SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF 3,5-SUBSTITUTED 2-ACYLMETHYL-1,3,4-THIADIAZOLES

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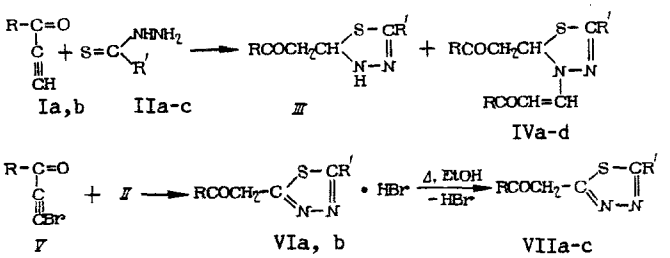
The 4-sulfamide oxy- and oxo-derivatives of 1,2,5-thiadiazoles are known to have bacterial activity [2-4, 6, 7]. The heterylthiomethyl-5-(4-chlorophenyl)-1,3,4-thiadiazoles-2-thiones exhibit in vitro antibacterial activity against Gram-positive and Gram-negative bacteria [1], whereas the 2-substituted 4-(2,6-xylylimino)-1,3,4-thiadiazolines exhibit antitubercular activity [5].

In our search for new antituberculosis preparations we synthesized several 2-acylmethyl-1,3,4-thiadiazoles and their 3- and 5-substituted analogs (III, IVa-d, VIa, b, VIIa-c). The compounds 2-benzoylmethyl-5-methylamino-Δ^4-1,3,4-thiadiazoline (III) and 3-acylvinyl-2-acylmethyl-5-R^1-Δ^4-1,3,4-thiadiazolines (IVa-d) were synthesized by reacting terminal α-acetylene ketones (Ia, b) with 4-methyl-, 4-phenylthiosemicarbazide, and thiobenzhydrazide in an alcohol medium at 20°C. The compounds 2-benzoylmethyl-5-R^1-1,3,4-thiadiazoles (VIa, b, VIIa-c) were obtained by reacting 1-bromo-2-benzoylacetylene (V) with 4-methyl- (IIa), 4-phenylthiosemicarbazide (IIb), and thiobenzhydrazide (IIc), respectively, in alcohol or acetonitrile.

The synthesized compounds appear as crystalline white or yellow substances that are insoluble in water and soluble in proton (EtOH) and aprotonic (acetone, chloroform, DMSO) solvents.



R=Ph (Ia, III, IVa-c, V, VIa, b, VIIa-c), thienyl-2 (Ib, IVd), R^1=NHMe (IIa, III, IVa, VIa, VIIa), NHPh (IIb, IVb, VIb, VIIb), Ph (IIc, IVc, d, VIIc).

The structure of compounds III, IVa-d, VIa, b, and VIIa-c were confirmed by IR and PMR spectroscopy (Table 1).

The IR spectra of the compounds had absorption bands for the C=S bond (670-700 cm^{-1}), the C=O group (1630-1670 cm^{-1}), the C=C bonds (1525-1545 cm^{-1} for compounds IVa-d), the NH group (3175-3320 cm^{-1} for compounds III, IVa, b; VIIa, b), and a broad $^+NH_2$ group band (2600-3150 cm^{-1}) for the bromide IVa.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a UR-20 spectrometer in KBr pellets. PMR spectra were recorded on a Tesla BS-487C spectrometer (80 MHz) in DMSO-d_6. Internal standard was HMDS. Characteristics of the synthesized compounds are given in Table 1. Element analysis data satisfy the calculated values.

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	mp, °C	Empirical formula	PMR spectrum, δ, ppm
III	66	123—4	$C_{11}H_{13}N_3OS$	3,01 (3H, CH_3), 4,09 (2H, CH_2), 7,60—8,24 (7H, Ph, CH_χ, NH), 11,42 (1H, NH)
IVa	70	151—2	$C_{20}H_{19}N_3O_2S$	—
IVb	67	163—4	$C_{25}H_{21}N_3O_2S$	3,98 (2H, CH_2), 6,31 (2H, $COCH{=}CH_\chi$), 7,0—8,02 (16H, Ph, NCH=), 10,00 (NH)
IVc	79	143—5	$C_{25}H_{20}N_2O_2S$	3,79 (2H, CH_2), 6,28 (2H, $COCH{=}CH_\chi$), 7,43—8,20 (16H, Ph, NCH=)
IVd	80	175—7	$C_{21}H_{16}N_2O_2S_3$	3,75 (2H, CH_2), 6,27 (2H, $COCH{=}CH_\chi$), 7,13—8,12 (12H, C_4H_3S, Ph, NCH=)
VIIa	74	160—1	$C_{11}H_{11}N_3OS$	2,9 (3H, CH_3); 4,8 (2H, CH_2); 7,6—8,0 (6H, Ph, NH)
VIa	84	237—3	$C_{11}H_{12}BrN_3OS$	3,09 (3H, CH_3), 5,0 (2H, CH_2), 7,6—8,1 (5H, Ph), 8,9 (2H, NH_2^+)
VIIb	85	212—5	$C_{16}H_{13}N_3OS$	4,94 (2H, CH_2), 7,03—8,14 (10H, Ph), 10,36 (1H, NH)
VIIc	75	175—7	$C_{16}H_{12}N_2OS$	4,90 (2H, CH_2), 7,52—8,04 (10H, Ph)

2-Benzoylmethyl-5-methylamino-Δ^4-1,3,4-thiadiazoline (III) and 3-Benzoylvinyl-2-benzoylmethyl-5-methylamino-Δ^4-1,3,4-thiadiazoline (IVa). A solution of 0.65 g (5 mmoles) of benzoylacetylene (Ia) in 10 ml of ethanol was added upon slow stirring for 1 h to a solution of 0.53 g (5 mmoles) of 4-methylthiosemicarbazide in 15 ml of ethanol, heated to 40°C. The resultant precipitate was filtered off and recrystallized from ethanol to yield 0.75 g (66%) of III. After separating III, the solution was partially evaporated and kept for 24 h at 0°C. The resultant precipitate was filtered off and recrystallized from ethanol to yield 0.15 g (16%) of IVa.

