results of the distillation and subsequent analysis are shown in Table II.

Analytical Methods Employed.—Iodine numbers were determined by the standard Wijs (one-half hour) method. Molecular weights were determined cryoscopically in benzene on methyl esters only. Per cent. hydroxyl was determined by a method recently developed by C. L. Ogg, W. L. Porter and C. O. Willits,[14] of this Laboratory.

Acknowledgment.—The authors are indebted to J. C. Cowan and W. Bond of the Northern Regional Research Laboratory for conducting the molecular distillation, and to E. F. Jordan, Jr., of the Eastern Regional Research Laboratory for assistance in conducting some of the laboratory work.

Summary

The catalytic air oxidation of methyl oleate has been studied.

The high-boiling, previously uncharacterized portion of the oxidation products, obtained in 30 to 40% yield, has been fractionated by molecular distillation, yielding oxygenated polymers of dimeric and higher complexity. It is believed that these polymers are oxygen linked.

A methyl ester fraction with a boiling point intermediate between that of methyl oleate and the polymers has been isolated and extensively studied for the first time. By oxidative splitting of this fraction with potassium permanganate in acetone solution, it has been shown to consist mainly of methyl esters of several isomeric monohydroxy derivatives of one or more mono-unsaturated acids in which the double bond has been shifted from the 9,10-position, and methyl esters of dimeric acids.

(14) Ogg, Porter and Willits, *Ind. Eng. Chem., Anal. Ed.*, in press.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY,[1] PHILADELPHIA, PENNSYLVANIA]

Nicotinic Acid. Water-insoluble Esters and Amides

BY C. O. BADGETT, RAYMOND C. PROVOST, JR., CLYDE L. OGG AND C. F. WOODWARD

Attention has been directed[2] to the need for water-insoluble forms of nicotinic acid, thiamin, and riboflavin for use in the practical fortification of cereals, such as corn grits and white rice, which are often rinsed prior to cooking. Although nicotinic acid and nicotinamide have been successfully employed in the fortification of wheat flour, their water solubility makes them disadvantageous for enrichment of the food products mentioned above.

The present paper describes the preparation of *n*-alkyl esters and N-(*n*-alkyl) amides of nicotinic acid in an attempt to obtain derivatives having the desired water-insolubility and biological activity. The N-phenyl-, N-cyclohexyl- and N-(2-pyridyl)-nicotinamides were also prepared for biological comparison.

n-Alkyl esters of nicotinic acid, in which the length of the alkyl group ranged from C_2 to C_{18}, were prepared by the reaction of the corresponding alcohols with nicotinyl chloride.[3] N-(*n*-Alkyl) nicotinamides, in which the alkyl group ranges from C_6 to C_{18}, were prepared by the following methods: reaction of *n*-alkyl amines with nicotinyl chloride,[3] aminolysis of nicotinic esters,[4,5] and the reaction of amines with nicotinic acid.[5] The latter two methods were recently employed[5] in the synthesis of the following N-substituted nicotinamides for antispasmodic and anticonvulsant tests: benzyl-, *n*-amyl-, allyl- and dibutylaminopropyl-.

Published data indicate that methyl nicotinate is active in bacterial metabolism, whereas the ethyl-, *n*-propyl- and *n*-butyl esters of nicotinic acid are active in animal metabolism and exhibit some specificity as essential factors for bacteria. N-Methyl and N,N-diethyl nicotinamide were active in tests on dogs and on dysentery bacilli.[6]

Preliminary biological data, obtained by C. A. Elvehjem, L. J. Teply and W. A. Krehl, on several of the higher amides and esters prepared in this study are summarized in Tables I and II. Although most of these derivatives are relatively inactive in *Lactobacillus arabinosus*, there is some indication that the esters are active in animal metabolism. Since N-phenyl nicotinamide was about two-thirds as active as nicotinic acid in dog assays, it is believed that the N-alkyl nicotinamides will also be active under similar test conditions.

