SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1,4-SUBSTITUTED THIOSEMICARBAZIDES AND 1,2,4-TRIAZOLES

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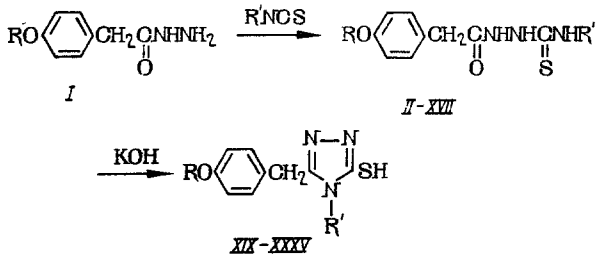
In recent years reports of the interesting biological properties of 1,2,4-triazole derivatives have been appearing at an ever increasing rate. Compounds with antidepressant [1, 2], antimicrobial [3], and antiviral [4] activity have been detected among substituted mercapto- and aminotriazoles. Of particular interest are the substituted thiosemicarbazides that constitute the starting compounds for the preparation of 1,2,4-triazoles; their biological properties have received relatively little attention. Substituted thiosemicarbazides, in contrast to thiosemicarbazide itself, which is a convulsant [5], are known to have anticonvulsant properties [6]. Taking this as our starting point, we have continued our work initiated with [7] by moving on to the synthesis of substituted thiosemicarbazides and 1,2,4-triazoles by the reaction sequence



$R = CH_3, \ldots, iso\text{-}C_4H_9$; $R' = CH_3$, $CH_2{=}CHCH_2$, $o\text{-}ClC_6H_4$.

The starting compounds were 4-alkoxyphenylacetohydrazides [8], reaction of which with isothiocyanates of various structures formed the substituted thiosemicarbazides (II)-(XVII). Cyclization of these in alkaline solution gave the 1,2,4-triazoles (XIX)-(XXXV). The synthetic compounds were chromatographically pure crystalline substances. Their mass spectra showed the molecular ions and characteristic fragment ions.

Examination of the antidepressant properties of the substituted thiosemicarbazides revealed that none prevent nicotine tremor or arecoline seizure, i.e., they are devoid of central n- and m- cholinolytic properties. Administration of the thiosemicarbazides with $R' = CH_3$, $CH_2{=}CHCH_2$ does not produce antagonism toward corazole and electroshock seizure. Replacement of these groups by phenyl in the thiosemicarbazides with $R = C_3H_7$ and C_4H_9 [8] produces a weak anticorazole effect. However, replacement of the alkoxybenzyl substituent by 4-bromophenoxy (XVIII) or 2,4-dichlorophenoxy [9] when a phenyl group is attached to the nitrogen in position 4 causes the activity in all tests to disappear. Thiosemicarbazides (XIV) and (XVII) show protective action against maximal electroshock seizure [$ED_{50} < 170$ mg/kg (130.3-221.0 mg/kg) and 135 mg/kg (96.3-189.0 mg/kg) respectively]; the weak anticorazole effect persists. Our results are consistent with published work [6], which imply that the attachment of an aromatic nucleus to the nitrogen in position 4 is accompanied by increase in the activity toward maximal electroshock seizure. Thus the presence of an aromatic ring seems to be a necessary condition for enhancement of the antidepressant properties of thiosemicarbazide derivatives.

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TABLE 1. 1,4-Substituted Thiosemicarbazides (II)-(XVII) and Substituted 1,2,4-Triazoles (XIX)-(XXXV)

