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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF METHYL 3-ISONICOTINOYL-DITHIOCARBAZATE AND S,S'-DIMETHYL DITHIOCARBONATE ISONICOTINOYLHYDRAZONE, AND THEIR REACTIONS WITH AMINES AND HYDRAZINES

H. Foks[1], J. Mieczkowska[1], M. Janowiec[2], Z. Zwolska[2], and Z. Andrzejczyk[2]

Methyl 3-isonicotinoyldithiocarbazates and S,S'-dimethyl dithiocarbonate isonicotinoylhydrazone were prepared. Their reactions with primary and secondary amines, diamines, and hydrazines were studied. The newly obtained derivatives did not show tuberculostatic activity in vitro.

Keywords: 1,3-diazacycloalkanes, 1,2-diaziridine, S,S'-dimethyl dithiocarbonates, 1,3-dithiolane, isonicotinehydrazide, S-methyl dithiocarbazates, 1,2,4-triazoles, tuberculostatic activity.

Among the papers on synthesis and reactivity of 3-acyldithiocarbazates, Hoggart's report describing preparation of the compounds by reaction of carbon disulfide with phenylhydrazides in ethanolic potassium hydroxide still seems to be the most important one [1]. It was shown that reaction of 3-acyldithiocarbazates with hydrazine gave derivatives of 4-amino-5-methylthio-3-phenyl-1,2,4-triazole, while heated in pyridine they were transformed into 5-mercapto-2-phenyl-1,3,4-oxadiazoles. Mechanisms of the cyclizations were presented by Young and Wood, who also found that in concentrated sulfuric acid 3-acyldithiocarbazates were transformed into 2-substituted 5-methylthio-1,3,4-thiadiazoles [2]. Analogous reactions were performed with methyl-3-nicotinoyl derivative by Yoshida [3]. A considerable number of alkyl esters of 2-, 3-, and 4-pyridylthiocarbazoic acids were obtained by Kubota who studied the influence of the compounds on respiratory function of mitochondria [4]. The highest activity was found for derivatives possessing bulky alkyl residues, and QSAR analysis showed a good correlation of the activity with Hansch's hydrophobic constant II [5]. Possible applications of isonicotinoyldithiocarbazoic acid esters as rubber vulcanization accelerators, insecticides, fungicides, therapeutics, and components of light-sensitive emulsions were indicated in related patents [6, 7].

In the paper mentioned above Kubota described picolyl and isonicotinoyl derivatives of S,S'-dimethyl dithiocarbonate, formed as by-products during synthesis of the related monoesters [4]. Similar phenyl derivatives were obtained by Ruefenacht by methylation of methyl 3-benzoyldithiocarbazate with methyl iodide or dimethylsulfate [8]. The chemical properties of the dithiocarbonates have not been described yet, except our reports on the reactivity of S,S'-dialkyl dithiocarbonate pyrazinoylbenzoylhydrazones and their tuberculostatic activity [9, 10].

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[1] Department of Organic Chemistry, Medical University of Gdansk, 80-416 Gdansk, Poland; e-mail: hfoks@farmacja.amg.gda.pl. [2] Department of Microbiology, Institute of Tuberculosis Pulmonary Diseases 01-138 Warszawa, Poland. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 918-925, July, 2002. Original article submitted January 14, 2002.

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The synthesis of 3-isonicotinoyldithiocarbazate (**1**) is known and described in two papers [4, 7]. The compound was obtained by reaction of isonicotinehydrazide with carbon disulfide and methyl iodide in ethanol in the presence of potassium hydroxide. It was found that the yield of the reaction was unsatisfactory, and the process was modified by replacing the potassium hydroxide with triethylamine.