As was to be expected, the higher *n*-alkyl esters and amides of nicotinic acid were insoluble in water. Since the rinsing of fortified cereals would not result in saturation of the wash water with the vitamin, the solubility data herein reported are indicative of the maximum vitamin loss that could be incurred. The actual loss in practice would probably be far less than the saturation value.

Experimental

The preparation of *n*-octyl nicotinate is representative of the method employed in the preparation of the fourteen

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Gunderson, *Science*, **98**, 277 (1943).

(3) Hukusima, *J. Chem. Soc.*, Japan, **61**, 121 (1940).

(4) Pictet and Sussdorff, *Arch. sci. phys. nat.*, Geneve, [4] **5**, 118; *Chem. Zentr.*, **69**, I, 677 (1898).

(5) Billman and Rendall, THIS JOURNAL, **66**, 540 (1944).

(6) For an excellent review of compounds functionally related to nicotinic acid, see Elvehjem and Teply, *Chem. Rev.*, [4] **33**, 185 (1943).

Table I

n-Alkyl Nicotinic Acid Esters

No.	n-Alkyl group	Boiling point, °C.	Mm.	Density$^{25}_{4}$	n^{25}D	Melting point of picrate, °C.	Analyses, %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Ethyl[a]	88	3.5	1.1047	1.5008	147.5–148.0				
2	Propyl[a]	72–73	0.2	1.0711	1.4964	129.5–130.0	65.45	65.41	6.66	6.82
3	Butyl[a]	75–76	.15	1.0471	1.4933	113.5–114.0	67.08	66.88	7.30	6.99
4	Amyl[a]	93	.22	1.0217	1.4847	98.5–99.0	68.39	68.76	7.77	8.15
5	Hexyl	103–104	.2	1.0133	1.4897	87.5–88.5	69.56	69.35	8.21	8.27
6	Heptyl	116	.19	0.9939	1.4846	92.5–93.5	70.58	70.55	8.59	8.93
7	Octyl	116–117	.2	.9871	1.4856	89.5–90.0	71.49	71.43	8.93	9.18
8	Nonyl	133.5	.28	.9852	1.4853	99.5–100.0	72.25	71.83	9.29	9.42
9	Decyl	140–141	.25	.9714	1.4847	94.0–94.5	72.96	72.45	9.56	9.06
10	Undecyl	159–160	.5	.9606	1.4829	103.5–103.8	73.60	74.09	9.81	9.69
11	Dodecyl	F. p., 22.7		.9356	1.4750	99.5–100.5	74.18	74.16	10.03	9.81
12	Tetradecyl	M. p., 40.2–40.8		....	....	102.4–103.0	75.18	75.12	10.41	10.10
13	Hexadecyl	M. p., 46.7–47.0		....	....	103.0–103.5	76.03	76.17	10.73	10.69
14	Octadecyl	M. p., 55.3–55.8		....	....	107.7–107.9	76.75	76.59	11.00	10.98

No.	Analyses, %: Nitrogen Calcd.	Nitrogen Found	Picrate nitrogen Calcd.	Picrate nitrogen Found	Solute in 100 cc. solution at 25°C.[b] g.	Nicotinic acid equivalent,[d] g.	Biological activity,[c] as compared with that of nicotinic acid, on— *L. arabinosus*, %	Dogs
1	..	..	14.73	14.36	5.60	4.58	7.5	Equal
2	8.48	8.57	14.21	13.83	0.950	0.708	5.2	..[e]
3	7.80	8.21	13.72	13.27	.261	.179	5.1	..
4	7.25	7.51	13.26	12.98	.081	.052	5.3	..
5	6.76	6.62	12.74	12.96	.046	.027	4.8	..
6	6.33	6.86	12.44	12.29	.040	.022	4.2	..
7	5.95	5.93	12.06	11.68	.019	.010	4.0	..
8	5.62	5.92	11.71	11.62	.020	.010	...	..
9	5.32	5.03	11.39	11.38	.017	.008	...	..
10	5.05	4.96	11.06	10.80	.017	.007	...	..
11	4.81	4.59	10.76	10.33	.015	.006	2.5	Fair
12	4.38	4.33	10.21	10.23	.012	.005	...	..
13	4.03	4.09	9.71	9.71	.013	.005	...	..
14	3.73	3.70	9.26	9.41	.014	.005	...	..

