INDOLE DERIVATIVES

LXXXIV.* HYDROXAMIC ACIDS OF THE INDOLE SERIES

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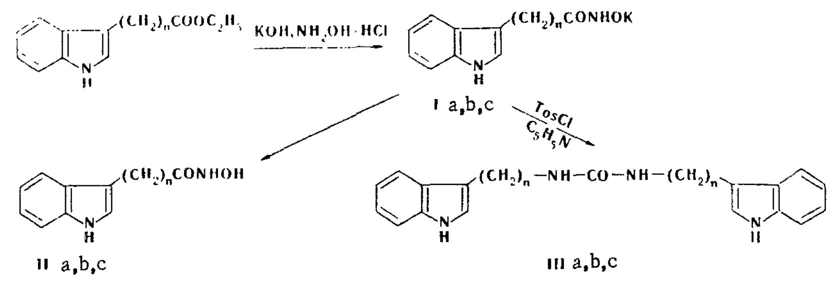
3-Indolylalkylhydroxamic acids were obtained and subjected to the Lossen rearrangement and reaction with phenyl isocyanate.

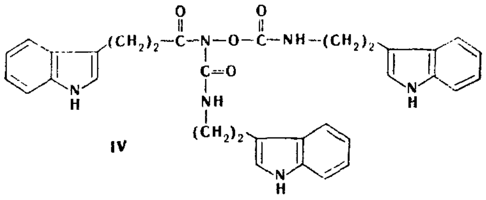
Hydroxamic acids are of interest as substances with potential biological activity and as starting materials for the synthesis of diverse derivatives [2]. We have accomplished the synthesis of some hydroxamic acids of the indole series and have studied some of their properties.

The hydroxamic acids were obtained in good yields by reaction of acid esters with hydroxylamine in the presence of KOH.



I, II, III a n=1; b n-2; c n-3

The Lossen rearrangement occurred during the reaction of salts of the hydroxamic acids with the chlorides of strong acids [3]. Thus, N,N'-diskatylurea (IIIa) is formed on treatment of potassium 3-indolylacetohydroxamate (I) with p-toluenesulfonyl chloride in pyridine; the reaction proceeds similarly with 4-(3-indolyl) butanohydroxamic acid. However, in the case of potassium 3-(3-indolyl)propiohydroxamate, in addition to the symmetrical urea (IIIb), the product of the reaction of 2 moles of the initially formed 2-(3-indolyl)ethyl isocyanate with 1 mole of hydroxamic acid – N,O-bis[2-(3-indolyl)ethylcarbamoyl]-N-[3-(3-indolyl)propionly]hydroxylamine (IV) – can be isolated. The formation of a product of this type was previously observed in the Lossen rearrangement with benzhydroxamic acid [4].



IV

The structure of symmetrical ureas IIIa, IIIb, and IIIc was established on the basis of spectral data and a comparison with authentic samples. The structure of IV is in good agreement with the results of ele-

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* See [1] for communication LXXXIII.

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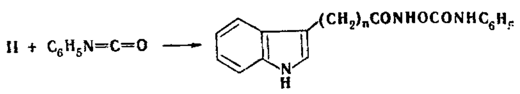
mentary analysis, the IR spectra, and the chemical properties. Thus the IR spectrum of this substance contains absorption bands at 1690, 1730, and 1750 cm^{-1}, which correspond to three C=O groups. Symmetrical urea IIIb is formed on heating and hydrolysis of IV; this is characteristic for compounds of this type [4].

We also carried out the reaction of hydroxamic acids with phenyl isocyanate and isolated a number of O-carbamoyl derivatives of hydroxamic acids of the indole series (V).



V a,b,c

V a n=1; b n=2; c n=3

The structure of the carbamoyl derivatives of the hydroxamic acids is in good agreement with the results of elementary analysis and the IR spectra.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer.

3-(3-Indolyl)propiohydroxamic Acid (IIb). A solution of 18.55 g (0.331 mole) of KOH in 50 ml of methanol, prepared by refluxing and cooling to 40°, was added to a solution of 15.85 g (0.23 mole) of hydroxylamine hydrochloride in 85 ml of methanol, prepared in the same manner. The mixture was cooled to 10°, and 21.5 g (0.099 mole) of ethyl 3-(3-indolyl)propionate was added with vigorous stirring. The precipitate was removed by filtration and washed with methanol. The filtrate was allowed to stand at 20° for 18 h. The methanol was removed by vacuum distillation, and the residue was washed several times with ether, triturated in 50 ml of water, and acidified with acetic acid to pH 6. The mixture was allowed to stand at 5° for 2 h, and the precipitate was removed by filtration and washed several times with cold water to give 17.8 g (85%) of a product with mp 155-156° (from water). Found: C 64.9; H 5.8; N 13.8%. $C_{11}H_{12}N_2O_2$. Calculated: C 64.7; H 5.9; N 13.7%. IR spectrum: 1645 (C=O); 3190, 3400 (NH, OH) cm^{-1}.

3-Indolylacetohydroxamic Acid (IIa). This compound, with mp 126-127° (from water) (mp 126-127° [5]), was similarly obtained in 85% yield.

4-(3-Indolyl)butanohydroxamic Acid (IIc). This compound, with mp 123-124° (from water), was similarly obtained in 72.5% yield. Found: C 66.3; H 6.2; N 12.8%. $C_{12}H_{14}N_2O_2$. Calculated: C 66.0; H 6.4; N 12.8%. IR spectrum: 1638 (C=O), 3190, 3410 (NH, OH) cm^{-1}.

