SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PHENYLENEDIOXAMIC AND DERIVATIVES

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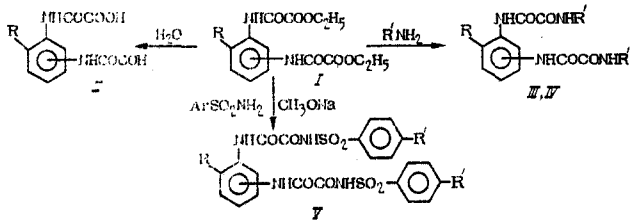
In a search for new biologically active compounds, esters of phenylenedioxamic acids (I) were synthesized, and their transformations by hydrolysis, aminolysis and hydrazinolysis were studied.



Given are compounds, position of substituent in the ring, : p-, H, —; IIa: p-, H, —; IIb: m-, H, —; IIa: m-, CH_3, —; IIIa: m-, CH_3, CH_3; IIIb: m-, CH_3, OH; IIIc: m-, CH_3, C_6H_4COO-*o*; IIId: m-, H, OH; IIIe: m-, H, C_6H_4OH-p; IIIf: m-, H, C_6H_4COO-*o*; IIIg: m-, H, CH_2CH_2Cl; IIIh: p-, H, C_6H_4OH-p; IIIi: p-, H, C_6H_4COOH-*o*; IIIj: p-, H, CH_2CH_2Cl; IIIk: p-, H, $CH_2CH_2N(C_2H_5)_2$; IIIl: p-, H, $C_6H_5CH_2$; IVa: p-, H, HN_2; IVb: m-, H, NH_2; IVc: m-, CH_3, NH_2; Va: m-, H, CH_3; Vb: m-, H, NH_2; Vc: p-, H, NH_2; Vd: p-, H, CH_3.

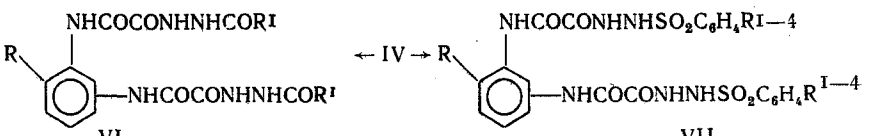
Esters I were obtained by acylation of phenylenediamines with oxalic acid monoethyl ester chloride [10] or by diethyl oxalate [3]. Esters I readily undergo hydrolysis with the formation of phenylenedioxamic acids (Table 1). According to the data in [9], acid IIc does not exist in the free state. However, our data show that this conclusion is incorrect. Acids IIa-c are characterized by two ionization constants (pK_{a1} 2.9-3.1; pK_{a2} 3.6-3.7), and form water-insoluble precipitates with several metal cations (Fe^{3+}, Co^{2+}, Cu^{2+}, Ag^{+}, etc.).

In the IR spectra of IIa-c, stretching vibration bands were observed, ν_{max}, cm^{-1}: 3330-3280 (NH), 1740 (CO in COOH), 1700-1670 (amide CO). On transition to triethylammonium salts, bands corresponding to the carboxylic CO group disappear in the IR spectra and COO^- bands appear (1600, 1390 cm^{-1}). The UV spectra of IIa-c have one absorption maximum in the 252-285 nm region (log ε 4.0-4.2).

Esters I have a fairly high electrophilicity, and with aliphatic, aromatic and heterocyclic amines form amides III. In the IR spectra of the latter, stretching vibration bands were observed at ν_{max}, cm^{-1}: 3500-3150 (NH) and 1710-1660 (CO).

Arenesulfonamides of phenylenedioxamic acids (Va-d, see Table 1) were obtained by condensation of sodium salts of arenesulfonamides with esters I in absolute methanol. Sulfonamides V have acidic properties (pK_{a1} 3.72-3.85; pK_{a2} 4.51) and their ammonium salts with metal cations give water-insoluble precipitates.

In the IR spectra of Va-d there are stretching vibration bands of NH (3350-3210 cm^{-1}), CO (1720-1680 cm^{-1}) and SO_2 groups (1360-1350, 1180-1170 cm^{-1}). The UV spectra of Va-d are characterized by one absorption maximum in the 280 nm region (log ε 4.43-4.47).