[a] Previously reported. [b] With an accuracy of ±0.005 g. [c] Molar basis. [d] Solubility of nicotinic acid is 1.77 g. [e] Indicates no test.

esters whose properties are summarized in Table I. All melting points reported herein are corrected values.

***n*-Octyl Nicotinate.**—Thionyl chloride, 35.7 g., was added with stirring during twenty minutes to a cooled mixture of 36.9 g. of nicotinic acid and 47.4 g. of pyridine in a 500-cc., 3-necked flask equipped with a dropping funnel, a reflux condenser, and a mercury-sealed stirrer. The reaction mixture was then heated for one hour at 100°. Octanol-1, 42.9 g., was added over a period of five minutes, and the resulting mixture was heated at 95–100° for three hours. The reaction mixture was poured into 500 cc. of water and made slightly alkaline with dilute ammonium hydroxide. The water-insoluble portion was then separated and washed in turn with dilute sodium carbonate solution and water. The original water solution, from which the ester had been separated, was then extracted twice with 100-cc. portions of diethyl ether. The combined ether extract was added to the washed ester fraction, and the solution was dried over anhydrous sodium sulfate. After the drying agent was removed by filtration, the filtrate was fractionally distilled under reduced pressure. The 46.2-g. portion distilling at 116° (0.18 mm.) was pure n-octyl nicotinate and represented 65.5% of the theoretical yield; n^{25}D 1.4856, d^{25}_{4} 0.9871. Melting point of picrate was 89.5–90.0°.

In the preparation of C_{14}, C_{16} and C_{18} esters, an excess of nicotinyl chloride was employed to ensure practically complete esterification of the alcohol and minimize the difficulty encountered in separating the ester from any unreacted alcohol by fractional distillation. To ensure complete separation of these higher esters from the corresponding alcohols, the dried ether extract, obtained as described above, was saturated with dry hydrogen chloride, and the precipitated ester hydrochloride was filtered and washed with cold ether. The ester obtained by subsequent treatment of the hydrochloride with sodium carbonate solution was free of the alcohol employed in the esterification.

The N-(n-alkyl)-nicotinamides (Table II) were prepared by one or more of the following three methods. The detailed procedures for the preparation of N-(n-decyl)-nicotinamide are applicable to all amides herein reported.

N-(*n*-Decyl)-nicotinamide, Method A.—A mixture consisting of 24.6 g. of nicotinic acid and 31.4 g. of n-decylamine was heated at 200–235° for fifteen minutes. The reaction mixture was then made slightly alkaline by the addition of sodium carbonate solution while a temperature of 75° was maintained. The aqueous layer was withdrawn, the residual liquid N-(n-decyl)-nicotinamide layer was washed with hot water, and the crude amide was then separated and dried in a vacuum desiccator. The dried product was dissolved in chloroform, and the solution was clarified by boiling with activated carbon and filtering. The amide was precipitated from the warm filtrate by the addition of petroleum ether. The solution was then cooled and the crystalline product filtered. The 43.5 g. of material melting at 64.0–66.0° represented 83.0% of the theoretical yield. Repeated recrystallization of the amide from a mixture of petroleum ether and chloroform yielded

