concerning the chemical and biological aspects of these studies will be forthcoming.

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2′-(3-Dimethylaminopropylthio)cinnamanilide and Related Compounds: A New Class of Potent and Relatively Specific Serotonin Inhibitors

JOHN KRAPCHO, BERNARD RUBIN, ANNE M. DRUNGIS, ERVIN R. SPITZMILLER, CHESTER F. TURK, JUNE WILLIAMS, BRADFORD N. CRAVER, AND JOSEF FRIED

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

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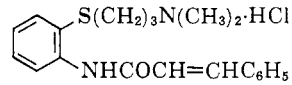
We wish to report the discovery of a new class of serotonin inhibitors show ng activity of a high order. Characteristic of these compounds is I



I

which *in vitro* at concentrations ranging from 0.0005 to 0.03 mcg./ml. inhibited the spasmogenic effect of 0.2 mcg./ml. of serotonin on the excised rat uterus. This corresponds to 157 times the antiserotonin activity of BAS[1] with a potency range of 60 to 407 times BAS at $p = 0.05$. The specificity of action of I was evident from the findings that concentrations as high as 2 mcg./ml. failed to inhibit the contractile response to acetylcholine (0.4 mcg./ml.) of the rat uterus and that concentrations of 0.5 to 8 mcg./ml. were necessary to inhibit histamine (2 mcg./ml.)-induced contractions of excised guinea pig ileum.

In vivo antiserotonin activity of I has been demonstrated in dogs and mice. Intravenous doses of about 150 mcg./kg. of I in pentobarbitalized-flaxedilized dogs produced 50% inhibition of the bronchoconstrictor effect of *i.v.* serotonin (20 mcg./kg.). About 4 mg./kg. *i.v.* of BAS was required for a similar degree of inhibition. Pretreatment of mice with oral doses of 32–128 mg./kg. of I partially to completely inhibited spontaneous head-twitch caused by 500 mg./kg. i.p. of *dl*-5-hydroxytryptophan. In contrast, BAS failed to inhibit this type of head-twitch after oral doses as high as 310 mg./kg.

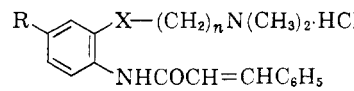
Compounds related to I have been synthesized (Table I) and studied on the excised rat uterus in order to define the structure–activity relationships in this series. The introduction of a chlorine atom into the *ortho* (II) or *para* (III) position of the cinnamoyl group gave compounds having essentially the same activity as I; replacement of the cinnamoyl moiety, however, by dihydrocinnamoyl (IV), benzoyl (V), and propionyl (VI) yielded compounds having activity comparable to BAS. Substitution of a diethylamino (VII) for the dimethylamino group in I scarcely altered activity. Oxidation of I to the sulfone (VIII) led to a compound of considerably lower activity. The *para* isomer of I, 4′-(3-dimethylaminopropylthio) cinnamanilide (IX), which no longer possesses the *ortho* relationship of the non-basic nitrogen and the basic substituent, exhibited little or no antiserotonin activity at 2 mcg./ml.

TABLE I

Compound	M.p., °C. (cor.) hydrochloride salt	Compound	M.p., °C. (cor.) oxalate salt
I	146–148	IV	124–126
II	144–145	V	152–153
III	148–150	VI	131–133
VII	179–181	VIII	189–191
IX	238–240		

Other structural variants of I (Table II) are represented by the general formula II.

TABLE II



II

Cpd.	R	X	*n*	M.p., °C (cor.)
X	H	O	4	165–167
XI	H	O	3	179–181
XII	CH_3O	O	3	223–225
XIII	H	O	2	212–214
XIV	H	CH_2	1	189–191

The oxygen analog of I (XI) had antiserotonin activity comparable to that exhibited by I. It is of interest that the introduction of a methoxyl group into this compound (XII) led to considerable deactivation. Decreasing the length of the side chain by one carbon atom (XIII) resulted in minor reduction of activity, whereas an increase by one carbon atom (X) yielded a considerably less active compound. Moderate activity was shown by a compound (XIV) which contained only methylene groups in the side chain. The *meta* isomer of IV, 3′-(3-dimethylaminopropoxy)cinnamanilide maleate (XV), m.p. 136–138° corr., showed little or no antiserotonin activity at 2 mcg./ml.

The following examples are illustrative of the synthetic procedures used. Reaction of 2-aminobenzenethiol with 3-dimethylaminopropyl chloride in the presence of sodium methoxide or sodamide gave 2-(3-dimethylaminopropylthio)aniline. This intermediate exhibited no significant antiserotonin activity. Acylation with cinnamoyl chloride gave I. The alkylation of *o*-nitrophenol with 3-dimethylaminopropyl chloride yielded 2-(3-dimethylaminopropoxy)nitrobenzene. Catalytic reduction of this compound followed by reaction of the resulting amine with cinnamoyl chloride gave XI. In a similar manner, 2-(2-dimethylaminoethyl)nitrobenzene (from *o*-nitrophenethyl bromide and dimethylamine) was converted to XIV.

Further laboratory investigations of I and related compounds are in progress. Papers describing chemical and biological aspects in more detail will be forthcoming.

(1) BAS is 1-benzyl-2-methyl-3-(2-aminoethyl)-5-methoxyindole hydrochloride. The antiserotonin activity of this compound was reported by E. N. Shaw and D. W. Woolley, *J. Pharm. Expll. Therap.*, **116**, 164 (1956).