Given are compounds, the position of the substituent in the ring, m-CH_3, 3-pyridyl VIb: m-, CH_3, C_6H_5; VIc: m-, H, 3-pyridyl; VId: m-, H, C_6H_5; VIe: p-, H, 3-pyridyl; VIf: p-, H, C_6H_5; VIIa: p-, H, NO_2; VIIb: m-, H, CH_3; VIIc: p-, H, NO_2; VIId: p-, H, CH_3; VIIe: p-, H, $NHCOOCH_3$; VIIf: m-, CH_3, CH_3; VIIg: m-, CH_3, NO_2; VIIh: m-, CH_3, $NHCOOCH_3$.

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TABLE 1. Derivatives of Phenylenedioxamic Acids

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %
IIa	78,5	254—5	11,00	$C_{10}H_8N_2O_6$	11,1
IIb	72,8	239—41	10,95	$C_{10}H_8N_2O_6$	11,1
IIc	81,3	210—2	10,40	$C_{11}H_{10}N_2O_6$	10,5
IIIa	67,2	>250	19,00	$C_{13}H_{16}N_4O_4$	19,2
IIIb	53,3	162—3	18,64	$C_{11}H_{12}N_4O_6$	18,9
IIIc	51,2	160—2	11,01	$C_{25}H_{20}N_4O_8$	11,7
IIId	60,1	180—3	14,70	$C_{10}H_{10}N_4O_6$	14,8
IIIe	56,7	268—70	12,75	$C_{22}H_{18}N_4O_6$	12,9
IIIf	56,7	193—5	11,31	$C_{24}H_{18}N_4O_8$	11,4
IIIg	72,8	262—5	14,69	$C_{14}H_{16}N_4Cl_2O_4$	14,9
IIIh	63,5	260—5	12,97	$C_{22}H_{18}N_4O_6$	12,9
IIIi	54,2	>270	11,81	$C_{24}H_{18}N_4O_8$	11,4
IIIj	60,5	260—5	14,70	$C_{14}H_{16}Cl_2N_4O_4$	14,9
IIIk	71,5	258—60	17,32	$C_{22}H_{36}N_6O_6$	17,5
IIIℓ	69,8	318—20	12,91	$C_{24}H_{22}N_4O_4$	13,0
IVa	88,4	>320	29,79	$C_{10}H_{12}N_6O_4$	29,97
IVb	79,9	>310	29,65	$C_{10}H_{12}N_6O_4$	29,97
IVc	89,5	223—5	28,05	$C_{11}H_{14}N_6O_4$	28,5
Va	63,2	223—8	9,91	$C_{24}H_{22}N_4S_2O_8$	10,0
Vb	65,7	226—8	14,81	$C_{22}H_{20}N_6S_2O_8$	15,0
Vc	61,4	255—8	15,03	$C_{22}H_{20}N_6S_2O_8$	15,0
Vd	66,3	253—5	10,10	$C_{24}H_{22}N_4S_2O_8$	10,0

TABLE 2. Acyl- and Arenesulfohydrazides of Phenlenedioxamic Acids

Compound	Yield, %	mp, °C	Found N, %	Empirical formula	Calculated N, %
VIa	49,2	203—6	22,01	$C_{23}H_{20}N_8O_6$	22,2
VIb	56,5	210—3	16,42	$C_{25}H_{22}N_6O_6$	16,7
VIc	51,6	237—40	22,68	$C_{22}H_{18}N_8O_6$	22,9
VId	62,4	260—3	17,92	$C_{24}H_{20}N_6O_6$	18,0
VIe	49,6	240—5	22,78	$C_{22}H_{18}N_6O_6$	22,9
VIf	60,4	>290	18,26	$C_{24}H_{20}N_6O_8$	18,0
VIIa	67,4	199—203	16,70	$C_{22}H_{18}N_8S_2O_{12}$	16,98
VIIb	69,2	184—8	14,00	$C_{24}H_{24}N_6S_2O_8$	14,4
VIIc	65,7	206—10	16,72	$C_{22}H_{18}N_8S_2O_{12}$	16,98
VIId	71,4	196—9	14,10	$C_{24}H_{24}N_6S_2O_8$	14,3
VIIe	59,6	120—3	15,65	$C_{26}H_{26}N_8S_2O_{12}$	15,9
VIIf	62,7	163—5	13,55	$C_{25}H_{26}N_6S_2O_8$	13,9
VIIg	74,7	146—8	16,62	$C_{23}H_{20}N_8S_2O_{12}$	16,8
VIIh	68,6	195—8	15,20	$C_{27}H_{28}N_8S_2O_{12}$	15,4

