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REACTION OF ACYLACETYLENES AND METHYL PROPIOLATE WITH N,N′-BIS(DITHIOCARBOXY)PIPERAZINE

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The reaction of N,N′-bis(dithiocarboxy)piperazine with acetylenic ketones and methyl propiolate gave N,N′-bis(acylvinyldithiocarbo)- and N,N′-bis(methoxycarbonylvinyldithiocarbo)piperazines. Heating the compounds obtained with perchloric acid leads to intramolecular cyclization with the formation of N,N′-bis[2-acyl(methoxycarbonyl)methyl-1,3-dithietanium]piperazine perchlorates.

The reaction of N-methyldithiocarbamic acid with propiolic acid in the presence of PCl_3 leads to 5-methyl-4-oxo-1,3-thiazine-6-thione [1], while the reaction of the triethylammonium salt of N,N-diethyldithiocarbamic acid with the dimethyl ester of acetylenedicarboxylic acid (DMEADC) in acetonitrile gives 2-(N,N-diethylamino)-4,5-dicarbomethoxy-1,3-dithiol [2] in 88% yield. The trimethylammonium salt of dithiobenzoic acid reacts analogously with DMEADC to give 2-phenyl-4,5-dicarbomethoxy-1,3-dithiol [3].

We have previously studied the reaction of α-acetylenic ketones with N,N-dialkyldithiocarbamic acids in acetonitrile at 20°C leading to the formation of S-acylvinyl-N,N- dialkyldithiocarbamates and carried out their heterocyclization to give 1,3-dithietanium perchlorates by the action of perchloric acid [4, 5].

In the present work, we studied the reaction of terminal and substituted α-acetylenic ketones (Ia)-(Ie) and methyl propiolate (If) with N,N′-bis(dithiocarboxy)piperazine (II) in order to synthesize new functionally substituted piperazines, which hold promise as pharmacological agents.

Samples of (II) were synthesized by the reaction of anhydrous piperazine with carbon disulfide in 1:2 ratio in an aprotic solvent such as chloroform or acetonitrile and were used in the reaction without separation from the reaction mixture. The reaction of dithiocarbamic acid (II) with terminal acylacetylenes (Ia) and (Ib) in 1:2 mole ratio in chloroform at 20°C gives N,N′-bis[benzoylvinyldithiocarbo]piperazine (IIIa) and N,N′-bis[(thenoyl-2)- vinyldithiocarbo]piperazine (IIIb) in 88-94% yields.

The reaction of substituted acylacetylenes (Ic)-(Ie) with (II) was carried out in chloroform in the presence of triethylamine at 60°C. The yields of (IIIc)-(IIIe) were 52-85%.

The reaction of methyl propiolate (If) with (II) was carried out in acetonitrile with a 2:1 reagent ratio at 20°C. The yield of (IIIf) was 18%.

The IR spectra of (IIIa)-(IIIf) have bands for a conjugated carbonyl group at 1615-1630 cm^{-1} (1690 cm^{-1} for (IIIf)), C=C bonds at 1570-1600 cm^{-1}, C-N bonds at 1250-1270 cm^{-1}, and C-S bonds at 702-705 cm^{-1}. The PMR spectral data for (IIIa)-(IIIf) are given in Table 1.

Careful heating of (IIId)-(IIIf) in excess 57% perchloric acid leads to the formation of N,N′-bis(2-acyl(methoxycarbonyl)methyldithietanium]piperazine perchlorates (IVd)-(IVf). Salts (IVd)-(IVf) are white, high-melting, crystalline compounds, which are soluble in hot water, aqueous ethanol, acetone, and DMSO. The IR spectra of perchlorates (IVd)-(IVf) have bands at 1670-1705 cm^{-1} (C=O), 1610-1620 cm^{-1} (C=N), 1460 cm^{-1} (CH_2), 700-705 cm^{-1} (C-S), and 1080-1120 cm^{-1} (ClO_4^-). The PMR spectral data for these compounds are given in Table 1.

