A Novel Serotonin Antagonist 2,2'-bis[3-(2-*N*,*N*-Dimethylaminoethyl)indolyl]sulfide (BDIS)

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Received September 27, 1984

A novel serotonin antagonist, 2,2'-bis[3-(2-*N*,*N*-dimethylaminoethyl)indolyl]sulfide (BDIS) was synthesized in one step from the reaction of *N*,*N*-dimethyltryptamine with thionyl chloride.

J. Heterocyclic Chem., **21**, 1901 (1984).

It is known or speculated that a number of disease states such as mental depression, behavioral disorders, anorexia, hypertension, sleep disorders, *etc* [1] have been related to the serotonergic functions in humans. The current concept of 5-hydroxytryptamine (5-HT) receptors is as complicated as its relationship to the disease states. Gaddum and Picarelli [2] proposed M- and D-receptors based on their experiment of morphine and dibenamine blockade of serotonin receptors in the guinea pig ileum. Edvinsson *et al.* [3,4], however, demonstrated that an intracranial serotonin receptor is different from the M- or D-receptors in both cat and human. The existence of another serotonin receptor different from either M- or D-receptor was also observed by Humphrey [5]. From *in vitro* binding studies of various tissues, Snyder *et al* [6,7] defined two distinct receptor bidning sites; 5-HT_1 (or S_1) and 5-HT_2 (or S_2) which could be labeled with high affinity by [^{3}H]-serotonin and [^{3}H]-spiperone, respectively. Leysen *et al* [8,9] also observed the similar findings. However, differentiation of multiple serotonin receptors remains limited because of the lack of

Scheme I Chemical Ionization Mass Spectral Fragmention Pattern

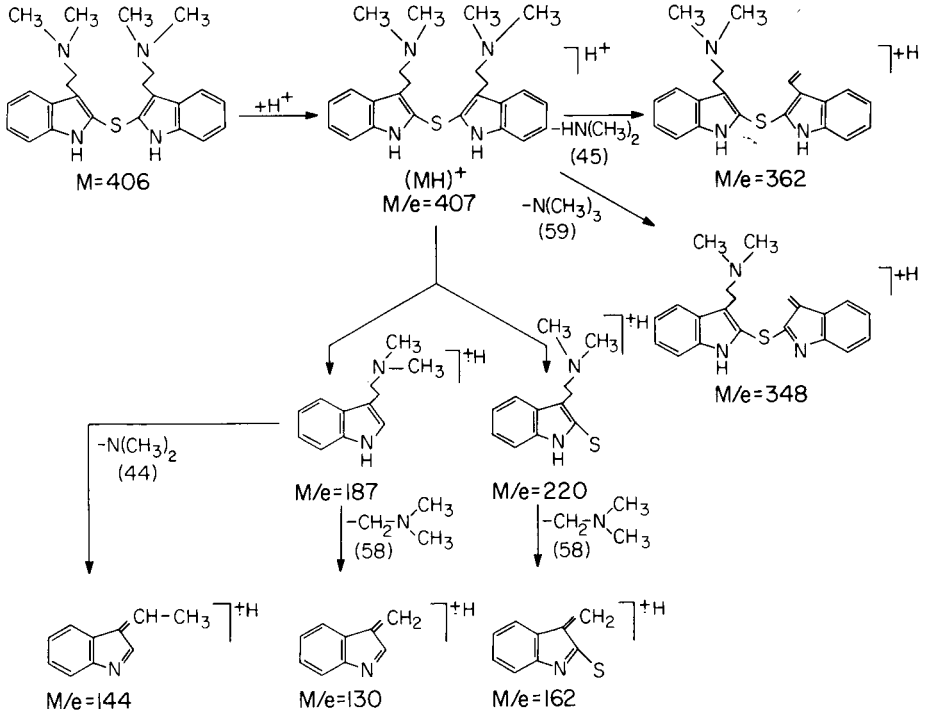
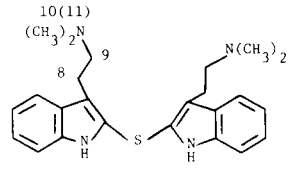


Table 1. ^{1}H and ^{13}C NMR Data



BDIS

$CDCl_3$/TMS (PPM)

Position / Type	1	2	3	3a	4	5	6	7	7a	8	9	10 (11)
^{1}H	11.80 (s)	-	-	-	5.45 (d)	7.00 (t)	7.03 (t)	7.08 (d)	-	3.15 (t)	2.75 (t)	2.49 (s)
^{13}C		123.90	117.46	127.20	118.97	123.15	119.65	111.66	136.85	22.41	59.91	45.42

more highly specific serotonin receptor antagonists.

