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Effects of Thiophene Analogues of Chloroamphetamines on Central Serotonergic Mechanisms

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Ring-chlorinated thienylisopropylamines, thiophene analogues of chloroamphetamines, have been synthesized and their effects on serotonergic mechanisms in the rat brain have been evaluated. With 4,5-dichlorothienylisopropylamine (**3e**), a pharmacological profile similar to that of *p*-chloroamphetamine, consisting in a marked and long-lasting serotonin depletion and a rather strong and prolonged inhibition of synaptosomal uptake of serotonin, was found. Chloro substitution in position C_3 of the thiophene ring did not determine brain serotonin depletion nor serotonin uptake inhibition but enhanced brain MAO inhibitory activity present in all these compounds. 3,5-Dichlorothienylisopropylamine (**3g**) was the only compound of the series in which the inhibition of serotonin uptake was more marked than the serotonin depleting property.

Ring-halogenated amphetamines affect predominantly brain serotonin (5-HT) metabolism.[1] *p*-Chloroamphetamine (PCA) has been extensively studied in this regard, and it is known that this drug exerts multiple actions on 5-HT metabolism. PCA inhibits tryptophan hydroxylase,[2] releases serotonin from storage granules,[3,4] blocks serotonin reuptake into the serotonergic neurons,[4] and inhibits 5-HT metabolism by monoamine oxidase (MAO).[5] After treatment of rats with a high enough dose of PCA, some of the effects of this drug become irreversible. Thus, brain levels of 5-HT are markedly reduced for several months and the 5-HT synaptosomal uptake system shows also a long-term inhibition.[6] The selective neurotoxic actions of PCA on 5-HT neurons in the brain may result from the formation of a neurotoxic metabolite or from the prolonged permanence of the drug inside the neuron.[7] In any case, the continual uptake of PCA into the 5-HT neurons seems necessary to obtain neuronal destruction.[8] This continual uptake of PCA is possible due to the long half-life of this drug in the organism.[9] Human studies have shown that PCA, like other blockers of 5-HT reuptake, is an effective antidepressant.[10] However, the possibility of a toxic destruction of 5-HT neurons has perhaps prevented more extensive trials with this drug in psychiatry.

Fuller and Molloy[11] suggested that the multiple actions of PCA were potentially dissociable and, in fact, some PCA analogues which only retain some pharmacological features of the parent drug have already been developed.[12,13] With this aim, we have prepared some ring-chlorinated thienylisopropylamines, thiophene analogues of chloroamphetamines, and have studied their effects on some aspects of brain 5-HT dynamics. The bioisosteric equivalence of the benzene and thiophene rings is well known,[14] and we have recently found in our laboratory new examples of this bioequivalence.[15-17] On the other hand, the substitution of benzene by thiophene could perhaps lead in the present case to chloroamphetamines analogues more easily metabolized in the brain and, in consequence,

Scheme I

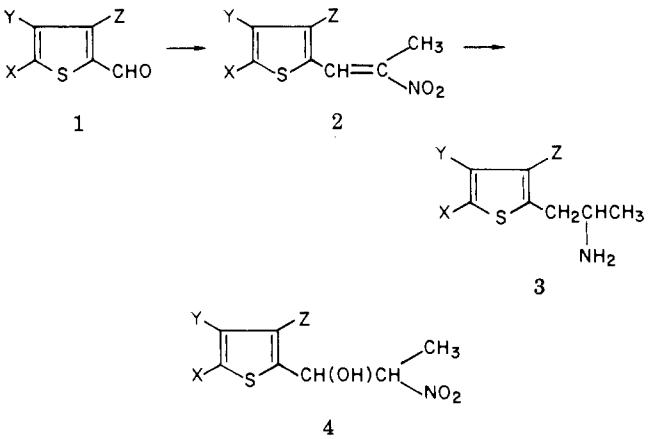

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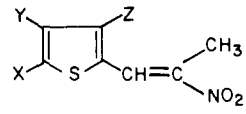
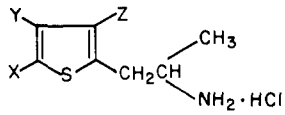
Table I. 1-(2-Thienyl)-2-nitropropenes