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TABLE 1. PMR Spectra of Dithiocarbamates (IIIa)-(IIIf) and Perchlorates (IVd) and (IVe) (δ, ppm, (J, Hz))

Compound	$=CHCO$, CH_2CO *	R	R^1	$-N(CH_2CH_2)_2N-$
(IIIa)	7,10 d (1H, $^3J=15,3$)	7,64–8,11 m (10H)	8,80 d (1H, $^3J=15,3$)	4,44 s (8H)
(IIIb)	7,68 d (1H, $^3J=9,27$)		8,79 d (1H, $^3J=9,27$)	4,43 s (8H)
(IIIc)	7,39 s (1H)	7,63–8,02 m (20H)		3,94 s (8H)
(IIId)	7,62 s (1H)	7,30–8,21 m (16H)		4,01 s (8H)
(IIIe)	7,48 s (1H)	6,80–8,04 m (16H)		4,01 s (8H)
(IIIf)	6,33 d (1H, $^3J=10,74$) 6,45 d (1H, $^3J=16,33$)	3,72 s (3H)	8,56 d (1H, $^3J=10,74$) 8,54 d (1H, $^3J=16,33$)	4,41 s (8H)
(IVd)	4,89 s (4H)	7,40–8,22 m (6H)	7,46–7,88 m (10H)	4,07 s (8H)
(IVe)	4,75 s (4H)	7,51–7,90 m (6H)	7,32–7,90 (10H)	4,05 s (8H)

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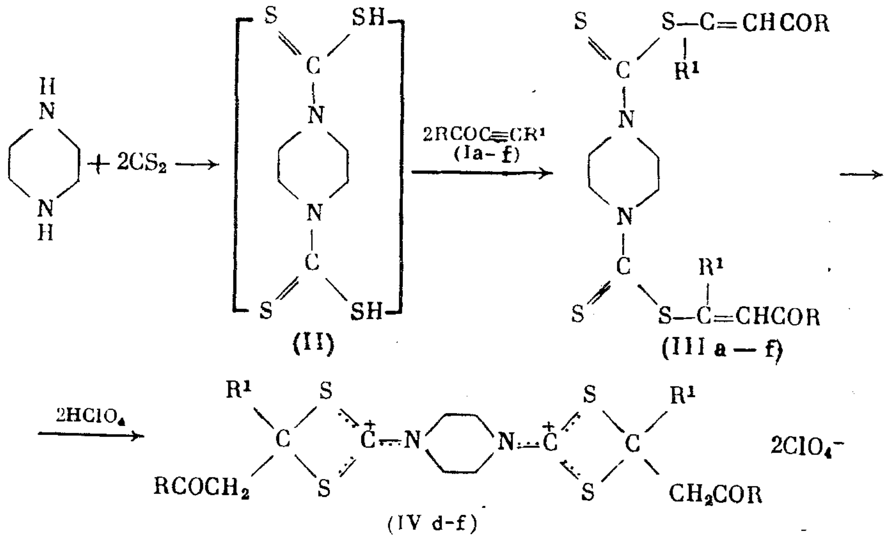
*For (IVd) and (IVe).



$R = Ph$, $R^1 = H$ (a); R = 2-thienyl, $R^1 = H$ (b); $R = R' = Ph$ (c); R = 2-thienyl, $R^1 = Ph$ (d); R = 2-furyl, $R^1 = Ph$ (e); $R = OMe$, $R^1 = H$ (f).

