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SYNTHESIS AND TRANSFORMATIONS OF SULFIDES OF THE THIOPHENE SERIES.

39.* SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF SOME 2,5-DISUBSTITUTED 3-THIENYLALKYLAMINES

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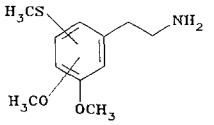
A number of isomeric 3-thienylalkylamines containing methylthio and methoxy groups in the α positions of the thiophene ring have been synthesized. It has been shown that they possess a weak activity of the stimulating and antidepressant type.

It is known that substituted phenethylamines are compounds of interest as potential psychotropic agents [2, 3]. Recently [4, 5], it has been shown that the sulfur analogs of natural psychotomimetic agents — mescaline and isomescaline (3,4,5- and 2,3,4-trimethoxyphenethylamines), type (I) — are psychomimetic agents 6-12 times more powerful than mescaline, while the corresponding dithio analogs have no appreciable influence on the central nervous system [5]. It has also been reported that all sulfur analogs of mescaline are readily deaminated by monoamine oxidase and are more suitable for this purpose than the corresponding oxygen compounds [4], although no direct correlation has been detected between the degree of decomposition by the enzyme and the psychotomimetic activity (for man).

Taking into account the frequently observed similarity in the biological activities of thiophene and benzene analogs [6], it appeared desirable to investigate within the plan considered above the corresponding derivatives of the thiophene series.

The present paper describes the synthesis and some psychopharmacological properties of substituted 3-thienyl alkylamines (II-IV) bearing methylthio and methoxy groups in the α positions of the thiophene nucleus.



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*For communication 38, see [1].

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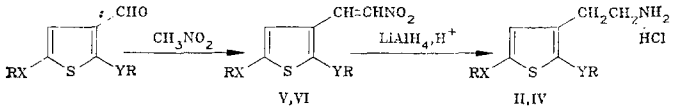
TABLE 1. Characteristics of the Compounds Synthesized

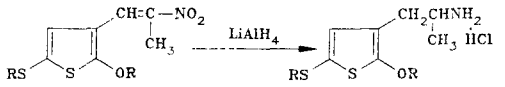
Compound	mp[a], °C	UV spectra (in ethanol), λ_{max}, nm (ε)	PMR spectrum[b], δ, ppm	Mass spectrum, m/z (I, %)	Found, %					Empirical formula, mol. wt.	Calculated, %					Yield, %
					C	H	Cl	N	S		C	H	Cl	N	S	
V	88—89	215 (11 550) 280 (13 105) 385 (11 995)	2,35 (3H, s, SCH_3), 4,02 (3H, s, OCH_3), 6,90 (1H, s, 4-H), 7,30 (1H, d, J=14 Hz, CH=CH), 7,70 (1H, d, J=14Hz, CH=CH)	231 (100), 216 (10), 188 (80), 170 (50)	41,4	3,8	—	4,6	27,6							79
VI	111—112	215 (11 020) 268 (9 918) 308 (13 003) 380 (7 052)	2,45 (3H, s, SCH_3), 3,94 (3H, s, OCH_3), 6,27 (1H, s, 4-H), 7,42 (1H, d, J=14 Hz, CH=CH), 8,27 (1H, d, J=14 Hz, CH=CH)	231 (94), 216 (5), 185 (100), 170 (100)	41,5	3,9	—	5,9	27,4	$C_8H_9NO_3S_2$, 231,29	41,5	3,9	—	6,06	27,7	52
VII[c]	49—50	215 (13 450) 282 (12 342) 380 (10 918)	2,33 (6H, s, CH_3, SCH_3), 3,97 (3H, s, OCH_3), 6,97 (1H, s, 4-H)	245 (59), 215 (11), 188 (100), 183 (36), 169 (36)	—	—	—	—	—	$C_9H_{11}NO_3S_2$, 245,22	—	—	—	—	—	—
II[d]	137—139	203 (12 278) 230 (3 837) 280 (7 290)	2,30 (3H, s, SCH_3), 2,69 (2H, t, J=7 Hz, CH_2CH_2), 3,05 (2H, t, J=7 Hz, CH_2CH_2), 3,83 (3H, s, OCH_3), 6,79 (1H, s, 4-H)	203 (50), 173 (100), 172 (50), 158 (90), 157 (30), 130 (17), 129 (20)	40,3	5,9	14,8	5,9	26,8							70
IV[d]	160—161	202 (10 522) 238 (4 797) 275 (7 273)	2,19 (3H, s, SCH_3), 2,98 (4H, m, CH_2CH_2), 3,74 (3H, s, OCH_3), 6,11 (1H, s, 4-H)	203 (75), 174 (34), 173 (17), 159 (100), 131 (20), 130 (22)	39,9	5,9	14,7	5,8	26,8	$C_8H_{13}NOS_2 \cdot HCl$, 239,78	40,1	5,9	14,8	5,9	26,8	40
III[d]	111—112	202 (5 823) 238 (2 911) 280 (9 747)	1,15 (3H, d, CH_3CH), 2,24 (3H, s, SCH_3), 2,63 (2H, d, CH_2CH), 3,43 (1H, m, $CHCH_3$), 3,78 (3H, s, OCH_3), 6,76 (1H, s, 4-H)	217 (18), 174 (100), 159 (89), 149 (74), 131 (17)	42,8	6,3	13,7	5,8	24,8	$C_9H_{15}NOS_2 \cdot HCl$, 253,74	42,6	6,4	14,0	5,5	25,2	38

