COMMUNICATIONS TO THE EDITOR

A NEW CLASS OF POTENT CENTRAL NERVOUS SYSTEM DEPRESSANTS

Sir:

Although the first 2-amino-2-oxazolines (pseudoureas) were synthesized over fifty years ago,[1,2] compounds containing that grouping have until now received only cursory pharmacological examination.[3] We now wish to report the synthesis, in the course of a systematic search for new psychotherapeutic agents, of the previously unknown 2-(1-naphthylamino)-2-oxazoline (I). This compound represents a new structural type of central nervous system depressant, which displays a unique pharmacological profile.

Treatment of α-naphthyl isocyanate with β-bromoethylamine[4] in benzene solution led to 1-(1-naphthyl)-3-(2-bromoethyl)-urea (II), m.p. 146.8–147.2°; $\lambda_{max.}^{KBr}$ 3.10, 6.19, 6.41, 6.60, 6.70; (*Anal.* Calcd. for $C_{13}H_{13}N_2OBr$: C, 53.3; H, 4.47; N, 9.56; Br, 27.3. Found: C, 53.1; H, 4.37; N, 9.76; Br, 27.1). Alternatively, II could be synthesized by treating β-bromopropionyl chloride[5] with sodium azide under thermal-rearrangement conditions to afford the previously unknown β-bromoethyl isocyanate, which was not isolated but allowed to react directly with α-naphthylamine affording the desired compound. The urea II readily underwent intramolecular cyclization in boiling water[6] to give a solution of 2-(1-naphthylamino)-2-oxazoline hydrobromide, from which dilute ammonium hydroxide precipitated the free base I, m.p. 123.4–124.6; $\lambda_{max.}^{KBr}$ 3.36, 3.55, 5.98, 6.08, 6.38, 6.64; (*Anal.* Calcd. for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.70; N, 13.2. Found: C, 73.5; H, 5.60; N, 13.1).

Treatment of I with anhydrous hydrochloric acid in methylene chloride solution afforded the corresponding hydrochloride salt, m.p. 150.2–150.8°; $\lambda_{max.}^{KBr}$ 3.28, 3.53, 6.00, 6.18, 6.28, 6.33, 6.41, which reverted in boiling 2-propanol to 1-(1-naphthyl)-3-(2-chloroethyl)-urea (IV), m.p. 145.6–146.4; $\lambda_{max.}^{KBr}$ 3.07, 6.14, 6.40, 6.65; (*Anal.* Calcd. for $C_{13}H_{13}N_2OCl$: C, 62.8; H, 5.27; N, 11.3. Found: C, 63.1; H, 5.26; N, 11.1). The synthesis of IV could also be accomplished from β-chloroethyl isocyanate[7] and α-naphthylamine or by treating 1-(1-naphthyl)-3-(2-hydroxyethyl)-urea (V)[8] with thionyl chloride in refluxing chloroform. Acidic degradation of I with boiling 3*N* hydrochloric acid leads to V.

The iodo analog, 1-(1-naphthyl)-3-(2-iodoethyl)-urea (VI), m.p. 176.0–178.0°; $\lambda_{max.}^{KBr}$ 3.09, 6.17, 6.39, 6.60, 6.68; (*Anal.* Calcd. for $C_{13}H_{13}N_2OI$: C, 45.9; H, 3.85; N, 8.24. Found: C, 45.9; H, 3.94; N, 8.25) was prepared by refluxing II with excess sodium iodide in acetone solution.[9]

Following oral or parenteral administration of the oxazoline I to cats, dogs and monkeys, marked quieting was observed accompanied by muscle relaxation and increased ease of handling. In potentiation of hydroxydione (21-hydroxypregnanedione sodium succinate) anesthesia, I proved somewhat more potent than either reserpine or chlorpromazine, while all three drugs depressed the spontaneous motility of mice to a similar degree. Spinal cord depressant activity could be demonstrated with lower doses of I than were required with the distant structural relative, 2-amino-5-chlorobenzoxazole.[10] Metrazole convulsions were facilitated by pretreatment with I, as is the case with reserpine.[11]

(1) R. H. Wiley and L. L. Bennett, Jr., *Chem. Revs.*, **44**, 464 (1949); J. W. Cornforth, "Heterocyclic Chemistry," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. II, pp. 384–386, 390.

(2) For more recent chemical studies, see A. F. McKay and coworkers, THIS JOURNAL, **78**, 486, 1618, 6144 (1956); *Can. J. Chem.*, **35**, 8 (1957), and earlier papers.

(3) C. J. Rose, H. A. Shonle and K. K. Chen, *Pharmaceutical Archives*, **11**, 81 (1940); R. Gebauer, German Patent 694,133 (July 26, 1940); *C.A.*, **35**, 5259 (1941).

(4) M. Engelmann, U. S. Patent 2,027,031 (Jan. 7, 1936); *C.A.*, **30**, 1519 (1936).

(5) C. S. Hamilton and C. L. Simpson, THIS JOURNAL, **51**, 3158 (1929); R. Dahlbom, *Acta Chem. Scand.*, **7**, 873 (1953).

(6) In accord with earlier observations in the β-haloalkylurea series, alkali-catalyzed cyclization of II proceeded via alkylation on nitrogen to produce 1-(1-naphthyl)-2-imidazolidone (III), m.p. 180.4–181.6°, $\lambda_{max.}^{KBr}$ 3.17, 3.32, 3.57, 5.97, 6.31, 6.72 (*Anal.* Calcd. for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.70; N, 13.2. Found: C, 74.2; H, 5.61; N, 13.3).

(7) H. Wenker, THIS JOURNAL, **58**, 2608 (1936); W. Siefken, *Ann.*, **562**, 75 (1949).

(8) K. W. Charlton and A. R. Day, *J. Org. Chem.*, **1**, 552 (1936).

(9) In animals the β-bromoethyl urea II displays a spectrum of pharmacological actions similar to I, although much higher doses are required. Since it can be demonstrated that any efficient solvolytic medium (*e.g.*, methanol, dimethylformamide) will effect *in vitro* cyclization of the urea II to the oxazoline I at room temperature, it seems highly probable that a similar *in vivo* conversion is involved in the pharmacodynamics of II. Further investigation of this novel metabolic transformation is contemplated. Neither the iodo nor chloro analog is as active as II when evaluated by the technique of anesthesia potentiation in rats. The whole picture of *in vivo* transformation to an active species by intramolecular alkylation, as well as varying potency among halogen analogs is reminiscent of the β-haloethylamine adrenergic blocking agents (G. E. Ullyot and J. F. Kerwin, "Medicinal Chemistry," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1956, p. 234).

(10) W. H. Funderburk and R. T. Woodcock, *Fed. Proc.*, **14**, 311 (1955); K. Kamijo and G. B. Koelle, *ibid.*, **14**, 356 (1955); D. F. Marsh, *ibid.*, **14**, 366 (1955).

(11) The detailed pharmacology of I will be published elsewhere.

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BIS-(CYCLOPENTADIENYL)-TITANIUM DICHLORIDE—ALKYLALUMINUM COMPLEXES AS CATALYSTS FOR THE POLYMERIZATION OF ETHYLENE

Sir:

The recent publications of Natta and coworkers[1,2] on the use of bis-(cyclopentadienyl)-

(1) G. Natta, P. Pino, G. Mazzanti, U. Giannini, E. Mantica and M. Peraldo, *Chim. e. ind. (Milan)*, **39**, 19 (1957); *C.A.*, **51**, 7049 (1957).

(2) G. Natta, P. Pino, G. Mazzanti and U. Giannini, THIS JOURNAL, **79**, 2975 (1957).