SYNTHESIS OF CERTAIN DERIVATIVES OF 3-PHENYL-5-METHYL-4-ISOXAZOLECARBOXYLIC ACID

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3,5-Disubstituted isoxazole-4-carboxylic acids have recently found wide use for the synthesis of new acid- and penicillinase-resistant penicillins [1]. Among them we should mention oxacillin and cloxacillin, which have proved to be the most effective preparations in the treatment of Staphylococcus infections and have found practical application in medicine.

We were interested in synthesizing the hydrazide and certain hydrazones of one of the acids of this series for a study of their biological activity. For this purpose, we selected the more readily available 3-phenyl-5-methyl-4-isoxazolecarboxylic acid (I), used in the synthesis of oxacillin. The initial acid (I) was produced according to the procedure that we developed earlier [2]. The hydrazide of acid I was synthesized by the reaction of the corresponding acid chloride with hydrazine hydrate in an alcohol-ether solution (method A), and also by the reaction of the methyl ester of acid I with hydrazine in ethanol medium (method B). The yield of the hydrazide according to method A was somewhat lower (70%) than according to method B (74.5%). The use of the ethyl ester of the acid I in the synthesis of the hydrazide both in ethanol medium and in a medium of high-boiling alcohols (propyl, n-butyl, and amyl), despite prolonged heating (20 h), did not give positive results. Nor were we able to produce the hydrazide from the acid I and hydrazine in toluene medium in the presence of activated aluminum oxide with azeotropic distillation of water.

In the subsequent interaction of the hydrazide of acid I with various ketones (acetone, methyl ethyl ketone, acetophenone) and aldehydes (benzaldehyde, o-chlorobenzaldehyde, p-bromobenzaldehyde, m-nitrobenzaldehyde, p-diethylaminobenzaldehyde, salicylaldehyde, vanillin, furfural, and 4,5-dibromofurfural) in ethanol medium, we obtained hydrazones, representing colorless or slightly yellowish needle-like crystals, difficultly soluble in cold alcohol and insoluble in water.

The preparations obtained were tested for antimicrobial activity in vitro with respect to six strains of microorganisms: Staphylococcus 209P, Enterococcus, Proteus, Escherichia coli, anthracoid bacillus, and the paratyphus microbe. The minimum bacteriostatic concentration was determined by the method of successive two-fold dilutions in meat-peptone broth. Not one of the compounds inhibited growth of the microorganisms at concentrations of 200 μg/ml or below. The results of tests for antitubercular activity will be reported separately.

EXPERIMENTAL

3-Phenyl-5-methyl-4-isoxazolecarboxylyl Chloride was produced in 88.4% yield. Colorless liquid, bp 160-162° (20 mm). According to the literature data [3], bp 162-165° (20-30 mm). Crystallizes upon standing. Mp 24-25°.

Methyl Ester of 3-Phenyl-5-methyl-4-isoxazolecarboxylic Acid. A 44.2 g portion of the acid chloride was dissolved with cooling in 50 ml of methanol, and the solution boiled with a reflux condenser on a water bath for 2 h. The product that precipitated upon cooling was filtered, washed with a small amount of methanol and water. Yield 42.4 g (99%). Colorless rhombic crystals. Mp 78-78.5°. Found, %: C 66.50, 65.25; H 5.00, 5.09; N 6.30, 6.42. $C_{12}H_{11}NO_3$. Calculated, %: C 66.4; H 5.07; N 6.45.

3-Phenyl-4-methyl-4-isoxazoylhydrazide. A. To a cooled solution of 25 ml hydrazine hydrate in 200 ml of absolute alcohol, a solution of 11.25 g (0.05 mole) of the acid chloride I in 100 ml of ether was added drop-wise with vigorous mixing. After three-hour mixing at room temperature, the solution was evaporated to dryness. The solid residue was washed with water, alcohol, and ether. Yield 8.68 g (70%).

