hot by suction and washed with warm water. The air-dried product was immediately recrystallized from hot ethanol and yielded 51 Gm. (92%), m.p. 101.5–102.5°.

Anal.—Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.10; H, 6.40; N, 5.81.

1 - (2 - Hydroxyethyl) - 2 - phenyl - 3 - pyrrolidinomethylindolizine—Six milliliters of 37% aqueous formaldehyde (0.075 mole) and 5.34 Gm. of pyrrolidine (0.075 mole) were combined with 30 ml. of dioxane and allowed to stand for 15 min. at room temperature. 1-(2-Hydroxyethyl)-2-phenylindolizine, 3.57 Gm. (0.015 mole), was dissolved in the mixture which was then allowed to stand at room temperature for 24 hr. The reaction mixture was transferred to an evaporating dish and the solvent was removed by blowing cold air over the surface. Scratching with a glass rod during evaporation failed to induce crystallization and a viscous oil was obtained. The oil was transferred to a 50-ml. conical flask with the aid of about 3 ml. of ethanol and placed in the freezer compartment of the refrigerator. The product crystallized after 1 week in the refrigerator. The crystals were removed by filtration, washed with 50% ethanol, and recrystallized from hot DMF–water. The yield was 2.9 Gm. (62%), m.p. 122–124°.

Anal.—Calcd. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.65; H, 7.54; N, 8.72.

REFERENCES

(1) Harrell, W. B., and Doerge, R. F., *J. Pharm. Sci.*, **56**, 225(1967).
(2) Mannich, C., and Krosche, W., *Arch. Pharm.*, **250**, 647 (1912).
(3) Collonna, M., Bruni, P., and Monti, A., *Gazz. Chem. Ital.*, **94**, 509(1964).
(4) Chichibabin, A. E., *Chem. Ber.*, **60**, 1607(1927).
(5) Barrett, P. A., *J. Chem. Soc.*, **1958**, 325.

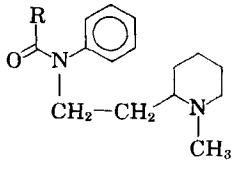
New Compounds: Amides Derived from 2-(2-Pyridyl)ethylamines

By JOSEPH SAM*

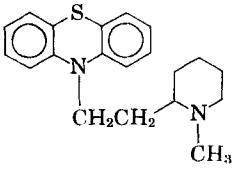
Basic amides containing the pyridylethyl- and piperidylethylamino groups have been prepared either from 2-vinylpyridines, 2-(2-aminoethyl)pyridines, or from substituted 2-(2-aminoethyl)piperidines. The amides possess some of the structural characteristics of the phenothiazine tranquilizers.

Amides, in general, exhibit a depressant effect on the central nervous system. Phenacetin, an analgesic amide, and barbital, an hypnotic amide derivative, were forerunners of many other biologically active amides (1).

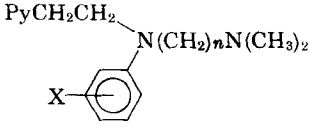
Based on (*a*) the general CNS depressant properties of amides, (*b*) the presence of the 1,3-propylenediamine entity in many biologically active compounds, and (*c*) the similarity of the reactions of the NH of the phenothiazine ring to the NH of amides, it was of interest to prepare some amides (I) possessing structural characteristics of the phenothiazine tranquilizers (II).



