# N-Dialkylaminoalkyl-N-(pyridylethyl)anilines

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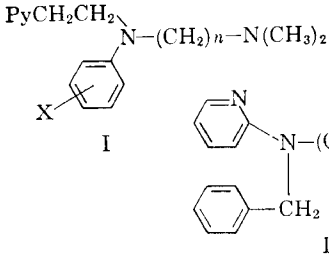
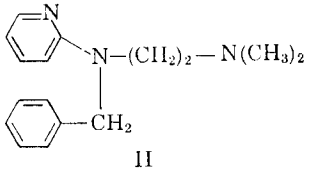
**A series of N-dialkylaminoalkyl-N-(pyridylethyl)anilines has been prepared and on pharmacological evaluation significant hypotensive, anti-inflammatory, analgesic, and tranquillizing effects noted.**

STRUCTURE-ACTIVITY relationships among the antihistamines and the phenothiazine type tranquillizer drugs (1) has indicated the criticality associated with small structural changes with such compounds. In this paper, a series of N-dialkylaminoalkyl-N-(pyridylethyl)anilines (I) envisioned as congeners of tripelennamine (II)



I



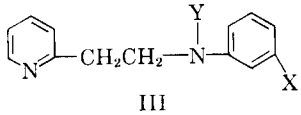
II

Py = 2-pyridyl, 2-pyridyl-5-ethyl, 4-pyridyl; $n$ = 2, 3; X = H, $CH_3$—, Cl, $CH_3O$—

has been synthesized and evaluated pharmacologically. In contrast to II, the pyridine ring of I is separated from the nitrogen by the ethylene group and the benzyl group of II has been herein replaced by a phenyl group directly attached to the nitrogen. In addition, substituents previously demonstrated to enhance activity in antihistamines and tranquillizing drugs have been introduced on the phenyl ring of I. In particular, the substitution of X = *m*-chloro, affords a group relationship paralleling that noted with the chlorine atom and ring nitrogen in chlorpromazine. The linking element between the nitrogens was varied to provide carbon chains, 2 and 3 atoms in length, whereas substitution on the more basic nitrogen was retained as the flat dimethylamino group (2).

A convenient synthetic route for I involved pyridylethylation of the N-dimethylaminoalkylanilines following the method of Levine (3). With these relatively high boiling pyridylethylated products, difficulties associated with reversibility (4) of the formed product to its reactants during distillation, seriously restricted the yields. See Table I.

A variety of other synthetic routes evaluated proved ineffective. Thus, pyridylethylanilines III, Y = H, could not be successfully alkylated with dialkylaminoalkyl halides following conventional procedures (5) or by fusion at elevated temperatures (6).



III

Y = H (IIIa), X = Cl
Y = —$COCH_2Cl$ (IIIb), X = Cl
—$COCH_2N(CH_3)_2$ (IIIc), X = Cl
—$CH_2CH_2OH$ (IIId), X = H
—$CH_2CH_2Cl$ (IIIe), X = H

The compound III, Y = H, gave the chloroacetamide (IIIb) which was converted to the dimethylacetamide (IIIc) which failed to yield the desired I on treatment with lithium aluminum hydride. Refractoriness to reduction of certain amides by lithium aluminum hydride has been noted by others (7–10).

As another alternative, the compound IIId did not yield the desired haloethyl derivative (IIIe) on treatment with thionyl chloride or 48% hydrobromic acid (11).

On pharmacological evaluation, the noted responses confirmed previous conclusions (1, 5) on the significance of structural variations on activity. Thus, hypotension was confined to the variants Py = 4-pyridyl with a 3+ response (12) being noted with compounds 12, 13, and 16 which had $LD_{min.}$ of 400, 500, and 350 mg./Kg. s.c., respectively.

Significant analgesia (13) was obtained with compounds 1, 7, and 13 with an $ED_{50}$ of 90, 150, and 250 mg./Kg. s.c., respectively, all having X = *m*-chloro.

Interestingly, virtually all compounds evaluated for antihistamine effect showed no effect whatever with the exception of some potentiation with compound 7 and slight inhibition with compound 9.

