The Natural Products Laboratory
Department of Chemistry
Western Reserve University

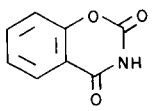
The Chemistry of Heterocycles. IV.

2*H*-Pyrido[4,3-*e*]-1,3-oxazine-2,4(3*H*)-dione, Its Precursors and Some 3-Substituted Derivatives. (1-3)

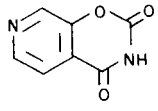
J. D. Crum (4) and C. H. Fuchsman (5)

The preparation of 2*H*-pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (II) and the anisoyl, benzoyl, 4-chlorobenzoyl, *trans*-cinnamoyl, 3,5-dinitrobenzoyl, 2-furoyl, and 2-naphthoyl derivatives substituted at position 3 of II together with their infrared and ultraviolet spectra are described. The 3-substituted 2 and 4-(2-pyridylethyl) and hydroxymethyl derivatives of quinolinimide and cinchomeronimide were also prepared and their spectra recorded.

In continuation of our interest in the chemistry of 2*H*-1,3-benzoxazine-2,4(3*H*)-dione (I) (1) we wish to report herein our work relative to the synthesis of one of the four possible pyrido-analogs, 2*H*-pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (II). A second analog, 2*H*-pyrido[2,3-e]-1,3-oxazine-2,4-(3*H*)-dione (III) was recently reported (6) while the present work was in progress. The physiological and therapeutic significance of isonicotinic acid and related compounds suggests possible areas of interest in the compounds herein reported.



I



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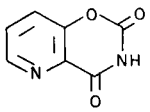
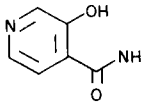


III



IV

To parallel the preparation of I by reaction of salicylamide with ethyl chlorocarbonate in pyridine solution (1), the preparation of II required the preliminary synthesis of 3-hydroxyisonicotinamide (IV). This amide (IV) was not known (7), and its immediate precursors were not readily available. Accordingly, cinchomeronic acid was treated with acetic anhydride to give cinchomeronic anhydride which was converted to cinchomeronimide (V) by reaction with acetamide. This amide on Hofmann rearrangement gave 3-aminoisonicotinic acid (VI), which on diazotization and subsequent decomposition of the diazonium salt yielded 3-hydroxyisonicotinic acid (VII). The hydroxy acid (VII) was esterified with methanol and the resulting ester (VIII) treated with aqueous ammonia to yield the desired hydroxy amide (IV).

Treatment of 3-hydroxyisonicotinamide (IV) with ethyl chlorocarbonate in anhydrous pyridine at room temperature yielded the pyridine-soluble compound, *O*-carboethoxy-3-hydroxyisonicotinamide (IX) which was isolated by quenching the reaction mixture in a large volume of water. Such an intermediate was not isolated in the previously reported preparation of (I) (1). Prolonged heating of the pyridine reaction mixture yielded the desired pyridine insoluble pyridoöxazinedione (II).

Attempts to extend this reaction to other pyrido-analogs using 2-hydroxynicotinamide and 2-hydroxy-6-methylnicotinamide were unsuccessful with the starting amides being recovered unchanged. This unreactivity of the 2-hydroxynicotinamides was attributed to the likelihood that they exist largely as the respective pyridone tautomers, and thus effectively lack a hydroxyl group to participate in the formation of the *O*-carboethoxy intermediates.

The preparation of 3-acyl derivatives of II was accomplished by the preliminary formation of the sodium salt of II and its subsequent reaction with acyl halides. The treatment of the oxazinedione (II) with sodium ethoxide in alcohol (1), was unsuitable because II, unlike I, is rather insoluble in alcohol. The treatment of a dimethylformamide suspension of II with sodium hydride in a manner similar to that

recently described for III (6) was satisfactory, but did not yield the salt in pure form. In the published procedure describing the conversion of III to 3-alkyl derivatives (6), the dimethylformamide was removed by pouring the reaction mixture into a large excess of water. We have observed that the 3-acyl derivatives of II are, however, readily hydrolysed. Therefore, the crude sodium salt was freed of mineral oil and dimethylformamide by filtration and washing of the salt with benzene and the acylation then effected by treating the dry salt with a benzene solution of the respective acyl chloride and refluxing for several hours.

