PHARMACOLOGICAL STUDY OF 2-CHLORO-3-ORGANYLAMINO DERIVATIVES OF BENZO[b]THIOPHENE SULFONE

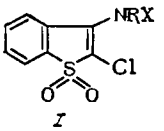
S. K. Germane, V. É. Udre, and R. O. Vitolinya

UDC 612.214:547.735

Benzo[b]thiophene derivatives display a wide range of biological activity. Some of these compounds possess psychotropic, analgesic, and antihistamine activity, and also exert an effect on the cardiovascular system [1-6].

The object of the present work was to synthesize 2-chloro-3-organylamino derivatives of benzo[b]thiophene sulfone and to study their psychotropic activity, and their effect on the cardiovascular system in order to compare their structures and pharmacological action.

2-Chloro-3-organylamino derivatives of benzo[b]thiophene sulfone (I) were obtained by the method described in [7], by adding primary or secondary amines or amino alcohols to the $C_2 = C_3$ double bond of 2,3-dichlorobenzo[b]thiophene sulfone. The reaction takes place with loss of hydrogen chloride, which combines with an excess of the corresponding amine.



I

X = H, OH, NH_2; R is an alkene or cycloalkene.

Pharmacological studies were performed on BALB/c mice of both sexes weighing 18-22 g, on white female rats weighing 200-250 g, and on cats of both sexes weighing 2.3-3.7 kg.

The compound was introduced intraperitoneally in increasing doses 15-30 min before the performance of the experiment. Solutions of the compounds in dimethyl acetal were prepared for intraperitoneal injection. A corresponding volume of an isotonic solution of sodium chloride or of the solvent used was injected into the control animal.

Experimental data were treated statistically. Student's criteria [8] were used to evaluate the difference between the average magnitudes. Differences were considered significant for a level of probability P = 0.05.

The effect of the compounds on the motor coordination and muscular tone was studied by the "rotating rod" method [9] and the "chimney" test [10]; the effect on the duration of the action of hypnotic drugs — hexenal (70 mg/kg, intravenously), medinal (150 mg/kg, intraperitoneally), and chloral hydrate (300 mg/kg, intraperitoneally) — was also studied. The duration of sleep in minutes was determined from the moment of loss of the righting reflex until its reestablishment. In addition, the potentiation indices of (I) for the narcotic effect of the drugs were determined. The analgesic action was studied by the "hot plate" method [11]. The antispasmodic action was determined by the maximum electric shock test [12], and with convulsions induced by the introduction of Corazole (0.5% solution, intravenously at a speed of 0.05 ml/sec). Amphetamine stereotype [13] was used to evaluate the adrenergic and dopaminergic processes. The effect on the temperature of the body was determined in experiments on white mice, the temperature was taken before the introduction of the compound and every 30 minutes for 4 hours after introduction. The temperature was taken

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 10, No. 10, pp. 16-21, October, 1976. Original article submitted February 24, 1976.

in the rectum with an electrothermometer. The mean effective dose which caused a hypothermic effect of 3° and greater was determined. The acute toxicity of the compounds was also studied in experiments on white mice. A number of measurements were made in experiments on cats (narcotized with chloralose, 90 mg/kg, intraperitoneally); the total arterial pressure and breathing were recorded, the effect of the substance on the electrical stimulation of cardiac fibers of the vagus nerve (30 Hz, 0.05 μsec, 10 V) and the effect of the substance on the hemodynamic action of acetyl choline (0.3 μg/kg), adrenaline (1.2 μg/kg), and histamine (1 μg/kg) were studied. The mean effective concentrations of the substances which lowered the effect of acetyl choline (10^{-7} g/ml) and barium chloride (10^{-4} g/ml) were determined using isolated lengths of rat colon.

The results of experiments are given in Table 1. It was found that in low doses none of the compounds studied had a significant effect on the behavior or motor activity of experimental animals. On increasing the dose, a general quieting of the animals was observed, and this was accompanied by a decrease in the motor activity, some relaxation of the skeletal muscles and a disturbance in the coordination of movements.