Compound	R	R'	Yield, %	Melting point, °C	R_f	Found, %		Formula	Calculated, %	
						N	S		N	S
II	C_3H_7	CH_3	98,5	172—3	0,74	14,60	11,10	$C_{13}H_{19}N_3O_2S$	14,93	11,39
III	iso-C_3H_7	CH_3	93,9	142—3	0,72	14,81	11,25	$C_{13}H_{19}N_3O_2S$	14,93	11,39
IV	C_4H_9	CH_3	95,6	167—9	0,73	14,40	11,11	$C_{14}H_{21}N_3O_2S$	14,22	10,85
V	iso-C_4H_9	CH_3	97,6	139—50	0,70	14,51	10,65	$C_{14}H_{21}N_3O_2S$	14,22	10,85
VI	CH_3	CH_2=$CHCH_2$	87,8	148—9	0,[illegible]	15,23	11,28	$C_{13}H_{17}N_3O_2S$	15,04	11,47
VII	C_2H_5	CH_2=$CHCH_2$	88,7	137—8	0,[illegible]	14,17	10,65	$C_{14}H_{19}N_3O_2S$	14,32	10,92
VIII	C_3H_7	CH_2=$CHCH_2$	84,5	136—8	0,[illegible]	13,83	10,18	$C_{15}H_{21}N_3O_2S$	13,67	10,43
IX	iso-C_3H_7	CH_2=$CHCH_2$	87,2	147—6	0,[illegible]	13,42	10,21	$C_{15}H_{21}N_3O_2S$	13,67	10,43
X	C_4H_9	CH_2=$CHCH_2$	89,8	142—3	0,[illegible]	13,22	9,74	$C_{16}H_{23}N_3O_2S$	13,07	9,97
XI	iso-C_4H_9	CH_2=$CHCH_2$	90,0	146—7	0,[illegible]	12,88	10,12	$C_{16}H_{23}N_3O_2S$	13,07	9,97
XII	CH_3	o-ClC_6H_4	83,2	121—5	0,[illegible]	12,26	9,31	$C_{16}H_{12}ClN_3O_2S$	12,01	9,16
XIII	C_2H_5	o-ClC_6H_4	70,6	157—7	0,[illegible]	11,70	8,65	$C_{17}H_{14}ClN_3O_2S$	11,52	8,81
XIV	C_3H_7	o-ClC_6H_4	76,1	121—2	0,[illegible]	11,29	8,36	$C_{18}H_{16}ClN_3O_2S$	11,12	8,48
XV	iso-C_3H_7	o-ClC_6H_4	71,5	92—5	0,[illegible]	11,03	8,53	$C_{18}H_{16}ClN_3O_2S$	11,12	8,48
XVI	C_4H_9	o-ClC_6H_4	72,8	129—31	0,[illegible]	10,49	8,06	$C_{19}H_{18}ClN_3O_2S$	10,72	8,18
XVII	iso-C_4H_9	o-ClC_6H_4	69,3	111—2	0,60	10,81	8,12	$C_{19}H_{18}ClN_3O_2S$	10,72	8,18
XIX	CH_3	CH_3	[illegible],2	190—2	0,84	17,58	13,81	$C_{11}H_{13}N_3OS$	17,85	13,62
XX	C_2H_5	CH_3	[illegible],6	149—50	0,83	16,56	12,58	$C_{12}H_{15}N_3OS$	16,85	12,86
XXI	C_3H_7	CH_3	[illegible],5	138—40	0,82	16,13	12,29	$C_{13}H_{17}N_3OS$	15,94	12,17
XXII	iso-C_3H_7	CH_3	[illegible],3	136—7	0,80	16,20	11,82	$C_{13}H_{17}N_3OS$	15,94	12,17
XXIII	C_4H_9	CH_3	[illegible],9	141—[illegible]	0,81	15,36	11,67	$C_{14}H_{19}N_3OS$	15,15	11,56
XXIV	iso-C_4H_9	CH_3	[illegible],3	144—[illegible]	0,79	15,40	11,90	$C_{14}H_{19}N_3OS$	15,15	11,56
XXV	C_2H_5	C_6H_5	92,6	197—[illegible]	0,71	13,[illegible]	10,45	$C_{17}H_{17}N_3OS$	13,49	10,29
XXVI	C_3H_7	C_6H_5	85,7	219—[illegible]1	0,70	12,[illegible]	10,11	$C_{18}H_{19}N_3OS$	12,60	9,85
XXVII	iso-C_3H_7	C_6H_5	93,2	148—[illegible]	0,68	12,[illegible]	9,98	$C_{18}H_{19}N_3OS$	12,60	9,85
XXVIII	C_4H_9	C_6H_5	86,2	119—[illegible]20	0,69	12,[illegible]	9,21	$C_{19}H_{21}N_3OS$	12,37	9,44
XXIX	iso-C_4H_9	C_6H_5	92,3	189—[illegible]90	0,67	12,49	9,38	$C_{19}H_{21}N_3OS$	12,37	9,44
XXX	CH_3	CH_2=$CHCH_2$	98,4	91—[illegible]	0,69	16,31	12,03	$C_{13}H_{15}N_3OS$	16,07	12,27
XXXI	C_2H_5	CH_2=$CHCH_2$	98,8	126—7	0,68	15,29	11,52	$C_{14}H_{17}N_3OS$	15,36	11,64
XXXII	C_3H_7	CH_2=$CHCH_2$	96,2	74—5	0,66	14,42	10,87	$C_{15}H_{19}N_3OS$	14,72	11,08
XXXIII	iso-C_3H_7	CH_2=$CHCH_2$	95,6	76—8	0,64	14,39	11,21	$C_{15}H_{19}N_3OS$	14,72	11,08
XXXIV	C_4H_9	CH_2=$CHCH_2$	92,7	50—1	0,65	13,75	10,48	$C_{16}H_{21}N_3OS$	13,88	10,57
XXXV	iso-C_4H_9	CH_2=$CHCH_2$	97,5	83—4	0,63	14,06	10,72	$C_{16}H_{21}N_3OS$	13,88	10,57

Evaluation of the antibacterial properties of triazoles (XIX)-(XXXV) revealed that all are devoid of *in vitro* antimicrobial action toward *Staphylococcus aureus* and *Shigella flexneri*. We examined compounds (XXII), (XXVII), and (XXXIII) *in vivo*. A single administration of these compounds does not cause changes in the behavior and state of white mice (dose 2000 mg/kg). Chemotherapeutic experiments revealed that infected mice treated with these preparations (dose 1000 mg/kg) died at the same time as the control animals. Consequently these compounds have no therapeutic action toward infection by *S. aureus*.

