Serotonin Inhibitors. II.[1] 2′-(3-Dimethylaminopropylthio)cinnamanilide and Related Compounds

JOHN KRAPCHO, ERVIN R. SPITZMILLER, CHESTER F. TURK, AND JOSEF FRIED

The Squibb Institute for Medical Research, New Brunswick, New Jersey

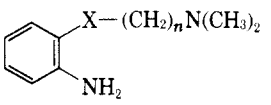
Received August 22, 1963

Although almost a century has passed since the demonstration that the vasoconstrictive power of blood increases after clotting, it was only in 1948 that the material responsible for the added vasoconstrictor activity was isolated in crystalline form, assigned the name serotonin, and then identified as 5-hydroxytryptamine.[2] Subsequent findings of significant quantities of serotonin in the brain, gastrointestinal tract, and malignant carcinoids stimulated a great deal of work in this field.[3] Despite these extensive investigations, the role which serotonin plays in human physiology or pathology is still uncertain. It is not unreasonable to hope that this role may become more clearly defined by employing a highly selective serotonin inhibitor in those disorders in which serotonin has been implicated.

We have recently reported[1] the *in vitro* and *in vivo* antiserotonin activity of 2′-(3-dimethylaminopropylthio)cinnamanilide hydrochloride (Table II, **1**), a potent and highly selective serotonin inhibitor, and the effect of some structural changes on the antiserotonin activity. The synthesis of **1** and related compounds and their *in vitro* activity on the isolated rat uterus are reported herein.

The results obtained with the additional compounds emphasize the importance of the cinnamoyl group for high antiserotonin activity. Thus, replacement of that group by phenylpropiolyl (**8**), α-propylcinnamoyl (**7**), crotonyl (**5**), sorbyl (**6**), phenacetyl (**10**), and cinnamyl (**30**) led to compounds of lower activity. Benzylation of the amido group (**27**) also resulted in decreased activity. Variations in the basic group showed the amino compound (**24**) slightly less potent than the corresponding methylamino (**23**) and dimethylamino (**14**) analogs.

TABLE I



No.	X	n	B.p. °C.	B.p. mm.	Formula	% Nitrogen Calcd.	% Nitrogen Found
A	S	3	115–118	0.3	$C_{11}H_{18}N_2S$[a]	13.32	13.30
B	S	2	115–119	0.4	$C_{10}H_{16}N_2S$	14.27	14.09
C	O	4	130–133	0.5	$C_{12}H_{20}N_2O$	13.45	13.14
D	O	3	110–114	0.2	$C_{11}H_{18}N_2O$	14.42	14.69
E	O	2	100–102	0.1	$C_{10}H_{16}N_2O$	15.54	15.12
F[b]	2-[3-(4-Methyl-1-piperazinyl)propylthio]aniline				$C_{14}H_{23}N_3S$	15.83	16.01
G[b]	2-[2-(Methylphenethylamino)ethylthio]aniline				$C_{17}H_{22}N_2S$	9.78	9.51
H[c]	N-[2-(2-Aminophenylthio)ethyl]phthalimide				$C_{16}H_{14}N_2O_2S$	9.39	9.28
I[b]	2-(3-Dimethylaminopropoxy)-4-methoxyaniline				$C_{12}H_{20}N_2O_2$	12.49	12.34
J[b]	5-Chloro-2-(3-dimethylaminopropoxy)aniline				$C_{11}H_{17}ClN_2O$	12.25	12.06
K[b,d]	N-[2-(3-Dimethylaminopropylthio)phenyl]benzylamine				$C_{18}H_{24}N_2S$	9.33	9.39
L[b]	4-(3-Dimethylaminopropylthio)aniline				$C_{11}H_{18}N_2S$	13.32	13.23
M[b]	3-(3-Dimethylaminopropoxy)aniline				$C_{11}H_{18}N_2O$	14.42	13.53[e]

[a] The dihydrochloride melted at 233–235° (from 95% ethanol). *Anal.* Calcd. for $C_{11}H_{18}N_2S \cdot 2HCl$: Cl, 25.03; N, 9.89. Found: Cl, 24.93; N, 9.66. [b] B.p., °C. (mm.): F, 171–174 (0.2); G, 177–183 (0.2); I, 135–138 (0.2); J, 141–146 (0.2); K, 179–183 (0.4); L, 133–138 (0.1); M, 116–119 (0.1). [c] M.p. 115–117° (from benzene). [d] Prepared in 60% yield by sodium borohydride reduction (in methanol) of N-benzylidene-2-(3-dimethylaminopropylthio)aniline; b.p. 182–189° (0.4 mm.). *Anal.* Calcd. for $C_{18}H_{22}N_2S$: N, 9.39. Found: N, 9.49. The latter compound was obtained in 78% yield by heating equivalent quantities of A and benzaldehyde in xylene for 4 hr. [e] Analysis and infrared spectra indicated contamination by a small quantity of the starting nitro compound.