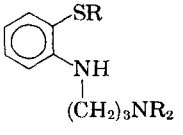
I



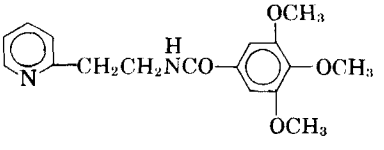
II



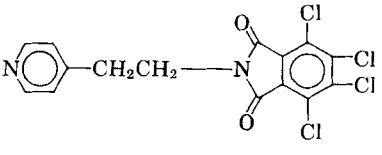
III



IV



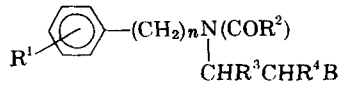
V



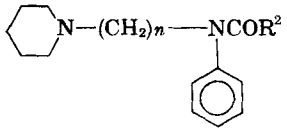
VI

Shapiro and associates (2) prepared some similar compounds (III) which were related to the antihistamine, tripelennamine [*N*-benzyl-*N'*,*N'*-dimethyl-*N*-(2-pyridyl)ethylenediamine] and to the phenothiazine tranquilizers. Nieforth (3) prepared

Received April 11, 1967, from Bristol Laboratories, Syracuse, NY 13201
Accepted for publication June 9, 1967.
* Present address: Department of Pharmaceutical Chemistry, University of Mississippi, University, MS 38677



