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AMINOACYL DERIVATIVES OF DIARYLGLYCOLIC ACID HYDRAZIDES AND THEIR ANALGESIC ACTIVITY

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Arylhydrazides of disubstituted glycolic acids were previously bound to exhibit analgesic acitivity [1] which is potentiated when an aminoacyl fragment is introduced into their structure [2].

For the purpose of broadening the investigative area in the search for substances with analgesic activity, we synthesized unsubstituted hydrazides of diaryglycolic acids and their various β-N-acyl derivatives.

The starter diaryglycolic acid hydrazides (Ia-e) (Table 1) were obtained by the rehydrazionation of diaryglycolic acid cylohexylidene hydrazides [5] by hydrazine hydrate in accordance with the following arrangement:

$$C_6H_{10}{=}NNHCOC(OH)(C_6H_4R)_2 \longrightarrow \xrightarrow{} H_2NNHCOC(OH)(C_6H_4R)_2$$

Ia-e

R=H(Ia—IIIa), m-CH_3(Ib -IIIb) p-CH_3(Ic-IIIc), p-F(Id-IIId) p-Cl(Ie -IIId).

N-chloroacetyl (IIa-e) and N-α-bromopropionyl (IIIa-e) diarylglycolic acid hydrazides were synthesized by the interaction of chloroacetic chloroanhydride and α-bromopropionyl chloroanhydride with hydrazides I(a-e) (Table 1).

Ia-e → (+$ClCH_2COCl$) $ClCH_2CONHNHCOC(OH)(C_6H_4R)_2$ IIa-e

Ia-e → (+$BrCH(CH_3)COCl$) $BrCH(CH_3)CONHNHCOC(OH)(C_6H_4R)_2$ IIIa-e

The halide acyl derivatives of diarylglycolic acid hydrazides II and III upon reacting with secondary amines were converted to the corresponding aminoacyl derivatives (IVa-e, Va-d) (Table 2).

IIa-e + $CH_3N(CH_2CH_2)_2HN$ →
→ $CH_3N(CH_2CH_2)_2NCH_2CONHNHCOC(OH)(C_6H_4R)_2$
IVa-e

IIIa-d + $HN(C_2H_5)_2$ →
→ $(C_2H_5)_2NCH(CH_3)CONHNHCOC(OH)(C_6H_4R)_2$
Va-d

The IR-spectra of compounds IVd, e, and Va have two absorption bands of nonequivalent amide carbonyls in the 1610-1630 cm^{-1} and 1700-1710 cm^{-1} regions [3] and stretching vibration bands of the hydroxyl and two NH groups in the 3400-3420 cm^{-1} region.

EXPERIMENTAL (CHEMICAL)

The purity of the synthesized compounds was confirmed by TLC on Silufol UV-254 plates in a 10:9:1 benzene-ether-acetone system, iodine developer. IR-spectra was recorded on a UR-20 instrument in petroleum jelly. Element analysis data satisfied the calculated values.

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TABLE 1. Properties of Compounds IIa-e, and IIIa-e

Compound	Yield, %	mp, °C (solvent for crystallization)	Empirical formula
Ia	85	170—171 (ethanol)	$C_{14}H_{14}N_2O_2$
Ib	94	129—130 (benzene)	$C_{16}H_{18}N_2O_2$
Ic	73	179—180 (ethyl acetate)	$C_{16}H_{18}N_2O_2$
Id	58	184—185 (ethanol)	$C_{14}H_{12}F_2N_2O_2$
Ie	84	198—199 (toluene)	$C_{14}H_{12}Cl_2N_2O_2$
IIa	82	180—181 (benzene)	$C_{16}H_{15}ClN_2O_3$
IIb	75	158—159 (benzene)	$C_{18}H_{19}ClN_2O_3$
IIc	70	152—153 (benzene)	$C_{18}H_{19}ClN_2O_3$
IId	80	145—146 (benzene)	$C_{16}H_{13}ClFN_2O_3$
IIe	78	133—134 (benzene)	$C_{16}H_{13}Cl_3N_2O_3$
IIIa	74	181—182 (toluene)	$C_{17}H_{17}BrN_2O_3$
IIIb	85	151—152 (toluene)	$C_{19}H_{21}BrN_2O_3$
IIIc	74	185—186 (toluene)	$C_{19}H_{21}BrN_2O_3$
IIId	81	127—128 (toluene)	$C_{17}H_{15}BrF_2N_2O_3$
IIIe	75	177—178 (toluene)	$C_{17}H_{15}BrClN_2O_3$

Benzyl Hydrazide (Ia). An alcohol solution of 2 g (6.2 mmole) of benzyl cyclohexylidene hydrazide [5] and 5 g (0.1 mole) of hydrazine hydrate was boiled for 15 min, cooled, and decanted into 200 ml of water. The precipitate was filtered off. Yield was 85%, mp 170-171°C (from ethanol). The synthesized hydrazide Ia was identical to the substance obtained by method [4]. Compounds Ib-e were obtained in a similar manner.

