with that of the "abnormal" product. After two recrystallizations from ethanol, the melting point was 109–110°. The melting point was not depressed by admixture with the 1,3-diphenylisochromane obtained previously.

Anal. Calcd. for $C_{21}H_{18}O$: C, 88.08; H, 6.34. Found: C, 87.45; H, 6.12.

CHICAGO 16, ILL. RECEIVED NOVEMBER 11, 1950

[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Some β-(2-Pyridyl)- and β-(2-Piperidyl)-propionamides*

BY FREEMAN H. MCMILLAN AND JOHN A. KING

Series of the substances named in the title were prepared for pharmacological evaluation of their central stimulant action. 3-(2-Pyridyl)-propanol-1 was oxidized to 3-(2-pyridyl)-propionic acid which was converted to 17 amides. Eight of these were catalytically hydrogenated to the corresponding piperidyl amides.

Although the physiological actions of N,N-diethylnicotinamide, assigned the non-proprietary name nikethamide by the Council on Pharmacy and Chemistry of the American Medical Association,[1] were first reported in 1924[2,3] and this compound has subsequently enjoyed considerable use in medical practice as a respiratory stimulant and analeptic, there has been relatively little study of its homologs, analogs and isosteres. In the pyridine series amides of pyridine-2,3- and -3,4-dicarboxylic acid are claimed[4] as analeptics, as are the amides of N-substituted - 2,3 - dimethylpiperidine - 4,4 - dicarboxylic acid,[5] and N,N-diethylpyridine-3-acetamide.[6] Several furyl carboxylic and acetic acid amides[5,7,8] and amides of a pyranyl malonic acid[5] and pyrone carboxylic acids[9,10] are reported to have stimulant properties. Other amides so reported are those of several isoxazole[11–16] and benzisoxazole[17] carboxylic acids, of methyl-β-(1-morpholinyl)-ethylmalonic acid,[5] and of nuclear carboxylic acids of the pyrazole,[18] pyrazine[19] and thiazole[20] series. It is noteworthy that in practically all of the amides claimed to have analeptic properties the carboxyl group is attached directly to the heterocyclic nucleus; the few exceptions are a small number of substituted malondiamides, a few furan derivatives, a single pyridine derivative,[6] and, as the only mention of heterocyclic substituted alkanamides higher than acetamides as analeptics, a series of ω-(3,5-dimethylisoxazolyl)-alkanamides.[13] It seemed desirable to us to learn if this neglect of higher alkanamides was justified and, particularly, to learn if the 3-carboxylic and -acetic amides were unique in the pyridine series in their display of stimulant properties.

In connection with other work[21] which required the preparation of β-(2-piperidyl)-propionic acid dimethylamide and cyclic lactam (3-ketoöctahydropyrrocoline) it was desirable to have a ready source of the requisite corresponding acid or its pyridyl precursor. The most frequently mentioned synthesis of β-(2-pyridyl)-propionic acid consists[22] of the condensation of chloral with α-picoline, followed by hydrolysis, dehydration and reduction; this method was used by us at the start of our work and, while the over-all yield of 30 to 40% was considered satisfactory, the initial condensation reaction was somewhat troublesome. Other methods which have been described in the literature for the preparation of the acid are: condensation of α-picoline with mesoxalic ester, giving a 40% yield of ethyl β-(2-pyridyl)-acrylate which could be reduced to the propionate[23]; preparation of β-(2-pyridyl)-ethyl bromide, its metathesis with sodium cyanide, then hydrolysis to the acid[24]; and the addition of hydrogen cyanide to 2-vinylpyridine followed by hydrolysis, giving the acid in 30% over-all yield.[25]

Because objections were to be had to each of the above methods, a more convenient synthesis of β-(2-pyridyl)-propionic acid was sought and was found in the acid permanganate oxidation of the

* Presented before the Division of Medicinal Chemistry at the 119th meeting of the American Chemical Society, Cleveland, Ohio, April 9, 1951.

