Synthesis and biological properties of dithiocarbamic acid derivatives XII.* Biological properties of mixed anhydrides of *N*-methyl-*N*-methoxycarbonylcarbamic and *N*,*N*-dialkyldithiocarbamic acids

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A synthesis of novel mixed anhydrides prepared by the reaction of *N*-methyl-*N*-methoxycarbonylcarbamoyl chloride with alkaline salts of *N*,*N*-dialkyldithiocarbamic acid is described. Studying the physicochemical properties of compounds prepared it was found that in dependence on substituents attached to the nitrogen atom of the dithiocarbamic group the compounds decomposed to form carbon disulfide and an appropriate alkyl *N*,*N*-dialkylaminocarbonyl-*N'*-methylcarbamate. Compounds prepared were examined on contact and systemic insecticidal, acaricidal, ovicidal, fungicidal, and herbicidal activities. Mixed anhydride of *N*-methyl-*N*-methoxycarbonylcarbamic and *N*,*N*-dimethyldithiocarbamic acids showed high activity as mordant of cultural plants and mixed anhydride of *N*-methyl-*N*-methoxycarbonylcarbamic and *N*,*N*-di(1-methylethyl)-dithiocarbamic acids showed very high fungicidal and antipowdery mildew activities. The structure of prepared mixed acid anhydrides and alkyl *N*,*N*-dialkylaminocarbonyl-*N'*-methylcarbamates was proved by spectral methods.

Описан синтез новых смешанных ангидридов, получаемых по реакции *N*-метил-*N*-метоксикарбонилкарбамоилхлорида со щелочными солями *N*,*N*-диалкилдитиокарбаминовой кислоты. При исследовании физико-химических свойств полученных соединений было найдено, что в зависимости от заместителей на атоме азота дитиокарбаминовой группы, они разлагаются с образованием сероуглерода и соответствующего алкил-*N*,*N*-диалкиламинокарбонил-*N'*-метилкарбамата. Полученные соединения исследовались на контактную и системическую инсектицидную, акарицидную, овицидную, фунгицидную и гербицидную активность. Смешанные ангидриды *N*-метил-*N*-метоксикарбонилкарбаминовой и *N*,*N*-

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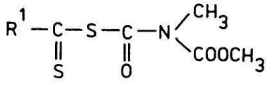
-диметилдитиокарбаминовой кислот проявили высокую активность в качестве протравы культивируемых растений, а смешанные ангидриды *N*-метил-*N*-метоксикарбонилкарбаминовой и *N*,*N*-ди(1-метилэтил)-дитиокарбаминовой кислот проявили очень высокое фунгицидное действие против мучнистовой роси. Структуры полученных смешанных кислотных ангидридов и алкил-*N*,*N*-диалкиламинокарбонил-*N'*-метилкарбаматов были доказаны с помощью спектральных методов.

Continuing the study of the synthesis and biological activity of dithiocarbamic acid derivatives we prepared novel compounds of the formula



by the reaction of *N*-methyl-*N*-methoxycarbonylcarbamoyl chloride with sodium and potassium salts of *N*,*N*-dialkyldithiocarbamic acid, respectively (Table 1). In infrared spectra all compounds showed two intense $\nu(C=O)$ bands. The band at higher wavenumber 1733 cm^{-1} is assigned to the ester group, while the band at $\tilde{\nu} \approx 1672$ cm^{-1} to the carbamic group. The medium intensity bands at $\tilde{\nu} \approx$ ≈ 1240 cm^{-1} and 1200 cm^{-1} are characteristic of the (N—C(S)—S) group; the $\nu(C=S)$ band is observed at $\tilde{\nu} \approx 647$ cm^{-1}, the ν(C—N) band at $\tilde{\nu} \approx 1330$ cm^{-1} and the ν(C—O) band at $\tilde{\nu} \approx 1310$ cm^{-1}.