No significant differences between individual compounds were observed as far as their overall action was concerned, but for the mean effective values which characterize the psychotropic activity of the compounds, a relationship between activity and the substituents in the 3 position of benzo[b]thiophene sulfone was noted. N-Alkyl- and N-arylpiperazino derivatives of benzo[b]thiophene sulfone display depressing activity; they exert analgesic and hypothermic action, they cause a disturbance of the coordination of movement and a relaxation of the skeletal muscles. Piperazine derivatives also increase the hypnotic action of cortical and basal narcotics. The potentiating action was most pronounced with alkylpiperazine derivatives of benzo[b]thiophene sulfone when hypnotics of the barbiturate series were used (Medinal and sodium barbiturate).

N-Alkyl piperazine derivatives of benzo[b]thiophene sulfone also reduce the duration of stereotypic movement in white rats, and prolong the latent period.

Hydroxyamino and diamino derivatives of benzo[b]thiophene sulfone have similar ED_{50} values for analgesic, hypothermic, and muscle weakening action, but they differ considerably from piperazine derivatives in their influence on the effects of amphetamine, a dopaminomimetic compound.

Cycloamino derivatives of benzo[b]thiophene sulfone display some depressing activity (see Table 1, compounds 18, 20, and 21); this kind of activity is not observed in the remaining compounds, even at near-lethal doses.

Cycloamino derivatives of benzo[b]thiophene sulfone (compounds 17, 19, 20, and 21) increase the effects of amphetamine.

Hydroxyamino derivatives of benzo[b]thiophene sulfone (compounds 11 and 12) possess antispasmodic activity as well as depressing action on the central nervous system. These compounds reduce amphetamine stereotypy in rats, as do also piperazine derivatives.

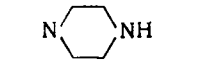
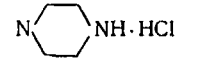
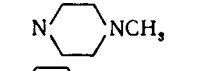
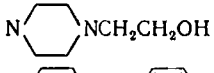
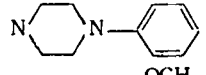
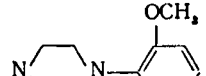
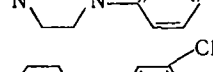
In experiments on cats it was observed that N-alkyl and N-aryl piperazine derivatives of benzo[b]thiophene sulfone (compounds 2, 5, and 6) in doses of 0.5-3 mg/kg give a pressor effect (10-30 mm mercury) or cause an increase in the arterial pressure followed by a decrease (compounds 1 and 3). Compounds with piperazine (compound 18) and diamino (compounds 7/5) substituents also cause some hypertensive reaction.

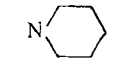
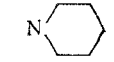
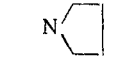
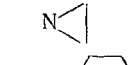
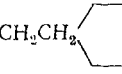
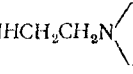
Derivatives of benzo[b]thiophene sulfone with branched hydroxyalkyl amino (compounds 11 and 12), cycloamino (compound 18), and ethylenediamino (compound 14) substituents give a temporary depressor effect (10-40 mm mercury) in doses of 0.5-2 mg/kg.

Some piperazine derivatives of benzo[b]thiophene sulfone in doses of 0.5-2 mg/kg display antihistamine activity (compounds 1, 3, and 6) and adrenosensitizing activity (compounds 2 and 6); diamino derivatives (compounds 14 and 15) also increase the pressor reaction of adrenaline.

All the substances studied show approximately the same degree of antagonism in relation to the spasmogenic action of barium chloride on isolated lengths of rat intestine. Piperazine derivatives (compound 1 and 6), piperidine (compound 18), and ethylene diamine derivatives (compound 14) decreased the smooth muscle contraction caused by acetyl choline in very low concentrations (10^{-6} g/ml).