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TABLE I.—N-DIALKYLAMINOALKYL-N-(PYRIDYLETHYL)ANILINES (I)

| No. | X | *n* | M.P.,[a] °C. (R.S.)[b] or B.P., °C. (mm.) | Formula | Analyses, %[c] Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Py = 2-Pyridyl | | | | | | |
| 1 | 3-Cl | 2 | 140–148 (0.03) | $C_{17}H_{22}ClN_3$ | 67.2 | 67.0 | 7.3 | 7.2 | 13.8 | 14.1 |
| | [d] | | 180–183 (A) | $C_{29}H_{28}ClN_9O_{14}$ | 45.7 | 45.9 | 3.7 | 3.3 | 16.5 | 16.9 |
| 2 | 3-Cl | 3 | 138 (0.02) | $C_{18}H_{24}ClN_3$ | 68.0 | 68.4 | 7.6 | 7.9 | 13.2 | 12.9 |
| 3 | 4-Cl | 2 | 152–154 (0.09) | $C_{17}H_{22}ClN_3$ | .. | .. | .. | .. | .. | .. |
| | [d] | | 142–145 (B) | $C_{29}H_{28}ClN_9O_{14}$ | 45.7 | 45.6 | 3.7 | 3.6 | 16.5 | 16.7 |
| 4 | 4-Cl | 3 | 166–170 (0.05) | $C_{18}H_{24}ClN_3$ | [e] | .. | .. | .. | .. | .. |
| | [d] | | 160–163 (A) | $C_{30}H_{30}ClN_9O_{14}$ | 46.4 | 46.5 | 3.9 | 3.8 | 16.2 | 16.6 |
| 5 | 4-$CH_3O$ | 2 | 152–154 (0.07) | $C_{18}H_{25}N_3O$ | 72.2 | 72.1 | 8.4 | 8.4 | 14.0 | 14.3 |
| | [d] | | 179–180 (C) | $C_{30}H_{31}N_9O_{15}$ | .. | .. | .. | .. | 16.6 | 16.9 |
| | | | | Py = 5-Ethyl-2-Pyridyl | | | | | | |
| 6 | H | 3 | 170–174 (0.05) | $C_{20}H_{29}N_3$ | .. | .. | .. | .. | 13.5 | 13.6 |
| | [d] | | 160–163 (C) | $C_{32}H_{35}N_9O_{14}$ | 49.9 | 50.3 | 4.6 | 4.6 | 16.4 | 16.3 |
| 7 | 3-Cl | 2 | 172–174 (0.20) | $C_{19}H_{26}ClN_3$ | .. | .. | .. | .. | 12.7 | 12.4 |
| 8 | 3-Cl | 3 | 158–160 (0.03) | $C_{20}H_{28}ClN_3$ | .. | .. | .. | .. | 12.2 | 12.0 |
| 9 | 4-Cl | 3 | 170–172 (0.02) | $C_{20}H_{28}ClN_3$ | 69.4 | 69.3 | 8.2 | 7.8 | 12.2 | 12.3 |
| | | | | Py = 4-Pyridyl | | | | | | |
| 10 | H | 2 | 154–156 (0.02) | $C_{17}H_{23}N_3$ | .. | .. | .. | .. | 15.6 | 15.5 |
| | [d] | | 176–177 (D) | $C_{29}H_{29}N_9O_{14}$ | 47.9 | 48.1 | 4.0 | 4.2 | 17.3 | 17.6 |
| 11 | 2-Cl | 3 | 156 (0.09) | $C_{18}H_{24}ClN_3$ | .. | .. | .. | .. | 13.2 | 12.7 |
| 12 | 3-Cl | 2 | 164–168 (0.02) | $C_{17}H_{22}ClN_3$ | 67.2 | 67.0 | 7.3 | 7.3 | 13.8 | 14.0 |
| 13 | 3-Cl | 3 | 178–180 (0.02) | $C_{18}H_{24}ClN_3$ | .. | .. | .. | .. | 13.2 | 12.8 |
| | [d] | | 188–189 (D) | $C_{30}H_{29}ClN_9O_{14}$ | 46.4 | 46.4 | 3.9 | 4.2 | 16.2 | 15.6 |
| 14 | 4-Cl | 2 | 168–170 (0.07) | $C_{17}H_{22}ClN_3$ | .. | .. | .. | .. | 13.8 | 13.8 |
| | [d] | | 165–166 (D) | $C_{29}H_{28}ClN_9O_{14}$ | 45.7 | 45.7 | 3.7 | 3.8 | 16.5 | 16.7 |
| 15 | 4-Cl | 3 | 168–170 (0.05) | $C_{18}H_{24}ClN_3$ | .. | .. | .. | .. | 13.2 | 13.0 |
| 16 | 3-$CH_3$ | 2 | 158–160 (0.05) | $C_{18}H_{25}N_3$ | 76.3 | 75.9 | 8.9 | 9.0 | 14.8 | 14.5 |
| | [d] | | 178–179 (D) | $C_{30}H_{31}N_9O_{14}$ | 48.6 | 48.5 | 4.2 | 4.4 | .. | .. |