We also examined the hypoglycemic activity of the thiosemicarbazide derivatives. Among the test compounds 1-(4-isobutoxyphenylacetyl)-4-methylthiosemicarbazide (V) and 1-(4-isobutoxyphenylacetyl)-4-allylthiosemicarbazide (XI) show definite hypoglycemic activity, reducing the blood glucose content by 18 and 20% respectively. The other compounds are inactive. Thus, the thiosemicarbazide derivatives include compounds with hypoglycemic activity.

EXPERIMENTAL CHEMICAL PART

Mass spectra were recorded on an MX-1303 spectrometer with direct sample insertion into the ionization chamber. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates developed with iodine vapor using an ultrachemiscope.

1,4-Substituted thiosemicarbazides (II)-(XVII). A mixture of (I) (0.01 mole) and the isothiocyanate (0.01 mole) in ethanol (10 ml) was refluxed for 30 min in the case of (II)-(V) and for 2 h in the case of (VI)-(XVII) and then left for 2-3 h. The precipitate was filtered off and recrystallized from ethanol. The TLC system was methanol—ether (2:1) (Table 1). Mass spectrum: (VIII): 307 (M^+), 289, 274, 208, 176, 149, 133, 107; (XII): 349 (M^+), 331, 319, 223, 180, 149, 121.

1-(4-Bromophenoxyacetyl)-4-phenylthiosemicarbazide (XVIII) was prepared like (XII)-(XVII). The yield was 2.32 g (90.2%), mp 172-174°C. Found, %: N 11.28, S 8.31. $C_{15}H_{14}BrN_3O_2S$. Calculated, %: N 11.05, S 8.43. R_f 0.64 in methanol-ether (2:1).

3-Mercapto-4-methyl(phenyl)-5-(4-alkoxybenzyl)-1,2,4-triazoles (XIX)-(XXIX). To (II)-(V) (0.025 mole) or 1-(4-alkoxyphenylacetyl)-4-phenylthiosemicarbazide (0.025 mole) [8] was added a solution of potassium hydroxide (0.04 mole) in water (30 ml). The mixture was refluxed for 2 h. The cooled solution was acidified with acetic acid; the precipitate was filtered off and recrystallized from methanol. The TLC system was methanol—ether (1:1) (Table 1). Mass spectrum: (XXI): 235 (M^+), 220, 202, 175, 161, 147, 121, 107, 91.

3-Mercapto-4-allyl-5-(4-alkoxybenzyl)-1,2,4-triazoles (XXX)-(XXXV). Compound (VI)-(XI) (0.005 mole) and potassium hydroxide (0.0075 mole) were dissolved in water (10 ml) and refluxed for 1 h. Acetic acid was added to the cooled solution to pH 5.0. The precipitate was filtered off and recrystallized from ether. The TLC system was methanol—ether (1:2), (Table 1). Mass spectrum: (XXXII): 261 (M^+), 246, 228, 220, 147, 121.

EXPERIMENTAL PHARMACOLOGICAL PART

We evaluated the antidepressant activity of the 1,4-substituted thiosemicarbazides in tests on 240 mice. Compounds were administered intraperitoneally as suspensions in Tween-80. The anticonvulsant effect of the compounds was assayed toward convulsive states induced by administration of corazole [10], nicotine [11], or arecoline [12], and by the maximal electroshock seizure method [13]. For several compounds we evaluated ED_{50} in mg/kg weight [14].

We assessed antibacterial properties of the substituted 1,2,4-triazole by serial dilution in nutrient agar followed by infection with *S. aureus* 209P or *S. flexneri* 114. We assayed the chemotherapeutic activity of the compounds in generalized infection of white mice caused by intraperitoneal administration of one lethal dose of *S. aureaus*. Compounds were administered as a single internal dose several minutes before infection.

The hypoglycemic activity was determined with the orthotoluidine reagent. Preparations were administered intraperitoneally in 100 or 250 mg/kg doses to groups of five or more rats for each dose. The test and control animals were decapitated 2.5 h after administration of the preparation and blood samples were taken.

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