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INDOLE DERIVATIVES

CXV.* SYNTHESIS AND SOME TRANSFORMATIONS OF 5-(3-INDOLYL)ISOXAZOLE-3-CARBOXYLIC ACID

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UDC 547.759'786.1.07

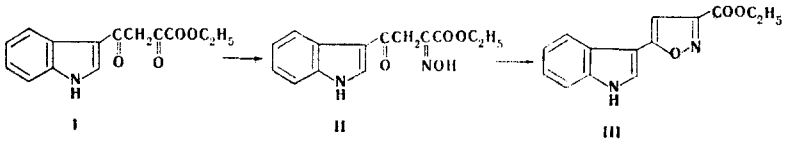
5-(3-Indolyl)isoxazole-3-carboxylic acid and its amide and hydrazide were obtained from ethyl 5-(3-indolyl)isoxazole-3-carboxylate. When 5-(3-indolyl)isoxazole-3-carboxylate is heated, it undergoes decarboxylation with isomerization to 3-(ω-cyanoacetyl)indole; when it is heated in alcohol with hydrazine and phenylhydrazine in the presence of copper, it undergoes isomerization to 5-(3-indolyl)pyrazole-3-carboxylic and 1-phenyl-5-(3-indolyl)-pyrazole-3-carboxylic acids. 5-(3-Indolyl)pyrazole-3-carboxylic acid hydrazide is formed when a solution of ethyl 5-(3-indolyl)isoxazole-3-carboxylate is refluxed with hydrazine in 96% alcohol.

Very interesting physiologically active compounds have been found among indolylazoles [2]. Least study has been devoted to indolyloxazoles. To obtain the latter we used ethyl 4-(3-indolyl)butane-2,4-dioate (I) [3].

Monooxime II was obtained by the action of hydroxylamine on ester I in the presence of acetic acid. Its IR spectrum contains a broad band at 3200-3230 cm^{-1}, which merges with a narrow band at 3310 cm^{-1} (NH and OH stretching vibrations). There is also a carbonyl band of an ester group at 1620 cm^{-1}. It can be assigned to the vibrations of a carbonyl group attached to an indole ring [4] and is superimposed on the band of the C=N bond.

The PMR spectrum of monooxime II contains a singlet of the two equivalent protons of the side chain at 4.24 ppm. As in the case of I, the indole ring 2-H proton gives a singlet at 8.27 ppm. This indicates rapid exchange of the protons of the NH group, which is characteristic for compounds with a carbonyl group attached to the indole ring [5].

Ethyl 5-(3-indolyl)isoxazole-3-carboxylate (III) was obtained by the action of hydroxylamine on I in the presence of pyridine. It was shown by thin-layer chromatography (TLC) that the initial product is oxime II, which slowly undergoes cyclization to III.



I II III

* See [1] for communication CXIV.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 936-938, July, 1978. Original article submitted July 14, 1977.

0009-3122/78/1407-0754$07.50

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Found, %			Empirical formula	Calc., %			IR spectrum, cm^{-1}	Yield, %
		C	H	N		C	H	N		
II	180—181	61,3	5,8	10,0	$C_{14}H_{14}N_2O_4$	61,3	5,1	10,2	3310, 3200—3230, 1740, 1620, 1615	—
III	163—164	65,4	4,6	10,9	$C_{14}H_{12}N_2O_3$	65,6	4,7	10,9	3320, 1730, 1615	66
IV	233—234	63,3	3,8	12,5	$C_{12}H_8N_2O_3$	63,2	3,5	12,3	3260, 1710, 1597, 2500—2900	85
V	231—233	63,8	4,0	18,8	$C_{12}H_9N_3O_2$	63,4	4,0	18,5	3400, 3320, 3200, 1670, 1630, 1600	47
VI	237—238	71,6	4,4	15,3	$C_{11}H_8N_2O$	71,7	4,4	15,2	3230, 2270, 1640	70
VII	238—239	59,4	4,2	23,4	$C_{12}H_{10}N_4O_2$	59,5	4,2	23,1	3360, 3285, 3220, 3170, 1690, 1605	69
VIII	258	63,6	5,1	19,8	$C_{15}H_{14}N_4O_2$	63,8	5,0	19,8	3360, 3180, 1695, 1630, 1610	—

The IR spectrum of isoxazole III contains a band of carbonyl vibrations of an ester group at 1730 cm^{-1}, a C=N band at 1615 cm^{-1}, and a rather broad NH band of an indole ring at 3320 cm^{-1}. In the PMR spectrum the proton of the isoxazole ring forms a singlet at **6.94 ppm** [6], and 2-H of the indole ring gives a doublet at 8.03 ppm. The remaining protons of the indole ring form multiplets at 7.05-7.2, 7.4-7.5, and 7.8-7.9 ppm.

Hydrolysis of ester III gave 5-(3-indolyl)isoxazole-3-carboxylic acid (IV), the successive action of phosphorus pentachloride and ammonia on which gave amide V. When acid IV was heated, it underwent violent decomposition to give a complex mixture, from which 3-(ω-cyanoacetyl)indole (VI) was isolated in low yields. Compound VI was the chief product when acid IV was heated in quinoline, dimethylacetamide (DMA), and dimethylformamide (DMF). Rearrangement to β-keto nitriles is characteristic for isoxazole-3-carboxylic acids [7, 8].