VII



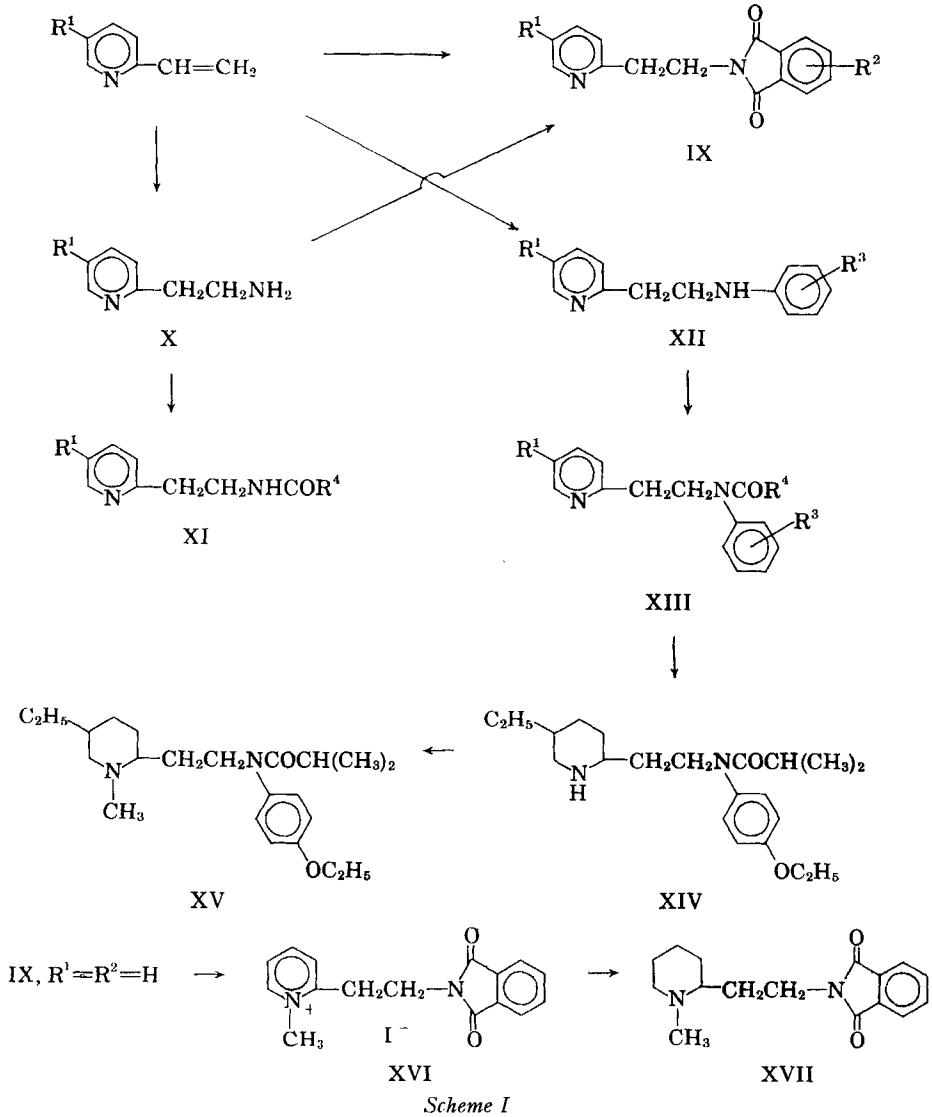
VIII

some 2-aminobenzenethiol derivatives (IV) related to the phenothiazine tranquilizers and to reserpine. Perron and Sam (4) noted tranquilizing properties in the 3,4,5-trimethoxybenzamide (V) of 2-(2-pyridyl)ethylamine; Lewis (5) observed analgesic properties with the phthalimide (IX) $R^1 = R^2 = H$; and VI was prepared as an intermediate to bis-quaternary hypotensive agents (6). Compounds possessing structure I are closely related to potent analgesic amides (VII and VIII, respectively) described by Fancher and associates (7) and Carabateas and co-workers (8).

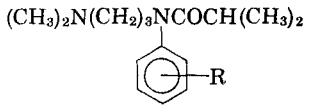
The procedures described by Reich and Levine (9) and Shapiro and associates (2) were employed for the preparation of the phthalimides (IX) and pyridylethylanilines (XII). The preparation of the *N*-methylpiperidine derivative (XV) was accomplished *via* hydrogenation of XIII followed by methylation, whereas XVII was obtained from IX *via* the methiodide (XVI) followed by reduction. The amides (XI) were prepared by reacting X with the appropriate acid chloride. (Scheme I.)

Several related compounds possessing structures XVIII and XIX were prepared for comparison purposes. The latter compounds are related to analgesic anilides described by Wright and Brabander (10).

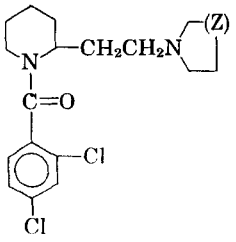
Preliminary pharmacological evaluation did not indicate any pronounced biological activity in the compounds that were studied.



Scheme I



XVIII



XIX (Z = CH_2, CH_2O)

EXPERIMENTAL[1]

2-(2-Aminoethyl)-5-ethylpyridine—The procedure described by Magnus and Levine (12) for the preparation of 2-(2-aminoethyl)pyridine was followed. A mixture of 214 Gm. (4 moles) of ammonium chloride, 266 Gm. (2 moles) of 5-ethyl-2-vinylpyridine, 300 ml. of water, and 400 ml. of methanol was refluxed for 3 days. The methanol was distilled *in vacuo*. The aqueous solution was cooled, poured into ice water, and neutralized with excess 40% sodium hydroxide. The oily layer was extracted with chloroform and dried over anhydrous potassium carbonate. Distillation of the solvent and then the residual oil gave 192 Gm. (64%) of distillate, b.p. 90–95° (2 mm.).

Anal.—Calcd. for $C_9H_{14}N_2$: C, 71.9; H, 9.38; N, 18.76. Found: C, 72.1; H, 9.56; N, 18.55.

Amides (Table I)—*Method A*—A mixture of 0.2 mole of amine, 40.4 Gm. (0.4 mole) of triethylamine, 0.4 mole of acid chloride, and 600 ml. of dry benzene was refluxed on a steam bath for 18–24 hr. Thereafter, the mixture was cooled, washed with water, and 10% sodium hydroxide, respectively, and dried over anhydrous potassium carbonate. The benzene solution was distilled and the residual material either recrystallized or distilled.

Method B—A mixture of 0.5 mole of the desired vinylpyridine and 73.6 Gm. (0.5 mole) of phthalimide was treated with 0.5 mole of a surfactant[2] and heated slowly and carefully to 175–180° and kept at this temperature for 3 hr. The oil, consisting of a single phase, was cooled and treated with 100 ml. of chloroform and filtered. The filtrate was concentrated and the residual oil crystallized.