[a] Melting points were taken on the Fisher-Johns melting point apparatus and are uncorrected. [b] R.S. = recrystallizing solvent; A = water; B = acetone; C = methyl ethyl ketone; D = acetonitrile. [c] Analyses are by Weiler & Strauss, Oxford, England. [d] Dipicrate of compound immediately above. [e] Chlorine: Calcd.: 11.2; Found: 11.3.

Tranquillizing activity reflected by reduction in motor activity of rats (4) was noted with the following: the compound No./$LD_{min.}$/% reduction in activity/dosage tested: 6/250/59/50; 12/400/47/100; 14/250/69/100.

Tranquillizing activity was also manifest in the capacity of compound 10 ($LD_{min.}$ 200) and 16 to prevent audiogenic seizures in mice (14) with a $PD_{50}$ of 72 and 75 mg./Kg.

Anti-inflammatory effectiveness (15) was noted with the following compounds showing 80–100% protection at 50 mg./Kg.: 1, 6, 9, 15, and 16, whereas the following showed 50–63% protection at 50 mg./Kg.: 4, 10, 12, 13, and 14. It is of interest that this latter category has representation in virtually all of the structural variants in the series.

## EXPERIMENTAL

**N - Dimethylaminoalkylanilines.**—These intermediates were prepared by familiar procedures (16, 17) and are described in Table II.

**N - Dimethylaminoethyl - N - (2 - [2 - pyridyl]-ethyl) - *p* - methoxyaniline (Table I, Compound 5).**—A solution of 10.5 Gm. (0.1 mole) of 2-vinylpyridine, 19.4 Gm. (0.1 mole) of *N*-dimethylaminoethyl - *p* - methoxyaniline (Table II, compound 12), and 6.0 Gm. (0.1 mole) of acetic acid in 150 ml. of ethanol was heated under reflux for 24 hours. After removal of the solvent and basifying with aqueous sodium hydroxide, the separated oil was extracted with three 100-ml. portions of ether. The ether extracts were combined, dried (magnesium sulfate), filtered, the ether removed, and the residue distilled. After a forerun of 8.6 Gm. (44%) of the reactant aniline there was obtained 11.7 Gm.(40%) of product, boiling at 152–154° (0.07 mm.).

The other compounds of Table I were similarly prepared. The compound X = alkoxy gave the highest yield; those compounds with X = H or $CH_3$ afforded yields in the range 18–30%, whereas X = Cl gave yields of 2–12%. Many of the compounds were further characterized as their dipicrates.

**N - (2 - [2 - Pyridyl]ethyl) - *m* - chloroaniline (IIIa) (3).**—A mixture of 52.5 Gm. (0.5 mole) of 2-vinylpyridine, 63.8 Gm. (0.5 mole) of *m*-chloroaniline, 30.0 Gm. (0.5 mole) of glacial acetic acid in 125 ml. of methanol, after 8 hours reflux afforded 73.0 Gm. (64%) of crude product (m.p., 29–32°). On recrystallization (pentane) it melted at 54–55°.

*Anal.*—Calcd. for $C_{13}H_{13}ClN_2$: C, 67.1; H, 5.6; N, 12.0. Found: C, 67.2; H, 5.6; N, 12.1

**N - (2 - [2 - Pyridyl]ethyl) - *p* - chloroaniline.**—Prepared as above, melted at 61–62° (hexane).

*Anal.*—Calcd. for $C_{13}H_{13}ClN_2$: C, 67.1; H, 5.6; N, 12.0. Found: C, 66.8; H, 5.6; N, 11.9.

The picrate melted at 152–153° (ethanol).

*Anal.*—Calcd. for $C_{19}H_{16}ClN_5O_7$: C, 49.4; H, 3.5; N, 15.2. Found: C, 49.8; H, 3.7; N, 14.7.