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(2) E. S. Faust, *Schweiz. med. Wochschr.*, **54**, 229 (1924); *Lancet*, **208**, 1336 (1925); *C. A.*, **19**, 3114 (1925).

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(5) H. Martin and H. Gysin (to J. R. Geigy A.-G.), U. S. Patent 2,447,194, Aug. 17, 1948.

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(25) W. E. Doering and R. A. N. Weil, *ibid.*, **69**, 2461 (1947).

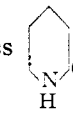
TABLE I

β-(2-PYRIDYL)-PROPIONAMIDES 

No.	R¹	R²	Preparative method[a]	Yield, %	M.p., °C.[b]	B.p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1[c]	-H	-H	A	68	128-129										
			B	64											
2	$-CH_3$	-H	A	60	63.5-65	132	0.4			65.90	7.37	17.06	65.81	7.64	16.85
3	$-C_2H_5$	-H	A	80	47.5-48.5	119-121	.15			67.39	7.92	15.72	66.91	7.75	15.85
4	$-C_3H_7$-*n*	-H	C	26		114-115	.1	1.5200	1.0482			14.57			14.61
5	$-C_3H_7$-*i*	-H	A	47	75-77					68.72	8.39	14.57	68.85	8.21	14.46
6[d]	$-C_4H_9$-*n*	-H	A	77		129-130	.15	1.5157		69.95	8.80	13.58	70.00	8.92	13.84
7[e]	$-C_6H_5$	-H	D	76	109.5-110					74.31	6.24	12.38	74.10	6.08	12.47
8	$-CH_2CH_2OH$	-H	D	52	102.5-104					61.83	7.26	14.42	61.50	7.26	14.68
9	$-CH_2CH_2NEt_2$	-H	E	68		150	.06	1.5154	1.0283			16.85			16.88
10[f]	$-CH_3$	$-CH_3$	A	75		115-117	.8	1.5304	1.0833						
11[g]	$-C_2H_5$	$-C_2H_5$	A	52		107	.1	1.5152	1.0386			13.58			13.54
12	$-C_3H_7$-*n*	$-C_3H_7$-*n*	A	56		122	.5	1.5073	1.0046			11.96			11.80
13	$-C_3H_7$-*i*	$-C_3H_7$-*i*	A	7		102-104	.15	1.5074	1.0101			11.96			11.67
14[h]	$-C_4H_9$-*n*	$-C_4H_9$-*n*	A	33		122	.1	1.5009				10.68			10.44
			C	17											
15	$-C_6H_5$	$-CH_3$	D	48	67-69	154	.3			74.97	6.71		74.82	6.41	
16	Piperidine		E	76		133-135	.4	1.5413	1.0907			12.85			12.69
17	Morpholine		E	76		126-130	.2	1.5444	1.1690	65.43	7.32	12.72	65.27	7.06	12.80

[a] See Experimental. [b] Melting points and boiling points are uncorrected. [c] Ref. 24; m.p. reported, 129–130°. [d] Hydrochloride, m.p. 103–104°. *Anal.* Calcd. for $C_{12}H_{18}N_2O\cdot HCl$: Cl, 15.09. Found: Cl, 14.89. [e] Hydrochloride, m.p. 203–204°. *Anal.* Calcd. for $C_{14}H_{14}N_2O\cdot HCl$: Cl, 13.50. Found: Cl, 13.57. [f] Ref. 21. [g] Methiodide, m.p. 107.5–108.5°. *Anal.* Calcd. for $C_{13}H_{21}IN_2O$: I, 36.45. Found: I, 36.54. [h] Dihydrochloride (prepared in anhydrous ether), m.p. 72.5–73°. *Anal.* Calcd. for $C_{16}H_{26}N_2O\cdot 2HCl$: Cl, 21.2. Found: Cl, 20.4.