The 3-pyridylethyl derivatives of II may be prepared, without catalysis, by the methods used for the preparation of such derivatives of I (8) and of III (6). By contrast the preparation of the corresponding, previously unknown, derivatives of cinchomeronimide and quinolinimide required base catalysis, consistent with the reports of similar reactions with phthalimide (9,10). The opposite situation exists in the addition of formaldehyde to the imides, in aqueous solution. Thus, cinchomeronimide and quinolinimide formed 3-hydroxymethyl derivatives quite readily, as does phthalimide (11). Under similar conditions, II did not react with formaldehyde.

TABLE I

Carbonyl Absorption (cm^{-1}) of Pyridine Dicarboximides, Pyridoöxazinediones and Related Compounds

Compound	M.p.	Pyridine Ring-bonded 4	3	2	Urethane	Acyl	Carbonate
3-Hydroxyisonicotinamide (IV)	237-237.5	1705					
O-Carboethoxy-3-hydroxyisonicotinamide (IX)	(188(a)) 320	1680					1750
Cinchomeronimide (V)	231	1725	1777				
N-hydroxymethylcinchomeronimide	172	1710	1783				
N-[2-(2-Pyridylethyl)]cinchomeronimide	134-5	1705	1775				
N-[2-(4-Pyridylethyl)]cinchomeronimide	121-2	1710	1782				
Quinolinimide	241.5-243.5		1770	1700			
N-Hydroxymethylquinolinimide	156-60		1785	1735			
N-[2-(2-Pyridylethyl)]quinolinimide	110-2		1780	1720			
N-[2-(4-Pyridylethyl)]quinolinimide	189-90		1780	1710			
2*H*-Pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (II)	320	1715			1780		
3-Anisoyl (IIb)	122-4	1708			1785	1730	
3-Benzoyl (IIc)	140-1	1715			1787	1745	
3-(4-Chlorobenzoyl) (IId)	193-7	1715			1780	1735	
3-*trans*-Cinnamoyl (IIe)	194	1705			1785	1730	
3-(3,5-Dinitrobenzoyl) (IIf)	208-10	1710			1785	1745	
3-(2-Furoyl) (IIg)	161-161.5	1720			1790	1720	
3-(2-Naphthoyl) (IIh)	217-220	1710			1780	1725	

(a) Change in color from yellow to white without melting.

TABLE II

Ultraviolet Spectral Data

Compound					
3-Hydroxyisonicotinamide (IV)	212 (1.1);	240s (0.34);	312b (0.33)		
O-Carboethoxy-3-hydroxyisonicotinamide (IX)	208 (1.7);	221 (2.1);	250s (0.42);	310b (0.31)	365b (0.31)
Cinchomeronimide (V)	208 (1.5);	220s (1.1);	231s (0.74);	275b (0.33)	
N-hydroxymethylcinchomeronimide	208 (1.6);	222s (1.1);	230s (0.79);	275b (0.26)	
N-[2-(2-Pyridylethyl)]cinchomeronimide	210 (2.5);	262b (0.71);	281s (0.49);		
N-[2-(4-Pyridylethyl)]cinchomeronimide	210 (2.5);	262s (0.60)			
Quinolinimide	213 (1.9);	225s (1.4);	234s (1.0);	269b (0.28)	
N-hydroxymethylquinolinimide	213 (1.8);	227s (1.3);	237s (0.66);	268b (0.29)	
N-[2-(2-Pyridylethyl)]quinolinimide	212 (2.5);	262b (0.69)			
N-[2-(4-Pyridylethyl)]quinolinimide	213 (2.4);	258s (0.50)			
2*H*-Pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (II)	208 (1.3);	295b (0.33)			
3-Anisoyl (IIb)	208 (2.1);	218b (1.9);	290 (2.3)		
3-Benzoyl (IIc)	208 (2.1);	235b (1.4);	254s (0.93);	277b (0.42)	
3-(4-Chlorobenzoyl) (IId)	208 (2.3);	245 (1.9)			
3-*trans*-Cinnamoyl (IIe)	208 (2.1);	218b (1.9);	290 (2.3)		
3-(3,5-Dinitrobenzoyl) (IIf)	218b (3.3);	293 (0.28)			
3-(2-Furoyl) (IIg)	212 (1.7);	263 (1.6)			
3-(2-Naphthoyl) (IIh)	211 (3.2);	243 (4.9);	286b (1.03)		