Under similar conditions at a benzoylacetylene:4-methylthiosemicarbazide ratio of 2:1, 1.3 g (70%) of compound IVa only was obtained.

3-Benzoylvinyl-2-benzoylmethyl-5-phenylamino-Δ-1,3,4-thiadiazoline (IVb) was synthesized in a similar fashion from 0.65 g (5 mmoles) of benzoylacetylene and 0.42 g (2.5 mmoles) of 4-phenylthiosemicarbazide (IIb). Yield was 0.72 g (67%) of IVb.

3-Benzoylvinyl-2-benzoylmethyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (IVc). A solution of 0.65 g (5 mmoles) of benzoylacetylene in 5 ml of MeOH was slowly added with stirring to a solution of 0.76 g (5 mmoles) of thiobenzhydrazine (IIc) in 15 ml of MeOH. The mixture was stirred for 2 h at 20°C and left overnight. The resultant precipitate was filtered off and recrystallized from a 1:1 mixture of ethanol and ether. Yield was 0.81 g (79%) of IVc.

3-Thenoylvinyl-2-thenoylmethyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (IVd) was obtained in a similar manner as IVc from 0.68 g (5 mmoles) of thenoylacetylene (Ib) and 0.76 g (5 mmoles) of thiobenzhydrazide (IIc). Yield was 0.84 g (80%).

2-Benzoylmethyl-5-methylamino-1,3,4-thiadiazole Hydrobromide (VIa). A 1.06-g (10 mmoles) portion of 4-methylthiosemicarbazide (IIa) was added to a solution of 2.09 g (10 mmoles) of 1-bromo-2-benzoylacetylene V in 25 ml of acetonitrile. The mixture was stirred at 20°C for 1.5 h and the precipitate was filtered off and recrystallized from a 5:1 mixture of acetonitrile and methanol to yield 2.65 g (84%) of VIa. $C_{11}H_{12}BrN_3OS$.

2-Benzoylmethyl-5-methylamino-1,3,4-thiadiazole (VIIa). A 0.43-ml portion of triethylamine was added to a solution of 1.34 g (4.3 mmoles) of hydrobromide VIa in 75 ml of ethanol and 120 ml of water and the mixture is heated for 0.5 h up to boiling. After the solution was cooled, the resultant precipitate was filtered off and vacuum-dried over $CaCl_2$. Yield 0.73 g (74%) of VIIa.

2-Benzoylmethyl-5-phenylamino-1,3,4-thiadiazole (VIIb) was obtained in a similar manner as VIa from 0.52 g (2.5 mmoles) of 1-bromo-2-benzoylacetylene V and 0.42 g (2.5 mmoles) of 3-phenylthiosemicarbazide (IIb) in 15 ml of acetonitrile to yield 0.8 g (85%) of hydrobromide VIb. mp 210-214°C. $C_{16}H_{14}BrN_3OS$. Compound VIb was heated to boiling in a 10:1 mixture of ethanol and water. After cooling, the yield was 0.53 g (85%) of VIIb.

2-Benzoylmethyl-5-phenyl-1,3,4-thiadiazole VIIc. A solution of 1.05 g (5 mmoles) of 1-bromo-2-benzoylacetylene (V) in 10 ml of MeOH was added slowly with stirring to a solution of 0.76 g (5 mmoles) of thiobenzhydrazide (IIc) in 10 ml of methanol cooled to −30°C. The reaction mixture was heated to 0°C and the resultant precipitate was filtered off and recrystallized from ethanol to yield 1.05 g (75%) of VIIc.

TABLE 2. Tuberculostatic Activity of 3,5-Substituted 2-Acylmethyl-1,3,4 -thiadiazoles III, IVa-d, VIa, VIIa-c

Compound	Minimum inhibitory concentration (strain H37RV), μg/ml	LD_{50}, mg/kg
III	25,0—12,5	
IVa	25,0	
IVb	12,5	>2200
IVc	25,0	
IVd	10,0	>2200
VIa	>50	670
VIIa	>50	
VIIb	12,5	>1000
VIIc	>50	

EXPERIMENTAL (BIOLOGICAL)

The tuberculostatic activity of the synthesized compounds was tested by the double series method.

The results of the tuberculostatic activity tests of the synthesized compounds are given in Table 2.

The nature of the substituent in positions 2 and 5 of the heterocyclic ring did not have any significant effect on antituberculosis activity in the examined 2-acylmethyl-Δ^4-1, 3,4-thiadiazolines (III, IVa-d).

Of all the examined compounds, the highest level of tuberculostatic activity (10 μg/ml) against strain H37Rv was exhibited by IVd which has a thenoylmethyl substituent in position 2 of the thiadiazole ring and a thenoylvinyl substituent in position 3.

The tested compounds exhibited a low level of toxicity.

Thus, the results of our experiments indicate that 2-acylmethyl- and 2-acylmethyl-3-acylvinyl-1,3,4-thiadiazoles exhibit tuberculostatic activity that is comparable to that of the antitubercular preparations on hand.

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