compd	X	Y	Z	yield, %	mp, °C	formula	analyses
2a	H	H	H	70	69[a]	$C_7H_7NO_2S$	
2b	Cl	H	H	75	102-103	$C_7H_6ClNO_2S$	C, H, N
2c	H	H	Cl	57	74	$C_7H_6ClNO_2S$	C, H, N
2d	H	Cl	H	87	60-61	$C_7H_6ClNO_2S$	C, H, N
2e	Cl	Cl	H	84	103-104[b]	$C_7H_5Cl_2NO_2S$	C, H, N
2f	H	Cl	Cl	52	91-92	$C_7H_5Cl_2NO_2S$	C, H, N
2g	Cl	H	Cl	79	72-73	$C_7H_5Cl_2NO_2S$	C, H, N

[a] Lit.[29] mp 68.5 °C (EtOH). [b] Lit.[31] mp 107 °C (EtOH).

Table II. 1-(2-Thienyl)isopropylamines



compd	X	Y	Z	yield, %	mp, °C	formula	analyses
3a	H	H	H	53	146[a]	$C_7H_{12}ClNS$	
3b	Cl	H	H	46	135	$C_7H_{11}Cl_2NS$	C, H, N
3c	H	H	Cl	41	172	$C_7H_{11}Cl_2NS$	C, H, N
3d	H	Cl	H	45	167	$C_7H_{11}Cl_2NS$	C, H, N
3e	Cl	Cl	H	58	162-163	$C_7H_{10}Cl_3NS$	C, H, N
3f	H	Cl	Cl	40	184	$C_7H_{10}Cl_3NS$	C, H, N
3g	Cl	H	Cl	62	181	$C_7H_{10}Cl_3NS$	C, H, N

[a] Lit.[29] mp 143-144.5 °C (EtOH-Et_2O).

Table III. Effects on Serotonergic Mechanisms in the Rat Brain

	% decrease of 5-HT[a]			% MAO inhibn,	% 5-HT uptake inhibn		
						in vivo[a]	
compd	4 h	24 h	7 days	in vitro[b]	in vitro[b]	24 h	7 days
3a	4.3 ± 2.6			6.2 ± 2.9	5.3 ± 3.0		
3b	14.5 ± 2.7	15.4 ± 3.2		28.6 ± 6.0	17.7 ± 3.8	4.1 ± 2.0	
3c	2.8 ± 2.0			28.0 ± 5.4	6.6 ± 2.9		
3d	22.1 ± 3.8	18.3 ± 4.1		15.5 ± 3.7	18.7 ± 3.4	6.7 ± 2.1	
3e	49.3 ± 7.5	50.7 ± 9.6	41.6 ± 7.1	23.4 ± 5.2	40.5 ± 7.3[d]	30.4 ± 5.8	32.4 ± 6.7
3f	10.3 ± 3.1	11.7 ± 2.9		72.7 ± 11.1[c]	27.5 ± 3.7	0.4 ± 1.8	
3g	12.1 ± 2.2	13.3 ± 3.3		44.0 ± 8.5[c]	19.4 ± 4.0	24.5 ± 5.1	
PCA	48.6 ± 8.0	47.6 ± 8.3	63.7 ± 10.4	33.6 ± 6.2[c]	38.4 ± 7.0[d]	45.5 ± 8.6	34.3 ± 7.1

[a] (±)-*p*-Chloroamphetamine hydrochloride (PCA) was given at 7.5 mg/kg ip; all other compounds were given at 15 mg/kg ip. Each value is the mean ± SE of four to seven experiments. Control value of brain 5-HT was 0.73 ± 0.02 μg/g (mean ± SE of 22 experiments). [b] The concentration of test compounds used for MAO inhibition or uptake inhibition studies was 1 and 0.2 μM, respectively. Each value is the mean ± SE of five determinations. [c] The following IC_{50} values were found: **3f**, 0.25 μM; **3g**, 2.5 μM; PCA, 3.7 μM. [d] The IC_{50} values of **3e** and of PCA were 0.45 and 0.50 μM, respectively.

with effects of shorter duration on 5-HT metabolism.

