INDOLE DERIVATIVES.

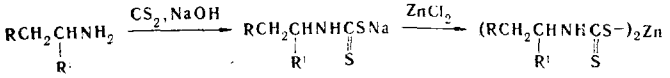
XCVIII.* SYNTHESIS AND GERMISTATIC ACTIVITY OF INDOLYLALKYLDITHIOCARBAMATES

N. N. Suvorov, E. N. Sidorenko, L. Kh. Vinograd, N. M. Przhiyalgovskaya, T. N. Zykova, T. A. Gus'kova, G. N. Pershin, and M. V. Vasin

UDC 547.754:543.422.25.4:615.33

Indolylalkyldithiocarbamates were obtained by reaction of indolylalkylamines with carbon disulfide and sodium hydroxide. Their effect on pathogenic bacteria and fungi was investigated.

Previously unknown sodium and zinc salts of indolyl- and arylalkyldithiocarbamic acids were synthesized via the following scheme:



I a-e II a-e III a,b,e

I—III a R = 3-indolyl R^1 = H; b R = 5-methoxy-3-indolyl R^1 = H; c R = 3-indolyl R^1 = CH_3; d R = 4,5,6-trimethoxy-3-indolyl R^1 = H; e R = 3,4-dimethoxyphenyl R^1 = H

The best results were achieved when the reaction was carried out in aqueous solutions. The chief reaction product in acetone is the corresponding thiourea. The solubility of the side products increases in a water—acetone mixture, and this hinders the isolation and purification of the dithiocarbamates. It was found by means of thin-layer chromotography (TLC) that the corresponding thiuram disulfide and isothiocyanate are also always formed in the course of the reaction of the dithiocarbamate and thiourea. The thiuram disulfide arises due to oxidation of the dithiocarbamate, while the isothiocyanate is formed as a result of its cleavage. A large portion of the isothiocyanate is then converted to the thiourea [2].

The sodium dithiocarbamates IIa-e proved to be insufficiently stable. The zinc salts (IIIa, b, e), which are more stable and are insoluble in water, were obtained by an exchange reaction with zinc chloride.

The IR spectra of the synthesized dithiocarbamates contain intense absorption bands at 3200-3400 cm^{-1} (NH) and 1490-1500; this is characteristic for the dithiocarbamate group [3]. In addition to the absorption at 225 and 285 nm characteristic for the indole ring, two intense maxima at 260 and 290 nm, which are characteristic for dithiocarbamates [4], and a less intense maximum at 340 nm appear in the UV spectra of the sodium dithiocarbamates.

*See [1] for Communication XCVII.

D. I. Mendeleev Moscow Chemical-Engineering Institute. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1371-1374, October, 1974. Original article submitted November 19, 1973.

TABLE 1. Dithiocarbamates

Compound	Dec. point °C	Empirical formula	Found, %					Calc., %					Yield %
			C	H	N	S	H_2O	C	H	N	S	H_2O	
IIa	220	$C_{11}H_{13}N_2NaS_2 \cdot H_2O$	47,6	4,8	10,1	22,9	17,9	47,7	4,7	10,1	23,2	18,7	92
IIb	133	$C_{12}H_{13}N_2NaOS_2 \cdot 2,5H_2O$	43,5	5,4	8,4	19,4	23,0	43,3	5,4	8,4	19,2	22,2	92
IIc	116	$C_{12}H_{13}N_2NaS_2 \cdot 2,5H_2O$	45,2	6,1	8,7	19,8	14,0	45,4	5,7	8,8	20,2	14,2	92
IId	159	$C_{14}H_{17}N_2NaO_3S_2 \cdot 2H_2O$	43,4	5,8	7,3	16,1	18,5	43,6	5,5	7,3	16,6	18,6	92
IIe	210	$C_{11}H_{14}NNaO_2S_2 \cdot 1,5H_2O$	43,2	5,3	4,4	—	—	43,1	5,5	4,5	—	—	—
IIIa	126	$C_{22}H_{22}N_4S_4Zn$	46,9	3,6	10,4	23,8	—	49,3	4,1	10,4	23,9	—	84
IIIb	135	$C_{24}H_{26}N_2O_2S_4Zn$	48,2	4,3	9,4	21,1	—	48,4	4,4	9,4	21,5	—	84
IIIe	165	$C_{22}H_{28}N_2O_4S_4Zn$	46,8	5,2	4,4	22,0	—	46,8	4,9	4,8	22,2	—	—