a) The solvent for compounds (V-VII) was heptane, and for (II) and (IV) ethanol—ether. b) The PMR spectra of compounds (II-IV) were taken in D_2O, and those of (V-VII) in CCl_4. c) For the results of elementary analysis, see [7]. d) The mass spectra of the bases are given.

As the initial compounds for their synthesis we used 2-methoxy-, 5-methylthio-, and 5-methoxy-2-methylthiothiophene-3-carbaldehydes, accessible methods of obtaining which we had developed previously [7, 8]. The isomeric aldehydes were converted by Knoevenagel condensation with nitromethane [9] into the nitrovinyl derivatives (V and VI), which were then reduced with lithium tetrahydroaluminate in ether [10] to the corresponding alkylamines (II) and (IV). 3-(2-Aminopropyl)-2-methoxy-5-methylthiothiophene (III) was obtained similarly from the 2-methoxy-5-methylthio-3-nitroprop-1-enylthiophene (VII) that we have described previously [8].* The optimum yields of the amines (in the form of hydrochlorides) were obtained when using 2-2.5 moles of $LiAlH_4$ per 1 mole of nitrovinyl derivative.



V,VI II,IV



VII III

II, V X=S, Y=O; IV, VI X=O, Y=S; R=CH_3

The 2,5-disubstituted 3-thienylalkylamines (II-IV) obtained were tested in the pharmacological laboratory NIIBIKhS [Scientific-Research Institute for the Biological Testing of Chemical Compounds] (Kupavna) using a special set of tests employed for revealing preparations with a central neuropsychotropic action [11]. The following aspects were studied: the acute toxicity of the substances in a single intraperitoneal administration to male mice, and also the influence of these substances on the behavior of the animal, the body temperature, the motor orienting activity, and the number of movements in 10 min, and their influence on the effects of hexenal (60 mg/kg), apomorphine (2 mg/kg), phenamine (2 mg/kg), arecoline (25 mg/kg), reserpine (2 mg/kg), and corazole [pentylenetetrazole] (150 mg/kg). All the preparations were administered intraperitoneally 40 min before the experiment except for reserpine, which was administered 4 h before the substances tested. The doses of the substances were 10-20% of the LD_{50} values.