Chemistry. All the 1-(2-thienyl)isopropylamine derivatives **3** (Table II) reported in this work are racemic mixtures and were prepared by the sequence of reactions shown in Scheme I. 2-Thiophenealdehydes **1**, obtained from the appropriate thiophene by known methods or adaptations thereof, were heated at 60 °C for 2 weeks with nitroethane in the presence of catalytic amounts of *n*-butylamine to afford the corresponding 1-(2-thienyl)-2-nitropropenes **2** (Table I). Attempts made in order to synthesize these nitropropenes by the much quicker method of Profft and Wolf[18] always led to the intermediate alcohol **4**, identified by IR, NMR, and analyses data, as the main product. Compounds **2** were reduced by lithium aluminum hydride to the corresponding 1-(2-thienyl)-isopropylamines **3** (Table II), which were isolated as their hydrochlorides.

Pharmacological Results and Discussion. In preliminary studies the new thiophene derivatives and *p*-chloroamphetamine (PCA) were given ip to rats at a fixed dose of 7.5 mg/kg. This dose of PCA is known to induce marked effects on central serotonergic mechanisms.[6] Compound **3e** only decreased brain serotonin (5-HT) by 14.5% 4 h later, whereas PCA decreased 5-HT by 48%. The effect of all other thiophene derivatives was even less pronounced. Since, in general, PCA was about two times more toxic than the thiophene derivatives (Table IV), a double dose (15 mg/kg) of these compounds was used for the subsequent in vivo studies.

The effect of the thiophene derivatives on the brain concentration of 5-HT is shown in Table III. Chloro substitution in position C_4 and C_5 of the thiophene ring produced the highest reduction of brain 5-HT, and with compound **3e** (4,5-dichloro derivative) the marked decrease

Table IV. Effects on Locomotor Activity and Acute Toxicity in Mice

	locomotor act. in mice, counts/30 min[a]				
	5 mg/kg ip		10 mg/kg ip		approx LD_{50} in
compd	30 min	270 min	30 min	270 min	mice, ip
control	88	47	88	47	
3a	47	61	203[c]	59	162
3b	167[b]	103[b]	303[c]	131[c]	113
3c	48	69	81	67	101
3d	165[b]	75	375[c]	72	128
3e	225[c]	66	291[c]	77	133
3f	114	59	246[c]	82	121
3g	94	73	76	89	135
PCA	324[c]	129[b]	451[c]	242[c]	64

[a] Shown are the means obtained with at least eight animals (experimental groups) or with 90 animals (control groups). Test compounds were administered ip, and locomotor activity was measured at the intervals of time indicated. [b] Significantly different from controls, $p < 0.05$ (Wilcoxon matched-pairs signed-rank test). [c] $p < 0.01$.

of brain 5-HT persisted for 1 week at least. Chloro substitution in position C_3 (**3c**) did not produce, however, a decrease of brain 5-HT. The results obtained are thus parallel to those previously shown in the series of chloroamphetamines, in which brain 5-HT levels are reduced by 3-chloroamphetamine but not by 2-chloroamphetamine.[19] Positions C_4 and C_5 of the thiophene ring appear then to be equivalent to positions C_4 and C_3 of the benzene ring. Yet, thiophene derivatives monochlorinated at position C_4 (**3d**) or C_5 (**3b**) lowered brain 5-HT, whereas 3-chloroamphetamine only strongly lowered brain 5-HT when combined with desipramine to inhibit the para hydroxylation of amphetamine.[11]

Compound **3e** was also the most potent blocker of 5-HT uptake, either in vitro or in vivo. This compound mimics very closely the effects of PCA on serotonergic mechanism of the brain. PCA is approximately twofold more potent than compound **3e** but shows also a twofold higher toxicity. Of all other thiophene derivatives, only compound **3g** blocked to a relatively high degree 5-HT uptake when given in vivo (Table III). Compound **3g** was only a weak depletor of brain 5-HT so it seems that the structural requirements in this series for blocking 5-HT uptake or for inducing permanent loss of 5-HT from serotonergic neurons are not the same.