As was previously noted in the case of the 3-acyl derivatives of I (1), the three carbonyl groups bonded to the 3-nitrogen in II were distinguishable by their infrared stretching frequencies. The carbonyl absorption in cinchomeronimide and in II, closest to that found in 3-hydroxyisonicotinamide, was assigned to the carbonyl group bonded to the 4-position of the pyridine ring. The other carbonyl absorption was assigned to the carbonyl bonded to the 3-position of the pyridine ring for cinchomeronimide or to the urethane carbonyl group in the pyridoöxazinedione (II). The third carbonyl group, present in the 3-acyl compounds, absorbed at positions intermediate to those corresponding to the amide and the urethane carbonyls of the oxazinedione (II). A comparison of the infrared spectrum of quinolinimide to that of cinchomeronimide, led to assignment of the carbonyl bonded to the 2-position on the pyridine ring (Table I).

The stretching frequencies of the imide carbonyl groups were not notably affected by the replacement of the imide proton by a hydroxylmethyl or pyridylethyl group. Similarly the absorptions of the oxazinedione carbonyl groups were not substantially altered by the replacement of the acidic oxazinedione hydrogen atom by a pyridylethyl group.

The following generalizations describe the data. The amide carbonyl attached to the pyridine ring at the 4-position absorbed typically at 1705-1720 cm^{-1}, at the 3-position it absorbed at 1770-1785 cm^{-1}, and at the 2-position it absorbed at 1700-1735 cm^{-1}. In the pyridoöxazinediones, the urethane carbonyl absorbed at 1780-1787 cm^{-1}. In the 3-acyl substituted pyridoöxazinediones described in this work, the acyl carbonyl absorbed at 1720-1745 cm^{-1}. A large shift in carbonyl absorption was observed only in the case of *O*-carboethoxy-3-hydroxyisonicotinamide where the amide carbonyl absorption was lowered to 1680 cm^{-1}. A second carbonyl absorption at 1750 cm^{-1} was assigned to the carbonate carbonyl.

The ultraviolet spectra of these compounds in methanol generally contained a characteristic absorption maximum in the region 208-213 mμ which can be attributed to the conjugated aromatic-carbonyl structures. Where more highly chromophoric groups appear, as in the 3-naphthoyl substituted pyridoöxazinedione, additional strong absorption appeared also at greater wavelengths. In the case of the 3-(3,5-dinitrobenzoyl)-derivative the recorded broad maximum at 218 mμ suggests a combination of an expected maximum at 208-212 mμ and one at 218 mμ.

EXPERIMENTAL

Cinchomeronimide (V).

A mixture of 250 g. (1.49 moles) of cinchomeronic acid and 600 g. (5.88 moles) of acetic anhydride was heated to boiling and 477 g. of distillate removed. The residue was cooled to room temperature, combined with 250 g. (4.22 moles) of acetamide, and refluxed for 3 hours. After remaining overnight the solid residue was broken up, triturated with water, filtered, washed and dried to a final weight of 204.5 g. (92% yield), m.p. 231° in agreement with 229-230° (12), 226-227° (13), 231-232° (14), 229° (15) previously reported.

3-Aminoisonicotinic acid (VI).

To 1200 g. of 10% aqueous sodium hydroxide cooled to 7° was added 81 g. (0.51 mole) of bromine and 74.1 g. (0.50 mole) of (V). The resulting solution was heated to 80°, cooled to 37°, and adjusted to *p*H 5.5 by the addition of 125 ml. of glacial acetic acid. The resulting suspension was refrigerated overnight and filtered. The solids, washed with 20 ml. of water and 25 ml. of methanol, were dried yielding 57.5 g. (82% yield) of VI, m.p. 295-297° in agreement with 280° (16), 292° (dec.) (17), 308 (dec.) (18), 319-320° (13), 308° (dec.) (19), previously reported.

3-Hydroxyisonicotinic acid (VII).