TABLE 2. Yields, Physical Constants, and Elemental Analysis Data of Dithiocarbamates (IIIa)-(IIIf) and Perchlorates (IVd)-(IVf)

Compound	Yield, %	mp, °C	Found, %				Chemical formula	Calculated, %			
			C	H	N	S(Cl)		C	H	N	S(Cl)
(IIIa)	94	209–210	57,6	4,5	5,6	25,5	$C_{24}H_{22}N_2O_2S_4$	57,8	4,4	5,6	25,7
(IIIb)	88	233–234	46,8	3,8	5,6	36,5	$C_{20}H_{18}N_2O_2S_6$	47,1	3,5	5,5	36,7
(IIIc)	85	187–190	66,6	4,8	4,3	19,4	$C_{36}H_{30}N_2O_2S_4$	66,5	4.6	4,3	19.7
(IIId)	60	193–194	58,1	4,1	4,4	28,8	$C_{32}H_{26}N_2O_2S_6$	58,0	3.9	4.2	29,0
(IIIe)	52	188–190	61,0	4,3	4,4	20,2	$C_{32}H_{26}N_2O_4S_4$	60,9	4,1	4,4	20,3
(IIIf)	18	193–195	41,4	4,3	6,9	31,2	$C_{14}H_{18}N_2O_4S_4$	41,4	4,4	6,9	31,5
(IVd)	73	198–200	44,5	3,2	3,2	22,3 (7,9)	$C_{32}H_{28}Cl_2N_2O_{10}S_6$	44.4	3,2	3,2	22,3 (8.2)
(IVe)	80	203–205	46,2	3,4	3,4	15,6 (8,3)	$C_{32}H_{28}Cl_2N_2O_{12}S_4$	46,2	3.4	3,4	15,4 (8,5)
(IVf)	74	226–227	27,5	3.2	4,7	20,9 (11,6)	$C_{14}H_{20}Cl_2N_2O_{12}S_4$	27,7	3,3	4,6	21.1 (11,7)

EXPERIMENTAL

The IR spectra were taken in KBr pellets on a Specord spectrometer. The PMR spectra were taken on Jeol FX 90Q spectrometer at 89.55 MHz in CD_3OD and $CDCl_3$ with HMDS as the internal standard.

The indices of the synthesized compounds and their PMR spectra are given in Tables 1 and 2.

N,N′-Bis(benzoylvinyldithiocarbo)piperazine (IIIa). A sample of 0.76 g (0.01 mole) CS_2 was added slowly with rapid stirring to a solution of 0.43 g (5 mmoles) anhydrous piperazine in 10 ml $CHCl_3$. The reaction mixture was stirred for 0.5 h and then a solution of 1.3 g (0.01 mole) benzoylacetylene in 10 ml chloroform was added to dithiocarbamic acid (II). The mixture was stirred for 20 h at ~20°C and cooled. The precipitate was filtered off and recrystallized from ethanol to give 2.34 g (94%) (IIIa). Product (IIIb) was obtained analogously.

Dithiocarbamates (IIIc)-(IIIe) were obtained by the reaction of substituted α-acetylenic ketones (Ic)-(Ie) with (II) in the presence of an equimolar amount of triethylamine at 60°C for 3 h (Tables 1 and 2).

N,N′-Bis(methoxycarbonylvinyldithiocarbo)piperazine (IIIf). A sample of 1.9 g (25 mmoles) CS_2 was added to a solution of 0.86 g (0.01 mole) anhydrous piperazine in 15 ml acetonitrile and stirred for 1 h. A solution of 1.68 g (0.02 mole) methyl propiolate (If) was added and stirred for 14 h at ~20°C. The precipitate was filtered off and recrystallized from ethanol to give 0.64 g (18%) (IIIf) (Tables 1 and 2).

N,N′-Bis(2-thenoylmethyl-2-phenyl-1,3-dithietanium)piperazine Perchlorate (IVd). A sample of 3.31 g (5 mmoles) (IIIf) was dissolved in 15 ml 57% perchloric acid (d_4^{20} 1.49 g/cm^3), carefully heated on a water bath to 60°C, and stirred for 1 h. The solution was cooled. The precipitate formed was washed with cold water and recrystallized from ethanol to give 3.14 g (73%) (IVd).

Perchlorates (IVe) and (IVf) were obtained by analogy (Tables 1 and 2).

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