TABLE 1. Pharmacological Activity of Benzo[b]thiophene Sulfone Derivatives

Compound No.	NRX	LD_{50}, mg/kg	ED_{50}, mg/kg					Potentiation index				Change in amphetamine stereotypy*	
			"rotating rod" test	"chimney" test	analgesic activity	hypothermia of 3° and greater	electric shock	chloral hydrate	Medinal*	hexenal		min	%
								dose of 20 mg/kg	dose of 20 mg/kg	dose of 20 mg/kg	dose of 100 mg/kg		
1		79 (68÷92)	9,3 (7,8÷11,1)	>20	>50	7 (3,7÷13,3)	>50	1,20	2,49†	3,10†	—	−18,5	7,4
2		1350 (1106÷1647)	95 (68÷133)	125 (83÷181)	>500	140 (108÷182)	>500	2,98†	2,68†	4,58†	5,08†	−34,5	16,5†
3		145 (127÷165)	32 (25÷41)	50 (33÷75)	31 (22÷43)	93 (7,8÷11,1)	>100	2,05†	6,23†	2,31†	3,42†	−121,5	60,4†
4		760 (623÷927)	330 (254÷429)	350 (265÷462)	140 (90÷127)	70 (37÷133)	>500	1,85†	0,98	1,58†	2,65†	−22,6	8,8
5		>5000	>1000	>1000	500 (333÷750)	37 (29÷49)	>500	1,75†	6,13†	3,20†	—	−6,5	2,2
6		>5000	>1000	>1000	>1000	80 (59÷109)	>500	2,35†	6,11†	0,82	1,71†	+12,0	5,7
7		>5000	165 (127÷215)	>500	375 (289÷488)	315 (250÷409)	>500	1,23	2,60†	2,79†	4,15†	+8,6	4,5
8	$NHCH_2CH_2OH$	1250 (947÷1650)	230 (169÷313)	390 (323÷464)	170 (110÷264)	200 (143÷280)	>500	1,85†	1,54†	2,04†	2,92†	+30,6	22,2†

9	$NH(CH_2)_2CH_2OH$	8600 (7610÷9718)	400 (267÷600)	>700	750 (540÷1043)	600 (455÷792)	>800	2 36†	1,60†	2,58†	3,58†	+6,2	3,5
10	$NH(CH_2)_5CH_2OH$	>5000	250 (179÷350)	>500	>500	250 (179÷350)	>500	1,43	2,35†	2,75†	4,39†	+1,0	0,5
11	$NHCHCH_2CH_2OH$ CH_3	660 (574÷759)	170 (81÷357)	>500	375 (289÷488)	165 (127÷215)	450 (363÷558)	1,00	2,08†	1,94†	3,44†	—14,3	6,1
12	CH_3 $N—CH_2CH_2OH$	345 (278÷428)	250 (179÷350)	>500	>500	250 (179÷350)	315 (250÷409)	1,39	2,20†	2,24†	5,68†	—23,7	11,7†
13	$N(CH_2CH_2OH)_2$	250 (172÷362)	225 (178÷283)	260 (208÷325)	>500	120 (103÷139)	>500	3,02†	0,72†	2,57†	2,82†	+22,1	12,3†
14	$NH(CH_2)_2NH_2$	1350 (1106÷1647)	250 (170÷360)	>500	700 (540÷910)	26 15÷44	>500	1,13	2,11†	2,10†	2,20†	—8,0	3,5
15	$NH(CH_2)_2CHCH_2OH$ NH_2	670 (588÷764)	>500	>500	>500	>500	>500	0,85	2,46†	1,34	2,05†	—12,0	4,7
16	$NHCH(CH_2)_3N(C_2H_5)_2$ CH_3	750 (641÷878)	250 (179÷350)	375 (288÷487)	>500	250 (179÷350)	>500	1,21	0,68	1,45†	2,19†	+6,6	10,6
17		7200 (5901÷8784)	250 (179÷350)	>500	>500	>500	>500	1,16	1,87†	1,92†	2,07†	+72,5	51,4†
18		1650 (1269÷2145)	155 (116÷208)	155 (116÷208)	270 (169÷432)	42 (31÷37)	>500	1,06	3,98†	3,63†	3,83†	+13,5	7,0
19		9000 (7438÷ ÷10 890)	250 (179÷350)	>500	>500	300 (252÷357)	>500	0,74	2,62†	2,65†	4,42†	+27,0	15,6†
20		2150 (1344÷3440)	200 (143÷280)	370 (218÷629)	120 (87÷166)	26 (18÷38)	>500	2,24†	1,54†	0,75†	1,27†	+21,8	10,6†
21		860 (754÷980)	170 (81÷357)	>500	225 (129÷427)	170 (81÷357)	>500	1,73†	3,70†	1,26†	2,11†	+34,8	17,5†
22		880 (759÷1021)	140 (119÷165)	155 (134÷180)	>500	130 (114÷148)	>500	1,91†	1,18	2,65†	3,77†	—0,6	0,3

