SYNTHESIS AND BACTERIOSTATIC ACTIVITY OF THIOSEMICARBAZONES AND ISONICOTINOYLHYDRAZONES OF PYRUVIC ACID

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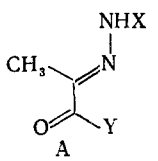
UDC 615.281.221.1:547.482.23].012.1

On the basis of available information on the antituberculosis activity of several hydrazones of pyruvic acid [1-3], we synthesized a series of thiosemicarbazones (I-VII) and isonicotinoylhydrazones (IX-X) of pyruvic acid (see Table 1) and investigated their antituberculosis activity.

Judging from the PMR spectra, the compounds obtained under the conditions studied exist in one stereoisomeric form relative to the C—N bond, since one observes only one singlet of the methyl protons of CH_3—C—N in the region 2.08-2.27 ppm in pyridine, and the NH protons of the hydrazone fragment occur in the region 9.9-11.4 ppm in dimethyl sulfoxide. The location of the NH signals of the hydrazone fragment in a weak field shows the presence of a hydrogen bond. For example in compound VI it was shown that in strongly polar media, on going from methanol to hexamethylphosphorotriamide this signal shifts toward the weak field, since its position is observed to be linearly dependent on E_T (see Fig. 1). These data show the intermolecular character of the hydrogen bond and its intensification in the indicated series of solvents.

The absence of intramolecular hydrogen bonds is indicated by the shift of the NH signal in chloroform, in dilution, to a stronger field; by the NH absorption frequency (3375 cm^{-1}) in IR spectra for dilute solutions of compound VI in chloroform and carbon tetrachloride; and also by the identity of the carbonyl absorption band frequency with that of the starting pyruvic amide.

Evidently, the thiosemicarbazones of pyruvic acid dialkylamides exist predominantly in stereoisomeric form A, stabilized by the dipolar repulsion of C=N and C=O.



A

The UV spectra of compounds I-VII are quite similar exhibiting a hypsochromic $n\rightarrow\pi^*$ shift of the absorption band when the solvent is changed from chloroform to water, which evidently results from hydrogen-bonding with water molecules.

Bacteriostatic activity was investigated for compounds I, III, VI, and VIII-X. The study was carried out by the method of serial dilution of the Preyss liquid medium. We used as test strains mycobacteria of the human type H37Rv, sensitive to all preparations; and two strains taken from tuberculosis patients which are resistant to 50 μg of streptomycin and to 5 μg of tubazide. The isonicotinoylhydrazone of pyruvic acid (VIII) inhibits the growth of sensitive mycobacteria at a concentration of 1 μg/ml. Isonicotinoylhydrazones IX-X were inactive.

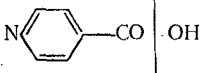
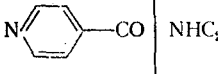
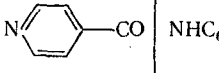
In the series of tested thiosemicarbazones there was insignificant activity except for compound III, which inhibited the growth of mycobacteria at a concentration of 50 μg/ml.

Thus, change in the structure of isonicotinoylhydrazone VIII by the introduction of either an amide or a thiosemicarbazone causes a loss of bacteriostatic activity.

S. M. Kirov Military-Medical Academy, Leningrad. Leningrad Tuberculosis Research Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 12, pp. 26-29, Decmeber, 1977. Original article submitted April 25, 1977.