In the IR spectra of acylhydrazides VIa-f there are stretching vibration bands ν_{max}, cm^{-1}: 3360-3150 (NH), 1720-1610 CO); in the spectra of arenesulfohydrazides, 3310-3180 (NH), 1740-1680, 1620-1540 (CO), 1370-1320, 1190-1170 (SO_2). The UV spectra of acyl- and arenesulfohydrazides are characterized by one absorption maximum in the 260-307 nm region (log ε 4.14-4.50) and 250-287 (log ε 4.08-4.50), respectively.

As was expected, the acidic properties of arenesulfohydrazides VIIa-h (pK_{a1} 4.25-6.00; pK_{a2} 6.84-8.80) are less pronounced than those of arenesulfonamides V.

EXPERIMENTAL (CHEMICAL)

The IR spectra were run on a UR-20 spectrophotometer (GDR) in KBr tablets and in chloroform, the UV spectra – on a SF-26 spectrophotometer in 0.5 N potassium hydroxide solution. The ionization constants were determined potentiometrically in 60% dioxane, on a EV-74 ionometer.

4-Methyl-1,3-phenylenedioxamic Acid (IIc). A 1.6 g portion of ester I is dissolved with heating in 60 ml of 10% aqueous solution of potassium hydroxide. The solution is acidified by hydrochloric acid (1:1) to pH 2.0 and the precipitate that separates, is filtered and crystallized from ethanol.

Compounds IIa, b were obtained in a similar way.

Di-(4-hydroxyanilide) of 1,4-Phenylenedioxamic Acid (IIIh). A mixture of 3.08 g (0.01 mole) of ester I and 2.18 g (0.02 mole) of p-aminophenol is heated in 5 ml of DMFA for 15 min, then diluted with water, and acidified by HCl (1:1) to pH 2.0. The precipitate that separates is filtered and crystallized.

TABLE 3. Anti-exudative Acitivity of Phenylenedioxamic Acid Derivatives IIIa-e,IIIi, Va-d, VIa-f, VIIa-h and Mephenamic Acid

Compound	Depression of formalin-induced edema, %	Compound	Depression of formalin-induced edema, %
IIIa	16	VIc	2
IIIb	14	VId	14
IIIc	4	VIe	8
IIId	26	VIf	3
IIIe	33	VIIa	14
IIIi	9	VIIb	21
Va	12	VIIc	2
Vb	33	VIId	11
Vc	9	VIIf	28
Vd	29	VIIg	32
VIa	12	VIIh	25
VIb	2	Mephenamic acid	33

Compounds IIIc, IIIe-f, IIIi, IIIℓ are obtained in similar way.

Di-β-chloroethylamide of 1,3-Phenylenedioxamic Acid (IIIg). Alcoholic solutions of 3.08 g (0.01 mole) of ester I and β-chloroethylamine, obtained from 2.32 g (0.02 mole) of β-chloroethylamine hydrochloride and 1.12 g (0.02 mole) of potassium hydroxide, are mixed together, and the mixture is left to stand overnight. The precipitate that separates is filtered and crystallized.

Compounds IIIa-b, IIId, IIIj are obtained in a similar way.

Dihydrazides of phenylenedioxamic acids (IV) are obtained by the method described in [4].

Diarenesulfonamides of pheneylenedioxamic acids (IV) are obtained by the method described in [5] and purified by reprecipitation from a sodium hydroxide solution by an acid.