TABLE II

N-SUBSTITUTED NICOTINAMIDES

No.	Substituent	Melting point, °C.	Melting point of picrate, °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	*n*-Hexyl	44.6–44.9	147.1–147.6	69.86	69.70	8.79	8.70
2	*n*-Heptyl	51.8–52.1	151.2–151.6	70.87	70.50	9.16	9.03
3	*n*-Octyl	61.4–61.9	144.6–144.9	71.75	71.62	9.47	9.34
4	*n*-Nonyl	73.1–73.4	147.9–148.4	72.54	72.59	9.74	9.79
5	*n*-Decyl	72.1–72.4	151.0–151.6	73.23	72.77	10.00	9.74
6	*n*-Undecyl	71.1–71.8	152.3–152.8	73.86	73.82	10.22	9.97
7	*n*-Dodecyl	77.6–77.8	153.5–154.0	74.43	74.18	10.38	10.13
8	*n*-Tridecyl	81.8–82.2	153.9–154.2	74.94	74.60	10.60	10.34
9	*n*-Tetradecyl	80.9–81.2	154.2–154.5	75.42	74.97	10.77	10.29
10	*n*-Hexadecyl	87.7–87.9	155.4–155.8	76.25	76.38	11.06	10.66
11	*n*-Octadecyl	91.7–92.0	155.1–155.7	76.95	76.63	11.29	11.29
12	Phenyl[a]	116.8–117.2	186.2–186.9	72.71	72.40	5.09	5.67
13	Cyclohexyl	140.0–140.4	198.8–199.1	70.55	70.49	7.90	7.43
14	2-Pyridyl	136.4–136.6	225.3–225.7[b]	66.32	66.30	4.55	4.60

No.	Analyses, % Nitrogen Calcd.	Nitrogen Found	Picrate nitrogen Calcd.	Picrate nitrogen Found	Solute in 100 cc. solution at 25°C.[c] g.	Nicotinic acid equivalent, g.	Biological activity,[d] as compared with that of nicotinic acid, on— L. arabinosus, %	Dogs
1	13.58	13.51	16.09	16.20	0.062	0.037	0.25	....[e]
2	12.72	12.27	15.58	15.61	.014	.008	0.05	....
3	11.96	11.57	15.11	15.09	.023	.012	..	....
4	11.28	11.17	14.67	14.58	.018	.009	0.2	....
5	10.68	10.67	14.25	14.11	.022	.010	..	....
6	10.21	10.05	13.86	13.20	.026	.012	..	....
7	9.65	9.56	13.48	13.40	.018	.008	..	....
8	9.20	9.32	13.13	13.00	.036	.014	..	....
9	8.80	8.81	12.79	12.35	.020	.008	Less than 1	....
10	8.09	7.91	12.17	12.18	.038	.014	Less than 1	....
11	7.48	7.49	11.60	11.65	.024	.008	Less than 1	....
12	14.14	14.01	16.39	16.38	.016	.010	0.32	Approx. $^2/_3$
13	13.72	13.39	16.16	15.98	.098	.060	..	....
14	21.09	20.97	19.18[b]	18.98	.021	.012	..	....

[a] Previously reported. [b] Dipicrate. [c] With an accuracy of ±0.005 g. [d] Molar basis. [e] Indicates no test.

a product of analytical purity which melted at 72.1–72.4°. Melting point of picrate was 151.0–151.6°.

Method B.—A reaction mixture consisting of 61.8 g. of ethyl nicotinate and 70.8 g. of *n*-decylamine was heated at 214–250° for 190 minutes in a reaction flask equipped with an efficient fractionating column having a reflux head. During the heating period, 10.6 g. of ethyl alcohol distilled from the reaction mixture. The residue in the distillation flask was dissolved in 500 cc. of chloroform and the amide isolated as in Method A. The 90.8 g. of N-(*n*-decyl)-nicotinamide melting at 69.8–70.4° represented 82.7% of the theoretical yield. After several recrystallizations from chloroform and petroleum ether, the amide melted at 72.2–72.6°.