An interesting transformation was observed in the reaction of ester III with hydrazine. Hydrazide VII, which gives a hydrazone (VIII) with acetone, was obtained when III was heated in methanol. 5-(3-Indolyl)pyrazole-3-carboxylic acid hydrazide (IX), identical to a sample obtained from ethyl 5-(3-indolyl)pyrazole-3-carboxylate and hydrazine [3], was isolated when the same reaction was carried out in 96% ethanol. It has been shown [9] that when 5-alkyl- and 5-arylisoxazole-3-carboxylic acids are heated with hydrazine and phenylhydrazine in alcohol in the presence of copper metal, the acids undergo conversion to the corresponding 5-alkyl-(aryl)pyrazole-3- and 1-phenylpyrazole-3-carboxylic acids. We carried out the same reactions with acid IV and isolated 5-(3-indolyl)pyrazole-3-carboxylic and 1-phenyl-5-(3-indolyl)pyrazole-3-carboxylic acids, which were described in [3]. Isomerization did not occur when acid IV was heated with hydrazine and phenylhydrazine in alcohol in the absence of copper; acid IV was isolated in unchanged form, and resinification occurred in the case of prolonged heating with phenylhydrazine.

The amide, hydrazide, and sodium salt of 5-(3-indolyl)isoxazole-3-carboxylic acid have weak antibacterial and antifungal activity.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in a mixture of d_6-acetone and d_6-DMSO were recorded with a Varian CFT-20 spectrometer. The course of the reactions and the individuality of all of the compounds were monitored by thin-layer chromatography (TLC) on Silufol UV-254 (elution with ether—petroleum ether).

Ethyl 4-(3-Indolyl)butane-2,4-dionate Monooxime (II). A 1.18-g of anhydrous potassium acetate was added to a solution of 0.73 g of hydroxylamine hydrochloride in 10 ml of ethanol, after which the mixture was stirred, and the precipitate was removed by filtration. The filtrate was added dropwise to a suspension of 1 g of ester I in a mixture of 20 ml of ethanol and 5 ml of acetic acid, and the mixture was heated for 15 min. The ethanol and acetic acid were removed by vacuum distillation, and the residue was mixed with 20 ml of water. The mixture was allowed to stand overnight, and the resulting precipitate was removed by filtration and recrystallized from isopropyl alcohol to give 0.6 g of II.

Ethyl 5-(3-Indolyl)isoxazole-3-carboxylate (III). Pyridine (5 ml) was added to a solution of 2.5 g (36 mmole) of hydroxylamine hydrochloride in 80 ml of ethanol, and 8.6 g (33 mmole) of I was added in portions with vigorous stirring at 50°C. The mixture was then refluxed on a water bath until the initially formed oxime

disappeared (3.4 h) according to TLC data, after which an equal volume of water was added, and the mixture was allowed to stand until it was completely cooled. The precipitate was removed by filtration and recrystallized from dilute alcohol to give 5.6 g of III.

5-(3-Indolyl)isoxazole-3-carboxylic Acid (IV). A mixture of 5.4 g (21 mmole) of III, 50 ml of alcohol, and 20 ml of 20% sodium carbonate was refluxed for 30 min, after which 150 ml of water was added to the resulting solution, and the mixture was refluxed for 10 min with activated charcoal. It was then filtered, and the cold filtrate was acidified with hydrochloric acid. The precipitate was recrystallized from 80% alcohol to give 4.1 g of IV.

5-(3-Indolyl)isoxazole-3-carboxamide (V). A 1.2-g sample of IV was mixed in 100 ml of absolute ether, and 0.97 g of phosphorus pentachloride was added to the cooled mixture. The resulting mixture was stirred until IV dissolved, and the resulting ether solution of acid chloride IV was added with stirring to 25 ml of cold 20% ammonium hydroxide. The precipitate was recrystallized from dilute alcohol to give 0.56 g of V.

5-(3-Indolyl)isoxazole-3-carboxylic Acid Hydrazide (VII). Hydrazine hydrate (5 ml) was added to a solution of 2.56 g (0.01 mole) of III in 50 ml of methanol, and the mixture was refluxed until the III vanished. It was then cooled, and the precipitate was removed by filtration and recrystallized from dilute alcohol to give 1.68 g of VII.

5-(3-Indolyl)pyrazole-3-carboxylic Acid Hydrazide (IX). Hydrazine hydrate (3 ml) was added to a solution of 0.64 g (2.5 mmole) of III in 10 ml of ethanol, and the mixture was refluxed until the III vanished. It was then cooled, and the precipitate was removed by filtration and recrystallized from alcohol to give 0.31 g of IX with mp 289-290°C (288-290°C [3]).

3-(ω-Cyanoacetyl)indole (VI). A solution of 3 g (13 mmole) of IV in 15 ml of DMA was refluxed for 30 min, after which it was poured into water, and the resulting precipitate was removed by filtration and recrystallized from alcohol to give 1.7 g of VI. PMR spectrum: 4.23 (s, CH_2), 8.23 (s, indole ring H_2), 7.2-7.3, 7.5-7.6, and 8.1-8.3 ppm (indole ring protons).

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