Method C—A mixture of 24.1 Gm. (0.2 mole) of 2-(2-aminoethyl)pyridine (11) and 0.2 mole of anhydride was heated at 170–180° for 2 hr. and then cooled. The residual solid was recrystallized from a suitable solvent.

Method D—A mixture of 24.5 Gm. (0.2 mole) of 2-(2-aminoethyl)pyridine and 0.2 mole of ester was heated on a steam bath for 20 hr. and then vacuum distilled.

1 - (2,4 - Dichlorobenzoyl) - 5 - ethyl - 2 - (2 - morpholinoethyl)piperidine—The procedure described under *Method A* was followed. From 22.6 Gm. (0.1 mole) of 5-ethyl-2-(2-morpholinoethyl)-piperidine and 21 Gm. (0.1 mole) of 2,4-dichlorobenzoyl chloride there was obtained 31 Gm. (77%) of product, b.p. 234–236° (0.7 mm.) (13).

A methiodide was prepared in 87% yield as described under *Method E* and was recrystallized from methanol, m.p. 235–236° (13).

1 - (2,4 - Dichlorobenzoyl) - 5 - ethyl - 2 - (2 - pyrrolidinoethyl)piperidine—The procedure described under *Method A* was followed. From 19 Gm. (0.09 mole) of 5-ethyl-2-(2-pyrrolidinoethyl)-piperidine and 21 Gm. (0.1 mole) of 2,4-dichlorobenzoyl chloride there was obtained 28 Gm. (81%) of product, b.p. 218–220° (1.0 mm.) (13).

A methiodide was prepared in 98% yield as described under *Method A* and recrystallized from methanol, m.p. 205–207° (13).

Quaternary Ammonium Iodides—*Method E*—A solution of 0.02 mole of the requisite tertiary amine in 50 ml. of acetonitrile was treated with 14 Gm. (0.1 mole) of methyl iodide and refluxed on a steam bath for 4 hr. The solution was either filtered to remove the product or concentrated to dryness and then recrystallized from a suitable solvent.

2 - [2 - (p - Ethoxyanilino)ethyl] - 5 - ethylpyridine—The procedure described by Reich and Levine (9) was followed using 133 Gm. (1.0 mole) of 5-ethyl-2-vinylpyridine, 137 Gm. (1.0 mole) of *p*-phenetidine, 60 Gm. (1.0 mole) of acetic acid, and 300 ml. of methanol. One hundred and ninety grams of product, boiling at 168–176° (0.1 mm.), was obtained.

Anal.—Calcd. for $C_{17}H_{22}N_2O$: C, 75.51; H, 8.20. Found: C, 75.70; H, 8.38.

N - [2 - (1 - Methyl - 2 - piperidyl)ethyl]phthalimide Hydriodide—A mixture of 39 Gm. (0.1 mole) of 1-methyl-2-(2-phthalimidoethyl)pyridinium iodide, 200 ml. of methanol, and 0.4 Gm. of platinum oxide catalyst was hydrogenated at 60 p.s.i. at 50° for 18 hr. The resulting mixture was treated with 800 ml. of methanol, heated to reflux, filtered, and cooled. The product (30 Gm., 75%) was removed by filtration, m.p. 230–231°.

Anal.—Calcd. for $C_{16}H_{21}IN_2O_2$: C, 48.01; H, 5.29. Found: C, 48.20; H, 5.29.

N - (p - Ethoxyphenyl) - N - [2 - (5 - ethyl - 2-piperidyl)ethyl]isobutyramide—A solution of 40 Gm. (0.12 mole) of *N*-(*p*-ethoxyphenyl)-*N*-[2-(5-ethyl-2-pyridyl)ethyl]isobutyramide in 150 ml. of glacial acetic acid was hydrogenated at 58 p.s.i. in the presence of 0.4 Gm. platinum oxide catalyst for 30 hr. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The residual material was treated with 100 ml. of concentrated sodium hydroxide solution. The oily layer was extracted with ether and dried over anhydrous potassium carbonate. Distillation of the ether solution gave 36 Gm. (88%) of product, b.p. 200–205° (1.0 mm.); n_D^{26} 1.5161.