To a suspension of 41.2 g. (0.290 mole) of VI in 600 ml. of water, was added 30 ml. of concentrated sulfuric acid. The mixture was heated to 52° to dissolve the solids and then cooled to 8°. A solution of 20.7 g. (0.300 mole) of sodium nitrite in 180 ml. of water, cooled to 10°, was combined with the sulfuric acid suspension, over a 20 minute period, with the reaction temperature maintained at 8-10°. The solution was heated to 82°, cooled to 65°, 30 ml. of glacial acetic acid was added, and followed by 70 ml. of concentrated ammonium hydroxide to raise the *p*H to 4.5. After refrigeration overnight, the reaction mixture was filtered and washed with 40 ml. of water and dried to yield 32.6 g. (79%) of the product, m.p. 317-319° (dec.) (14), 312° (20), 314° (15).

Anal. Calcd. for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.88; H, 3.35; N, 10.20.

Methyl 3-hydroxyisonicotinate (VIII).

To 400 ml. of methanolic solution containing 109 g. of hydrogen chloride was added 99.6 g. (0.716 mole) of VII and the mixture refluxed for 4 hours. The resulting solution was neutralized to *p*H 7.2 with 10% aqueous sodium carbonate and extracted with four 200 ml. portions of chloroform. Evaporation of the solvent yielded 70.7 g. of VIII (64% yield). Concentration of the aqueous phase after chloroform extraction to 1 l. and acidification with hydrochloric acid to *p*H 4.5 led to precipitation of 26.6 g. of unreacted acid, which was resubjected to the esterification procedure to bring the overall esterification yield to 83%. Recrystallization of the product from ligroin yielded analytically pure material, m.p. 78-79° in agreement with 78.5-80.5° (21) previously reported.

Anal. Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.30; H, 4.59; N, 8.98.

3-Hydroxyisonicotinamide (IV).

To 6.72 g. (0.0049 mole) of VIII was added 203 ml. of concentrated ammonium hydroxide. Complete solution occurred within 1 hour at room temperature. The solution was concentrated to 55 ml., refrigerated overnight, filtered, and the procedure of concentration, refrigeration and filtration repeated until the residual liquid volume was 5 ml. giving 4.93 g. (73% yield) of IV. Recrystallization from water gave material, m.p. 237-237.5°.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.03; H, 4.24; N, 20.31.

O-Carboethoxy-3-hydroxyisonicotinamide (IX).

To a stirred suspension of 2.0 g. of IV in 5 ml. of pyridine, was added over a 10 minute period 4.0 ml. of ethyl chloroformate. The mixture was heated to 73° in the next 8 minutes and the resulting solution poured into 30 ml. of water. The yellow precipitate was filtered and the resulting yellow solid dried at 80° giving 1.96 g. (64% yield) of IX. Recrystallization from ethanol gave material which turned white at 188° and melted at 320°.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.69; N, 13.33. Found: C, 51.17; H, 4.68; N, 13.59.

2*H*-Pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (II).

To a stirred suspension of 5.0 g. (0.0359 mole) of IV in 9.1 g. of pyridine was slowly added 8.73 g. (0.080 mole) of ethyl chloroformate. The resulting clear solution was then refluxed for 30 minutes. The suspension was diluted with 150 ml. of water, refrigerated overnight and filtered. The product was washed with 10 ml. of water, and dried giving 4.45 g. (75% yield) of material melting at 320°. Analytically pure material was prepared by recrystallization from dioxane.

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.35; H, 2.75; N, 16.92.

This product was also prepared by dissolving IX in pyridine, refluxing and then proceeding as above.

2*H*-Pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione-sodium (IIa).

To a suspension of 6.56 g. of II in 45 ml. of dimethylformamide cooled to 5°, was added 1.64 g. of a 58.6% suspension of sodium

hydride in mineral oil. The mixture was stirred gently, cooled for about 30 minutes and filtered through fritted glass. The solids were washed with 25 ml. of benzene and dried in a vacuum oven to a constant weight of 7.06 g. This salt was used without further purification.

3-Anisoyl-2*H*-pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (IIb).

To a suspension of 0.93 g. (0.0050 mole) of the crude sodium salt of II in 25 ml. of benzene was added a solution of 0.85 g. (0.0050 mole) of anisoyl chloride in 7 ml. of benzene. The mixture was refluxed for 2 hours and then filtered hot. The solid was washed with 20 ml. of hot benzene and the combined filtrates evaporated to dryness yielding 0.51 g. (34%) of product. Recrystallization first from ligroin and then twice from ethanol yielded IIb, m.p. 122-124°.