The thioester **1** was obtained in 70% yield and reacted with morpholine and ethanolamine. Products of the reaction with morpholine depended on the reaction conditions. Reaction of equimolar amounts of the reagents in ethanolic solution gave, despite the temperature, the salt **2** only, which after acidification was transformed back into the starting compound. However, prolonged reflux with an excess of morpholine gave 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol (**3**). Direct heating of the compound **1** with morpholine for 5 min gave a morpholine derivative of the thiosemicarbazide **4**, while after 2 h of heating 2-morpholino-5-(pyridin-4-yl)-1,3,4-oxadiazole (**5**) was isolated. Reaction of the compound **1** with ethanolamine gave a good yield of 4-(2-hydroxyethyl)-5-(pyridin-4-yl)-1,3,4-triazole-2(3H)-thione (**6**).

Subsequently, the synthesis and reactivity of S,S'-dimethyl dithiocarbonate isonicotinoylhydrazone were studied. The compound was isolated earlier as a side product in synthesis of the monoester **1** [4]. To increase the yield of the diester, the amounts of potassium hydroxide and methyl iodide were doubled and, as a result, the S,S'-dimethyl dithioester of the methylpyridinium salt **7** was formed as the main product. The compound **7** became a sole product when the ratio of hydrazide : carbon disulfide : base (KOH or TEA) : methyl iodide was 1 : 1 : 2 : 3, respectively. The use of potassium hydroxide was advantageous, as with TEA the obtained product was sometimes contaminated with triethylamine hydroiodide. The prepared diester **7** was reacted with several amines, including morpholine, 4-phenylpiperazine, *n*-propylamine, aniline, *p*-chloroaniline, ethanolamine, alkyldiamines, hydrazine, methylhydrazine, and dimethylhydrazine.

Heating of the S,S'-dithioester **7** with morpholine, phenylpiperazine, or propylamine resulted in cyclization to 2-amino-substituted 1,3,4-oxadiazoles **8-10**. The structure of the compound **9** was confirmed by transformation of the earlier obtained oxadiazole **5** into pyridinium methiodide.

Different results were observed for reactions of the diester with aniline or *p*-chloroaniline. Analysis of the NMR, IR, and MS spectra proved that in these cases products **11** and **12** were formed as a result of replacement of one of the S-methyl group by amine.

The reaction of the diester **7** with ethanolamine gave 3-(β-hydroxyethylamino)-4-(β-hydroxyethyl)-substituted 1,2,4-triazole **13**. The product **6** treated with an excess of methyl iodide in basic medium was transformed into methylthio derivative **14**.