Dibenzoylhydrazide of 4-Methyl-1,3-phenylenedioxamic Acid (VIb). A 2.3 ml portion of benzoyl chloride is added dropwise, with constant stirring, to a solution of 2.94 g (0.01 mole) of IVb in 20 ml of 6% potassium hydroxide. The mixture is stirred for 5 h. The transparent solution is acidified by HCl (1:1) to pH 2.0, and the precipitate that separates is filtered and crystallized.

Compounds IVa, VIc-f are obtained in a similar way.

Di(4-Nitrobenzenesulfohydrazide) of 1,3-Phenylenedioxamic Acid (VIIa). p-Nitrobenzenesulfonyl chloride (4.44 g, 0.02 mole) is added in portions, with constant stirring, to a solution of 2.26 g (0.01 mole) of IVa in 20 ml of 12% potassium hydroxide. At the end of the reaction, the mixture is acidified by HCl (1:1) to pH 2.0, and the precipitate is filtered and crystallized.

Compounds VIIb-h are obtained in a similar way.

EXPERIMENTAL (BIOLOGICAL)

The compounds studied were examined by the E. Yu. Strel'nikov method [8] for their anti-inflammatory activity on male white mice, weighing 18-20 g each, as compared with mephenamic acid.

The compounds tested and mephenamic acid were introduced into the femoral fat of the posterior paw, using 100 mg per kg of body weight of the animal. A control experiment was set up at the same time. An anti-exudative effect was indicated from the ratio of differences in weight between the edematour and edematous paws obtained in the main experiment, and the data obtained with respect to mice in the control group. The results are given in Table 3.

In the group of amides III, the derivative of meta-phenylenedioxamic acid IIIa showed the highest activity (at the level of mephenamic acid). Introduction of a substituent into the benzene ring (IIIc) or transfer of the oxamoyl residue to the para-position (IIIi) leads to a sharp decrease in activity.

Among arenesulfonamides V, the meta-derivative Vb also showed the highest activity. The corresponding para-isomer is much less active.

Among the acylhydrazides of dioxamic acids VI, VII, the arenesulfonyl derivatives VII display the highest activity. The nitro derivative VIIg has equivalent anti-exudative activity to that of mephenamic acid.

It should be noted that, on the whole, the anti-inflammatory activity of the dioxamic acid derivatives is less than that of the corresponding oxamic acid derivatives [1, 2], but among phenylenedioxamic acids, compounds may possibly be found with a high activity.

The acute toxicity of the compounds was determined on white mice, weighing 20-22 g each, with peroral administration of suspension of the compound on Tween-80 by the method of I. V. Sanotskii [6]. The LD_{50} of the compounds studied is greater than 5000 mg/kg, and according to the K. K. Sidorov classification, they can be grouped as being practically nontoxic compounds (the LD_{50} of mephenamic acid is 620 mg/kg).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF MONO- AND TRICYCLIC DERIVATIVES OF 2-AMINO-3-CYANOPYRIDINE

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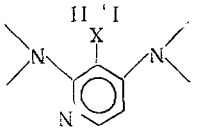
The broad spectrum of biological activity of bradykinin (BK) in the presence of common types of pathology (cardiovascular, inflammatory and other diseases), in which activated kininogenesis is observed, prompts the search for new compounds which restrict the activity of this peptide [2]. One of the promising paths for restricting the activity of BK is the use of its antagonists, i.e., compounds which selectively block its interaction with a receptor in tissues. This suggestion is based on abundant data on the use of antagonists of various biologically active compounds which restrict the activity of the corresponding biochemical systems in the organism (in particular, blocking agents or adrenergic, cholinergic and other systems).

Examination of the literature data shows that in order to have antikinin activity, low-molecular-weight compounds should contain one or several aromatic rings in their struc-



Va: R = H, R′ = CH_2Ph; Vb: NRR′ = $N(CH_2)_5$; Vc: R = R′ = H; Vd: RR′N = $N(CH_2CH_2)_2O$; Ve: R = H, R′ = $PhCH_2CH(CH_3)$; Vf: R = H, R′ = $3,4\text{-}(OMe)_2C_6H_2CH_2CH_2$.

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