One new 5-HT blocking agent, ketanserin, currenlty undergoing clinical trials as an antihypertensive agent [10-12], was demonstrated to be specific and potent in the rat frontal cortex for the 5-HT_2 receptor [13-15]. However, its mode of action as a hypotensive agent has not been unambiguously determined whether the observed clinical activity is related to 5-HT_2 [12] or alpha-adrenoreceptor [16] blocking activity. As a part of our program to develop specific serotonin antagonists related to 5-HT, we synthesized 2,2′-bis[3-(2-*N,N*-dimethylaminoethyl)indolyl]sulfide (BDIS). We wish to report here its synthesis, structure determination, and preliminary biological activities.

The title compound (BDIS) was obtained in low yield (about 30%) as the hydrochloride salt [17] in one step by the treatment of *N,N*-dimethyltryptamine with thionyl chloride in chloroform at room temperature. Although similar reactions of ethyl indole-2-carboxylate with thionyl chloride to form bis(2-ethoxycarbonyl-3-indolyl)sulfide were observed [18,19], the formation of indole-2-sulfide bond has not been reported in the literature. Furthermore, the mechanism of reaction for formation of these products is not well understood.

The structural assignment was made on the basis of elemental analysis, ^{1}H- and ^{13}C-nmr spectra (Table 1) as well as the analysis of mass spectral fragmentation pattern (Scheme 1). The ^{1}H nmr spectrum at 270 MHz clearly indicated the absence of one hydrogen on the five membered ring portion of the indole ring, which corresponds to H-2. This was confirmed by homonuclear decoupling experiments. The spectrum also shows that four hydrogens consisted of two doublets (H-4 and H-7) and two triplets (H-5 and H-6), which clearly indicates the unsubstitution on the benzene ring. Additionally, two pseudotriplets (δ 3.15 and 2.75) and a singlet (δ 2.49) indicated the presence of dimethylamino moiety. Selective decoupling experiment together with the spectral comparison to that of *N,N*-dimethyltryptamine allowed the assignment of ^{13}C nmr spectrum (Table 1). In addition, the mass spectral pattern (Scheme 1) and elemental analysis [20] provided crucial information for the structure as a sulfur bridged dimer of *N,N*-dimethyltryptamine.

In vitro serotonergic blocking activity of BDIS was determined in the rabbit aortic and rat stomach fundus tissues. In the rabbit aortic tissue, the receptor blocking activity at a concentration of $4.6 \times 10^{-6} M$ was characterized as competitive serotonin antagonist, which resembles that of ketanserin [21]. Preliminary antihypertensive activity was tested in adult male Sprague-Dowley rats anesthetized with sodium pentobarbital (50 mg/kg, IP). Under this condition the average blood pressure drop and heat rate reduction were 14 ± 4 (mm Hg) and 39 ± 9 (beat/minute), respectively.

The compound was tested in an anticonvulsant screening system [22]. BDIS induces convulsion-on-handling [23] and lowers intravenous pentylenetetrazole seizure threshold but anticonvulsant effects occur in a spontaneous epileptic rodent [23]. The behavioral effects induced resemble those of reserpine but without ptosis. These behavioral results suggest that the compound has a behavioral profile consistent with serotonin antagonist [24].

Based on these interesting *in vitro* and *in vivo* activities of BDIS, further biological evaluation of the compound as well as the structure-activity relationship of this new class of serotonin antagonists are warranted.

Acknowledgements.

One of the authors (CKC) would like to express his gratitude to Dr. Howard C. Ansel, Dean, and Dr. James T. Stewart, Professor and Head of the Department of Medicinal Chemistry and Pharmacognosy, the University of Georgia College of Pharmacy, for their support. The critical review of this manuscript by Professor C. Dewitt Blanton, Jr. is greatly appreciated.

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