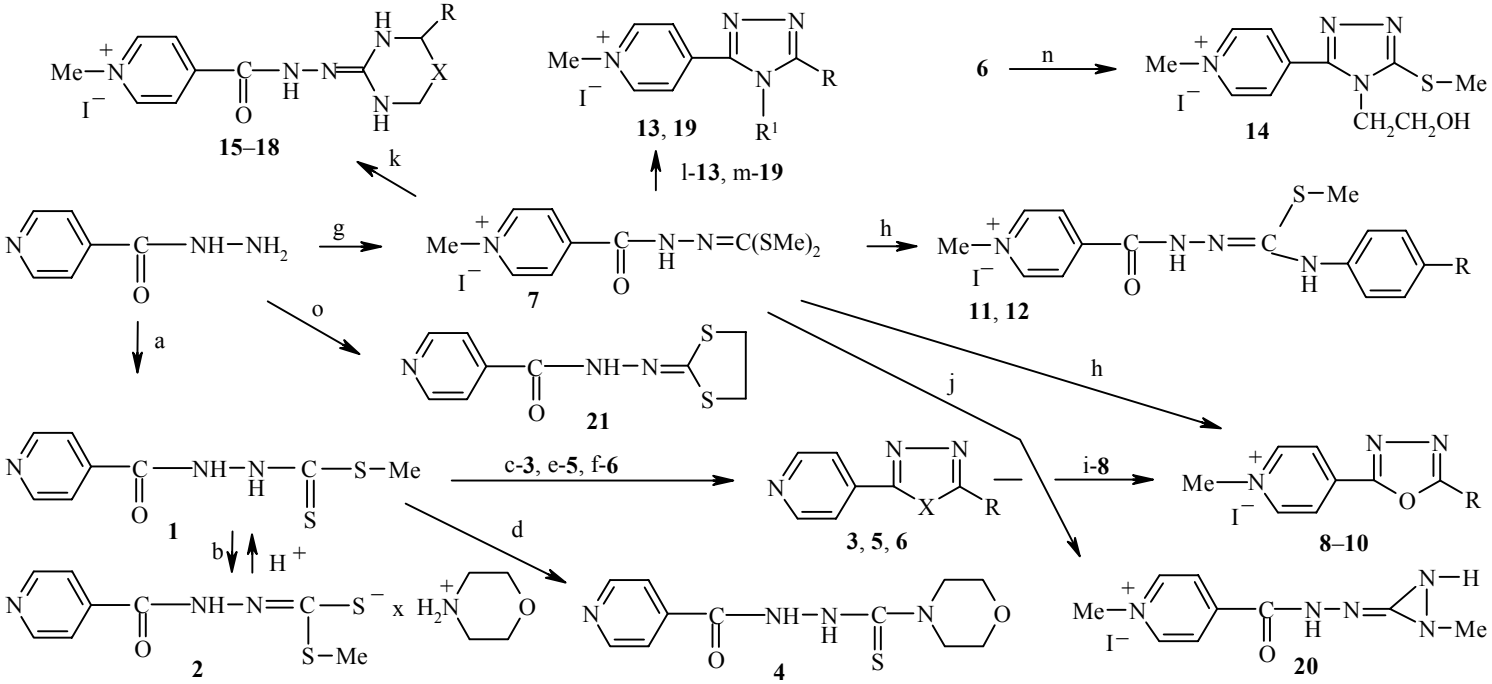
Short heating (approximately 10 min.) of the diester **7** with alkylenediamines in ethanol gave crystalline derivatives of N'-(1,3-diazacycloalkane-2-ylidene)isonicotinehydrazides **15-18**. 4-Amino-2-hydrazino-1,2,4-triazole **19** was formed by heating with 100% hydrazine hydrate in ethanol. The methylhydrazine reacted with the diester **7** to give compound **20** containing a diaziridinylidene group. Under analogous conditions dimethylhydrazine did not react.

The diester **7** was isolated only as its pyridinium salt, while an attempted synthesis of a cyclic diester **21** by reaction with ethylene bromide gave a 1,3-dithiolane derivative, in which the pyridinium nitrogen was not quaternized.

The compounds **7-20** were examined for their tuberculostatic activity towards *Mycobaterium tuberculosis* $H_{37}Rv$ strain and two "wild" strains isolated from tuberculotic patients: one resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), ethambutol (ETB), and rifampicine (RFP), another fully susceptible to the drugs administered.

In vitro investigations were performed by a classical test tube method of successive dilutions with Youman's liquid medium containing 10% of bovine serum [11].

The determined minimum concentrations inhibiting the growth of tuberculous strains (MIC) for most of the compounds examined were within the limits 250-1000 μg/ml, which showed that the newly obtained



	3	5	6	8	9	10	11	12	13	15	16	17	18	19
X	O	O	$N(CH_2)_2OH$	—	—	—	—	—		—	—	CH_2	CMe_2	
R	SH		SH			$NH(CH_2)_2Me$	H	Cl	$NH(CH_2)_2OH$	H	Me	H	H	$NHNH_2$
R'	—	—	—	—	—	—	—	—	$(CH_2)_2OH$	—	—	—	—	NH_2

a) CS_2, EtOH, Et_3N, MeI; b) EtOH, morpholine; c) EtOH, 1:2,5 morpholine, boiling, H^+; d) morpholine, boiling, 5 min., H^+ ; e) morpholine, boiling; f) $H_2NCH_2CH_2OH$, H^+; g) CS_2, EtOH, 2KOH, 3MeI; h) EtOH, amines, boiling; i) MeI; j) EtOH, $MeHNNH_2$; k) EtOH, $H_2N–CHR–X–CH_2–NH_2$; l) EtOH, $H_2NCH_2CH_2OH$; m) EtOH, $H_2NNH_2·H_2O$; n) EtOH, KOH, MeI; o) CS_2, EtOH, 2KOH, $BrCH_2CH_2Br$

