[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# Pyridine Derivatives Related to 4-Amino-N-(2-diethylaminoethyl)-benzamide (Pronestyl[1])[2]

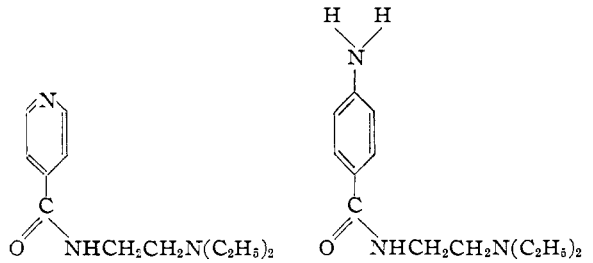
BY HARRY L. YALE AND JACK BERNSTEIN

RECEIVED JUNE 14, 1956

A number of dialkylaminoalkylamides of pyridinecarboxylic acids are described. All of the compounds were screened for possible utilization in the treatment of cardiac arrhythmias.

In 1935, procaine (2-diethylaminoethyl 4-aminobenzoate) was introduced for the treatment of acute cardiac arrhythmias such as those which may occur during anesthesia. Subsequently, it was found that 4-amino-N-(2-diethylaminoethyl)-benzamide (Pronestyl[1]) was a more useful drug for this purpose.[3]

Our interest in pyridine compounds led us to the synthesis of a series of dialkylaminoalkylamides of various pyridinecarboxylic acids related to Pronestyl. The first compound prepared in this series was N-(2-diethylaminoethyl)-isonicotinamide (I), since it possesses structural similarity to Pronestyl (II).




I II

N-(2-Diethylaminoethyl)-isonicotinamide was prepared by the reaction (a) of methyl isonicotinate and 2-diethylaminoethylamine or (b) of isonicotinyl chloride and 2-diethylaminoethylamine in dry benzene. The distilled bases obtained by either method gave identical crystalline monohydrochlorides, m.p. 110–111°, and identical crystalline dihydrochlorides, m.p. 194–196°. These constants were at variance with those reported in the literature, where a "hydrochloride" of N-(2-diethylaminoethyl)-isonicotinamide, prepared from isonicotinyl chloride and 2-diethylaminoethylamine in benzene, has been described as a "brown sludge"[4] or as a solid, m.p. 247°.[5] In addition, we found that N-(3-diethylaminopropyl)-isonicotinamide (III) formed a dihydrochloride, m.p. 152°; a "hydrochloride" of III had previously been described as a "brown sludge."[4,6]

From the reaction between methyl isonicotinate and N,N-diethyl-N′-methylethylenediamine (IV) only isonicotinic acid was obtained; the desired compound was prepared by the reaction of isonicotinyl chloride and IV in dry benzene.

**Pharmacological Evaluation.**—The pharmacological evaluation of these compounds in experimentally induced arrhythmia in dogs has been reported elsewhere.[7,8] The most active and least toxic compound in this series was found to be N-(2-diethylaminoethyl)-isonicotinamide.

**Acknowledgment.**—The authors are indebted to Mr. W. A. Lott for his advice and encouragement during this investigation. The microanalyses were carried out by Mr. J. F. Alicino and his associates.

## Experimental Part[9]

**N-(2-Diethylaminoethyl)-isonicotinamide (Method A).**—A mixture of 1188 g. (8.7 moles) of methyl isonicotinate and 2042 g. (17.6 moles) of 2-diethylaminoethylamine, in a distillation apparatus equipped with a short fractionating column, was so heated as to allow the methanol to distil from the mixture as it was formed; the still-head temperature was kept at 60–90°. During 5 hours a total of 490 ml. of distillate was collected. The reaction mixture was then concentrated *in vacuo* to remove excess 2-diethylaminoethylamine (maximum still-head temperature 95° (35 mm.)). The residue weighed 1924 g. Distillation gave 1857 g. (96% yield) of product, b.p. 173.0–173.5° (0.2 mm.), $n^{24}D$ 1.5273.

**N-(2-Diethylaminoethyl)-isonicotinamide (Method B).**—To 12 g. (0.075 mole) of sublimed isonicotinyl chloride hydrochloride suspended in 40 ml. of dry benzene was added, with ice-cooling and stirring, 9.6 g. (0.08 mole) of 2-diethylaminoethylamine in 40 ml. of dry benzene. A gummy mass separated. The mixture was stirred and refluxed for 2 hours, cooled and treated with an excess of aqueous sodium hydroxide. The benzene layer was separated, the aqueous layer was extracted with ether, the benzene and ether extracts were dried, concentrated and distilled to give 8.8 g. (53% yield) of product, b.p. 158–160° (0.1 mm.).

