SYNTHESIS AND STUDY OF RHODANINES WITH POSSIBLE PSYCHOSTIMULANT ACTION

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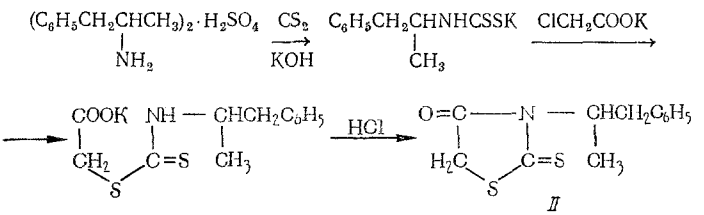
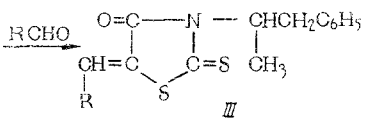
Psychostimulant substances have acquired great importance in medicine in recent times. Besides the long-known caffeine, phenylalkylamine derivatives (phenamine, pervitine, and phenatine), diphenylmethane derivatives, and oxazolidine derivatives (pyridrol, meridil, and azoxodone) and others [1] belong to this class.

We set ourselves the task of synthesizing rhodanine (r-thio-4-thiazolidone) derivatives based on phenamine and studying their properties. Phenamine sulfate (d,l-1-phenyl-2-aminopropane sulfate) (I) and carbon disulfide served as starting materials for the synthesis; they were brought into reaction with each other in aqueous KOH solution. The dithiocarbamate obtained was not isolated, but was brought directly into condensation with monochloroacetic acid neutralized with K_2CO_3. When the reaction mixture was heated with hydrochloric acid, conversion of the N-(α-methyl-β-phenyl)ethyl-S-thiocarbamylthioglycolic acid to the previously undescribed 3-(α-methyl-β-phenyl)ethylrhodanine (II) took place, whose synthesis may be represented by the scheme:



Utilizing the lability of the hydrogen atoms in the 5-position of the rhodanine molecule [2], we have synthesized 5-substituted derivatives of II (designated as type III compounds) by condensation with aldehydes of the aromatic, polycyclic and heterocyclic series in glacial acetic acid, in the presence of anhydrous sodium acetate, according to the scheme:



Compounds of type III were obtained in high yields in this manner (see Table 1). Reactions of II with aliphatic aldehydes (isobutyraldehyde or isovaleraldehyde) or aliphatic ketones (cyclopentanone or cyclohexanone), carried out either in glacial acetic acid or in ammoniacal-alcoholic solution, did not lead to positive results. Contrary to this, the reaction of II with isatin or its N-methyl derivative took place very rapidly, whereupon the 2,3-dihydro-2-oxo-3-indolidene (IV) and 1-methyl-2,3-dihydro-2-oxo-3-indolidene (V) derivatives were obtained.

Upon study of the stability of the thiazolidine ring in the molecule of the substances obtained, it was observed that II, like other N-substituted rhodanine derivatives [3], is a rather labile substance, which undergoes hydrolysis in dilute or concentrated solutions of alkali or ammonia, and also in 10% Na_2CO_3 solution, which is indicated by a positive nitroprusside reaction (violet-rose coloration). Introduction of arylidene residues into the 5-position leads to considerable stabilization of the thiazolidine ring, as a result of which all the type III compounds resist hydrolysis under the conditions given above. To study the structure of the compounds synthesized, we took their absorption spectra in the ultraviolet region of the

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TABLE 1. 3-(α-Methyl-β-phenyl)ethylrhodanine and Its 5-Derivatives.