Benzyl Chloroacetyl Hydrazide (IIa). A solution of 2.4 g (10 mmole) of hydrazide Ia and 3 g of chloroacetic chloroanhydride in 15 ml of dioxane was heated for 2 h on a water bath. Hydrazide IIa was obtained after the solvent was removed. Yield was 82%, mp 180-181°C (from benzene). Compounds IIb-e were obtained in the same manner.

Benzyl α-Bromopropionyl Hydrazide (IIIa). A solution of 2.4 g (10 mmole) of hydrazide Ia and 2.5 g of α-bromoproprionyl chloroanhydride in 30 ml of dioxane was heated for 2 h on a water bath. After the solvent was removed the yield of IIIa was 73%, mp 181-182°C (from toluene). Compounds IIIb-e were obtained in a similar manner.

Benzyl 1-N-Methylpiperazinoacetyl Hydrazide (IVa). A solution of 3.2 g (10 mmole) of hydrazide IIa and 4 g of 1-N-methylpiperazine in 30 ml of dioxane was boiled for 2 h. Hydrazide IVa was obtained after the solvent was removed. Yield was 60%, mp 214-215°C (from toluene). Compounds IVb-e were obtained in a similar manner.

Benzyl α-Dimethylaminopropionyl Hydrazide (Va). A solution of 1.9 g (5 mmole) of compound IIIa and 10 g of diethylamine in 15 ml of dioxane was heated for 2 h and cooled after which the end product was filtered at a 50% yield, mp 108-109°C (from ethanol). Compounds Vb-d were obtained in a similar manner.

EXPERIMENTAL (BIOLOGICAL)

Our pharmacological investigation was aimed at a search for analgesic activity in unsubstituted hydrazides of diarylglycolic acids Ia, c, d, and their acyl derivatives IIa, c-e, IIIb-e, IVa-e, and Va-d. The tests were conducted on 250 white nonpedigree mice of both sexes weighing 20 ± 2 g. Acute toxicity (LD_{50}) was determined by the ip injection of the examined compounds and the recording of animal deaths within a five-day period. Analgesic activity was measured by the "hot plate" test. The substances under study were administered ip at a dose of 50 mg/kg in the form a 2% starch-mucilage suspension.

The results of the biological tests are given in Table 3 from which one can see that all of the tested compounds are only slightly toxic. Their LD_{50} values are within the range of

TABLE 2. Aminoacyl Derivatives of Diarylglycolic Acid Hydrazides IVa-e and Va-d

Compound	Yield, %	mp, °C (solvent for crystallization)	Empirical formula
IVa	60	214—215 (toluene)	$C_{21}H_{26}N_4O_3$
IVb	44	167—168 (toluene)	$C_{23}H_{30}N_4O_3$
IVc	45	201—202 (toluene)	$C_{23}H_{30}N_4O_3$
IVd	48	232—233 (propanol)	$C_{21}H_{24}F_2N_4O_3$
IVe	57	227—228 (toluene)	$C_{21}H_{24}Cl_2N_4O_3$
Va	50	108—109 (ethanol)	$C_{21}H_{27}N_3O_3$
Vb	53	131—132 (2-propanol)	$C_{23}H_{31}N_3O_3$
Vc	56	148—149 (2-propanol)	$C_{23}H_{31}N_3O_3$
Vd	61	152—153 (2-propanol)	$C_{21}H_{25}F_2N_3O_3$

TABLE 3. Acute Toxicity and Analgesic Activity of Compounds I-V

Compound	LD_{50}, mg/kg	Duration of conditional defense reflex at peak activity, s
Ia	650	12,0±1,2
Ic	830	14,0±3,2
Ie	840	15,0±1,7
IIa	640	13,0±0,9
IIc	615	18,5±2,5
IId	500	17,0±1,3
IIe	540	17,0±1,8
IIIb	590	18,0±1,2
IIIc	610	17,0±2,0
IIId	760	16,5±1,4
IIIe	620	19,0±1,7
IVa	890	20,0±0,9
IVb	920	26,0±1,7
IVc	1030	19,0±0,4
IVd	915	25,0±1,8
IVe	950	25,0±1,9
Va	800	24,0±0,9
Vb	620	25,0±1,8
Vc	715	26,0±2,1
Vd	635	24,0±1,3

600-1000 mg/kg [6]. The analgesic activity of the unsubstituted diarylglycolic acid hydrazides is lower than that of the aryl hydrazides of these acids [1]. The introduction of a second aryl fragment into the hydrazide group results in a slight increase in the analgesic activity of the compounds with halide-containing residues (compounds IIc-e, IIIb-e) and in slightly increased activity for the aminoacyl derivatives IVa-e, Va-d. A similar effect was observed for the aryl hydrazides of the disubstituted glycolic acids.

The undertaken tests demonstrate the promise of finding analgesic preparations among the aminoacyl derivatives of disubstituted glycolic acid hydrazides.

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