Anal. Calcd. for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.38; N, 9.39. Found: C, 60.56; H, 3.45; N, 9.40.

The following 3-acyl derivatives of II were prepared by analogous procedures which differed from that given above only in the recrystallization step.

3-Benzoyl (IIc) 25% yield, m.p. 140-141°, analyzed without recrystallization.

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.09; H, 3.01; N, 10.44. Found: C, 62.86; H, 3.01; N, 10.48.

3-(4-Chlorobenzoyl) (IId) 32% yield, m.p. 195-197°, analyzed without recrystallization.

Anal. Calcd. for $C_{14}H_7ClN_2O_4$: C, 55.56; H, 2.33; N, 9.26; Cl, 11.71. Found: C, 55.41; H, 2.26; N, 9.03; Cl, 11.94.

3-*trans*-Cinnamoyl (IIe) 33% yield, m.p. 194°, analyzed without recrystallization.

Anal. Calcd. for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.52; H, 3.55; N, 9.62.

3-(3,5-Dinitrobenzoyl) (IIf) 39% yield. Recrystallized from ethanol gave material, m.p. 208-210°.

Anal. Calcd. for $C_{14}H_6N_4O_8$: C, 47.07; H, 1.69; N, 15.68. Found: C, 47.30; H, 1.93; N, 15.52.

3-(2-Furoyl) (IIg) 39% yield. Recrystallization first from ligroin, then twice from ethanol gave material, m.p. 161-161.5°.

Anal. Calcd. for $C_{12}H_6N_2O_5$: C, 55.82; H, 2.34; N, 10.86. Found: C, 56.03; H, 2.42; N, 10.67.

3-(2-Naphthoyl) (IIh) 10% yield, m.p. 217-220°, analyzed without recrystallization.

Anal. Calcd. for $C_{18}H_{10}N_2O_4$: C, 67.92; H, 3.17; N, 8.80. Found: C, 68.18; H, 3.44; N, 8.72.

Quinolinimide (X).

A mixture of 175 ml. of acetic anhydride and 153.6 g. (0.908 mole) of quinolinic acid was heated to remove 150 ml. of distillate, the residue cooled to about 100°, and 108 g. (1.83 moles) of acetamide added. The mixture was refluxed for 2.5 hours, cooled overnight and filtered. The solid was washed and triturated with water, refiltered, rewashed and dried giving 91.6 g. (68%) of X, m.p. 241.5-243.5° compared to 230° (22) and 233° (23) previously recorded.

3-[2-(2-Pyridylethyl)]-2*H*-pyrido[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (IIi).

To 3 ml. of 2-vinylpyridine was added 0.83 g. (0.0051 mole) of II and the mixture heated to 100° for 30 minutes. The mixture was cooled, diluted with 25 ml. of methanol, and filtered at 5°. The product was washed with 2 ml. of water and 4 ml. of methanol and dried *in vacuo* at 85° giving 0.82 g. Additional material (0.18 g.) was recovered by concentration and cooling the filtrate. The product (total weight 1.00 g., 73% yield), m.p. 137-138°, was analyzed without further purification.

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.23; H, 3.97; N, 15.43.

The following was prepared by analogous procedures, using 4-vinylpyridine in place of 2-vinylpyridine.

3-[2-(4-Pyridylethyl)]-2*H*-pyrido-[4,3-e]-1,3-oxazine-2,4(3*H*)-dione (IIj).

Yield, 55%. Recrystallization from ethanol gave material, m.p. 137-138°.

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.73; H, 4.25; N, 15.75.

N-[2-(2-Pyridylethyl)cinchomeronimide (Va).

A mixture of 5.0 g. (0.034 mole) of V in 3.5 ml. (0.033 mole) of 2-vinylpyridine to which 6 drops of 40% methanolic benzyltrimethylammonium hydroxide had been added, was refluxed for 20 minutes. On cooling it gave the solid product in quantitative yield. Recrystallization from ethanol gave material, m.p. 134-135°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.39; N, 16.59. Found: C, 66.25; H, 4.38; N, 16.77.

By analogous procedures the following compounds were prepared.

N-[2-(4-Pyridylethyl)]cinchomeronimide (Vb).