TABLE II

β-(2-PIPERIDYL)-PROPIONAMIDES 

No.	R¹	R²	Yield, %	M.p., °C.[a]	B.p., °C.[a]	Mm.	$n^{25}D$	d^{25}_4	Analyses, % N Calcd.	Found
18	$-C_4H_9$-*n*	-H	51	40–44	140–144	0.05			13.19	13.23
19[b]	$-C_6H_5$	-H	60	85–86					12.06	12.16
20[c]	$-CH_3$	$-CH_3$	34		91–93	.2	1.4942	1.0128		
21[d]	$-C_2H_5$	$-C_2H_5$	60		104–106	.3	1.4877	0.9809	13.19	13.23
22	$-C_3H_7$-*n*	$-C_3H_7$-*n*	71		110	.2	1.4815	0.9546	11.66	11.41
23	$-C_4H_9$-*n*	$-C_4H_9$-*n*	66		116–118	.1	1.4791		10.44	10.48
24	$-C_6H_5$	$-CH_3$	71		131	.1	1.5393	1.0573	11.37	11.59
25	Piperidine		69		115	.15	1.5096	1.0368	12.49	12.76

[a] Melting points and boiling points are uncorrected. [b] Hydrochloride, m.p. 202.5°. *Anal.* Calcd. for $C_{14}H_{20}N_2O\cdot HCl$: Cl, 13.52. Found: Cl, 13.46. [c] Ref. 21. [d] Methiodide, m.p. 161.5–162.5°. *Anal.* Calcd. for $C_{13}H_{27}IN_2O$: I, 35.8. Found: I, 36.0.

commercially available 3-(2-pyridyl)-propanol-1. Although this gave us no better yield (35–50%) than other methods the ease of the one-step reaction rendered it the most desirable synthesis of the acid.

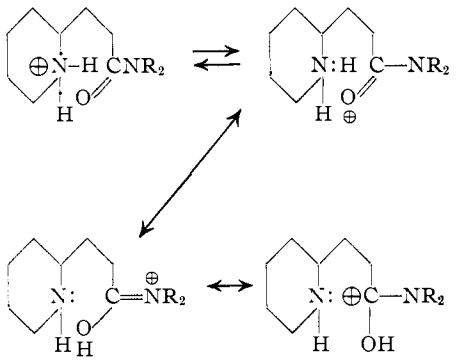
With a supply of the desired pyridyl acid thus assured, we proceeded with the preparation of series of N-substituted amides, all of which are new compounds. Although the three isomeric unsubstituted pyridyl propionamides are known (2-[24], 3-[26], 4-[24]), none of the N-substituted substances are reported in the literature, and in the piperidine series even the N-unsubstituted 2-, 3- or 4-propionamides are unreported. The two methods used by us for conversion of the pyridyl acid to its amides were: (1) aminolysis of an ester; and (2) thermal dehydration of a substituted ammonium salt. The reaction between methyl β-(2-pyridyl)-propionate and low-boiling amines (ammonia, methylamine and the like) was satisfactory but several days were required for the reaction to proceed to an acceptable extent; with higher-boiling amines (such as piperidine and morpholine) the aminolysis was carried out much more rapidly by heating the reactants under a distillation column and thereby removing the methanol formed in the reaction. The substituted ammonium salts of β-(2-pyridyl)-propionic acid were prepared by adding a slight excess of amine to the acid and these were heated to 200–220° to effect dehydration to the amide; in the case of low- or medium-boiling amines some loss of amine occurred, instead of loss of water, to leave considerable free acid. This amine loss was circumvented by slowly distilling the amine through the reaction mixture, thus ensuring ultimate conversion of all but a trace of the acid to the amide. This last procedure was found to be the most satisfactory for the synthesis of the pyridyl amides, and gave consistently good yields. The β-(2-pyridyl)-propionamides prepared are listed in Table I. An attempt was also made

(26) R. Graef, J. M. Fredericksen and A. Burger, *J. Org. Chem.*, 11, 257 (1946).

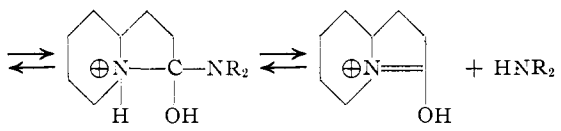
to prepare the diethanolamide but, as recently reported,[27] diethanolamine underwent bimolecular dehydration to yield only N,N′-bis-(β-hydroxyethyl)-piperazine.