Compound	R	Yield (in %)	M.p.(in °C)	Found (in %)		Empirical formula	Calc. (in %)		Ultraviolet spectra	
				N	S		N	S	λ_{max} (in mμ)	log ε
II	—	53.6	66—7	5.64	25.47	$C_{12}H_{13}NOS_2$	5.57	25.51	260 295.5	4.18 4.14
III	C_6H_5	88.2	102—3	4.26	18.82	$C_{19}H_{17}NOS_2$	4.12	18.87	234.5 275 365	4.05 4.13 4.62
III	p-BrC_6H_4	92.0	124—5	3.37	15.51	$C_{19}H_{16}BrNOS_2$	3.35	15.33	239 280 380	4.12 4.29 4.82
III	p-ClC_6H_4	86.5	125	3.92	17.49	$C_{19}H_{16}ClNOS_2$	3.75	17.15	240 291 398	3.83 3.97 4.51
III	p-$O_2NC_6H_4$	89.9	164—5	7.49	16.84	$C_{19}H_{16}N_2O_3S_2$	7.29	16.68	276 378	4.11 4.52
III	m-$O_2NC_6H_4$	65.2	162—3	7.26	16 95	$C_{19}H_{16}N_2O_3S_2$	7.29	16.68	262.5 367	4,16 4.44
III	o-$O_2NC_6H_4$	83.8	88—90	7.34	16.89	$C_{19}H_{16}N_2O_3S_2$	7.29	16.68	257 358	4.44 4,57
III	o-$CH_3OC_6H_4$	78,4	98—9	3.97	17.75	$C_{20}H_{19}NO_2S_2$	3.79	17.35	240 291 398	3.83 3.97 4.51
III	p-$(CH_3)_2NC_6H_4$	63,2	130—1	7.64	16.61	$C_{21}H_{22}N_2OS_2$	7 32	16.76	254 5 323 460	3.85 4,02 4 51
III	p-$(C_2H_5)_2NC_6H_4$	64,0	122—3	7.00	15.50	$C_{23}H_{26}N_2OS_2$	6.82	15.62	255 322 476	3.95 4.23 4.81
III	o-HOC_6H_4	74,5	174—5	4.17	17.57	$C_{19}H_{17}NO_2S_2$	3.94	18.04	280 400	3.97 4.52
III	3-CH_3O-4-HOC_6H_3	85.7	122—3	3.91	16.87	$C_{20}H_{19}NO_3S_2$	3.63	16.64	266 295 415	3.97 4,07 4.60
III	3,4-$(CH_3O)_2C_6H_3$	88.5	110—11	3.66	16.46	$C_{21}H_{21}NO_3S_2$	3.51	16.05	262 295 407	3.92 3,97 4.44
III	$C_6H_5CH=CH$	82.2	127—8	4.30	17.53	$C_{21}H_{19}NOS_2$	3.83	17.55	243.5 298 405	3.93 4.03 4.54
III	o-$HOOCC_6H_4$	89.0	117—20	3.91	16.62	$C_{20}H_{17}NO_3S_2$	3.65	16.72	296 367,5	4.08 4.52
III	β-$HOC_{10}H_6$	23.5	250	3.56	15.90	$C_{23}H_{19}NO_2S_2$	3.45	15.82	253 294 374	4.19 3,90 3,88
III	9-Anthraceno	81.8	122—2,5	3.23	14.56	$C_{27}H_{21}NOS_2$	3.19	14.59	255 287 341 428,5	4.92 4,05 4.23 3.91
III	Furyl	78.8	114—5	4.37	19.79	$C_{17}H_{15}NO_2S_2$	4.25	19.47	238 289 398	3.54 3.81 4.47
IV	—	86.8	272—3	7.43	16.62	$C_{20}H_{16}N_2O_2S_2$	7.36	16.85	258 420	4.13 4.56
V	—	55.8	195—6	7 18	16.34	$C_{21}H_{18}N_2O_2S_2$	7.10	16.26	259 420	4.17 4.61

spectrum. Compound II is characterized by 2 absorption bands, at 260 and 295.5 mμ. Thus, the α-methyl-β-phenylethyl radical, introduced into position 3 of the rhodanine molecule, leads to a hypsochromic shift of the maxima by 2.5-7.5 mμ. On introduction of substituents into the 5-position, a new intense band arises with maxima in the 365-460 mμ region (see Table 1), which apparently is connected with the presence of a long conjugation chain.

Pharmacological studies carried out in the central research laboratory of the L'vov Medicinal Institute under the direction of Professor V. M. Chernov showed that II, like phenamine, displays psychostimulant action. The substance is recommended for further study as a central nervous system stimulant.

EXPERIMENTAL

3-(α-Methyl-β-phenyl)ethylrhodanine (II). A solution of 0.12 mole of I in 500 ml of water was neutralized with 0.24 mole of KOH dissolved in 20 ml of water, and 0.24 mole of carbon disulfide was added dropwise, with cooling and stirring, along with a solution of 0.24 mole of KOH in ml of water. The reaction mixture was stirred for 5 h. The dark-gray crystalline precipitate formed was filtered off. Monochloroacetic acid (0.24 mole), neutralized with an equimolecular amount of potassium carbonate, was added to the filtrate, after which the mixture was stirred for another 1-1.5 h. The solution was acidified with concentrated hydrochloric acid to pH 3.0 and was heated to 90°C on a water bath. Thereupon a colorless oil was formed, which crystallized on cooling after 5 days. Compound II was obtained in 53.6% yield, mp 66-67°C (from dilute acetic acid). It is a colorless or slightly yellow crystalline substance, readily soluble in the cold in pyridine, acetone, dioxane, chloroform, methanol, ethanol, ether, or glacial acetic acid; and soluble on warming in benzene, xylene and dilute acetic acid; it is insoluble in water or petroleum ether.

5-Derivatives of II (Type III Compounds). A mixture of equimolecular amounts (about 0.01 mole) of II and the carbonyl compound, 2.51 g of anhydrous sodium acetate, and 15 ml of glacial acetic acid was boiled in a flask under reflux for 1 to 7 h, except in the case of isatin, reaction with which took place after 10 min. In the reaction of II with benzaldehyde, and also with its p-chloro-, p- or m-nitro-, or p-diethylamino-derivatives, precipitates were formed even during boiling (after 20 min to 2.5 h); but with salicylaldehyde, o-nitrobenzaldehyde or furfural, only after dilution of the reaction mixture with water. In the other cases, crystalline substances were isolated only upon repeated washing and trituration of the greasy reaction products with chilled water. The type III compounds were obtained in yields of 60-92%, except for the compound where R = β-$HOC_{10}H_6$- (23% yield), which was isolated by trituration of the grease formed with glacial acetic acid and with petroleum ether. For analysis, the type III compounds were recrystallized from solutions in diluted acetic acid or methanol. The compounds of type III which were obtained were crystalline materials of yellow, orange, or red color, soluble in chloroform, acetone, pyridine, dioxane, benzene, ether, or xylene in the cold; in ethanol, methanol, or glacial acetic acid on warming; and insoluble in water, petroleum ether, or dilute or concentrated solutions of hydrochloric acid, alkali, or ammonia.

Spectrophotometric determinations were carried out in an SF-4 spectrophotometer. The solutions (1-2 mg %) were made up in twice-distilled ethanol.

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