Experimental[4]

2-(3-Dimethylaminopropylthio)aniline. (A).—A slurry of 57.0 g. (1.0 mole) of sodium methoxide (Mathieson, 95% $NaOCH_3$) in 800 ml. of isopropyl alcohol was treated with a solution of 125 g. (1.0 mole) of 2-aminobenzenethiol in 200 ml. of isopropyl alcohol. The resulting solution was stirred for 30 min. at room temperature, treated with a solution of 134 g. (1.1 moles) of 3-dimethylaminopropyl chloride in 620 ml. of toluene, and the mixture was refluxed for 6 hr. The solvent was removed under reduced pressure; the residue was treated with 100 ml. of water and extracted with 300-ml. portions of ether. After drying over magnesium sulfate, the solvent was evaporated and the residue fractionated to give 170 g. (81%) of product.

Most of the other compounds of Table I were obtained, usually in 60–85% yields, by the alkylation of 2-or 4-aminobenzenethiol with the appropriate substituted alkyl chloride (in the preparation of H, N-(2-bromoethyl)phthalimide was used); the related oxy compounds were obtained by a similar alkylation of the appropriate nitrophenol, followed by catalytic or stannous chloride (in the preparation of J) reduction of the intermediate nitro compounds. In the case of C, the intermediate was obtained by the reaction of 2-(4-chlorobutoxy)nitrobenzene, b.p. 150–155° (0.1 mm.) (from *o*-nitrophenol, sodium methoxide, and tetramethylene chlorobromide in isopropyl alcohol–dimethylformamide) with sodium iodide and then dimethylamine in benzene.

2′-(3-Dimethylaminopropylthio)cinnamanilide Hydrochloride (1).—A solution of 24.8 g. (0.118 mole) of A in 50 ml. of chloro-

(1) Previous paper: J. Krapcho, B. Rubin, A. M. Drungis, E. R. Spitzmiller, C. F. Turk, J. Williams, B. N. Craver, and J. Fried, *J. Med. Chem.*, **6**, 219 (1963).

(2) The historical aspect of this work has been summarized by I. H. Page, *Physiol. Rev.*, **34**, 563 (1954).

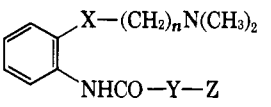
(3) I. H. Page, *ibid.*, **38**, 277 (1958); L. Gyermek, *Pharmacol. Rev.*, **13**, 399 (1961).

(4) Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected.

form was added dropwise (15 min.) to a stirred solution of 19.7 g. (0.118 mole) of cinnamoyl chloride in 150 ml. of chloroform while maintaining the temperature at 15–20°. The mixture was refluxed for 1 hr. and the solvent removed under reduced pressure. The residue was digested in 100 ml. of hot acetone, cooled, and filtered to give 42.0 g. (94%) of colorless solid, m.p. 146–148°. Crystallization from acetonitrile did not change the melting point. We had previously obtained the free base of this compound by another procedure.[5]

It was necessary to remove the chloroform in this preparation due to high solubility of **1** in this solvent; the products listed in Table II were usually isolated by dilution of the cooled reaction mixture with anhydrous ether. Most of the other compounds of Table II were obtained by acylation of the amines listed in Table I, usually in yields exceeding 80%, with the appropriate acid chlorides.