Several of the pyridyl amides were catalytically hydrogenated to the corresponding piperidyl amides, listed in Table II. The reductions, carried out in acetic acid in the presence of Adams platinum oxide, generally proceeded readily at slightly above room temperature. Some difficulty was originally encountered in the isolation of the reduction products, particularly with the amides of lower-boiling amines, in that when the acetic acid was removed under vacuum on the steam-cone there was intramolecular loss of an amine molecule to give 3-ketoöctahydropyrrocoline; this could be avoided, however, by keeping the bath temperature below 50° during removal of the acetic acid and satisfactory yields of the desired β-(2-piperidyl)-propionamides were thereby obtained, although even this low temperature solvent removal would not prevent the intramolecular loss of ammonia from the unsubstituted amide.

This cyclization bears some formal analogy to acid-catalyzed ester-interchange and can be visualized as proceeding *via* a similar mechanism. Because there probably would be little tendency for proton addition to an already positively charged molecule, the initial stage in the cyclization may be hydrogen bonding of the protonated nitrogen with the polarized carbonyl to yield the resonance



hybrid of the protonated amide which can also be in equilibrium with the protonated amide-amine, the over-all effect being ring-chain tautom-



erism. The more ready lactamization above 50° can be ascribed to a lowering of the activation energy for this tautomerism at the higher temperatures. Removal of the amine from the equilibrium by volatilization (as the acetate or, after dissociation, as the free base) drives the reaction to the right. That the base-strength of the amine is not a decisive factor was indicated by the lactamization of the unsubstituted amide (weakly basic ammonia) and non-lactamization of the anilide (weakly basic aniline) and dimethylamide (strongly basic dimethylamine) all under the same conditions; steric factors probably are also not governing, since the relatively unhindered monobutyl amide did not lactamize under the same conditions.

The pharmacological evaluation of the compounds herein reported will be described elsewhere by other workers; it can be stated here that none of the substances exhibited pronounced central stimulant activity in experimental animals.

We wish to acknowledge the technical assistance of Messrs. Charles Anderson and Kenneth Hutton.

Experimental

β-(2-Pyridyl)-propionic Acid.—In a twelve-liter three-necked flask equipped with a stirrer and a thermometer and surrounded by a cooling bath there was placed 3-(2-pyridyl)-propanol-1 (411 g., 3.00 moles), water (5 liters) and sulfuric acid (196 g., 2.00 moles). Powdered potassium permanganate (632 g., 4.00 moles) was added over a period of two hours while the reaction temperature was maintained at 50° by means of an ice-bath. After the addition was complete the mixture was held at 50° until the purple color of the permanganate had disappeared and was then heated to 80° and filtered. The filtrate was evaporated to dryness under vacuum on the steam-cone and the residue thus obtained was boiled with ethanol (2 liters) and charcoal (25 g.), for a few minutes. Filtration of this mixture and chilling of the filtrate yielded crystalline (166 g., 37% yield) β-(2-pyridyl)-propionic acid, m.p. 136.5–139°; reported,[25] 141°. Evaporation of the mother liquor under vacuum left a liquid residue which on distillation gave 50 g. (14% yield) of ethyl β-(2-pyridyl)-propionate, b.p. 103–104° (0.7 mm.); reported,[28] 95° (1 mm.).

N-Ethyl β-(2-Pyridyl)-propionamide (Procedure A).—β-(2-Pyridyl)-propionic acid (30.2 g., 0.20 mole) was placed in a reaction flask which was then heated to 200–220° while ethylamine was slowly distilled from another flask through the melt in the first flask. The excess amine and entrained water of reaction were condensed and returned to the second flask for recirculation of the amine. After two hours heating was stopped and the mixture was allowed to cool, after which it was taken up in benzene (200 cc.) and the benzene solution was washed with 50 cc. of 25% potassium carbonate solution to remove any unreacted acid. The benzene solution was dried (anhydrous potassium carbonate), the solvent was removed under vacuum and the residue was distilled to give 28.5 g. (80% yield) of material boiling at 119–121° (0.15 mm.). This later crystallized and melted at 47.5–48.5°.