TABLE 2. Spectral Characteristics of the Dithiocarbamates

Compound	UV spectrum, λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)				
IIa	223 (4,0)	259 (1,38)	286 (1,89)	291 (1,92)	345 (0,014)
IIb	225 (2,78)	260 (1,24)	289 (1,81)		342 (0,017)
IIc	223 (3,84)	261 (1,32)	287 (1,84)	291 (1,9)	340 (0,012)
IId	226 (3,72)	258 (1,49)	289 (1,82)		335 (0,021)
IIIa	—	—	—	—	—
IIIb	—	—	—	—	—

Compound	PMR spectrum, δ, ppm							Solvent
	β-H	α-H	CH_3	OCH_3	aromatic proton	2-H	NH	
IIa	2,75t*	3,85t	—	—	6,6—7,5m	7,04s	8,05s	CD_3OD
IIb	2,75t	3,75t	—	3,75s	6,6—7,3m	—	8,05s	CD_3OD
IIc	2,99m	4,88m	1,043g	—	6,6—7,6	7,14s	8,05s	CD_3OD
IId	3,05t	3,06t	—	3,72s 3,74s 3,94s	2-H and 7-H 6,72s 6,90s		—	$(CD_3)_2CO+CDCl_3$
IIIa	3,10t	3,82t	—	—	6,5—7,4m	7,14s	—	$(CD_3)_2CO+CDCl_3$
IIIb	3,15t	3,75t	—	3,75s	6,7—7,2m	—	—	$(CD_3)_2CO+CDCl_3$

*Symbols: s is singlet, d is doublet, t is triplet, and m is multiplet.

The presence of the signals of 2-H and NH protons in the PMR spectra, like the IR spectral data, constitutes evidence that only the aliphatic amino group reacts with carbon disulfide and that the indole ring does not participate in the reaction. It follows from the PMR spectra that all of the sodium salts contain crystallization water (3.50 ppm). The water content was also determined by the Fischer method. The amount of iodine consumed in the oxidation of the dithiocarbamate to thiuram disulfide was, of course, taken into account in the analysis. The actual water content was calculated from the formula $x = a - b$, where a is the water content (%) from titration data, and b is (18.016)100:molecular weight (%).

4,5,6-Trimethoxytryptamine was obtained by the Abramovich—Shapiro scheme in conformity with the patent data [5] with certain modifications. The alcoholic alkali solution was replaced by an aqueous alkali solution in the saponification of 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-oxo-β-carboline. This made it possible to follow the course of the reaction and terminate it after conversion of the insoluble carboline to

TABLE 3. Germostatic Activity of the Dithiocarbamates (in μg/ml)

Microorganism	Compound							
	IIa	IIb	IIc	IId	IIe	IIIa	IIIb	IIIe
Staphylococcus	15	125	>1000	>1000	125	15	125	250
Streptococcus	15	500	>1000	>1000	125	15	500	250
Escherichia coli	250	>1000	>1000	>1000	>1000	250	>1000	>1000
Salmonella typhosa	250	>1000	>1000	>1000	>1000	250	>1000	>1000
Dysentery bacillus	250	>1000	>1000	>1000	>1000	250	>1000	>1000
Diptheria bacillus	15	125	>1000	>1000	1000	15	125	250
Bacillus pyocyaneus	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Proteus vulgaris	>1000	>1000	>1000	>1000	>1000	>1000	>1000	>1000
Anthracoid spores	15	125	>1000	>1000	125	15	125	250
Tuberculosis bacillus (strain H-37)	1	2	2	4	>1000	—	—	4
Microsporone	2	8	4	15	>1000	8	4	8
Trichophyton	2	4	4	15	>1000	8	4	15
Achorion	2	8	4	15	>1000	8	4	15
Actinomycete	250	1000	125	1000	>1000	4	60	15
Candida	4	15—8	8	125	125	4	15	8

the soluble salt of 4,5,6-trimethoxy-3-(2-aminoethyl)-2-carboxylic acid. This acid was isolated in the individual state and characterized. Decarboxylation of the acid in a stream of argon made it possible to obtain 4,5,6-trimethoxytryptamine in purer form (mp 148-149°) in 85% yield.

The germostatic activity of the synthesized dithiocarbamates was tested with respect to 15 forms of inducers of infectious diseases, including the tuberculosis bacillus and five forms of pathogenic fungi. The results of the tests are presented in Table 3. It was established that the investigated compounds, except for IIe, suppressed the growth of the tuberculosis bacillus and pathogenic fungi to a greater extent than the growth of inducers of acute bacterial infections. Only IIa and IIIa have pronounced antimicrobial activity with respect to Gram-positive bacteria. The introduction of methoxy groups into the indole ring suppresses the activity (IIa,c,d, and IIIb).

Compounds IIa,b and IIIa,b were also studied in the case of experimentally induced candidosis of white mice, and compound IIIa was studied in the case of experimentally induced microsporia of guinea pigs, but the compounds proved to be inactive.