Reaction of 3-(3-Indolyl)propiohydroxamic Acid with p-Toluenesulfonyl Chloride. A solution of 2.8 g (14.8 mmole) of p-toluenesulfonyl chloride in 15 ml of pyridine was added with stirring in the course of 15-20 min to a solution of 3.6 g (14.8 mmole) of potassium 3-(3-indolyl)propiohydroxamate in 25 ml of dry pyridine, after which the mixture was allowed to stand at room temperature for 1 h. The dark-red solution was poured into 700 ml of cold water, and the aqueous mixture was allowed to stand for 2 days. The precipitated crystals were removed by filtration, washed with water, and dried. The resulting mixture of substances was separated by chromatography with a column packed with Al_2O_3 with successive elution with ethyl acetate–hexane (7 : 3) and ethyl acetate to give 1.2 g (42.1%) of IV with mp 137-139° (from absolute alcohol), which decomposes to give IIIb. Compound IV has R_f 0.52 during chromatography in a thin layer on Silufol plates in ethyl acetate–hexane (4 : 1). Found: C 69.0; H 5.6; N 14.6%. $C_{33}H_{32}N_6O_4$. Calculated: C 68.7; H 5.5; N 14.6%. IR spectrum: 1690, 1728, 1750 (C=O); 3250, 3390, 3430 (NH) cm^{-1}; also obtained was 0.55 g (21.4%) of urea IIIb with mp 157-158° (from alcohol) (mp 157° [6]). The latter has R_f 0.25 during chromatography in a thin layer on Silufol plates in ethyl acetate–hexane (4 : 1). Found: C 73.1; H 6.6; N 16.4%. $C_{21}H_{22}N_4O$. Calculated: C 72.9; H 6.4; N 16.2%. IR spectrum: 1620 (C=O); 3340, 3420 (urea NH, indole NH) cm^{-1}.

Reaction of 3-Indolylacetohydroxamic Acid with p-Toluenesulfonyl Chloride. The reaction and isolation of the products were carried out similarly to give 1.5 g (47.8%) of urea IIIa with mp 196-198° (from alcohol) and R_f 0.25 by chromatography in a thin layer on Silufol plates in ethyl acetate–hexane (4 : 1). Found: C 71.5; H 5.4; N 17.5%. $C_{19}H_{18}N_4O$. Calculated: C 71.7; H 5.6; N 17.6%. IR spectrum: 1615 (C=O); 3350, 3390 (NH) cm^{-1}.

Reaction of 4-(3-Indolyl)butanohydroxamic Acid with p-Toluenesulfonyl Chloride. The reaction and isolation of the products were carried out similarly to give 1.7 g (38.58%) of N,N'-bis[4-(3-indolyl)propylurea (IIIc) with mp 125-126° (from ethyl acetate) and R_f 0.22 by chromatography in a thin layer on Silufol plates in ethyl acetate–hexane (4:1). Found: C 73.7; H 6.6; N 14.8%. $C_{23}H_{26}N_4O$. Calculated: C 73.8; H 6.9; N 14.9%. IR spectrum: 1615 (C=O); 3310, 3360, 3390 (NH) cm^{-1}.

Hydrolysis of IV. A 0.95-g sample of IV was dissolved in a small amount of alcohol, and the solution was mixed with 1 N aqueous alcoholic alkali. The mixture was refluxed for 1.5 h and then diluted with water until turbidity was produced. The precipitated crystals were removed by filtration, washed with water, and dried to give 0.37 g of urea IIIb with mp 157-158° (from absolute alcohol). No melting-point depression was observed for a mixture of this product with urea IIIb obtained by Lossen rearrangement.

O-(N-Phenylcarbamoyl)-3-indolylacetohydroxamic Acid (Va). A 0.313-g (2.63 mole) sample of phenyl isocyanate was added dropwise at 20° to a solution of 0.5 g (2.63 mmole) of 3-indolylacetohydroxamic acid in 10 ml of anhydrous acetone, and the mixture was stirred for 10 min. The solvent was removed by distillation, and the residue was chromatographed with a column filled with silica gel (the ratio of sorbent to separable mixture was 40:1) with elution with ethyl acetate–hexane (3:7). The yield of product with mp 142-143° (from ethyl acetate–hexane) was 0.77 g (95%). Found: C 66.5; H 4.9; N 13.6%. $C_{17}H_{15}N_3O_3$. Calculated: C 66.7; H 4.8; N 13.6%. IR spectrum: 1670, 1770 (C=O); 3140, 3400 (NH) cm^{-1}.

O-(N-Phenylcarbamoyl)-3-(3-indolyl)propiohydroxamic Acid (Vb). This compound, with mp 144-145° (ethyl acetate–hexane), was similarly obtained in 97% yield. Found: C 66.7; H 5.2; N 13.1%. $C_{18}H_{17}N_3O_3$. Calculated: C 66.8; H 5.3; N 13.0%. IR spectrum: 1671, 1772 (C=O); 3135, 3400 (NH) cm^{-1}.

O-(N-Phenylcarbamoyl)-4-(3-indolyl)butanohydroxamic Acid (Vc). This compound, with mp 135-137° (from ethyl acetate–hexane), was similarly obtained in 95% yield. Found: C 67.0; H 5.5; N 12.3%. $C_{19}H_{19}N_3O_3$. Calculated: C 67.6; H 5.6; N 12.4%. IR spectrum: 1662, 1750 (C=O); 3165, 3410 (NH) cm^{-1}.

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