Method C.—Nicotinic acid, 36.9 g., and pyridine, 47.4 g., were added to a 500-cc., 3-necked flask equipped with a condenser, mercury-sealed stirrer, and dropping funnel. Thionyl chloride, 35.7 g., was added to the stirred mixture with cooling over a period of fifteen minutes. The reaction flask was heated on a steam-bath for four hours. *n*-Decylamine, 51.9 g., was then added dropwise to the mixture. Stirring and heating at 100° were continued for one hour. The reaction mixture was poured into 500 cc. of ice water and made slightly alkaline by the addition of a dilute sodium carbonate solution. The separated amide layer was washed thoroughly with hot 5% sodium carbonate solution and further purified as in Method A. The 50 g. of pure amide, melting at 72.2–72.8°, represented 65.5% of the theoretical yield.

Although the density and refractive index of the liquid esters were determined, no reliable comparison between the calculated and theoretical values for molecular refractivity could be made, since the empirical value for the pyridyl radical is questionable. Calculations made to establish a value for the pyridyl group on the basis of data previously reported yielded numerical values which were not in good agreement.

Solubility Determinations.—Solubility determinations on the nicotinic esters were made by the following general procedure. An excess of the ester was added to 200 cc. of distilled water and shaken at 24.0–25.0° for eighteen hours, after which the container was placed in a constant temperature bath at 25° for two to three days. Although it is recognized that these conditions did not necessarily ensure equilibrium, the procedure was considered sufficiently indicative for the purpose at hand. The undissolved ester was then removed by filtration or decantation, and the solubility of the ester was determined by saponification of the water solution. Samples of 10 to 15 ml. and 0.1 *N* acid and 0.1 *N* base were used. The aqueous solution was also titrated to determine the quantity of dissolved nicotinic acid caused by hydrolysis. With the one exception of ethyl nicotinate, hydrolysis was negligible for all esters. The solubility value herein reported for ethyl nicotinate was therefore determined on the aqueous solution obtained by shaking an excess of the ester with water at room temperature for one hour and then placing the mixture in the constant temperature bath for two hours. The solubility value for ethyl nicotinate, 5.6 g. per 100 ml. of water at 25°, indicates that this ester is more soluble than nicotinic acid, 1.77 g., under comparable conditions.

A saturated solution of the amides was made by the same procedure employed for the higher esters. Amide nitrogen determination was made on the aqueous solution by a Van Slyke procedure. One milliliter of saturated potassium hydroxide was added to 15 ml. of the aqueous sample, and the solution was refluxed for one hour. The hydrolyzed solution was washed into a 25-ml. volumetric flask and made to volume with water, and 1 ml. of this solution was analyzed for amino N by the Van Slyke manometric procedure. Since little or no amino nitrogen was detected prior to alkaline hydrolysis, it was concluded that hydrolysis of the amides by water was negligible.

It was expected that the water solubility of the amides and esters would vary inversely with the length of the *n*-alkyl group. The deviation from this anticipated result may have been due in part to the slight surface activity of the higher *n*-alkyl derivatives.

Acknowledgment.—The authors are indebted to C. A. Elvehjem, L. J. Teply and W. A. Krehl for the biological data herein reported.

Summary

The preparation of ten new esters and thirteen new amides of nicotinic acid is described. Preliminary biological and solubility data indicate these new compounds may be suitable water-insoluble anti-pellagra materials for the fortification of food products which are rinsed prior to cooking. However, the actual merit of these derivatives can be ascertained only by evaluation under conditions of intended use.

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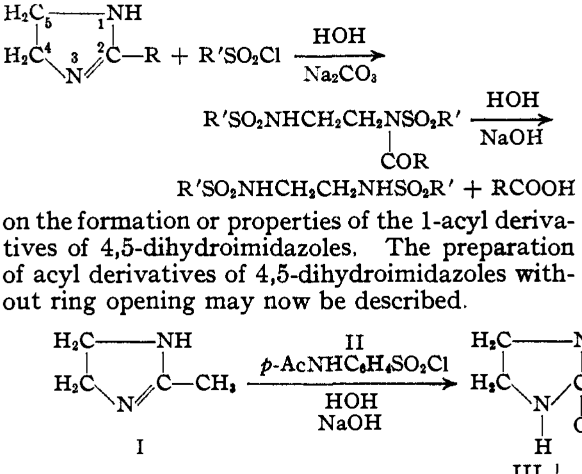
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO., ST. LOUIS, MISSOURI]