It is known that dithiocarbamic acid derivatives can occur in "thioureidic form" [1—3]. Therefore, the medium intensity band at $\tilde{\nu} \approx 1480$ cm^{-1} can be ascribed to the N···C vibration and the band at $\tilde{\nu} \approx 976$ cm^{-1} to the C···S stretching vibration. Ultraviolet spectra of compounds studied showed two bands. The first band at 264 nm can be assigned to the $\pi \rightarrow \pi^*$ transition localized in the S—C=S group [4] and the second band at ~297—298 nm to the $\pi \rightarrow \pi^*$ transition localized in the N—C=S group [5]. The ^{13}C NMR spectra of compounds studied showed characteristic signals; δ_r/ppm: 185 (C=S), 166 (C=O), 154 (O—C=O), 54(CH_3—O), 32 (CH_3—N). Similarly, the ^1H NMR spectra showed characteristic signals; δ_r/ppm: 3.26 (CH_3—N), 3.86 (CH_3—O).

A very interesting fact was observed after 6—10 months when compounds prepared were decomposed to carbon disulfide and alkyl *N*,*N*-dialkylaminocarbonyl-*N'*-methylcarbamates (Table 2). A decomposition of prepared compounds can be explained by the fact that the electronwithdrawing effect of the carbamic rest weakens the S—CO bond resulting in the splitting of carbon disulfide as denoted in the formula

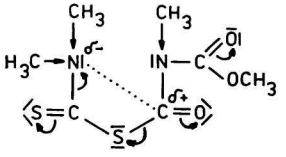
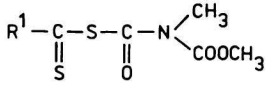


Table 1

A survey of the prepared compounds



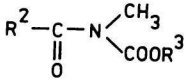
Compound	R^1	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield %	n(D, 20 °C) (M.p./°C)
				C	H	N	S		
I	$C_6H_{11}NH$	$C_{11}H_{18}N_2O_3S_2$	290.37	45.51	6.24	9.65	22.08	54.0	1.5409
				45.61	6.29	9.80	22.16		
II	$(CH_3)_2N$	$C_7H_{12}N_2O_3S_2$	236.29	35.58	5.12	11.85	27.11	81.9	(81—93)
				35.62	5.21	11.77	26.95		
III	$(C_2H_5)_2N$	$C_9H_{16}N_2O_3S_2$	264.35	40.89	6.10	10.58	24.21	85.4	(66—68)
				41.01	6.18	10.31	23.90		
IV	$(CH_3)_2CH$, CH_3 N	$C_9H_{16}N_2O_3S_2$	264.35	40.89	6.10	10.58	24.21	69.7	(87—89)
				40.94	6.08	10.40	24.11		
V	$(C_3H_7)_2N$	$C_{11}H_{20}N_2O_3S_2$	292.40	45.18	6.89	9.58	21.93	73.4	(61—63)
				45.22	6.99	9.61	22.11		
VI	$[(CH_3)_2CH]_2N$	$C_{11}H_{20}N_2O_3S_2$	292.40	45.18	6.89	9.58	21.93	72.2	(78—80)
				45.29	7.02	9.70	22.00		
VII	$(CH_2=CH—CH_2)_2N$	$C_{11}H_{16}N_2O_3S_2$	288.38	45.81	5.59	9.71	22.23	71.0	1.5845
				45.99	5.70	9.92	22.20		
VIII	$[(CH_3)_2CHCH_2]_2N$	$C_{13}H_{24}N_2O_3S_2$	320.44	48.72	7.55	8.74	20.01	80.7	(98—100)
				48.81	7.51	8.82	20.30		
IX		$C_{10}H_{16}N_2O_3S_2$	276.15	43.39	5.84	10.14	23.22	48.2	1.5862
				43.55	5.90	10.20	23.40		

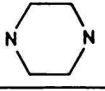
Table 1 (Continued)