0091-150X/77/1112-1609$07.50

TABLE 1. Pyruvic Acid Derivatives $CH_3-\overset{\overset{COY}{|}}{C}=NNHX$

Compound	X	Y	Yield, %	R_f*	mp, deg C	UV spectra, λ_{max} (log ε)		IR spectra in dimethyl sulfoxide (DMSO)		δ, ppm				Found %		Empirical formula	Calculated, %	
										DMSO			pyridine					
						H_2O	$CHCl_3$	1600—1800 cm^{-1}	3000—3600 cm^{-1}	amide NH	hydrazone NH	NH_2†	$CH_3-C=N$	N	S		N	S
I	$CSNH_2$	NHC_2H_5	60	0,70	217—9	290 (4,38)	302 (4,18)	1638 1665	3053 3173	8,5	10,2	8,5 (2H)	2,21	30,1	16,8	$C_6H_{12}N_4OS$	29,8	17,0
II	$CSNH_2$	NHC_3H_7	91	0,70	203—5	290 (3,53)	301 (3,80)	1615 1665	3055 3175	8,5	10,2	8,5 (2H)	2,21	27,5	15,7	$C_7H_{14}N_4OS$	27,8	15,8
III	$CSNH_2$	NHC_6H_5	59	0,80	218—9‡	298 (4,19)	287 (4,32)	1630 1665	3160 3270	10,1	10,4	8,6 8,8 (2H)	2,27	—	—	—	—	—
IV	$CSN(CH_3)_2$	NHC_6H_5	73	0,70	136—8	270 (4,16)	263 (4,11) 297 (4,09)	1680	3180	9,7	9,9	—	2,08	21,6	12,2	$C_{12}H_{16}N_4OS$	21,3	12,1
V	$CSNH_2$	$NCH_3C_6H_5$	36	0,75	200—2	283 (4,18)	295 (3,46)	1640	3020 3110 shoulder	—	10,2	6,5 8,1 (2H)	2,13	22,6	12,3	$C_{11}H_{14}N_4OS$	22,3	12,8
VI	$CSNH_2$	$N(C_2H_5)_2$	74	0,70	157—158	273 (4,26)	288 (4,33)	1620	3055	—	10,2	7,5 8,2 (2H)	2,17	25,9	14,8	$C_8H_{16}N_4OS$	25,8	14,8
VII	$CSNH_2$	$N(C_3H_7)_2$	38	0,70	152—154	275 (4,27)	287 (4,32)	1633	3033	—	10,2	7,4 8,2 (2H)	2,18	22,8	12,8	$C_{10}H_{10}N_4OS$	22,8	13,1
VIII		OH	95	0,90	216—7[2]	265 (4,01)	268 (3,98)	1693	3030	—	11,08 (2H) NH, OH	—	2,26	—	—	—	—	—
IX		NHC_2H_5	87	0,85	120—2	265 (4,93)	257 (4,08)	1620 1663 shoulder 1693	3060 3350	8,3	11,3	—	2,27	23,9	—	$C_{11}H_{14}N_4O_2$	23,9	—
X		NHC_6H_5	75	0,90	184—6	273 (4,12)	265 (4,07)	1603 1678 shoulder 1693	3070 3190	9,9	11,4	—	2,26	19,7	—	$C_{15}H_{14}N_4O_2$	19,8	—

Note. Compounds I, II, V, IX, and X were crystallized from water; III and IV from a chloroform–ether mixture; VI and VII from a water–ethanol mixture; VIII from dimethylformamide.

*Eluent benzene–ethanol (3:1), Silufol sheets, UV = 254.

†Broad signal.

‡According to [4], mp is 201-203°C.

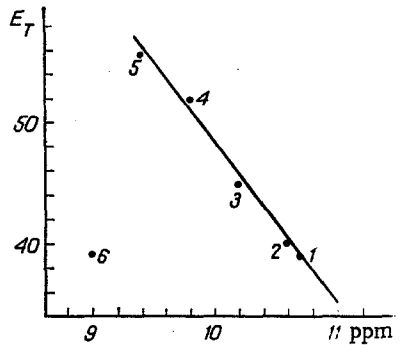


Fig. 1. Chemical shift of δ_{NH} in a solution of compound VI at a concentration of 0.2 M (0.46 M in chloroform). 1) in hexamethylphosphorotriamide; 2) in pyridine; 3) in dimethyl sulfoxide; 4) in ethanol; 5) in methanol; 6) in chloroform.

EXPERIMENTAL

PMR spectra were obtained on an R-2310 apparatus (60 MHz), in pyridine, using hexamethyldisiloxane as an internal standard. IR and UV spectra were obtained on UR-10 and SF-8 spectrophotometers.

Amides of Pyruvic Acid were obtained following the procedure of [5]. The ethylamide of pyruvic acid: bp 76°C (12 mm); mp 37°C. Found: %: N 12.29. $C_5H_9NO_2$. Calculated: %: N 12.19. The dipropylamide of pyruvic acid: bp 110°C (20 mm), n_D^{20} 1.441. Found: %: N 8.21. $C_9H_{17}NO_2$. Found: %: N 8.19.

Thiosemicarbazones and Isonicotinoylhydrazones of Pyruvic Acid. To a solution of 0.01 mole of the corresponding amide of pyruvic acid in 10 ml of 20% ethanol, acidified to pH 3.0 with dilute hydrochloric acid, was added 0.011 mole of thiosemicarbazide or isonicotinoylhydrazine in 10 ml of water. The mixture was stirred for 2 h. The precipitate was filtered off, washed with water (3 × 5 ml), and crystallized from an appropriate solvent.

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