Compounds IIa-d do not have appreciable radioprotective activity. Experiments were carried out with white mice. The compounds were injected prior to γ irradiation (^{60}Co/800-850 R) at a dose rate of 48-56 R/min (in 0.15 mmole/kg amounts).

EXPERIMENTAL

Chromatography was carried out on plates with a fixed layer of Silufol UV-254 silica gel in a benzene–acetone system (3:1). The spots were detected by means of an ultrachemiscope and also by spraying with an alcohol solution of p-dimethylaminobenzaldehyde containing hydrochloric acid. The IR spectra of mineral-oil suspensions were recorded with UR-10 and UR-20 spectrometers. The UV spectra of alcohol solutions were recorded with a Hitachi spectrophotometer. The PMR spectra were obtained with a Varian spectrometer at 60 MHz with tetramethylsilane as the internal standard.

β-(5-Methoxy-3-indolyl)ethyldithiocarbamate (IIb). A solution of 1.2 g (0.03 mole) of sodium hydroxide in 8 ml of water and 2.28 g (0.03 mole) of carbon disulfide were added to a suspension of 3.8 g (0.02 mole) of 5-methoxytryptamine in 30 ml of water, and the mixture was stirred vigorously at 8-10° for 2 h and allowed to stand overnight. The resulting orange solution of the dithiocarbamate was removed by filtration from the undissolved β,β'-(5-methoxy-3-indolyl)ethylthiourea and evaporated with a rotary evaporator at 30°. The crystalline orange precipitate was dissolved in acetone, the solution was filtered to remove the inorganic impurities, and the filtrate was vacuum evaporated. The residue was washed five to six times with 50-100-ml

portions of ether and dried in air to give 4.8 g (93%) of colorless crystals. The crystals were dissolved in 40 ml of absolute alcohol, and a 20-fold amount of absolute ether was added to give 3.36 g (65%) of shiny colorless plates of dithiocarbamate IIb.

Compounds IIa,c-e were similarly obtained (see Table 1).

Zinc β-(5-methoxy-3-indolyl)ethyldithiocarbamate (IIIb). A total of 4 ml of a 1% aqueous solution of zinc chloride (30 mmole) was added dropwise to a solution of 0.5 g (20 mmole) of IIa in 50 ml of water. After 1 h, the resulting precipitate was removed by filtration and washed with water. The still-moist precipitate was dissolved in the minimum amount of acetone, and after 12 h the precipitate was removed by filtration and vacuum dried over phosphorus pentoxide to give 0.43 g (84%) of colorless crystals of zinc dithiocarbamate IIIb.

Compounds IIIa, c-e were similarly obtained (see Table 1).

[Di-β,β'-(5-methoxy-3-indolyl)ethyl]thiourea. A solution of 3.8 g (0.02 mole) of tryptamine Ib in 40 ml of acetone was added with vigorous stirring in the course of 4 h to an emulsion of 1.68 g (0.03 mole) of potassium hydroxide and 2.28 g (0.03 mole) of carbon disulfide in 8 ml of water and 30 ml of acetone, and after 1 h the acetone was removed by vacuum evaporation. The yellow crystalline residue was washed with water and methanol and dried to give 2.2 g (50%) of crystals of the corresponding thiourea with mp 135° (from alcohol). The IR spectrum of the product was identical to that of the substance obtained in [6].

4,5,6-Trimethoxy-3-(2-aminoethyl)-2-indolylcarboxylic Acid. A 6.25-g (0.022 mole) sample of 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-oxo-β-carboline (mp 213-214°) was refluxed for 3.5 h with 12.4 g (0.22 mole) of potassium hydroxide in 120 ml of water. The resulting light-yellow solution was filtered, and the filtrate was acidified at 0° with ~10 ml of acetic acid to give 5.15 g (70%) of colorless crystals with mp 272-273° (decomp.). Found: C 54.7; H 6.2; N 7.9%. $C_{14}H_{18}N_2O_5$. Calculated: C 54.5; H 6.2; N 7.9%.

LITERATURE CITED

1. V. V. Vampilova, V. A. Velezheva, and N. N. Suvorov, Trudy MKhTI im. D. I. Mendeleeva, 80, 150 (1974).
2. J. D. Thorn and R. A. Ludwig, The Dithiocarbamates and Related Compounds, Amsterdam–London–New York (1962).
3. A. Usatenko and S. Bakalov, Zh. Prirodn. Soedin., 9, 27 (1968).
4. H. P. Koch, J. Chem. Soc., 401 (1949).
5. US Patent No. 3047578; Chem. Abstr., 58, 11421 (1963).
6. V. S. Murasheva, V. N. Buyanov, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 284 (1968).