TABLE II



No.	X	n	Y	Z	Salt[a]	M.p., °C.		—% Chlorine— Calcd.	Found	—% Nitrogen— Calcd.	Found	Anti-serotonin activity[b]
1	S	3	CH=CH	C_6H_5	I	146–148	$C_{20}H_{25}ClN_2OS$	9.41	9.29	7.43	7.45	++++
2	S	3	CH=CH	2-(Cl)C_6H_4	I	144–145	$C_{20}H_{24}Cl_2N_2OS$	17.24	17.32	6.81	6.55	++++
3	S	3	CH=CH	4-(Cl)C_6H_4	I	148–150	$C_{20}H_{24}Cl_2N_2OS$	17.24	17.09	6.81	6.77	++++
4	S	3	CH=CH	3,4,5$(CH_3O)_3C_6H_2$	I	81–83	$C_{23}H_{31}ClN_2O_4S$	7.59	7.57	6.00	6.23	++
5	S	3	CH=CH	CH_3	II	148–150	$C_{17}H_{24}N_2O_6S$	[c]		7.60	7.54	+++
6	S	3	CH=CH	$CH=CHCH_3$	I	125–127	$C_{17}H_{25}ClN_2OS$	10.40	10.10	8.22	8.16	+
7	S	3	C=CH | $(CH_2)_2CH_3$	C_6H_5	III	103–105	$C_{27}H_{34}N_2O_5S$	[d]		5.61	5.84	+++
8	S	3	C≡C	C_6H_5	I	143–145	$C_{20}H_{23}ClN_2OS$	9.46	9.64	7.47	7.65	++
9	S	3	CH_2CH_2	C_6H_5	II	124–126	$C_{22}C_{28}N_2O_5S$	[e]		6.48	6.34	+
10	S	3	CH_2	C_6H_5	I	101–103	$C_{19}H_{25}ClN_2OS$	9.71	9.65	7.67	7.66	+
11	S	3	CH_2	CH_3	II	131–133	$C_{16}H_{24}N_2O_6S$	[f]		7.86	8.00	+
12	S	3	.....	C_6H_5	II	152–153	$C_{20}H_{24}N_2O_6S$	[g]		6.93	7.15	++
13[h]	SO_2	3	CH=CH	C_6H_5	II	189–191	$C_{22}H_{26}N_2O_7S$	[i]		6.06	5.96	++
14	S	2	CH=CH	C_6H_5	I	163–165	$C_{19}H_{23}ClN_2OS$	9.77	9.80	7.72	7.63	+++
15	S	2	CH_2CH_2	C_6H_5	II	132–134	$C_{21}H_{26}N_2O_5S$	[j]		6.70	6.53	++
16	O	4	CH=CH	C_6H_5	I	165–167	$C_{21}H_{27}ClN_2O_2$	9.46	9.35	7.47	7.62	++
17	O	3	CH=CH	C_6H_5	I	179–181	$C_{20}H_{25}ClN_2O_2$	9.83	9.59	7.76	7.83	++++
18	O	2	CH=CH	C_6H_5	I	212–214	$C_{19}H_{23}ClN_2O_2$	10.22	10.03	8.08	8.18	+++
	Cinnamanilides:											
19[k]	2′-(3-Diethylaminopropylthio)				I	179–181	$C_{22}H_{29}ClN_2OS$	8.75	8.62	6.92	7.00	++++
20	2′-[3-(4-Methyl-1-piperazinyl)propylthio]				IV	222–224	$C_{23}H_{31}Cl_2N_3OS \cdot H_2O$[l]	14.58	14.55	8.64	8.59	+++
21[m]	2′[3-(Benzylmethylamino)ethylthio]				I	168–170	$C_{25}H_{27}ClN_2OS$	8.07	7.92	6.38	6.03	++++
22	2′-[2-(Methylphenethylamino)ethylthio]				I	85–87	$C_{26}H_{29}ClN_2OS \cdot H_2O$[n]	7.53	7.60	5.95	6.20	+
23[o]	2′-(2-Methylaminoethylthio)				I	162–164	$C_{18}H_{21}ClN_2OS$	10.16	10.03	8.03	7.81	+++
24[p]	2′-(2-Aminoethylthio)				I	181–183	$C_{17}H_{19}ClN_2OS$	10.59	10.32	8.37	8.45	++
25	2′-(3-Dimethylaminopropoxy)-4′-methoxy				I	223–225	$C_{21}H_{27}ClN_2O_3$	9.07	8.93	7.17	7.23	+
26	5′-Chloro-2′-(3-dimethylaminopropoxy)				I	180–182	$C_{20}H_{24}Cl_2N_2O_2$	17.94	18.20	7.09	6.93	+
27	N-Benzyl-2′-(3-dimethylaminopropylthio)				II	97–99	$C_{29}H_{32}N_2O_6S$	[q]		5.38	5.18	++
28	4′-(3-Dimethylaminopropylthio)				I	238–240	$C_{20}H_{25}ClN_2OS$	9.41	9.57	7.43	7.44	−
29	3′-(3-Dimethylaminopropoxy)				III	136–138	$C_{24}H_{28}N_2O_6$	[r]		6.36	6.24	−
30[s]	N-[2-(3-Dimethylaminopropylthio)phenyl]-cinnamylamine				I	93–95	$C_{20}H_{27}ClN_2S$	9.77	9.78	7.72	7.95	+