TABLE 1.Characteristics of the Newly Synthesized Compounds

Com-pound	mp, °C (solvent for crystallization)	Empirical formula	Found, % / Calculated, %			IR, cm^{-1}	^1H NMR, δ, ppm, DMSO-d_6*	Yield, %
			C	H	N			
1	2	3	4	5	6	7	8	9
2	147-149 (EtOH/Et_2O)	$C_{11}H_{18}N_4O_2S_2$	43.72 / 43.69	6.22 / 5.99	18.50 / 18.52	3083, 2912, 2720, 2472, 1643, 1515, 1440, 1232, 1055, 980, 880, 664	2.72 (3H, s, Me); 3.52, 4.12 (8H, 2m, morpholine); 8.1, 9.13 (4H, 2m, pyridine); 8.5 (2H, br. s, H_2N^+)	95
6	218-219 (H_2O)	$C_9H_{10}N_4OS$	48.41 / 48.63	4.63 / 4.53	25.15 / 25.20	3312, 1615, 1560, 1440, 1344, 1295, 1232, 1184, 1072, 1003, 923, 864, 720	3.74, 4.13 (4H, 2t, $2CH_2$); 3.96 (1H, br. s, OH); 7.83, 8.76 (4H, 2d, pyridine)	70
7	173-176 (MeOH)	$C_{10}H_{14}IN_3OS_2$	31.26 / 31.34	3.55 / 3.68	10.78 / 10.96	3375, 2352, 2992, 1680, 1520, 1483, 1263, 1135, 1092, 843	2.92 (6H, s, 2MeS); 4.85 (3H, s, MeN^+); 8.85, 9.67 (4H, 2d, pyridine)	90
8	280-284 (MeOH)	$C_{12}H_{15}IN_4O_2$	38.67 / 38.52	4.26 / 4.04	14.78 / 14.97	2992, 1603, 1444, 1372, 1280, 1184, 1135, 1072, 1024, 975, 912, 843, 730	3.9 (8H, m, morpholine); 4.6 (3H, s, MeN^+); 8.75, 9.37 (4H, 2d, pyridine)	38 (h) 80 (i)
9	230-232 (MeOH)	$C_{18}H_{20}IN_5O$	48.30 / 48.12	4.63 / 4.49	15.72 / 15.59	2992, 1600, 1500, 1280, 1232, 1072, 975, 843	3.55, 4.12 (8H, 2m, $4CH_2$); 4.62 (3H, s, MeN^+); 7.35 (5H, m, phenyl); 8.77, 9.35 (4H, 2d, pyridine)	37
10	240-243 (MeOH)	$C_{11}H_{15}IN_4O$	38.36 / 38.17	4.46 / 4.37	16.28 / 16.18	3440, 3152, 1632, 1504, 1375, 1104, 1072, 1040, 815, 672	1.1 (3H, t, CH_3); 1.87 (2H, m, CH_2); 3.60 (2H, m, N–CH_2); 4.65 (3H, s, MeN^+); 8.65, 9.38 (4H, 2d, pyridine)	38
11	133-135 (MeOH)	$C_{15}H_{17}IN_4OS$	42.21 / 42.05	4.18 / 4.00	13.31 / 13.08	3403, 3003, 1640, 1483, 1472, 1455, 1370, 1083, 843, 720	2.9 (3H, s, MeS); 4.52 (3H, s, MeN^+); 7.9 (5H, s, phenyl); 8.1, 9.2 (4H, 2d, pyridine)	51
12	235-237 (MeOH)	$C_{15}H_{16}ClIN_4OS$	38.72 / 38.93	3.36 / 3.48	12.02 / 12.10	3440, 2992, 1632, 1535, 1483, 1440, 1312, 992, 784, 704, 592	2.97 (3H, s, MeS); 4.55 (3H, s, MeN^+); 7.97 (4H, s, phenyl); 8.17, 9.25 (4H, 2s, pyridine)	43