Compound	R^1	Formula	M_r	w_i(calc.)/% / w_i(found)/%				Yield %	n(D, 20 °C) (M.p./°C)
				C	H	N	S		
X		$C_9H_{14}N_2O_4S_2$	278.33	39.84 39.92	5.07 5.20	10.06 10.12	23.04 23.30	60.0	(130—131)
XI		$C_{14}H_{20}N_4O_6S_4$	468.57	35.88 35.97	4.30 4.41	11.95 12.11	27.37 27.40	89.3	(149—151)

Table 2

A survey of the prepared alkyl *N*,*N*-dialkylaminocarbonyl-*N'*-methylcarbamates



Compound	R^2	R^3	Formula	M_r	w_i(calc.)/% w_i(found)/%			Yield %	B.p./°C (p/Pa)
					C	H	N		
XII	$(CH_3)_2N$	CH_3	$C_6H_{12}N_2O_3$	160.16	44.99	7.55	17.49		73 (26.6)
					45.11	7.61	17.61		
XIII	$(CH_3)_2N$	CH_2CH_2Cl	$C_7H_{13}ClN_2O_3$	208.63	40.58	6.23	13.42	58.6	93 (13.3)
					40.39	6.41	13.74		
XIV	$(CH_3)_2N$	$CH(CH_3)_2$	$C_8H_{16}N_2O_3$	188.22	50.47	8.51	14.89	59.6	74 (13.4)
					50.19	8.33	14.61		
XV	$(CH_3)_2N$	$CH_2—CH=CH_2$	$C_8H_{14}N_2O_3$	186.21	50.79	7.52	15.02	81.6	85 (20)
					50.80	7.53	14.72		
XVI	$(CH_3)_2N$	C_5H_9(cyclo)	$C_{10}H_{18}N_2O_3$	214.35	56.10	8.39	13.06	53.9	97 (13.3)
					55.93	8.38	13.01		
XVII	$(C_2H_5)_2N$	CH_3	$C_8H_{16}N_2O_3$	188.22	50.47	8.51	14.89		77 (13.3)
					50.22	8.40	14.72		
XVIII	$CH_3[(CH_3)_2CH]N$	CH_3	$C_8H_{16}N_2O_3$	188.22	50.47	8.51	14.84		80 (20)
					50.52	8.59	14.99		
XIX	$(CH_2=CH—CH_2)_2N$	CH_3	$C_{10}H_{16}N_2O_3$	212.34	56.56	7.59	13.19		83 (13.3)
					56.80	7.88	13.33		
XX		CH_3	$C_{12}H_{20}N_4O_6$	308.24	46.75	6.54	18.17		124 (13.3)
					46.81	6.68	18.36		

a) The yield was not evaluated.

When higher *N*-methyl-*N*-alkoxycarbamoyl chlorides were used in the reaction with alkaline salt of dithiocarbamic acid then primarily formed mixed acid anhydrides were decomposed into appropriate carbamates (compounds *XIII*—*XVI*) (Table 2). The structure of these compounds was proved by spectral methods.

Infrared spectra of these compounds showed two intense ν(C = O) bands, the first in the $\tilde{\nu}$ range 1714—1722 cm^{-1} belonging to the urea and the second band in the $\tilde{\nu}$ range 1668—1685 cm^{-1} belonging to the ester group.

The results of tests on fungicidal activity of mixed anhydrides prepared are summarized in Table 3 from which it appears that compounds *II* and *X* were the most active and compound *VI* showed antipowdery mildew activity. All these compounds were included into advanced stage of testing, the results of which are summarized in Table 4. These tests confirmed a high fungicidal activity of prepared compounds. Compound *II* was suggested for further research