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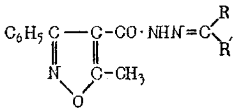
TABLE 1. Hydrazones with the General Formula



Compound	R	R¹	Yield (in %)	Mp (in degrees)	N found (in %)	Formula	N calculated (in %)
II	CH_3	CH_3	80,6	142—143	16,59, 16,48	$C_{14}H_{15}N_3O_2$	16,33
III	CH_3	C_2H_5	51,0	129,5—130	15,45, 15,38	$C_{15}H_{18}N_3O_2$	15,42
IV	H	C_6H_5	86,6	171—172,5	13,92, 13,81	$C_{18}H_{15}N_3O_2$	13,76
V	H	C_6H_4Cl-*o*	76,1	187—188*	12,26, 11,81	$C_{18}H_{14}ClN_3O_2$	12,37
VI	H	C_6H_4Br- p	91,3	184—185†	10,64, 10,78	$C_{18}H_{14}BrN_3O_2$	10,92
VII	H	$C_6H_4NO_2$-*м*	91,6	179—180	16,13, 16,35	$C_{18}H_{14}N_4O_4$	15,98
VIII	H	$C_6H_4N(C_2H_5)_2$-P	89,2	180—181	14,70, 14,76	$C_{22}H_{24}N_4O_2$	14,85
IX	H	$C_6H_4(OH)$- p	93,5	219—220,5	13,24, 13,46	$C_{18}H_{15}N_3O_3$	13,09
X	CH_3	C_6H_5	78,8	140—141	13,14, 13,40	$C_{19}H_{17}N_3O_2$	13,16
XI	H	M-CH_3O-p(OH)C_6H_3	86,5	207—208	11,90, 12,0	$C_{19}H_{17}N_3O_4$	11,97
XII	H	Furyl-2	81,1	185—185,5	14,40, 14,53	$C_{16}H_{13}N_3O_3$	14,22
XIII	H	4,5-Dibromofuryl-2	74,1	185,5—186‡	9,43, 9,44	$C_{16}H_{11}Br_2N_3O_3$	9,30

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* Found, %: Cl 9.83, 9.77. Calculated, %: Cl 10.45.

† Found, %: Br 20.75, 20.31. Calculated, %: Br 20.7.

‡ Found, %: Br 35.44, 35.16. Calculated, %: Br 35.18.

Colorless needle-like crystals. Mp 169-169.5° (from alcohol). Found, %: N 19.40, 19.50. $C_{11}H_{11}N_3O_2$. Calculated, %: N 19.35.

B. A 40 g portion of the methyl ester of I was dissolved in 20 ml of absolute ethanol, 15 ml of hydrazine was added, and the mixture boiled with a reflux condenser on a water bath for 3 h. The product that precipitated upon cooling was filtered, and washed with water, alcohol, and ether. Yield 16.34 g (74.5%). Mp 169-169.5° (from alcohol).

3-Phenyl-5-methyl-4-isoxazoylisopropylidenehydrazide (II). A 2.17 g portion (0.01 mole) of the hydrazide of I was dissolved in 10 ml of freshly redistilled acetone and the solution boiled with a reflux condenser on a water bath for 2 h. The acetone was partially evaporated, and the product that precipitated upon cooling was filtered and crystallized from methanol.

Compound III was produced analogously.

3-Phenyl-5-methyl-4-isoxazoylbenzylidenehydrazide (IV). A 2.17 g portion (0.01 mole) of the hydrazide of I was dissolved in heating in 30 ml of ethanol, 1.04 ml (0.01 mole) of freshly redistilled benzaldehyde added, and the mixture heated with a reflux condenser on a water bath for 2 h. This solution was cooled and the precipitated product filtered off, washed with ether, and crystallized from ethanol.

Substances V-XIII were synthesized analogously to IV. The data obtained and results of the analysis of the products are cited in Table 1.

LITERATURE CITED

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3. A. Quilico and R. Fusco, Gazz. Chim. Ital., 67, 589 (1937).