With regard to the in vitro inhibitory effect of the new thiophene derivatives on brain MAO activity, evaluated using 5-HT as a substrate, the highest activity was found with compound **3f** which was about 15-fold more potent than PCA in this regard. The highest inhibition of brain MAO was obtained in this series with thiophenes chlorinated in position C_3 (**3c**) and in some other position, C_4 (**3d**) or C_5 (**3b**), of the ring (Table III). The results are again parallel to those obtained in the benzene series in which 2,4-dichloroamphetamine shows an enhanced potency as an MAO inhibitor.[11] The presence of a chlorine atom in position C_3 of the thiophene ring is consequently of much importance for inhibition of brain MAO but not for depletion of brain 5-HT. The practical significance of the inhibition of brain MAO by compound **3f** remains, however, to be established since this compound is also a rather potent inhibitor of 5-HT uptake in vitro but loses this activity when administered in vivo.

The new thiophene derivatives were also tested for their effects on locomotor activity in mice (Table IV). With the exception of compounds **3c** and **3g**, the chloroamphetamine analogues induced a very significant, though short-lasting, increase of locomotion when given at 10 mg/kg. Only compound **3b**, like PCA, induced a stimulation of locomotor activity lasting more than 4 h. In some pilot studies carried out with rats (not shown in Table IV), a long-lasting increase of locomotor activity was also observed after compound **3b** or PCA. According to current theories[20,21] the effects of PCA and congeners on locomotor activity of rodents seem to be dependent on catecholaminergic rather than on serotonergic mechanisms. This may explain why compound **3e**, which induces a marked and long-lasting depletion of brain 5-HT and a prolonged inhibition of 5-HT synaptosomal uptake, does not produce, in contrast to PCA, a locomotor hyperactivity of long duration.

A brief comment should be finally made on the acute toxicity data reported in Table IV. The LD_{50} value found for PCA is much higher than that reported by other authors.[22] Yet, it is known that the acute toxicity of amphetamines and related compounds changes drastically depending on the aggregation state of the animals and on the ambient temperature. We never kept more than three animals to a cage and, on the other hand, room temperature never exceeded 18 °C. This may explain the lower toxicity found for PCA in the present study. By using identical experimental conditions, the new thiophene derivatives were found to be, on the average, half as toxic as PCA.

In summary, chloro substitution in positions C_4 and C_5 of the thiophene ring results in a compound which, like PCA, shows potent and long-lasting depleting effects on brain 5-HT. The 3,5-dichlorothiophene derivative is a 5-HT uptake blocker rather than a 5-HT depleting agent. Chloro substitution in position C_3 of the thiophene ring produces an enhanced brain MAO inhibitory activity.

Experimental Section

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values. IR and NMR spectra were recorded for all compounds and are consistent with assigned structures.

I. Chemical Methods. Chlorothiophenes. 2-Chlorothiophene was obtained by chlorination of thiophene.[23] 3-Chlorothiophene and 2,4-dichlorothiophene were made from the corresponding bromothiophene by a transhalogenation method.[24]

2-Thiophenealdehydes. 2-Thiophenealdehyde was obtained according to the method of Weston and Michaels.[25] The same method, except for the use of a longer reaction time (4 days), was applied to 2-chloro- and 3-chlorothiophene to yield 5-chloro-2-thiophenealdehyde[26] (59%) and 3-chloro-2-thiophenealdehyde[27] (53%), respectively. 4-Chloro-2-thiophenealdehyde was obtained by chlorination of 2-thiophenealdehyde according to the method of Iriarte et al.[28] The same method applied to 3-chloro- and 5-chloro-2-thiophenealdehyde afforded 3,4-dichloro-2-thiophenealdehyde[27] and 4,5-dichloro-2-thiophenealdehyde[27] in 75 and 90% yield, respectively. 3,5-Dichloro-2-thiophenealdehyde

was obtained following the method of Profft and Solft.[27]