Table 3

Fungicidal activity of the synthesized compounds

Compound	Mordant dose g·(100 kg)$^{-1}$		Sharvell test		Glass-slide method	*w*(*P. infestans*)/%		*w*(*E. graminis*)/%	
	100	10	As	Cc	Sf	0.5	0.1	0.1	0.04
I	96	40	*D*	*D*	*C*	2.5	0	2	0.5
II	100	94	*C*	*B*	*a*	+	0	3	2
III	100	29	*C*	*C*	*c*	+	2.5	1.5	1
IV	94	13	*D*	*C*	*d*	+	1.5	2.5	1.5
V	68	10	*D*	*C*	*c*	+	2.5	3.5	2.5
VI	23	0	*D*	*D*	*d*	+	2.5	4	3.5
VII	53	24	*D*	*C*	*d*	2.5	1	3	0
VIII	100	28	*C*	*B*	*b*	+	2.5	3	0.5
IX	64	13	*C*	*C*	*d*	1.5	1	1	0
X	100	95	*D*	*D*	*c*	+	2.5	2.5	0.5
XI	0	0	*D*	*D*	*d*	3	2.5	1	0.5
Dithio-cyanato-methan	100	100	—	—	—	—	—	—	—
Captan	—	—	*A*	*A*	*A*	—	—	—	—
Dithane M-45	—	—	—	—	—	4	4	—	—
Karathan	—	—	—	—	—	—	—	4	4

As — *Alternaria sp.*, Cc — *Cladosporium cucumerinum*, Sf — *Sclerotinia fructicola*; *A* = 10 ppm, *B* = 10—100 ppm, *C* = 100—1000 ppm, *D* = 1000 ppm, *a* = 2 ppm, *b* = 2—20 ppm, *c* = 20—200 ppm, *d* = 200 ppm. (The values express activity/%.) 4 — 0—15% of attacked area, 3 — 16—40% of attacked area, 2 — 41—60% of attacked area, 1 — 61—80% of attacked area, 0 — 81—100% of attacked area, + — phytotoxic, − — not tested.

Table 4

Advanced tests of fungicidal activity of some compounds prepared

Compound	ED_{50}/ppm			$ED_{50}/(g \cdot (100\ kg)^{-1})$
	Erysiphe graminis	*Erysiphe cichoraceraum*	*Sclerotinia fructicola*	*Fusarium nivale*
II	830	940	0.056	0.9
VI	20.2	145	—	—
X	—	—	—	0.79
Karathan	31.6	31	—	—
Captan	—	—	0.36	—
Dithio-cyanato-methan	—	—	—	0.2

of fungicidal activity having an advantage in more wide spectrum of activity as well as in accessibility of starting compounds.

Further research of compound *II* was directed to the study of physical and chemical properties as:

— a solubility in water which was determined to be 0.78 g dm^{-3} at 24 °C,

— a hydrolytic decomposition in water at 25 °C — an amount of compound (*w*/%) was decomposed after 14 days (75), after 21 days (90) and after 30 days (100).

— a shelf-live test after 14 days at 60 °C showed that the amount of decomposed compound was 75 mass %.

By thermoanalytical investigation of compound *II* it was found that a very rapid active decomposition begins at 120 °C and accomplishes at 200 °C. In this temperature range there are two decomposition stages in which 90 mass % of amount of compound is decomposed. The third stage of decomposition begins at 220 °C and accomplishes at 230 °C and 5 mass % of amount of compound is decomposed. The rest 5 mass % represents undefined rest and did not decompose even when temperature of 500 °C was used.

Table 5

Phytotoxicity of investigated compounds on winter wheat

Compounds	Dose of active compound $g \cdot (100\ kg)^{-1}$	Relative high of leaf (in control) %
II	300	85
	150	87
	75	95
	37.5	97
Vitavax standard	300	97
	150	99

The determination of phytotoxicity was carried out under greenhouse conditions and the results are summarized in Table 5. It was found that compound *II* was moderately phytotoxic on a model plant, winter wheat, as compared with the used standard Vitavax.

