.4 (m, 1H), 7.4-7.6 (m, 1H); ms: 242 (M^+, 9), 36 (M − 106, 100).

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