[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Amides of Nicotinic Acid and Related Acids. II

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In the first[4] of a series of articles on the preparation of compounds possessing antispasmodic and anticonvulsant activity, it was found that certain amides showed promise as antispasmodics and anticonvulsants. Further investigation of amides of various acids disclosed the fact that the benzyl amide of nicotinic acid possessed rather pronounced antispasmodic activity. However, the activities of other amides of nicotinic acid differ markedly. For example, nicotinamide[5] is relatively inert in regard to spasmodic or convulsant action while diethyl nicotinamide (Nikethamide)[6] possesses convulsant activity. It seemed, therefore, to be of interest to prepare other amides of nicotinic acid and related acids such as α-picolinic, γ-picolinic, quinoline-3-carboxylic, pyrazine monocarboxylic and pyrazine 2,3-dicarboxylic acids in order to compare their pharmacological activity. The amides were prepared by interaction of the appropriate amine either with the heterocyclic ester or the free acid.

It was thought that the activity of the benzyl amide might be due to the basicity and/or the solubility of the amine used in making the amide. Therefore, amines were selected which resemble benzylamine in structure or solubility. An amine which should have about the same solubility as benzylamine is *n*-amylamine, since a *n*-butyl group is considered approximately equivalent to a phenyl group in estimating solubility. An amine which should possess about the same basicity as benzylamine is allylamine, for in both compounds the amino group is attached to a carbon atom adjacent to a vinyl grouping. Accordingly, these amines were used. In addition to these, γ-di-*n*-butylaminopropylamine was used in the hope that even greater activity could be obtained since a number of amides synthesized from amines of this type approach that of atropine in pharmacological activity.[7] The amides prepared are listed in Table I.

TABLE I

Amides	M. p., °C.	B. p. °C.	Mm.	Yield	% Nitrogen Calcd.	Found
Benzyl nicotinamide	72–73			93.0	13.20	13.08
n-Amyl nicotinamide		170–171	1	49.4	14.58	14.67
Allyl nicotinamide[a]		158–161	1	50.0	17.29	17.20
Dibutylaminopropyl nicotinamide		226–230	2	60.1	14.42	14.12
				98.0[b]		
Benzyl γ-picolinamide	84.5–85.0			54.0[c]	13.20	12.95
n-Amyl γ-picolinamide		178–182	2	70.5	14.58	14.70
Allyl γ-picolinamide		158–159	2	51.8	17.29	17.22
Dibutylaminopropyl γ-picolinamide		236–240	2	78.2	14.42	14.13
				51.7[b]		
Benzyl α-picolinamide	87.0–87.5			73.3[c]	13.20	13.00
n-Amyl α-picolinamide		135–138	2	83.3	14.58	14.65
Allyl α-picolinamide		166–170	1	94.4	17.29	17.16
Dibutylaminopropyl α-picolinamide		209–212	1	92.1	14.42	14.22
Benzyl pyrazine monocarboxamide	116.0			31.0	19.72	19.64
N,N′-Dibenzyl pyrazine-2,3-dicarboxamide	171–171.5			78.2	16.18	16.29
N,N′-Diamyl pyrazine-2,3-dicarboxamide	145.5–146.0			20.0	18.30	18.14
Benzyl quinoline-3-carboxamide	139–139.5			47.8	10.77	10.91

[a] Pictet and Sussdorff, *Arch. Sci. phys. nat. Genève.*, [4] **5**, 122; *Chem. Zentr.*, **69**, 677 (1898). [b] Prepared according to Method "A." [c] Prepared according to Method "B."

Experimental

Two procedures were used in the preparation of the amides:

Method "A."—A xylene solution of the amine and acid was refluxed and the water evolved during the reaction collected in a calibrated water trap. Since the water could be measured, it was found possible to gage the speed and extent of completion of the reaction.

Obviously method "A" could not be used conveniently in the preparation of the amyl and allyl amides because of the low boiling points of the amines. It is interesting to note, however, that even when the *n*-amylamine salt of nicotinic acid was isolated and heated in refluxing xylene, dehydration could not be effected. Heating the salt to 180° in a vacuum of 2 mm. caused decomposition to the acid and amine.

Method "B."—The various amines were treated with the ethyl esters of nicotinic, α-picolinic, γ-picolinic and quinoline-3-carboxylic acids to yield the corresponding amides.

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(4) Billman and Hidy, THIS JOURNAL, **65**, 760 (1943).

(5) Supniewski, Hano and Taschner, *Bull. inter. acad. polon. sci., Classe med.*, 85–97 (1936); *Ber. ges. Physiol. expil. Pharmakol.*, **99**, 674 (1937); *C. A.*, **32**, 9280[3] (1938).

(6) Myers, *J. Hyg.*, **40**, 474 (1940).

(7) U. S. Patent 2,009,144, July 23, 1935.

α- and γ-Picolinic Acid Hydrochlorides.—Oxidation of the corresponding picolines yielded the acids which were then isolated as the hydrochlorides.[8]

Ethyl Esters.—The ethyl esters of nicotinic, α-picolinic and γ-picolinic acids were prepared in yields ranging from 78–85% according to a procedure described by LaForge[9] for the preparation of ethyl nicotinate.

Ethyl quinoline-3-carboxylate was prepared by a series of reactions consisting of the bromination of quinoline hydrobromide,[10] formation of the nitrile with cuprous cyanide,[11] subsequent hydrolysis with 70% sulfuric acid[10] and esterification according to the method used by LaForge.[9] A 55% yield of the ethyl ester based on 3-bromoquinoline was obtained.