The determination of fungicidal activity was carried out in the small-scale field experiments against

— *Tilletia foetida* on winter wheat, the results are given in Table 6, the compound showed a high degree of activity comparable with standard Agronal H;

— *Ustilago avena*, the results are given in Table 7, they confirmed a good activity of compound, however, it was nearly by one order lower than that of standard Vitavax;

— *Ustilago nuda*, the results are given in Table 8, compound *II* showed low activity against that of comparable standard;

Table 6

Small-scale field experiments against *Tilletia foetida* on winter wheat

Compound	Dose of active compound $g \cdot (100\ kg)^{-1}$	Inhibition degree of infection/%	
		Pstruša	Malinovo
II	100	96	96
Agronal H standard	200	100	100

Table 7

Results of the small-scale field experiment against *Ustilago avena*

Compound	ED_{50}(active compound)/$(g \cdot (100\ kg)^{-1})$	Relative activity in respect to standard
II	58.0	0.12
Vitavax standard	7.0	1

Table 8

Results of the small-scale field experiment on barley

Compound	Dose of active compound $g \cdot (100\ kg)^{-1}$	Inhibition degree of infection/%
II	300	19
	200	17
Vitavax standard	300	92
	200	89

— *Sphacelotheca destruens*, the results are given in Table 9, the compound reached the half activity of the standard Vitavax. Also alkyl *N*,*N*-dialkylaminocarbonyl-*N'*-methylcarbamates (Table 2) (compounds *XII*—*XX*) were examined on fungicidal activity, none of them showed a measurable fungicidal activity.

Table 9

Results of experiments against *Sphacelotheca destruens*

Compound	ED_{50}(active compound)/(g·(100 kg)$^{-1}$)	Relative activity in respect to standard
II	24.0	0.54
Vitavax standard	13.0	1

Although compound *II* showed a low toxicity against warmblooded animals and a high activity against *Sclerotinia fructicola* and *Tilletia foetida* on winter wheat, it was not included for its low stability into further stage of research.

Experimental

Infrared spectra of compounds prepared were recorded with a Specord 75 IR (Zeiss, Jena) instrument in tetrachloromethane ($c \approx 10^{-2}$ mol dm^{-3}, cell thickness 1.0 mm). The wavenumber calibration was checked against the spectrum of polystyrene.

Ultraviolet spectra were recorded with a Specord UV VIS (Zeiss, Jena) instrument in methanol ($c = 2 \times 10^{-5}$—1×10^{-4} mol dm^{-3}, cell thickness 1.0 cm).

^{1}H NMR spectra were recorded with a Tesla BS 487 C (80 MHz) instrument in C^2HCl_3 using TMS and HMDS as internal standards. ^{13}C NMR spectra were recorded with a FX-60 Jeol instrument in C^2HCl_3 using TMS and HMDS as internal standards.

Thermoanalytical investigation was performed on Thermoanalyzer 2 (Mettler) in the flow of pure nitrogen 7 dm^3 h^{-1} and at a rate 6 °C min^{-1} and for DTA Pt—Rh cells and freshly annealed Al_2O_3 as standard were used.

Fungicidal activity of prepared compounds was followed by both the *in vitro* and *in vivo* methods. Inherent activity was followed by the glass slide method on spores of fungi *Sclerotinia fructicola* (WINT.), *Aspergillus niger* TIEGH. and *Cladosporium cucumerinum* ELL. et ARRTH. after the Sharvell method using Captan (*N*-trichloromethylthio)-1,2,3,6-tetrahydrophthalimide) as standard. Antipowdery mildew activity was followed on *Erysiphe graminis* (on the living plants of spring barley, sort Dunajský trh) using Karathane (2,4-dinitrophenyl-6-isooctyl-2-butenoate) as standard and on tomatoes (*Phytophtora infestans* DE BY) using Dithane M-45 (a mixture of manganese(II) 1,2-ethanediyl bis(dithiocarbamate) with zinc(II) 1,2-ethanediyl bis(dithiocarbamate) as standard according to the known methods [6].

The mordant activity was determined on dead caryopsis of rye infected by conidia of fungi *Fusarium nivale* using Dithiocyanatomethan as standard after described method [7]. The mordant activity against *Tilletia foetida* on winter wheat, *Ustilago nuda*, *Ustilago avena*, and *Sphacelotheca destruens* was determined in the small-scale field experiments after [8].