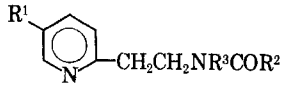
Anal.—Calcd. for $C_{21}H_{34}N_2O_2$: C, 72.79; H, 9.89. Found: C, 72.80; H, 9.70.

N - (p - Ethoxyphenyl) - N - [2 - (5 - ethyl - 1-methylpiperidyl)ethyl]isobutyramide—To 25 Gm. (0.07 mole) of *N*-(*p*-ethoxyphenyl)-*N*-[2-(5-ethyl-2-piperidyl)ethyl]isobutyramide, cooled in an ice bath, was added 7.8 Gm. (0.17 mole) of 98% formic acid. The mixture was allowed to warm slightly and then cooled while 7 ml. of 37% formaldehyde

[1] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected.

[2] Triton-B, Rohm and Haas, Philadelphia, Pa.

TABLE I—*N*-(2-PYRIDYLETHYL)AMIDES



R¹	R²	R³	Method	Recrystn. Solvent[a]	% Yield	M.p., °C. (B.p./mm.)	Molecular Formula	Anal., % Calcd. C	Calcd. H	Found C	Found H
H	$(C_6H_5)_2CH$	H	*A*	A–H	63	114–116	$C_{21}H_{20}N_2O$	79.7	6.37	79.9	6.53
C_2H_5	$(C_6H_5)_2CH$	H	*A*	M–W	74	116–117	$C_{23}H_{24}N_2O$	80.2	7.02	80.5	6.96
H	$NCCH_2$	H	*D*	M–E	58	(190–200/0.07) 118–120	$C_{10}H_{11}N_3O$	63.5	5.86	63.2	5.62
C_2H_5	3,4,5-$(CH_3O)_3C_6H_2$	H	*A*	E	73	98–99	$C_{19}H_{24}N_2O_4$	66.3	7.02	66.3	7.14
C_2H_5	CH_3	*p*-$C_2H_5OC_6H_4$	*A*	...	40	(197–199/0.5)	$C_{19}H_{24}N_2O_2$	73.1	7.74	73.1	7.85
C_2H_5	$(CH_3)_2CH$	*p*-$C_2H_5OC_6H_4$	*A*	...	89	(187–189/0.2)	$C_{21}H_{28}N_2O_2$	74.1	8.29	73.9	8.10
C_2H_5	*p*-$CH_3OC_6H_4$	*p*-$C_2H_5OC_6H_4$	*A*	E–H	71	68–69	$C_{25}H_{28}N_2O_3$	74.2	6.98	74.1	6.93
C_2H_5	$(CH_3)_2CH$	*m*-ClC_6H_4	*A*	...	56	(188–193/1.1)	$C_{19}H_{23}ClN_2O$	69.0	6.72	69.1	6.88
C_2H_5	$C_6H_4(CO)_2$[b]		*B*	C	43	94–97	$C_{17}H_{16}N_2O_2$	72.8	5.75	73.0	5.80
H	$C_6Cl_4(CO)_2$[c]		*C*	DMF	58	167–170	$C_{15}H_8Cl_4N_2O_2$[d]	46.2	2.07	46.4	2.27
H	$C_6H_4(CO)_2$[b]		*B*, *C*	C	80	96–98	$C_{15}H_{12}N_2O_2$[e]				
H	$C_6H_4(CO)_2$[b]		*E*	W	91	261–263	$C_{16}H_{15}IN_2O_2$[f,g]	48.7	3.83	48.8	3.71