**N - (2 - [2 - Pyridyl]ethyl) - N - (*m* - chlorophenyl)chloroacetamide (IIIb).**—A solution of 18.1 Gm. (0.16 mole) of chloroacetyl chloride in 250 ml. of acetonitrile was treated with 38 Gm. (0.16 mole) of N-(2-[2-pyridyl]ethyl)-*m*-chloroaniline, under cool-

TABLE II.—N-DIMETHYLAMINOALKYLANILINES

| No.[a] | X | n | B.P., °C. (mm.) | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | X-$C_6H_4NH(CH_2)_nN(CH_3)_2$ | | | | | | |
| 1 | H | 2 | 86–88 (1) | $C_{10}H_{16}N_2$ | 73.1 | 73.1 | 9.8 | 10.6 | 17.1 | 16.7 |
| 2 | H | 3 | 119–122 (4) | $C_{11}H_{18}N_2$ | .. | .. | .. | .. | 15.7 | 15.7 |
| 3 | 2-Cl | 2 | 158–160 (21) | $C_{10}H_{15}ClN_2$ | 60.5 | 60.7 | 7.6 | 7.9 | | |
| 4 | 2-Cl | 3 | 138 (4) | $C_{11}H_{17}ClN_2$ | 62.1 | 62.3 | 8.1 | 8.3 | 13.2 | 12.9 |
| 5 | 3-Cl | 2 | 132–134 (4) | $C_{10}H_{15}ClN_2$ | 60.5 | 60.5 | 7.6 | 7.9 | .. | .. |
| 6 | 3-Cl | 3 | 132–134 (1) | $C_{11}H_{17}ClN_2$ | 62.1 | 61.9 | 8.1 | 8.5 | .. | .. |
| 7[b] | 4-Cl | 2 | 157–162 (19) | .... | .. | .. | .. | .. | .. | .. |
| 8 | 4-Cl | 3 | 147–149 (2) | $C_{11}H_{14}ClN_2$ | .. | .. | .. | .. | 13.3 | 13.2 |
| 9 | 3,4-diCl | 2 | 102–104 (0.04) | $C_{10}H_{14}Cl_2N_2$ | 51.5 | 51.1 | 6.1 | 5.6 | .. | .. |
| 10 | 4-Br | 3 | 110–114 (0.02) | $C_{11}H_{17}BrN_2$ | .. | .. | .. | .. | 10.9 | 10.8 |
| 11[b] | 3-$CH_3$ | 2 | 111–113 (2) | .... | .. | .. | .. | .. | .. | .. |
| 12 | 4-$CH_3O$ | 2 | 133–137 (2) | $C_{11}H_{18}N_2O$ | .. | .. | .. | .. | 14.4 | 14.9 |

[a] Villani, F. J., Sperber, N., Lang, J., and Papa, D., *J. Am. Chem. Soc.*, **72**, 2724(1950), report compounds 1 and 5; Kyrides, L. P., Meyer, F. C., Zienty, F. B., Harvey, J., and Bannister, L. W., *ibid.*, **72**, 745(1950), report compounds 3, 7, and 12. [b] Used in subsequent work without analysis.

ing, followed by a 2-hour reflux. The solvent was removed, the residue, in water, basified with 40% aqueous sodium hydroxide, and the product extracted with ether and dried (anhydrous magnesium sulfate). After removal of the solvent and recrystallization (hexane), there was obtained 25 Gm. (51%), m.p. 58–59°.

*Anal.*—Calcd. for $C_{15}H_{14}Cl_2N_2O$: C, 58.3; H, 4.6; N, 9.1. Found: C, 58.3; H, 4.6; N, 9.1.

The hydrochloride melted at 186–188° (ethanol-ether).

*Anal.*—Calcd. for $C_{15}H_{15}Cl_3N_2O$: C, 52.1; H, 4.4. Found: C, 52.0; H, 4.4.

The picrate melted at 145–147° (ethanol).

*Anal.*—Calcd. for $C_{21}H_{17}Cl_2N_5O_8$: C, 46.9; H, 3.2; N, 13.0. Found: C, 46.7; H, 3.5; N, 13.1.