The investigations showed that substances (II-IV) possessed a moderate toxicity (the LD_{50} values (in mg/kg) amounted to 280 (213-366) for compound (II), 300 (246-366) for substance (IV), and 330 (270-392) for compound (III)), and they exhibited a weak activity of the stimulating and antidepressant type. One of them — 3-aminoethyl-2-methoxy-5-methylthiothiophene (II) — exhibited only stimulating properties: It caused some intensification of motor activity and the reactions of the animal to stimuli. In higher doses (100-200 mg/kg), the excitation became pronounced and was accompanied by spasms. Two other substances (III and IV), in small doses (1-10 mg/kg) caused weak stimulation of the animals; in higher doses their stimulating action was accompanied by sedative phenomena — ataxia, myorelaxation, and a fall in reactions to stimuli. This combination of stimulating and sedative properties is characteristic for the group of antidepressants. In the interaction tests, likewise, some differences were found in the action of the preparations. Isomer (II) shorted hexenal sleep, potentiated the effects of apomorphine, phenamine, and arecoline and weakly counteracted the development of reserpine ptosis and hypothermia. Compounds (IV) and (III) potentiated the effect of hexenal and intensified the effects of apomorphine, phenamine, and arecoline. However, the expression of both the stimulating action of the amine (II) and the antidepressant action of its isomer (III) and its homolog (IV) was weaker than for known standard preparations — caffeine and imipramine.

EXPERIMENTAL

UV spectra were taken on a Specord UV-vis spectrophotometer, PMR spectra on Varian DA-60IL and Tesla BS-497 (100 MHz) spectrometers with HMDS as internal standard. Molecular weights were determined by mass spectrometry, the mass spectra being obtained on a Varian MAT CH-6 instrument at an ionizing voltage of 70 V with a direct introduction of the sub-

*In one of the experiments with a deficiency of $LiAlH_4$, a small amount of a substance corresponding, according to the results of analysis and its IR and mass spectra, to the oxime of (2-methyl-5-methylthio-3-thienyl)acetone was isolated.

stance into the ion source. The constants, yields, elementary analyses, and mass, UV, and PMR spectra of the compounds synthesized are given in Table 1.

2-Methoxy-5-methylthio- and 5-Methoxy-2-methylthio-3-(β-nitrovinyl)thiophenes (V and VI). A solution of 1 g (5.34 mmole) of 2-methoxy-5-methylthio- or 5-methoxy-2-methylthiophene-3-carbaldehyde [7, 6] in 5 ml of ethanol was treated with 0.33 g (5.4 mmole) of CH_3NO_2, 0.04 g of $CH_3NH_2 \cdot HCl$, and 0.06 g of sodium carbonate and the mixture was left at 20°C for 12 h. The precipitate that had deposited was filtered off, washed with ethanol, dried, and recrystallized from heptane.

Hydrochlorides of 3-Aminoethyl-2-methoxy-5-methylthiothiophene (II), 3-(2-Aminopropyl)-2-methoxy-5-methylthiophene (III), and 3-Amino-5-methoxy-2-methylthiothiophene (IV). A solution of 10 mmole of one of the nitrovinyl derivatives (V) and (VI) in 100 ml of ether or of 2-methoxy-5-methylthio-3-nitroprop-1-enylthiophene (VII) in an atmosphere of Ar was added, in such a way that the mixture boiled gently, to a suspension of 20 mmole of $LiAlH_4$ in 30-40 ml of ether that had been distilled over $LiAlH_4$; the mixture was boiled for another 30 min and, after cooling, 5 ml of water and 20 ml of 20% aqueous K,Na tartrate (Seignette's salt; Rochelle salt) was added, the mixture was filtered, and the residue was washed on the filter with ether. The ether layer was separated and extracted with 2 × 15 ml of dilute HCl (1:10) and the acid extract was alkalinized with 10 ml of 20% aqueous NaOH. The oil that was liberated was extracted with ether, the extract was dried with $MgSO_4$, the ether was distilled off, and the residue (unpurified amine) was dissolved in a few ml of absolute ethanol, and 1 ml of an ethanolic solution of HCl and dry ether were added. The crystals of the hydrochloride that deposited were filtered off, washed with ether, dried, and reprecipitated from absolute ethanol with dry ether.

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