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
13	193-195 (MeOH)	$C_{12}H_{18}IN_5O_2$	36.72 / 36.84	4.43 / 4.63	18.11 / 17.90	3203, 1632, 1535, 1440, 1350, 1232, 1104, 1055, 750, 632	3.35, 3.60 (8H, 2m, $4CH_2$); 4.32 (3H, s, MeN^+); 5.4 (2H, br. s, 2OH); 7.58 (1H, br. s, NH); 8.46, 8.88 (4H, 2d, pyridine)	53
14	178-179 (MeOH)	$C_{11}H_{15}IN_4OS$	34.98 / 34.93	4.20 / 3.99	14.96 / 14.81	3360, 1632, 1563, 1504, 1440, 1375, 1280, 1184, 1043, 843	3.05 (3H, s, MeS); 4.0, 4.55 (4H, 2s, $2CH_2$); 4.25 (1H, s, OH); 4.72 (3H, s, MeN^+); 8.9, 9.5 (4H, 2d, pyridine)	80
15*[2]	274-276 (EtOH)	$C_{10}H_{14}IN_5O$	34.69 / 34.60	4.25 / 4.06	20.32 / 20.17	3163, 2944, 1600, 1520, 1463, 1083, 704, 658	3.85 (4H, s, $2CH_2$); 4.5 (3H, s, MeN^+); 8.7, 9.14 (4H, 2d, pyridine)	15
16	260-262 (MeOH)	$C_{11}H_{16}IN_5O$	36.72 / 36.58	4.63 / 4.46	19.54 / 19.39	3280, 1680, 1632, 1563, 1483, 1312, 1152, 864, 755, 675	1.47 (3H, d, Me); 3.4 (1H, m, CH); 4.0 (2H, m, CH_2); 4.5 (3H, s, MeN^+); 8.67, 9.12 (4H, 2d, pyridine)	14
17	252-255 (MeOH)	$C_{11}H_{16}IN_5O$	36.68 / 36.58	4.31 / 4.46	19.42 / 19.39	3440, 3264, 1660, 1584, 1552, 1360, 1264, 1215, 1152, 1072, 843, 752, 672	2.07 (2H, m, CH_2); 3.55 (4H, m, $2CH_2$); 4.67 (3H, s, MeN^+); 8.7 (2H, s, 2NH); 8.77, 9.52 (4H, 2d, pyridine); 10.2 (1H, s, NH)	12
18	273-275 (MeOH)	$C_{13}H_{20}IN_5O$	40.28 / 40.11	5.36 / 5.18	18.17 / 17.99	3200, 1632, 1552, 1504, 1295, 1163, 672	1.1 (6H, s, 2Me); 3.22 (4H, s, $2CH_2$); 4.52 (3H, s, MeN^+); 8.73, 9.15 (4H, 2d, pyridine)	30
19	212-213 (MeOH)	$C_8H_{12}IN_7$	28.98 / 28.84	3.84 / 3.63	29.72 / 29.43	3283, 1680, 1623, 1563, 1504, 1344, 1152, 1080, 752	3.75 (3H, br. s, 3NH); 4.55 (3H, s, MeN^+); 4.9 (2H, br. s, NH_2); 8.7, 9.5 (4H, 2d, pyridine)	60
20*[3]	228-229 (MeOH)	$C_9H_{12}IN_5O$	32.63 / 32.45	3.81 / 3.63	21.23 / 21.02	3415, 3003, 1683, 1632, 1563, 1504, 1472, 1424, 1184, 1024, 895	3.5 (3H, s, MeN^+); 4.6 (3H, s, MeN^+); 8.7, 9.35 (4H, 2d, pyridine)	45
21	203-205 (MeOH)	$C_9H_9N_3OS_2$	45.06 / 45.17	3.51 / 3.79	17.67 / 17.56	3175, 1643, 1535, 1320, 1284, 1040, 975, 832, 683	3.87 (4H, s, $2CH_2$); 7.95, 9.0 (4H, 2d, pyridine); 12.55 (1H, s, NH)	60

* **17** in DMSO-d_6 + TFA.

