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AMIDES AND HYDRAZIDES OF OXALIC ACID

XXXVII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED CARBAMIDOHYDROXAMIC ACIDS

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Hydroxamic acids are of interest as biologically active compounds having a wide spectrum of action (antimicrobial, antitumor, and anti-inflammatory) [1, 2], and also in connection with use in analytical practice [3].

The present work is devoted to a study of substituted carbamidohydroxamic acids (I) which have not been studied up till now in the chemical and biological respect. Synthesis of these compounds was performed according to the following scheme:

$$\underset{\text{II}}{RNHCOCOOC_2H_5} \xrightarrow{NH_2OH} \underset{\text{I}}{RNHCOCONHOH} \xleftarrow{RNH_2} \underset{\text{III}}{C_2H_5OOCCONHOH}$$

The acids, I, were prepared by two methods: A, by the reaction of oxalic ester polyamides (II) with hydroxylamine; and, B, by the aminolysis of ethoxycarbonylhydroxamic acid (III) with aliphatic or aromatic–aliphatic amines.

The acids I (see Table 1) are colorless (when R = $C_6H_4NO_2$ they are yellow) crystalline materials which are soluble in aqueous alkalis and in organic solvents.

The alcoholic solutions of the acids, I, give a cherry coloration with Fe^{3+} ions, and also give precipitates with a whole series of metal cations (Al^{3+}, Bi^{3+}, Pb^{2+}, Cu^{2+}, Mg^{2+}, U^{2+}, Mn^{2+}, Zn^{2+}).

In the IR spectra of I bands have been observed for the stretching vibrations of OH, NH, and two CO groups (see Table 1).

As a characteristic of the acidity of the compounds prepared, we determined the ionization constants of some of them (see Table 1). The pK_a values for the water-soluble acids Ia, Ie, and Id were determined in water; those of acids Ig, Ih, Ij, and I_l in 60% aqueous dioxane. It is evident from this table that in the case of the alkyl substituents the magnitude of pK_a essentially does not change. The correlation equation has the form: $pK_a = 7.85 - 0.06\sigma$, $r = 0.98$, $S = 0.06$.

The absolute value of ρ indicates that the reaction center is extremely insensitive to inductive effects of substituents.

The pK_a values of the acids with aryl substituents lie in the range 9.68 - 9.20, and decrease in the sequence of substituents: $C_2H_5O > CH_3 > H > NO_2$. The parameters for correlation of pK_a with the Hammett σ constants ($pK_{a\ calc.} = 9.75$; $\rho = 0.48$; $r = 0.99$; $S = 0.04$) indicate the presence of a linear dependence.

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TABLE 1. Substituted Carbamidohydroxamic Acids (I)

Compound	R	Yield, %	mp, °C	Found, % N	Molecular formula	Calc., % N	pK_a	IR spectrum, frequencies in cm^{-1} OH	NH (NHOH)	NH	CO (CONHOH)	CO
Ia	H	86	140—1	27,08	$C_2H_4N_2O_3$	26,92	7,93±0,03	3450	3300	3200	1630	1650
Ib	CH_3	78	200—2	23,93	$C_3H_6N_2O_3$	23,73	—	—	—	—	—	—
Ic	CH_2CH_2Cl	73	138—9	16,66	$C_4H_7ClN_2O_2$	16,76	—	—	—	—	—	—
Id	$CH_2C_6H_5$	87	161—2	14,41	$C_9H_{10}N_2O_3$	14,43	7,88±0,02	3400	3300	3200	1630	1650
Ie	Cyclo-C_6H_{11}	62	160—1	14,96	$C_8H_{14}N_2O_3$	15,05	7,75±0,02	3400	3300	3200	1630	1650
If	H_2	71	160—1	35,32	$C_2H_6N_3O_3$	35,29	—	—	—	—	—	—
Ig	C_6H_5	76	156(decomp.)	15,38	$C_8H_8N_2O_3$	15,55	9,57±0,04	3360	3320	3270	1660	1700
Ih	4-$CH_3C_6H_4$	81	150(decomp.)	14,22	$C_9H_{10}N_2O_3$	14,43	9,64±0,05	3430	3330	3290	1660	1700
Ii	4-$CH_3OC_6H_4$	78	170	13,28	$C_9H_{10}N_2O_4$	13,32	—	—	—	—	—	—
Ij	4-$C_2H_5OC_6H_4$	76	172	12,23	$C_{10}H_{12}N_2O_4$	12,50	9,68±0,04	—	—	—	—	—
Ik	4-$C_3H_7OC_6H_4$	78	153	11,56	$C_{11}H_{14}N_2O_4$	11,76	—	—	—	—	—	—
Il	4-$NO_2C_6H_4$	73	188	18,52	$C_8H_7N_5O_5$	18,70	9,20±0,04	3360	3320	3270	1690	1720
Im	4-$C_3H_7OOCC_6H_4$	77	161	10,72	$C_{12}H_{14}N_2O_5$	10,51	—	—	—	—	—	—
Im	4-iso-$C_3H_7OOCC_6H_4$	72	148	10,41	$C_{12}H_{14}N_2O_5$	10,51	—	—	—	—	—	—
Io	4-iso-$C_4H_9OOCC_6H_4$	70	153	10,23	$C_{13}H_{16}N_2O_5$	10,00	—	—	—	—	—	—
Ip	2-$NO_2C_6H_4$	87	183	18,80	$C_8H_7N_5O_5$	18,70	—	—	—	—	—	—
Iq	2-$C_2H_5OC_6H_4$	79	174—5	12,76	$C_{10}H_{12}N_2O_4$	12,50	—	—	—	—	—	—
Ir	2-$C_4H_9OC_6H_4$	89	137	11,27	$C_{12}H_{16}N_2O_4$	11,12	—	—	—	—	—	—
Is	2-COOH	91	188	12,29	$C_9H_8N_2O_5$	12,50	—	—	—	—	—	—