1-(2-Thienyl)-2-nitropropenes 2a–g. General Method. A mixture of the corresponding aldehyde (0.1 mol), nitroethane (7.5 g, 0.1 mol), and *n*-butylamine (1 mL) was heated for 2 weeks at 50–60 °C in a well-closed flask. Et_2O (33 mL) was added and the solution vigorously stirred for 2 h with 50 mL of a 35% $NaHSO_3$ solution. Little amounts of solid appeared which were separated by filtration. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated in vacuo. The residue was recrystallized from EtOH (see Table I).

1-(2-Thienyl)isopropylamines 3a–g. These compounds were prepared by $LiAlH_4$ reduction of the corresponding nitropropenes following a standard procedure.[29] To a stirred suspension of $LiAlH_4$ (0.95 g, 0.025 mol) in dry Et_2O (50 mL) was added a solution of the corresponding nitropropene (0.00925 mol) in dry Et_2O (60 mL) at such a rate as to cause gentle reflux. After the addition was over, the mixture was stirred at room temperature for 2 h and then ice-cooled, and, first, wet Et_2O (50 mL) and then enough H_2O to hydrolyze the mixture were added. The ethereal layer was separated and the aqueous layer extracted twice with Et_2O. The combined ethereal solutions were extracted twice with 2 N AcOH; the aqueous phase was alkalinized with 20% NaOH and extracted with Et_2O. The ethereal layer was dried ($MgSO_4$) and treated with ethereal HCl. The precipitate hydrochloride was filtered, dried, and recrystallized from absolute EtOH–Et_2O (see Table II).

***p*-Chloroamphetamine hydrochloride** was obtained following the procedure described in a patent.[30]

II. Pharmacological Methods. Compounds for pharmacological testing were dissolved in saline for ip administration or in the adequate solutions for in vitro studies (see below). The animals used were male rats from a Wistar-derived strain (200–300 g) or male ICR Swiss mice (20–25 g). After administration of test compounds, the animals were kept three to a cage and room temperature was not allowed to exceed 18 °C.

Endogenous Levels of 5-HT. Test compounds were administered ip to rats 4 h, 24 h, or 7 days before killing the animals. The whole brains were then rapidly removed, weighed, and homogenized in 0.1 N HCl. Serotonin was determined by a fluorometric method.[32]

Synaptosomal Uptake of 5-HT. Whole rat brains were extracted and homogenized in 8 vol of 0.25 M sucrose. Synaptosomal uptake was essentially measured according to the method of Snyder and Coyle[33] with minor modifications, using a 0.1 μM concentration of [^{14}C]-5-hydroxytryptamine creatinine sulfate (Amersham). Uptake was calculated as nanomoles of 5-HT/mg of pellet/5 min. For in vitro studies, test compounds were dissolved in a modified Krebs solution and added at a fixed 0.2 μM concentration. IC_{50} values of the most active compounds were also calculated. When compounds were given in vivo, the animals were killed 24 h or 7 days after ip administration.

Brain Monoamine Oxidase Activity. The oxidative deamination of 5-HT by brain MAO was measured using [^{14}C]serotonin, 1.2 μM, according to previously described methods.[34] Rats were killed by decapitation and whole brains were homogenized in 20 vol of phosphate buffer, pH 7.2, 67 mM. Test compounds were dissolved in the phosphate buffer and studied initially at a fixed 1 μM concentration (roughly the previously found IC_{50} of PCA[5]). In subsequent studies IC_{50} values of the most potent inhibitors were calculated.

Spontaneous Locomotor Activity. Spontaneous locomotor activity in mice was measured by means of a battery of five circular actophotometers, 25-cm external diameter with four photocells and a central light source. Every cross of two consecutive beams resulted in only one count, so only locomotion was measured. Thirty minutes and 4.5 h after drug injection, the animals were placed into the actophotometer and their activity was recorded for 30 min.

Locomotor activity in rats was measured using three circular actophotometers similar to those described above, of 50-cm external diameter.

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