**N - (Dimethylaminoacetyl) - N - (2 - [2 - pyridyl]-ethyl)-*m*-chloroaniline (IIIc).**—A mixture of N-(2-[2 - pyridyl]ethyl) - N - (*m* - chlorophenyl)chloroacetamide (11.4 Gm., 0.035 mole) and 5 Gm. (0.10 mole) of dimethylamine in 50 ml. of ethanol was maintained in a pressure bottle at 60–70° for 6 hours. After cooling and removal of the ethanol, the residue, in 100 ml. of water, was basified with 40% aqueous sodium hydroxide, salted with potassium carbonate, and the separated oil extracted with ether. After drying (magnesium sulfate) and removal of the ether, the product distilled to give 5.7 Gm. (51%) b.p. 152–168° (0.05 mm.) ($n_D^{29}$ 1.5624).

*Anal.*—Calcd. for $C_{17}H_{21}ClN_3O$: C, 64.0; H, 6.6; N, 13.2. Found: C, 64.3; H, 6.7; N, 12.7.

The dipicrate melted at 163–164° (ethanol).

*Anal.*—Calcd. for $C_{29}H_{27}ClN_9O_{15}$: C, 44.8; H, 3.5; N, 16.2. Found: C, 45.2; H, 3.6; N, 16.2.

Attempted reduction with lithium aluminum hydride in ether, after 14 hours reflux afforded only 52% of the reactant amide, IIIc: identified by analysis, and its dipicrate, not depressing the melting point of authentic dipicrate of IIIc.

**N - (2 - Hydroxyethyl) - N - (2 - [2 - pyridyl]-ethyl)aniline (IIId).**—A mixture of 52.5 Gm. (0.5 mole) of 2-vinylpyridine, 68.5 Gm. (0.5 mole) of 2-anilinoethanol, 30.0 Gm. (0.5 mole) of glacial acetic acid in 125 ml. of ethanol, under 13-hour reflux was processed as detailed for the compounds of Table II. After work-up and removal of the ether, the crystalline residue was triturated with pentane and recrystallized (hexane) to give 26.5 Gm. (23%), melting at 67–69°.

*Anal.*—Calcd. for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.5 N, 11.6. Found: C, 74.8; H, 6.9; N, 11.6.

An additional 20% of product was obtained from the pentane filtrate.

It is of interest that under these conditions no acetylation of the hydroxyl group was noted.

Attempts to convert the hydroxyl group to chlorine (thionyl chloride) or bromine (48% hydrobromic acid) afforded intractable tars.

## REFERENCES


(1) Burger, A., "Medicinal Chemistry," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 408, 531.
(2) *Ibid.*, p. 529.
(3) Reich, H. E., and Levine, R., *J. Am. Chem. Soc.*, **77**, 4913(1955).
(4) Shapiro, S. L., Rose, I. M., Roskin, E., and Freedman, L., *ibid.*, **80**, 1648(1958).
(5) Shapiro, S. L., Soloway, H., and Freedman, L., THIS JOURNAL, **46**, 333(1957).
(6) Mannich, C., and Margotte, E., *Ber.*, **68B**, 273(1935).
(7) Gaylord, N. G., "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 546, 555.
(8) Curtin, D. Y., and Gerber, S. M., *J. Am. Chem. Soc.*, **74**, 4052(1952).
(9) Eiter, K., and Mrazek, E., *Monatsh. Chem.*, **83**, 926 (1952).
(10) Wittig, G., and Hornberger, P., *Ann.*, **577**, 11(1952).
(11) Shapiro, S. L., Soloway, H., and Freedman, L., *J. Am. Chem. Soc.*, **80**, 6060(1958).
(12) Shapiro, S. L., Soloway, H., and Freedman, L., *ibid.*, **80**, 2743(1958).
(13) Bianchi, D., and Franceschini, J., *Brit. J. Pharmacol.*, **9**, 280(1954).
(14) Plotnikoff, N. P., and Green, D. M., *J. Pharm. Exptl. Therap.*, **119**, 294(1957).
(15) Siegmund, E., Cadmus, R., and Lu, G., *Proc. Soc. Exptl. Biol. Med.*, **95**, 729(1957).
(16) Biel, J. H., *J. Am. Chem. Soc.*, **71**, 1306(1949).
(17) Huttrer, C. P., Djerassi, C., Beears, W. L., Mayer, R. L., and Scholz, C. R., *ibid.*, **68**, 1999(1946).