In the case of those amines which were obtained in pressure cylinders the apparatus was modified by the omission of the second flask and the condenser. The gaseous amine was bubbled into the reaction mixture and the unreacted amine and entrained water escaped at the top of the column.

β-(2-Pyridyl)-propionamide (Procedure B).—Methyl β-(2-pyridyl)-propionate[24] (25 g., 0.15 mole) and concentrated aqueous ammonia (125 cc.) were well mixed and stored in a stoppered flask in the refrigerator for five days. Filtration of the crystals which formed followed by two successive concentrations of the filtrate gave a total of 14.6 g. (64% yield) of crystalline amide which, after recrystallization from isopropyl alcohol, melted at 127–129°.

N-(*n*-Propyl) β-(2-Pyridyl)-propionamide (Procedure C).—A mixture of methyl β-(2-pyridyl)-propionate (33.0 g., 0.20 mole) and *n*-propylamine (59.0 g., 1.00 mole) was refluxed for 15 hours. The excess amine was evaporated under vacuum and the residue, after two distillations, gave 10.0 g. (26% yield) of material boiling at 114–115° (0.1 mm.).

β-(2-Pyridyl)-propionanilide (Procedure D).—A mixture of β-(2-pyridyl)-propionic acid (30.2 g., 0.20 mole) and aniline (27.9 g., 0.30 mole) was heated at 200° under an air condenser for two hours. The hot mixture was poured into one liter of water and just enough alcohol was added to effect complete solution at the boiling point. The mixture was then boiled for a few minutes with charcoal (10 g.). After filtration an oil separated and rapidly crystallized.

(27) W. H. Rauscher, I. S. Goldstein and M. Breslau, THIS JOURNAL, **71**, 358 (1949).

(28) G. R. Clemo, W. McG. Morgan and R. Raper, *J. Chem. Soc.*, 1743 (1935).

One recrystallization from aqueous alcohol gave 34 g. (76% yield) of material, m.p. 109.5–110°.

N-(β-Diethylaminoethyl) β-(2-Pyridyl)-propionamide (Procedure E).—In a flask fitted with a twelve-inch helix-packed column there was placed methyl β-(2-pyridyl)-propionate (33.0 g., 0.20 mole) and β-diethylaminoethylamine (23.2 g., 0.20 mole). The mixture was heated so that only methanol would distil from the top of the column. During a five-hour period the temperature of the mixture slowly rose to 205°, at which time the reaction mixture was cooled and taken up in benzene (200 cc.). The benzene solution was washed with 50 cc. of 25% potassium carbonate solution and then dried over anhydrous potassium carbonate. The benzene was removed under vacuum and the residue was distilled through a 10-inch column with wire-screen packing and heated jacket to give 34 g. (68% yield) of product boiling at 150° (0.06 mm.).

N,N-Diethyl β-(2-Pyridyl)-propionamide Methiodide.—A mixture of N,N-diethyl β-(2-pyridyl)-propionamide (15.0 g., 0.073 mole) and methyl iodide (5.0 cc., 11.4 g., 0.08 mole) in benzene (100 cc.) was refluxed for one hour. An oil separated and soon crystallized. After two recrystallizations from acetone (300 cc.) the material melted at 107.5–108.5° and weighed 7.0 g. (28% yield).

N,N-Diethyl β-(2-Piperidyl)-propionamide.—A solution of N,N-diethyl β-(2-pyridyl)-propionamide (25 g., 0.12 mole) in glacial acetic acid (120 cc.) was reduced with hydrogen on a Parr shaker in the presence of 1.0 g. of Adams platinum oxide catalyst. The theoretical amount of hydrogen was taken up in about 2.5 hours. After removal of the catalyst the acetic acid was evaporated under vacuum with a bath temperature of *not over 50°*. The residue was taken up in benzene (500 cc.) and the benzene solution was washed with 240 cc. of 25% potassium carbonate solution. The carbonate wash was cross-extracted with 200 cc. of benzene and the combined benzene solutions were dried over anhydrous potassium carbonate. The benzene was removed under vacuum and the residue was distilled to give 15.5 g. (60% yield) of colorless material boiling at 104–106° (0.3 mm.).