Mixed anhydrides of N-methyl-N-methoxycarbonylcarbamic and N,N-dialkylthiocarbamic acids (I—XI)

To sodium or potassium salt of *N,N*-dithiocarbamic acid (0.1 mol) in propanone (100 cm^3) *N*-methyl-*N*-methoxycarbonylcarbamoyl chloride (0.1 mol) was added at 5—10 °C during 20 min with stirring. Then the reaction mixture was stirred for 1 h at 20 °C and for 2 h at 40 °C, after cooling it was poured into ice water (1000 cm^3) with stirring. The excluded solid compound was separated by filtration, dried and purified by crystallization from ethyl acetate or cyclohexane.

For compound *IV*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 0.98 (CH), 1.85 (N—CH), 3.26 (N—CH_3), 3.86 (CH_3O); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 184.92 (C=S), 166.74 (C=O), 154.52 (O—C=O), 54.15 (CH_3O), 32.33 (CH_3N), 11.26 (CH_3), 55.71 (CH—N).

For compound *VI*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 0.98 (CH), 1.07 (CH—N), 3.26 (CH_3N), 3.86 (CH_3O); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 185.96 (C=S), 166.22 (C=O), 154.40 (O—CO—), 63.64 (CH—N), 54.02 (CH_3O), 32.07 (CH_3N), 28.30 and 25.58 (CH), 20.25 and 19.86 (CH_3).

N,N-dialkylaminocarbonyl-N′-methylalkylcarbamates (XII, XVII—XX)

These compounds were prepared from decomposed mixed anhydrides of *N*-methyl-*N*-methoxycarbonyl carbamic and *N,N*-dialkyldithiocarbamic acids (approximately after six months) by separation of a liquid part, which was distilled under reduced pressure.

For compound *XII*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 2.95 ($(CH_3)_2N$), 3.00 (CH_3N), 3.74 (CH_3O); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 156.84 (C=O), 154.50 (O—CO), 53.14 (CH_3O), 37.03 ($(CH_3)_2N$), 33.13 (CH_3N).

For compound *XVII*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 1.15 (CH_2), 2.99 (CH_3N), 3.71 (CH_3O); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 156.19 (C=O), 154.89 (O—CO), 53.18 (CH_3O), 42.10 (CH_2N), 33.27 (CH_3N), 13.25 (CH_3—C).

N,N-dialkylaminocarbonyl-N′-methylalkylcarbamates (XIII—XVI)

To potassium or sodium salt of *N,N*-dithiocarbamic acid (0.11 mol) in propanone (160 cm^3) *N*-methyl-*N*-methoxycarbonylcarbamoyl chloride (0.1 mol) was added at 5—10 °C with stirring. The stirring was continued for 1 h at 15—20 °C and for 1 h at 40 °C. The reaction mixture was poured into ice water (1000 cm^3) with stirring. The excluded oily compound was extracted by addition of benzene (200 cm^3). The benzene solution was washed with water and dried with anhydrous sodium sulfate. Benzene was distilled off and the rest distilled under reduced pressure.

For compound *XIII*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 2.99 ($(CH_3)_2N$), 3.04 (CH_3N), 3.74 (CH_2O), 4.33 (CH_2Cl); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 156.35 (C=O), 153.36 (O—C=O), 65.71 (CH_2O), 42.07 (CH_2Cl), 37.14 ($(CH_3)_2N$), 33.11 (CH_3N).

For compound *XV*: ^{1}H NMR (C^2HCl_3)—δ_r/ppm: 2.97 ($(CH_3)_2N$), 3.00 (CH_3N), 3.18 (CH_2), 4.36 (CH); ^{13}C NMR (C^2HCl_3)—δ_r/ppm: 156.71 (C=O), 153.59 (O—C=O), 132.28 (CH), 117.86 (CH_2), 66.50 (CH_2O), 37.03 ($(CH_3)_2N$), 33.00 (CH_3N).

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