EXPERIMENTAL

Biological

The antimicrobial activity of the compounds prepared was studied by the method of twofold serial dilutions, on a spectrum which included Staphylococcus aureus 209-P, E. coli 675, and microspores. To culture the bacteria, we used Hottinger broth (pH 7.2-7.4); for fungi, Sabourand medium (pH 6.0-6.8). Activity was evaluated from the minimum bacteriostatic (MBS) and mycostatic (MMS) concentrations of the preparations, expressed in μg/ml.

Compound 1h displayed moderate activity with respect to microspores (MMS 25 μg/ml), Candida albicans (MMS 100 μg/ml), and Aspergillus niger (MMS more than 200 μg/ml). Acid Id displayed activity only with respect to the Staphylococcus (MBS 500 μg/ml). The remaining compounds (Ia, c, d, g, p, l, and q) did not show activity (MBS and MMS over 200 μg/ml).

Chemical

The IR spectra were taken on a UR-20 spectrometer in KBr disks (concentration of substance, 0.5%) using sodium chloride or lithium fluoride prisms. The pK_a values were determined on a pH-340 pH-meter.

(N-Cyclohexylcarbamido)hydroxamic Acid (Ie). A. To 1.99 g (0.01 mole) of ethyl cyclohexyloxamic acid in ethanol was added an alcoholic hydroxylamine solution prepared from 0.7 g (0.01 mole) of hydroxylamine hydrochloride and 0.6 g (0.01 mole) of potassium hydroxide, and the mixture was allowed to stand overnight. The solid which settled was filtered off and crystallized. Acids Ia-d and f-s were prepared similarly.

B. Compound III (3.99 g, 0.03 mole) was dissolved in 10 ml of ethanol, 5.94 g (0.06 mole) of cyclohexylamine was added, and the mixture was allowed to stand overnight. Then the reaction mixture was acidified with hydrochloric acid (1 : 1) to pH 3.0, and the precipitate was filtered off. The yield was 26%.

A mixed melting point test conducted with the two specimens showed no depression.

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INVESTIGATION OF THE ADSORPTION KINETICS OF DIFFERENT MOLECULAR WEIGHT METABOLITES BY ACTIVE CARBON

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Soviet and foreign research [1, 2] in experimental medicine has shown the merit of using sorption methods for the rapid removal of harmful endogenous and exogenous substances from blood. Selection of the sorbent for hemodialysis is determined by the substances to be removed. Ion-exchange resins (cation, anion, ampholites) are used for mineral salts and activated carbon, silica gel, and sephadex for organic components. Recently, in medical practice, active carbon has been used for the adsorption of the majority of substances of organic origin because of its availability and satisfactory adsorption properties.

To an extremely significant degree the effectiveness of all adsorption processes is determined by the capacity of the sorbent and the rate of sorption. Both of these parameters depend upon the structure of the sorbent, nature of the sorbed substance, and other factors.

Even though commercial carbons (AR-3, SKT, BAU) are available for hemosorption, information is not available in the literature concerning the relationship of active carbon to the sorption capacity with respect to the principal metabolite and the kinetic sorption of this metabolite with the structure, particle size, and nature of the carbon and molecular weight of the metabolite. It is obvious that knowledge of this dependence is necessary for determining the optimum activated carbon structure and particle size for hemodialysis and for making recommendations regarding the technology of active carbon production designed for the purpose of hemodialysis.

In the work presented here the kinetic adsorption of metabolites of different molecular weights on active carbon was investigated. The active carbons used in this study were hardened sintered carbons, IGI, prepared by the Institute of Combustible Minerals [3, 4] and carbons SKT-6A derived from peat moss and containing a resin binder. Their structures were characterized as micropore, mesopore, and macropore.

It is commonly known [5] that the adsorption properties of active carbons are principally due to the form of their porous structure. If the adsorbed molecule is not large, adsorption in the micropore is the determining factor. Large-sized pores function only as transport mechanisms. It is also known that the micropores are inaccessible to large molecules and that they are adsorbed from solution on the surface of the mesopores.

With the purpose of identifying the role of micropores and mesopores during the adsorption from solution of different molecular weight metabolites, we investigated six laboratory forms of IGI active carbon. They were identical in particle size compositions, but differed in the ratio of micropores to mesopores. In Table 1 is shown the characteristics of the investigated forms of IGI carbon. Samples of active carbon SKT-6A with very different microporosities (micropore—0.6 cm^3/g; mesopore—0.28 cm^3/g; macropore—0.3 cm^3/g) were studied for comparison.

The adsorption kinetics were determined for single component water solutions of low (creatinine, mol. wt. 113) and medium (bilirubin, mol. wt. 583 and vitamin B_{12}, mol. wt. 1357) molecular weight organic substances. Creatinine and bilirubin were selected as represenataive low- and medium-molecular weight toxic

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