Pyrazine-2,3-dicarboxylic Acid.—The acid was prepared by the oxidation of quinoxaline according to directions given by Gabriel and Sonn.[12]

Quinoxaline.—In the preparation of quinoxaline, it was found necessary to use a dilute solution of *o*-phenylenediamine and glyoxal bisulfite; otherwise, polymeric substances formed and little if any of the product was obtained. Since the method[12] for the preparation of quinoxaline is vague, we are including the procedure we used.

In a one-liter erlenmeyer flask containing 400 ml. of water at 70°, was placed 27.0 g. (0.25 mole) of *o*-phenylenediamine. A solution of 68.8 g. (0.26 mole) of glyoxal bisulfite in 300 ml. of water heated to 70° was then added with shaking. The shaking was continued for five minutes after completion of the mixing. The solution was allowed to cool to approximately 40° and 100 g. of potassium carbonate added. The quinoxaline separated and was extracted with 100 ml. and three 50-ml. portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate and distilled. Yields from 29.6 to 30.5 g. of product (90.8–93.5% of theoretical) boiling at 112–115° (17 mm.) were obtained.

Benzyl Nicotinamide.—In a 200-ml. erlenmeyer flask, connected by ground glass joints to a calibrated water trap, in turn attached to a reflux condenser, were placed 12.3 g. (0.10 mole) of nicotinic acid and 10.7 g. (0.10 mole) of benzylamine. The mixture was heated gently until it became homogeneous. Seventy-five ml. of anhydrous xylene was added and the mixture refluxed for one hundred and fifty hours in an oil-bath kept at 165–170°. At the end of this time, 1.95 ml. of water was found in the trap (1.80 ml.—theoretical amount). On cooling, the product formed pure white crystals. A yield of 19.7 g. (93.0% of theoretical) of product, m. p. 72–73°, was obtained.

***n*-Amyl-α-picolinamide.**—In a 250-ml. round-bottomed flask fitted with a reflux condenser were placed 15.1 g. (0.10 mole) of ethyl α-picolinate and 17.4 g. (0.20 mole) of *n*-amylamine. The mixture was heated in an oil-bath maintained at 125° for twenty-five hours. Distillation *in vacuo* yielded 1.8 g. (11.9% recovery) of ethyl α-picolinate, 16.0 g. (83.3%) of product boiling at 135–136° (2 mm.) and 1.0 g. of residue.

(8) Weidel, *Ber.*, **12**, 1992 (1879); *Org. Syn.*, **20**, 79 (1940).
(9) LaForge, THIS JOURNAL, **50**, 2479 (1928).
(10) Claus and Collischonn, *Ber.*, **19**, 2763 (1886).
(11) Gilman and Spatz, THIS JOURNAL, **63**, 1553 (1941).
(12) Gabriel and Sonn, *Ber.*, **40**, 4850–4860 (1907).

Summary

1. Benzyl nicotinamide has been prepared and found to possess antispasmodic activity.

2. A series of fifteen other amides of nicotinic acid and related acids has been prepared and submitted for pharmacological testing.

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[CONTRIBUTION FROM THE FERMENTATION DIVISION, NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Optical Isomers of 2,3-Butanediol Produced by Fermentation

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In connection with fermentation studies conducted at this Laboratory on the production of 2,3-butanediol, some of the properties of the isolated products have been determined. *levo*-2,3-Butanediol, previously unknown in pure form and not recognized heretofore as a fermentation product, has been identified as the chief substance formed by the action of *Bacillus polymyxa* on grain mash substrates.

Previous reports concerning fermentation butanediol have stated it to be essentially optically inactive, the slight *dextro* rotation sometimes observed being attributed to the presence of a relatively small quantity of the *dextro* isomer. The butanediol produced by Harden and Walpole,[2] the first investigators in the field, was examined by Walpole[3] and was reported to be essentially a mixture of two optically inactive glycols. This product had resulted from the action of *Bacterium lactis aerogenes* (*Aerobacter aerogenes*) on glucose. The butanediol prepared by Kluyver's process,[4] presumably using *Aerobacter aerogenes*, was investigated by Böeseken and Cohen[5] and found to have a specific rotation of +2.42° and a melting point of +25°. Attempts at resolution were unsuccessful. These data suggested that the principal constituent was *meso*-2,3-butanediol and that a small quantity of the *dextro*-rotatory isomer was also present.

During the past three years we have conducted numerous fermentations with *Aerobacter aerogenes*. The 2,3-butanediol isolated *en masse* from such liquors has consistently had a specific rotation of approximately +1.0° and has shown a tendency to crystallize at room temperatures. These observations are in essential agreement with the data presented by Böeseken and Cohen. The discrepancy in specific rotation is not especially significant, since we have observed that appreciable fractionation occurs during distillation of the glycol. Unless a quantity of glycol is distilled *in toto*, the rotation exhibited by any

(1) The Northern Regional Research Laboratory is one of four regional laboratories operated by the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.
(2) Harden and Walpole, *Proc. Roy. Soc.* (London), Series B, **77**, 399 (1906).
(3) Walpole, *ibid.*, Series B, **83**, 272 (1911).
(4) Kluyver and Scheffer, U. S. Patent 1,899,156.
(5) Böeseken and Cohen, *Rec. trav. chim.*, **47**, 839 (1928).