**N-(2-Diethylaminoethyl)-isonicotinamide Monohydrochloride.**—To a solution of 22 g. (0.1 mole) of distilled base (method A) in 100 ml. of methyl ethyl ketone was added, dropwise with stirring, 22 ml. of a 4.5 *N* ethereal HCl solution. The mixture was heated to remove the ether, 100 ml. of methyl ethyl ketone was added and the mixture refluxed until a clear solution had formed. The refluxing solution was treated with Darco, filtered and the filtrate allowed to cool. The product (20 g., 78% yield) separated as colorless crystals, m.p. 110–111°. The product was analytically pure.

**N-(2-Diethylaminoethyl)-isonicotinamide Dihydrochloride.**—To 11 g. (0.05 mole) of distilled base (method A) in 50 ml. of dry ether was added 25 ml. of a 4.5 *N* ethereal HCl

(1) Registered Trade Mark.

(2) Presented before the Division of Medicinal Chemistry at the 126th Meeting of the American Chemical Society, held in New York City, September 12–17, 1954.

(3) For a comprehensive survey of the literature on anti-arrhythmia drugs see J. T. DiPalma and J. E. Schults, *Medicine*, **29**, 123 (1950). See also, "Pronestyl Hydrochloride," E. R. Squibb & Sons, New York, N. Y., 1952, 4th Ed., for a survey of literature on the use of Pronestyl Hydrochloride.

(4) W. H. Linnell and A. F. Vyas, *Quart. J. Pharm. Pharmacol.*, **20**, 119 (1947).

(5) J. Bucki, P. Labhart and L. Ragaz, *Helv. Chim. Acta*, **30**, 507 (1947).

(6) We are of the opinion that the earlier workers in this field used an isonicotinic acid of questionable purity and consequently did not have pure products. With the very recent utilization of isonicotinic acid and methyl isonicotinate by the pharmaceutical industry these compounds became available to us, perhaps for the first time, in a high state of purity. For example, methyl isonicotinate, reported by L. Ternajgo, *Monatsh.*, **21**, 446 (1900), to melt at 8.5°, was found in our laboratory to melt at 16.5–17.0°.

(7) V. Lanzoni and B. B. Clark, *Circulation Research*, **3**, 335 (1955).

(8) B. B. Clark and B. Etstein, *New England J. Med.*, **253**, 217 (1955).

(9) All temperatures are uncorrected.

TABLE I

DIALKYLAMINOALKYLAMIDES OF PYRIDINECARBOXYLIC ACIDS

| Formula[f] RC(=O)– | Method | Yield, % | B.p., °C. | Mm. | Base Analyses, % Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| $NHCH_2CH_2N(CH_3)_2$ | A | 81 | 150–155 | 0.3[a] | ... | .. | 21.74 | ... | .. | 21.12 |
| $NHCH_2CH_2N(C_2H_5)_2$ | A,B | 77 | 173.0–173.5 | .2 | 65.12 | 8.65 | 18.99 | 64.97 | 8.45 | 18.84 |
| $NHCH_2CH_2CH_2N(C_2H_5)_2$ | A | 87 | 171–175 | .2 | 66.34 | 9.00 | 17.86 | 66.37 | 8.80 | 17.40 |
| $N(CH_3)CH_2CH_2N(C_2H_5)_2$ | B | 34 | 174–176 | .2 | 66.34 | 9.00 | 17.86 | 65.65 | 8.36 | 18.03 |
| $NHCH_2CH_2N(C_2H_5)_2$[g] | A | 85 | 198–200 | .3 | 70.82 | 7.80 | 15.49 | 69.19 | 7.07 | 14.83 |

| Hydrochloride Yield, % | M.p., °C. | Analyses, % Calcd. N | Calcd. Cl | Found N | Found Cl |
|---|---|---|---|---|---|
| 48 | 235–239[b] | 15.79 | 26.64 | 15.56 | 26.46 |
| 78 | 110–111[c] | 16.30 | 13.75 | 16.26 | 13.72 |
| 74 | 194–196[b] | 14.28 | 24.10 | 14.40 | 23.79 |
| 62 | 149–152[b] | 13.63 | 23.00 | 13.48 | 22.86 |
| 50 | 118–120[b] | 13.63 | ...[d] | 13.50 | ... |
| 66 | 221–223[b,e] | 12.20 | 20.59 | 11.90 | 20.15 |

[a] M.p. 104.5–106.0° (from $C_6H_6$). [b] Dihydrochloride. [c] Monohydrochloride. [d] Calcd.: C, 50.65; H, 7.52. Found: C, 50.75; H, 7.72. [e] German Patent 540,697 described the monohydrochloride. [f] R = 4-pyridyl. [g] R = 4-quinolyl.

solution. The colorless solid which separated was filtered and recrystallized from absolute ethanol–ether to give 10.8 g. (74% yield) of product, m.p. 194–196°.

