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.

BARRY M. BLOOM
RESEARCH LABORATORIES JOSEPH F. GARDOCKI
CHAS. PFIZER AND CO., INC. DUNCAN E. HUTCHEON
BROOKLYN, NEW YORK GERALD D. LAUBACH

RECEIVED JUNE 17, 1957

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).

titanium derivatives as catalysts for the low-pressure polymerization of ethylene prompt us to report some related work which we carried out several years ago. In several respects our results differ considerably from theirs.

An orange solution of bis-(cyclopentadienyl)-titanium dichloride in toluene (5 millimoles per liter) was treated with two moles of diethylaluminum chloride. The color immediately changed to a dark red, followed by a gradual change over a period of about an hour at room temperature to a green and finally to a blue solution. During this time ethane was evolved. (With triethylaluminum the formation of the blue solution was practically instantaneous; the slow reaction reported by Natta can be attributed to the insolubility of the dichloride in heptane.) Replacement of the toluene by *n*-heptane yielded a clear blue solution, from which a blue crystalline solid could be isolated by chilling in Dry Ice. After several recrystallizations it melted at 80–90°, apparently with some decomposition. Although the compound seemed to be thermally stable at room temperature, it was extremely sensitive to traces of oxygen. The compound is a complex of $(C_5H_5)_2Ti(III)Cl$ with what appears to be aluminum sesquichloride. *Anal.* Calcd. for $(C_5H_5)_2TiCl\cdot{}^1/_2(C_2H_5)_2AlCl\cdot{}^1/_2C_2H_5AlCl_2$: C, 46.28; H, 5.23. Found: C, 46.36; H, 5.26. Analysis of a heptane solution gave the ratios (normalized for total titanium) Ti(III or less), 0.95; Al, 1.05; Cl, 2.63. Magnetic susceptibility measurements showed the presence of one unpaired electron, while hydrolysis with thoroughly deaerated dilute mineral acid gave a green aqueous solution; the $(C_5H_5)_2Ti(III)$ ion is reported to be green.[3] There seems to be little doubt that, by analogy, the compound isolated by us and by Natta and co-workers from bis-(cyclopentadienyl)-titanium dichloride and triethylaluminum has the structure $(C_5H_5)_2TiCl\cdot(C_2H_5)_2AlCl$, the "sandwich" compound reacting with alkylaluminum compounds in a manner similar to titanium tetrachloride.

The blue complex prepared with diethylaluminum chloride is a very poor catalyst for the polymerization of ethylene, in agreement with the observations of Natta and co-workers on the complex prepared with triethylaluminum. A fresh mixture of bis-(cyclopentadienyl)-titanium dichloride and diethylaluminum chloride, however, is a highly active catalyst, as is the blue complex if the ethylene contains a trace of oxygen.[4] The color changes in the latter case indicate quite definitely that the oxygen is functioning to form a tetravalent titanium compound. Thus, ethylene containing 0.003 mole % oxygen was passed into a solution of 5 millimoles of bis-(cyclopentadienyl)-titanium dichloride and 10 millimoles of diethylaluminum chloride in a liter of toluene at 15–20°. The blue solution turned green, and 13 g. of polyethylene was formed in one hour. Under the same conditions ethylene containing 0.025% oxygen gave a brown solution; the addition of small amounts of a dilute solution of diethylaluminum chloride to maintain this color during the polymerization resulted in the formation of 174 g. of polyethylene in one hour. Thus, these catalysts are fully as active as the usual Ziegler type. There seems to be little doubt from these results that this *soluble* catalyst system depends for its catalytic activity on the presence of at least some tetravalent titanium. The polymers differ from polyethylene prepared with the usual Ziegler-type catalysts in being more linear (methyl content about 0.05% *vs.* about 0.9%) and higher melting (137° *vs.* 132°).

(3) G. Wilkinson and J. M. Birmingham, THIS JOURNAL, **76**, 4281 (1954).

(4) D. S. Breslow, Belgian Patent 551,283 (1957).

RESEARCH CENTER
HERCULES POWDER COMPANY
WILMINGTON 99, DELAWARE
DAVID S. BRESLOW
NORMAN R. NEWBURG

RECEIVED JULY 9, 1957

INHIBITION BY HYDROGEN PEROXIDE OF THE SECOND EXPLOSION LIMIT IN HYDROGEN-OXYGEN MIXTURES

Sir:

During a recent investigation of the gas-phase decomposition of hydrogen peroxide[1] in which we confirmed the partially homogeneous character of the reaction above 400°, we tried adding a number of gases to study their effect on the rate of peroxide decomposition. Of the various gases tested (H_2, O_2, NO, etc.) only hydrogen showed significant effects: a marked acceleration of the reaction in the temperature range 440–470° at total pressures in excess of 20 mm., in agreement with the findings of McLane[2] in a flow system. At lower pressures we observed explosive reactions of the hydrogen with the oxygen from decomposition of the peroxide. However, a remarkable feature of these explosions was that they occurred only after all, or nearly all, the hydrogen peroxide had disappeared although the mixtures were within the explosion range[3] for some time yet. This pointed out to a strong inhibiting action of hydrogen peroxide apparently not reported before.

To check this point further we added some hydrogen peroxide vapor to stoichiometric hydrogen–oxygen mixtures and determined the second limit by the usual withdrawal method. The preliminary results confirm, indeed, that hydrogen peroxide is an efficient explosion inhibitor, roughly ten times as efficient as water vapor under the same conditions. For instance at 458° the second limit was lowered from 28 mm. to 17 mm. by about 0.01 mole per cent. of hydrogen peroxide, while at 0.04 mole per cent., the explosions were suppressed entirely. There is some uncertainty in our results as to the exact concentration of peroxide at the moment of explosion because its decomposition rate depends on such continuously changing variables as total pressure and concentration of hydrogen gas in the system. Water vapor from the decomposing peroxide also acts as an inhibitor, but this is of minor importance in our case. That the above phenomenon has not been noticed previously is no doubt due to the fact that, unless special care is exercised, hydrogen peroxide will decompose quickly through a heterogeneous mechanism before the necessary

(1) P. A. Giguère and I. D. Liu, *Can. J. Chem.*, **35**, 283 (1957).

(2) C. K. McLane, *J. Chem. Phys.*, **18**, 972 (1950).

(3) B. Lewis and G. von Elbe, "Combustion, Flames and Explosions," Academic Press, Inc., New York, N. Y., 1951.