Quantitative yield. An analytical sample recrystallized from ethanol, melted at 121-122°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.39; N, 16.59. Found: C, 66.27; H, 4.42; N, 16.44.

N-[2-(4-Pyridylethyl)]quinolinimide (Xa).

Quantitative yield. An analyzed sample recrystallized from ethanol, melted at 189-190°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.39; N, 16.59. Found: C, 66.56; H, 4.51; N, 16.48.

N-[2-(2-Pyridylethyl)]quinolinimide (Xb).

For preparation of this compound the liquid after being refluxed was cooled to 60°, 9 ml. of chloroform added and the cooled suspension filtered. The product (58% yield), after two recrystallizations from ethanol, melted at 110-112°.

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.39; N, 16.59. Found: C, 66.21; H, 4.25; N, 16.49.

N-Hydroxymethylcinchomeronimide (Vc).

To 1.64 ml. of 37% U.S.P. formaldehyde diluted with 10 ml. of water, was added 3.0 g. (0.020 mole) of V. The mixture was boiled for 25 minutes during which time 0.8 ml. of additional formaldehyde solution was added. After remaining overnight, the suspension was filtered, and dried *in vacuo* yielding 3.0 g. (83%) of product, m.p. 172°. The sample was analyzed without further purification.

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 53.79; H, 3.40; N, 15.66.

By analogous procedures *N*-hydroxymethylquinolinimide (Xc) was prepared in 90% yield, m.p. 156-160°.

Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.20; H, 3.33; N, 15.80.

2-Hydroxynicotinic Acid (XI).

To a solution of 8 ml. of concentrated sulfuric acid in 438 ml. of water was added 15 g. (0.109 mole) of 2-aminonicotinic acid. The mixture was heated to 75° to dissolve the solids, cooled to 8° and a precooled solution of 9.0 g. (0.130 mole) of sodium nitrite in 75 ml. of water was added. After being maintained at 8° for 15 minutes, the mixture was heated to 85°, then cooled to 15°. The solids, washed with water, and dried *in vacuo* weighed 12.3 g. (81% yield) m.p. 217° in comparison with 255° decomp. (22), 217° (24), 255° decomp. (25), 255° (27), previously reported. The low melting point was attributed to the presence of some unreacted 2-aminonicotinic acid.

Methyl 2-hydroxynicotinate (XII).

This compound was prepared analogously to methyl 3-hydroxyisonicotinate noted above, except that the first chloroform extracts contained principally the methyl ester of undiazotized 2-aminonicotinic acid. Prolonged extraction with chloroform and reworking residues melting below 143° led to an ultimate accumulation of a 32% yield of product, whose melting point was 143-153° compared to 142-143° (26), and 153° (28) previously reported.

2-Hydroxynicotinamide (XIV).

The procedure paralleled that for the preparation of 3-hydroxyisonicotinamide and yielded 95% of a product melting at 273-274° in comparison with 266-267° (27) previously reported. The compound was analyzed without further purification.

Anal. Calcd. for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.51; H, 4.34; N, 20.27.

2-Hydroxy-6-methylnicotinamide (XV).

To 100 ml. of concentrated ammonium hydroxide was added 10 g. (0.0060 mole) of XIII, and the mixture stirred intermittently for 3 days. The solids did not completely dissolve and another 100 ml. of concentrated ammonium hydroxide was added and the suspension was boiled down to 50 ml., cooled and allowed to remain overnight. The product was filtered and dried to constant weight *in vacuo* weighing 8.50 g. (93% yield), m.p. 310°. A sample was analyzed without further purification.

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.12; H, 5.12; N, 18.41.

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(2) This investigation was supported in part by an Institution Grant, IN57B, to Western Reserve University by the American Cancer Society and in part by a National Service Foundation Grant for Science, GU405. This support is gratefully acknowledged.

(3) Taken in part from a dissertation submitted by Charles Herman Fuchsman in partial fulfillment of the requirements for the Ph.D. degree in Chemistry, Western Reserve University, September 1965.

(4) To whom inquiries concerning this paper should be sent.

(5) Present address, Ferro Chemical Division, Ferro Corporation, P. O. Box 349, Bedford, Ohio 44014.

(6) French Patent 1,339,175, Aug. 26, 1963, assigned to J. R. Geigy, S. A.

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Received June 7, 1966

Cleveland, Ohio 44106