*Experiments on white rats.
†$P < 0,05$.

The results obtained show that the organylamino derivatives of benzo[b]thiophene sulfone possess to a greater or lesser extent depressing activity, and some of them affect the stimulating action of amphetamine.

Hydroxyalkyl amino derivatives (compounds 11 and 12) with a branched alkyl chain (branched near the nitrogen atom) display antispasmodic activity. Compounds containing an unbranched hydroxyalkyl amino or diamino group (compound 15) do not possess such properties.

In addition to this, some benzo[b]thiophene sulfone derivatives possess hypotensive, antihistamine, and spasmolitic properties.

Comparison of the mean effective doses of amino derivatives of benzo[b]thiophene sulfones indicates that there are two factors which determine the most pronounced neurotropic activity of the derivatives — the presence of an alkylpiperazine substituent in the 3 position and the branched alkyl chain of the amino substituent.

Diamino derivatives of benzo[b]thiophene sulfone and some cycloamino derivatives are characterized by a very narrow interval between the depressing activity and a lethal effect.

The relationship which is found to exist between the depressing activity of the compound and its chemical structure indicates that it would be of interest to study new piperazino and hydroxyalkyl amino derivatives of benzo[b]thiophene sulfones.

LITERATURE CITED

1. E. Campaigne, D. R. Knapp, E. S. Neiss, et al., Adv. Drug. Res., 5, 1-54 (1970).
2. C. Kaiser and Ch. Zirkle, US Patent No. 3,546,232, 1970; Chem. Abstr., 74, 125,407 (1971).
3. Z. S. Ariyan and S. Y. Ma, German Patent No. 2,317,106, 1973; Chem. Abstr., 80, 27,092 (1974).
4. Z. S. Ariyan and S. Y. Ma, US Patent No. 3,790,600, 1974; Chem. Abstr., 80, 82,632 (1974).
5. C. Goldberg, R. Wandestrick, et al., Eur. J. Med. Chem. Chim. Ther., 9, No. 2, 123 (1974).
6. US Patent No. 3,528,994, 1970; Chem. Abstr., 74, 87,817 (1971).
7. V. É. Udre and M. G. Voronkov, Chemistry of Heterocyclic Compounds [in Russian], 1972, p. 1602.
8. M. L. Belen'kii, Elements of Quantitative Estimation of Pharmacological Activity [in Russian], Riga (1959).
9. N. W. Dunham and T. S. Miya, J. Am. Pharm. Assoc. Sci. Ed., 46, 208-209 (1957).
10. I. R. Boissier, Encephale, 1, 340-359 (1961).
11. N. B. Eddy and D. Leimbach, J. Pharmacol. Exp. Ther., 107, 385-393 (1953).
12. E. A. Swinyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, 319-330 (1952).
13. E. L. Shchelkunov, Farmakol. Toksikol., 5, 628-633 (1969).