*[2] MS, *m/z* (*I,* %): [M+1] – 219 (4.5), 205 (24.5), 142 (100), 127 (62.3), 98 (30.1).

*[3] MS, *m/z* (*I,* %): [M+1] – 205 (7.5), 191 (43.5), 142 (100), 127 (82.2), 78 (93.1).

derivatives were not active *in vitro*. Isonicotinic acid hydrazide (INH) transformation into these derivatives led to a significant decrease in biological activity. MIC of the most active compound **22** was 12.5 μg/ml for $H_{37}Rv$ strain and 25 μg/ml for another strains.

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were recorded on a Specord IR-75 spectrophotometer. The ^1H NMR spectra were determined on a Tesla Spectrometer BS-487C, 80 MHz, and the mass spectra with a Varian MAT 711 apparatus, at an electron beam energy of 70 eV. The results of elemental analyses (% C, H, N) for all the compounds obtained were in good agreement with the data calculated. Reaction yields and the physical constants of the compounds obtained are given in Table 1.

Methyl 3-isonicotinoyldithiocarbazate (1). To a suspension of isonicotinhydrazide (6.85 g, 50 mmol) in ethanol (15 ml), triethylamine (5.0 g, 50 mmol) was added, and then, through a reflux condenser, CS_2 (3.8 g, 50 mmol) was introduced dropwise. The reaction mixture was stirred until homogenization, and then methyl iodide (7.1 g, 50 mmol) was added dropwise. After 30 min 150 ml of water was added, the mixture was ice-cooled and the precipitate of ester **1** filtered off. The reaction yielded 9.5 g (83%) of **1**. After recrystallization from MeOH mp 249-252°C (decomp.), at *ca.* 190°C change of crystallographic system in accordance with Ref [4].

Methyl Ester 1 Morpholine Salt (2). Compound **1** (2.27 g, 10 mmol), ethanol (10 ml), and morpholine (0.9 g, 10 mmol) were refluxed for 15 min and allowed to stand. The product was precipitated with anhydrous diethyl ether. The precipitate of salt **2** on dissolving in water and acidifying with acetic acid gave the compound **1** back.

5-(Pyridin-4-yl)-1,3,4-oxadiazole-2-(3H)-thione (3). Compound **1** (2.27 g, 10 mmol) and (2 ml) morpholine dissolved in ethanol (10 ml) were refluxed for 4 h. The solvent was distilled off, then 5 ml of water was added and the mixture acidified with acetic acid. The precipitate was collected and recrystallized. Its mp and IR spectrum was as in Ref [3].

N'-Morpholinocarbothio-N-isonicotinoylhydrazine (4). Compound **1** (10 mmol) and morpholine (2 ml) were refluxed for 5 min. On cooling down 10 ml of water was added and the mixture acidified with acetic acid. The precipitate was collected and purified by recrystallization from ethanol. Its mp and IR spectrum was as in Ref [10].

2-Morpholino-5-(pyridin-4-yl)-1,3,4-oxadiazole (5). Compound **1** (10 mmol) and morpholine (2 ml) were refluxed for 2 h. On cooling down, water (20 ml) was added. The mixture was extracted with chloroform, the extract dried ($MgSO_4$), concentrated and the precipitate purified by recrystallization. Physical constants were as in Ref. [11].

4-(2-Hydroxyethyl)-5-(pyridin-4-yl)-1,2,4-triazole (6). Compound **1** (10 mmol) and ethanolamine (3 ml, 50 mmol) were refluxed for 1 h. On cooling down, water (10 ml) and acetic acid (3.5 ml) were added. The mixture was ice-cooled, and the precipitate collected and recrystallized.