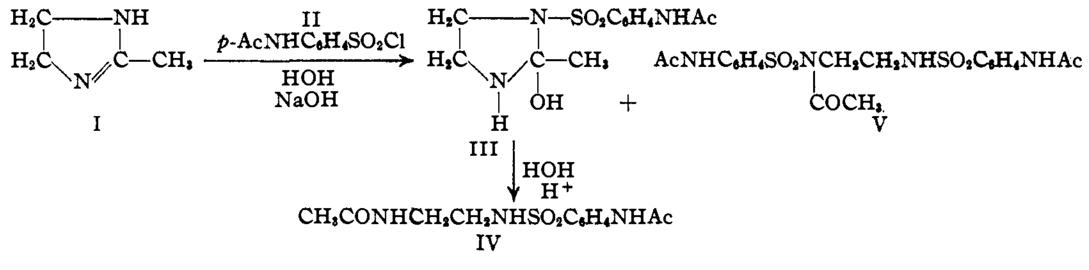
The Acylation of 4,5-Dihydroimidazoles

BY F. B. ZIENTY

The action of aromatic sulfonyl chlorides and carboxylic acid chlorides on 4,5-dihydroimidazoles in the presence of aqueous alkali causes ring opening to form triacyl and diacyl derivatives of ethylenediamine.[1] While N-acyl derivatives of imidazoles[2] and benzimidazoles[3] have been prepared, no information is available in the literature



on the formation or properties of the 1-acyl derivatives of 4,5-dihydroimidazoles. The preparation of acyl derivatives of 4,5-dihydroimidazoles without ring opening may now be described.



Reaction of 2-methyl-4,5-dihydroimidazole (I) with N-acetylsulfanilyl chloride (II) in water at 0–10° in the presence of an equivalent of alkali produced a 30% yield of 1-(N^4-acetylsulfanilyl)-2-hydroxy-2-methyl-tetrahydroimidazole (III), a considerable quantity of N-acetyl-N′-(N^4-acetylsulfanilyl)-ethylenediamine (IV), and a small amount of N-acetyl-N,N′-di-(N^4-acetylsulfanilyl)-ethylenediamine (V).

When the reaction was run at 60° a 98% yield of IV was obtained. It was found that III is very easily hydrolyzed to IV in the presence of mineral acids. The formation of hydroxy acylated imidazole derivatives is not new, since Gerngross[3] observed that the treatment of 1-benzoyl-benzimidazole with benzoyl chloride in anhydrous medium, followed by the addition of water, resulted in the formation of 1,3-dibenzoyl-benzimidazolol (VI).

Reaction of I and II in benzene, followed by quenching with water, resulted in the formation of a mixture consisting chiefly of III and V.

Compound IV was identified by mixed melting point with a sample prepared from N-acetylethylenediamine and II, and by alkali hydrolysis to the known N-sulfanilyl-ethylenediamine. The triacyl compound, V, was hydrolyzed by treatment with cold aqueous alkali to the known N,N′-di-(N^4-acetylsulfanilyl)-ethylenediamine which did not depress the melting point of a sample of this compound prepared from ethylenediamine and II, and which yielded on strong hydrolysis N,N′-disulfanilyl-ethylenediamine.

(1) Aspinall, *J. Org. Chem.*, **6**, 895 (1941); Ladenburg, *Ber.*, **28**, 3068 (1895).

(2) Lur'e, Starobogatov and Nikitskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 545 (1941); Gerngross, *Ber.*, **46**, 1909 (1913).

(3) Gerngross, *ibid.*, **46**, 1913 (1913); Bamberger and Berle, *Ann.*, **273**, 360 (1893).