[a] I, hydrochloride; II, oxalate; III, maleate; IV, dihydrochloride. These salts were crystallized from acetonitrile except **4** and **10** (acetone); **5**, **9**, **11**, **14**, **15**, **17**, and **20** (ethanol); **6** and **27** (butanone); **7** and **24** (2-propanol); **12**, **13**, and **28** (methanol); **22** (aqueous ethanol); **30** (ethyl acetate). [b] Activity measured on an isolated rat uterus. BAS = 1; ≥ 16–64 X = ++++; 4–16 X = +++; 1–4 X = ++; 1/4–1 X = +; and <1/4 X = −. Compound **1** was assayed directly against BAS and found to be 157 times more potent in this test. [c] Calcd.: C, 55.41; H, 6.57. Found: C, 55.45; H, 6.62. [d] Calcd.: C, 65.03; H, 6.87. Found: C, 64.91; H, 7.02. [e] Calcd.: C, 61.07; H, 6.52. Found: C, 60.94; H, 6.64. [f] Calcd.: C, 53.91; H, 6.79. Found: C, 54.05; H, 6.73. [g] Calcd.: S, 7.93. Found: S, 8.03. [h] Prepared by the oxidation of **1** with 28% H_2O_2 in acetic acid. [i] Calcd.: C, 57.13; H, 5.67. Found: C, 57.25; H, 5.61. [j] Calcd.: C, 60.26; H, 6.26. Found: C, 60.43: H, 6.47. [k] Obtained from the reaction of 2-(3-diethylaminopropylthio)aniline [S. C. Davis, G. L. Jenkins, A. M. Knevel, and C. Pagent, *J. Pharm. Sci.*, **51**, 840 (1962)] with cinnamoyl chloride. [l] Calcd.: C, 56.78; H, 6.84. Found: C, 57.00; H, 7.07. [m] This material was the major product of the alkylation of 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5H)-one with 2-(N-benzyl-N-methylamino)ethyl chloride.[5] [n] Calcd.: C, 66.29; H, 6.63. Found: C, 66.62; H, 6.80. [o] Obtained by treatment of **21** with ethyl chloroformate, followed by hydrolysis of the unpurified intermediate ethyl ester of 2′-{2-[carboxy(methyl)amino]ethylthio}cinnamanilide with 32% hydrogen bromide in acetic acid at room temperature. [p] Prepared in 47% yield by the reaction of excess hydrazine hydrate with 2′-(2-phthalimidoethylthio)cinnamanilide; m.p. 147–149° (from benzene). *Anal.* Calcd. for $C_{25}H_{20}N_2O_3S$: N, 6.54. Found: N, 6.68. The latter material was obtained in 76% yield by reaction of H with cinnamoyl chloride in the presence of an equivalent quantity of triethylamine. [q] Calcd.: C, 66.90; H, 6.20. Found: C, 66.74; H, 6.28. [r] Calcd.: C, 65.44; H, 6.41. Found: C, 65.47; H, 6.38. [s] Prepared in 66% yield by sodium borohydride reduction (in methanol) of N-cinnamylidene-2-(3-dimethylaminopropylthio)aniline; m.p. 73–75° (from hexane). *Anal.* Calcd. for $C_{20}H_{24}N_2S$: N, 8.64. Found: N, 8.66. The latter compound was obtained in 57% yield by heating equivalent quantities of A and cinnamaldehyde at 175–185° for 30 min.

Acknowledgment.—The authors are indebted to Dr. Bradford N. Craver and Dr. Bernard Rubin and their associates for the pharmacological data, to June Williams for the preparation of several of these compounds, and to Mr. Joseph Alicino and his staff for the analyses reported herein.

(5) J. Krapcho, E. R. Spitzmiller, and C. F. Turk, *J. Med. Chem.*, **6**, 546 (1963).