S,S'-Dimethyl Dithiocarbonate Isonicotinoylhydrazone Methiodide (7). To a suspension of isonicotinhydrazide (6.85 g, 50 mmol) in ethanol (15 ml) a solution of KOH (5.6 g, 100 mmol) in EtOH (20 ml) was added, then, through the reflux condenser, CS_2 (3.8 g, 50 mmol) was added portionwise. When the mixture became homogeneous, it was cooled down with water and MeI (21.3 g, 150 mmol) was added dropwise. After 24 h the precipitate of KI was filtered off. To the filtrate 150 ml of anhydrous Et_2O was added and the precipitate filtered off; mp after crystallization from MeOH: 173-176°C. Reaction yielded 17 g (90%) of dithioester **7**.

2-Morpholino-, 2-(4-Phenylpiperazino)- and 2-Propylamino-5-(pyridin-4-yl)-1,3,4-oxadiazole Methiodides (8-10). To a solution of dithioester **7** (1.2 g, 50 mmol) in 5 ml EtOH, 50 mmol of appropriate amine was added and refluxed for 2 h. Upon cooling down, the precipitate was collected and recrystallized.

Compound **8** was obtained as well by adding 25 mmol MeI to the solution of oxadiazole **5** (25 mmol) in 3 ml EtOH and allowing the mixture to stand for 12 h.

1-Isonicotinoyl-4-phenyl- and 4-(*p*-Chlorophenyl)-S-methylisothiosemicarbazide Methiodides (11 and 12). The solution of dithioester **7** (50 mmol) and aniline or *p*-chloroaniline (50 mmol) in EtOH (5 ml) was refluxed for 4 h. On cooling down, Et_2O was added and the oils precipitated. The ethereal solution was decanted, then a small amount of MeOH was added to the residue. Crystallization was initiated by rubbing with a glass rod. Products were purified by crystallization from MeOH.

3-(2-Hydroxyethylamino)-4-(2-hydroxyethyl)-5-(pyridin-4-yl)-1,2,4-triazole Methiodide (13). Compound **7** (1.2 g, 5 mmol) and ethanolamine (2 ml, 30 mmol) were refluxed for 3 h. Upon cooling down, the precipitate was collected.

4-(2-Hydroxyethyl)-3-methylthio-5-(pyridin-4-yl)-1,2,4-triazole Methiodide (14). Compound **6** (1.1 g, 5 mmol) was added to a solution of KOH (0.3 g, 5 mmol) in ethanol (15 ml), then methyl iodide (0.9 ml, 15 mmol) was added and the mixture was refluxed for 3 h. After cooling down, Et_2O was added and the ethereal solution was decanted from above the thick oil, which was treated with a small amount of MeOH. Crystallization was initiated by rubbing with a glass rod. The precipitate was filtered off and recrystallized from MeOH.

N'-(1,3-Diazacycloalkan-2-ylidene)isonicotinehydrazide Methiodides (15-18). Compound **7** (10 mmol), ethanol (10 ml) and an appropriate alkyldiamine (20 mmol) were refluxed for 0.5 h. After cooling down, the precipitates were collected and recrystallized.

4-Amino-3-hydrazino-5-(pyridin-4-yl)-1,2,4-triazole Methiodide (19). A solution of compound **7** (1.9 g, 5 mmol) in EtOH (10 ml) was treated with hydrazine hydrate (0.25 ml, 5 mmol) and refluxed for 10 min. On cooling down, the precipitate was filtered off and recrystallized.

N'-(1-Methyl-1,2-diaziridin-3-ylidene)isonicotinehydrazide Methiodide (20). Compound **7** (1.9 g, 5 mmol), ethanol (15 ml), and methylhydrazine (0.2 ml, 5 mmol) were refluxed for 10 min. On cooling down, the precipitate was filtered off.

N'-(1,3-Dithiolan-2-ylidene)isonicotinehydrazide (21). To a solution of KOH (1.2 g, 20 mmol) in EtOH (10 ml) isonicotinehydrazide (1.4 g, 10 mmol) was added, then CS_2 (0.6 ml, 10 mmol) was introduced dropwise through the reflux condenser. The mixture was clarified while stirring, then EtBr (0.86 ml, 10 mmol) was added and the mixture refluxed for 5 min. After cooling with ice 50 ml of water was added. The precipitate of compound **21** was filtered off and recrystallized from MeOH.

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