The distilled base obtained by method B was converted in similar fashion to a **monohydrochloride**, m.p. 110–111°, alone or mixed with the **monohydrochloride** described above, or to a **dihydrochloride**, m.p. 194–196°, alone or mixed with the dihydrochloride described above.

All of the compounds, their physical properties, and analyses will be found in Table I.

NEW BRUNSWICK, N. J.

---

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE AND TIERNAN, INC.]

# Some α-Amino Acids Containing a Sulfonamide Group

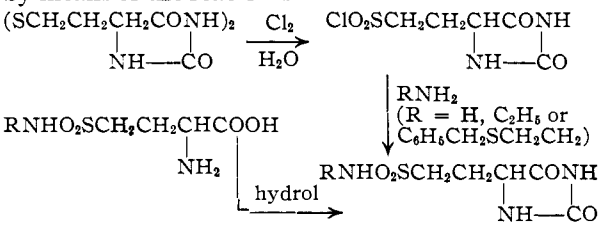
BY DAVID B. REISNER

RECEIVED APRIL 6, 1956

Structural analogs of glutamic acid containing a sulfonamide radical in place of the γ-carboxyl group have been synthesized and assayed as bacterial and viral growth-inhibitors.

Since the discovery by Woods[1] that sulfanilamide is an antagonist of PABA, a large number of synthetic antimetabolites has been reported in the literature. It was surprising to us that the substitution of a carboxyl group in α-amino acids by a sulfonamide radical has received little or no attention. McIlwain[2] prepared a series of α-aminosulfonic acids and included the amide of taurine but did not prepare any α-amino sulfonamides or α-amino acids possessing a sulfonamide group. As part of our researches on potential antimetabolites[3] we have prepared some *d,l*-γ-sulfamyl-α-amino acids. Since glutamic acid contains a γ-carboxyl group, our synthetic amino acids are structurally related to glutamic acid in somewhat the same manner that the sulfonamide drugs are related to PABA.

Syntheses of the amino acids were accomplished by means of the reactions




Conversion of homocystine hydantoin[4] to 5-(β-chlorosulfonyl)-ethylhydantoin was effected by chlorinating a suspension of the disulfide in water. Treatment of the sulfonyl chloride, suspended in ether, with ammonia or appropriate amine gave the desired sulfonamido-hydantoin. Subsequent hydrolysis of the hydantoin with aqueous barium hydroxide at approximately 160° afforded the corresponding amino acid (Table I). The synthesis of 3-(*p*-aminobenzamido)-3-carboxypropanesulfonamide (V) was undertaken because of its resemblance to the α-(*p*-aminobenzamido)-glutaric acid fragment of folic acid. It was prepared by acylating I with *p*-nitrobenzoyl chloride and reducing the resulting nitrobenzamide IV with hydrogen in the presence of 5% palladium–carbon catalyst.[5]

3-Amino-3-carboxypropanesulfonamide (I) suppressed multiplication of $T_2$ coliphage and inhibited growth of $T_2$ *E. coli* at 1 p.p.m. Its activity was reversed on addition of glutamic acid or glutamine. In view of its high order of *in vitro* antibacterial activity, compound I was tested in mice which had been infected with *E. coli* according to the procedure described by Scudi, *et al.*[6] Oral doses of 10 mg. of I given daily were ineffective in protecting the animals against infection.

(1) D. D. Woods, *Brit. J. Exptl. Path.*, **21**, 74 (1940).
(2) H. McIlwain, *J. Chem. Soc.*, 75 (1941).
(3) D. B. Reisner, THIS JOURNAL, **78**, 2132 (1956).
(4) J. V. Karabinos and J. L. Szabo, *ibid.*, **66**, 649 (1944).
(5) R. Mozingo, *Org. Syntheses*, **26**, 77 (1946).
(6) J. V. Scudi, S. J. Childress and O. J. Plekss, *Proc. Soc. Exptl. Biol. Med.*, **89**, 571 (1955).