[a] A, acetone; H, hexane; M, methanol; W, water; E, ether; C, cyclohexane. [b] NR^3COR^2, phthalimido. [c] NR^3COR^2, tetrachlorophthalimido. [d] Calcd. for Cl: 36.4. Found: Cl, 36.0. [e] *Reference 11.* [f] Methiodide. [g] Calcd. for I: 32.2. Found: I, 31.8.

solution was added. The resulting mixture was heated on a steam bath for 4 hr., cooled, and treated with 25 ml. of concentrated hydrochloric acid, and then concentrated under reduced pressure on a steam bath. The residual oil was neutralized with 15% sodium hydroxide solution, extracted with ether, and dried over anhydrous potassium carbonate. Distillation of the ether solution gave 20 Gm. (80%) of product, b.p. 187–190° (0.4 mm.); n_D^{26} 1.5141.

Anal.—Calcd. for $C_{22}H_{36}N_2O_2$: C, 73.29; H, 10.07. Found: C, 73.50; H, 10.02.

N - (3 - Dimethylaminopropyl) - N - (m - chlorophenyl)isobutyramide—Method *A* for the preparation of amides was followed using 25 Gm. (0.12 mole) of *N,N*-dimethyl-*N'*-(*m*-chlorophenyl)-1,3-propylenediamine (2); 28 Gm. (88%) of product was obtained, b.p. 132–135° (0.3 mm.); n_D^{26} 1.5157.

Anal.—Calcd. for $C_{15}H_{23}ClN_2O$: C, 63.70; H, 8.20. Found: C, 63.75; H, 8.20.

N - (3 - Dimethylaminopropyl) - N - (p - ethoxyphenyl)isobutyramide—The procedure described under *Method A* for the preparation of amides was followed, using 21 Gm. (0.1 mole) of *N,N*-dimethyl-*N'*-(*p*-ethoxyphenyl)-1,3-propylenediamine; 21 Gm. (72%) of product was obtained, b.p. 148–150° (0.4 mm.).

Anal.—Calcd. for $C_{17}H_{28}N_2O_2$: C, 69.82; H, 9.65. Found: C, 69.50; H, 9.35.

REFERENCES

(1) Burger, A., "Medicinal Chemistry," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1960, chap. 6.
(2) Shapiro, S., Soloway, H., Chodos, E., and Freedman, L., *J. Pharm. Sci.*, **50**, 1035(1961).
(3) Nieforth, K. A., *ibid.*, **52**, 1136(1963).
(4) Perron, Y. G., and Sam, J., U. S. pat. 2,870,156 (January 20, 1959); through *Chem. Abstr.*, **53**, 10264(1959).
(5) Lewis, J. R., *Arch. Intern. Pharmacodyn.*, **88**, 142 (1951); through *Biol. Abstr.*, **27**, 9727(1953); through *Chem. Abstr.*, **46**, 2680(1952).
(6) Irwin Neisler and Co., Brit. pat. 842,995 (August 4, 1960).
(7) Fancher, O. E., Hayoa, S., Strycher, W. G., and Sancilio, L. F., *J. Med. Chem.*, **7**, 721(1964).
(8) Carabateas, P. M., Wetterau, W. F., and Grumbach, L., *ibid.*, **6**, 355(1963).
(9) Reich, H. E., and Levine, R., *J. Am. Chem. Soc.*, **77**, 4913, 5434(1955).
(10) Wright, W. B., and Brabander, H. J., U. S. pat. 3,016,382(January 9, 1962); through *Chem. Abstr.*, **57**, 16485 (1962).
(11) Kirchner, F. K., McCormick, J .R., Cavallito, C. J., and Miller, L. C., *J. Org. Chem.*, **14**, 388(1949).
(12) Magnus, G., and Levine, R., *J. Am. Chem. Soc.*, **78**, 4127(1956).
(13) Sam, J., U. S. pat. 2,922,786(January 26, 1960).