NEW YORK 11, N. Y. RECEIVED JANUARY 15, 1951

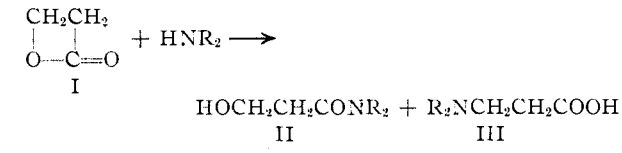
[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

β-Propiolactone. XI. Reactions with Ammonia and Amines

BY T. L. GRESHAM, J. E. JANSEN, F. W. SHAVER, R. A. BANKERT AND F. T. FIEDOREK

β-Propiolactone reacts with ammonia and primary and secondary amines to form the corresponding hydracrylamides and β-alanines and under certain conditions will give predominantly one or the other. Tertiary amines react with β-propiolactone to form the β-propiobetaine compounds.

β-Propiolactone[1] (I) reacts with ammonia and most primary and secondary amines to give both the amides (II) and the amino acids (III) and in some cases under favorable conditions will give predominantly one or the other. It would seem that the reactions between I and amines involve two different and competing reactions which open the



I

$$HOCH_2CH_2CONR_2 + R_2NCH_2CH_2COOH$$

II III

R = H, alkyl, aryl or heterocyclic radical

oxetane ring on different sides of the oxygen. The two competing reactions have been found to vary with the amine, the solvent and the order of addition.

No direct correlation was found between the formation of amino acids from the primary and secondary amines and the basic strength of the amines.[2] Dimethylamine added to an ethereal solution of I gives mostly amino acid, but diethylamine under the same conditions gives largely the amide. In acetonitrile solution ammonia, dimethyl-, ethyl- and dodecylamines give chiefly the amino acids; methyl-, diethyl- and propylamines under similar conditions give the amides with little or no isolable amino acids. In general the aromatic and cyclohexylamines give amino acids more consistently than the alkylamines but the reaction is slower and with some amines takes place only when heated. Alkylamines which have a high hydration constant[3,4] give mostly the amide even in acetonitrile and those having low hydration constants give amino acids.

The choice of solvent is important in determining where the lactone ring opens. With water as the solvent ammonia and I give mostly hydracrylamide and in acetonitrile the same reactants give excellent yields of β-alanine. With few exceptions water was the best solvent for amide formation and acetonitrile the best for amino acid.

In some cases the order of addition determines whether the product will be largely the amide or amino acid. When dimethylamine is added to I in ether the major product is the amino acid; however, if I is added to an ethereal solution of dimethylamine the major product is the amide. Simultaneous addition of I and dimethylamine to ether gives essentially an equal mixture (44 and 47%) of amide and amino acid, the net result indicating in this case that the rates of formation of the amide and amino acid are nearly the same.

There is evidence that the reactions of I with the different amines are nearly quantitative, but it is difficult to separate quantitatively the amide from the amino acid. This is in contrast to some of the other reactions of I where it was found[5] that the main reaction was accompanied by polyester formation. When an amino acid, obtained from an aliphatic amine, is the major component, it is usually a solid material and can be filtered from the soluble amide. If an amide is the major component it can be separated from the amino acid by distillation but even here some of the amino acid sublimes or distills over with the amide. The amino acids from the aromatic amines can be separated from the concomitant amides by basic extraction and al-

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(2) Choh-Hao Li and T. D. Stewart, *ibid.*, **59**, 2596 (1937).
(3) Moore and Winmill, *J. Chem. Soc.*, **91**, 1373, 1379 (1907).
(4) Moore and Winmill, *ibid.*, **101**, 1635 (1912).
(5) Gresham, Jansen, Shaver, Gregory and Beears, THIS JOURNAL, **70**, 1004 (1948).