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SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 2-ARYLMETHOXY-1,3-DI-(DIALKYLAMINO)PROPANES

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The previously synthesized compound 2-benzyloxy-1,3-dipiperidinopropane (VIb) [3] turned out to be an active local anesthetic. Therefore, in order to investigate the relationship between chemical structure and physiological activity in addition to searching for new drugs, we synthesized and examined that compound's structural analogs which had either not been previously known or which had not been tested for local anesthetic activity.

$n\text{-}C_6H_4[CH_2OCH(CH_2X)CH_2X']_2$
VII, VIII
$XCH_2CH(OR)CH_2X'$
Ib, h IId-g, IIb, IVb, Vb, c, VIa-i
X=X'=Cl (Ib, h), NEt_2 (IIb), NPr_2 (IVb), $N(CH_2)_4$ (Vb, c), $N(CH_2)_5$ (VIa-i, VIII); X=Br, X'=Cl (IId-g, VII);
R=H (VIa), CH_2Ph (Ib, IIIb-VIb)
$CH_2C_6H_4F\text{-}p$ (Vc, VIc), $CH_2C_6H_4Me\text{-}o$ (IId, VId),
$CH_2C_6H_4Me\text{-}m$ (IIe, VIe) $CH_2C_6H_4Me\text{-}p$ (IIf, VIf)
$CH_2C_6H_3Me_2\text{-}m,m'$ (IIg, VIg), CH_2-(1-naphthyl) (Ih, VIh)
COPh (VIi).

The amino esters IVb, Vb, and VId-h and VIII were synthesized by reacting secondary amines with the corresponding halogen esters Ib, h, IId-g, and VII which were synthesized by heating epichlorohydrin with halogenmethylarenes ($ArCH_2X$) or 1,4-di(bromomethyl)benzene in the presence of copper dihalides as catalysts. According to the PMR-spectra the synthesized halide esters Ib, h and IId-g, contained up to 10-15% of a mixture of 1-arylmethoxy-2,3-dihalogenpropanes. However, the amino esters IVb, Vb, VId-h derived from them, as well as the halogen ester VII and the amino ester hydrochloride VIII, constituted separate compounds after recrystallization.

The structure of the synthesized new compounds (Table 1) was confirmed by PMR-spectra which contained signals in the region (δ, ppm): 2.1-2.7 m (NCH_2), 3.4-3.6 d ($HalCH_2$), 3.5-3.7 q (OCH), 4.4-5.0 s (OCH_2) as well as

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	mp, °C or bp, °C (mm Hg)	Empirical formulas
Ih	36	165—107 (4)	$C_{14}H_{14}Cl_2O$
IId	66	164—106 (5)	$C_{11}H_{14}BrClO$
IIe	47	135—107 (3)	$C_{11}H_{14}BrClO$
IIf	73	158—160 (7)	$C_{11}H_{14}BrClO$
IIg	60	150—152 (4)	$C_{12}H_{16}BrClO$
IVb	58	115—117	$C_{22}H_{40}N_2O \cdot 2HCl$
		170—172 (1)*	$C_{22}H_{40}N_2O \cdot 2HCl$
Vb	72	154—156	$C_{18}H_{28}N_2O \cdot 2HCl$
		170—172 (4)*	
VId	70	192—194	$C_{21}H_{34}N_2O \cdot 2HCl$
		170—172 (1)*	
VIe	62	191—193	$C_{21}H_{34}N_2O \cdot 2HCl$
		175—177 (1)*	
VIf	68	222—224	$C_{21}H_{34}N_2O \cdot 2HCl$
		177—179 (1)*	
VIg	41	203—204	$C_{22}H_{36}N_2O \cdot 2HCl$
		183—185 (1)*	
VIh	67	228—230	$C_{24}H_{34}N_2O \cdot 2HCl$
VII	31	74—76	$C_{14}H_{18}Br_2Cl_2O_2$
VIII	32	269—271	$C_{34}H_{58}N_4O_2 \cdot 4HCl$

*Free base.

TABLE 2. Acute Toxicity, Local Anesthetic Activity, and Local Irritant Action of Amino Ester Hydrochlorides IIIb, IVb, Vb, c, VIa- and VIII

Compound	Acute toxicity (LD_{50}), mg/kg	Infiltration anesthesia	Conduction anesthesia		Local irritant action		
		Relative activity in comparison to novacaine*	Minimum effective concentration, mM	Half-excretion time, min	Degree of irritation by a 1% solution on a point scale	Tissue-irritating concentration, %	
						average	threshold
IVb	>1500	2,9	Slightly active		1,1	2,3	0,4
Vb	1230 (1051—1439)	1,4	10,3	25,0	0,8	8,0	0,7
VIb	323 (276—378)	5,2	1,8	14,4	1,1	3,8	0,2
VId	198 (139—281)	7,1	1,7	33,8	1,4	1,9	0,3
VIe	210 (168—262)	7,4	1,3	45,7	1,1	2,2	0,4
VIf	405 (332—494)	5,3	1,6	32,8	1,2	2,1	0,4
VIg	260 (205—330)	6,8	1,3	66,7	1,8	1,2	0,2
VIh	350 (302—406)	6,0	1,1	31,5	1,4	1,7	0,3
Novocaine	570 (539—602)	1,0	7,1	9,3	0,0	6,6	1,8
Trimecaine	391 (372—410)	1,7	5,0	10,8	1,2	3,6	0,1
Lidocaine	270 (204—356)	1,9	7,4	16,4	0,3	6,9	0,7
Pyromecaine	300 (287—313)	2,5	2,0	14,4	1,9	1,2	0,6
Dicain	44 (35—55)	5,6	0,3	13,4	2,6	0,6	0,1

*Values for compounds IIIb, Vc, VIa, c, i, and VIII are 0.8, 0.7, ~0, 1.6, 1.0, and 2.0 respectively.

Note: Limits of fluctuation are indicated in parentheses; data are statistically reliable ($P < 0.05$).

proton signals of the dialkylamino groups and aryl substituents. The UV-spectra of the benzene derivatives (IId-g, IVb, Vb, VId-g, VII, VIII) did not significantly differ and contained absorption bands in the region: λ_{max} 210-219 and 253-276 nm, log ε 3.5-3.9 and 2.3-2.8, respectively. However, the absorption bands of the naphthalene derivatives (Ih, VIh) were shifted toward the longwave side and were more intense (λ_{max} 224 and 280 nm, log ε 4.9-5.0 and 3.8, respectively).

Compounds Ib [2], IIIb [3], Vc [4], VIa [5], VIb [3], VIc [4], VIi [15], and the initial halogen methylarenes [6.8-11.16] have been described earlier.

The hydrochlorides of the synthesized aminoesters are readily soluble in water. The results of the pharmacological tests for those compounds are given in Table 2. We found that the local anesthetic action of these compounds increases in proportion to the length of their N-alkyl radicals (IIIb, IVb) or the number of the methylene

groups in the heterocyclic ring (Vb, VIb and Vc, VIc). The derivatives of the heterocyclic amines (Vb and VIb) are more active than their acyclic analogs (IIIb and IVb). The introduction of a fluoro substituent into the benzene ring decreases local anesthetic action whereas the introduction of one or two methyl substituents (VIb-g) just as the replacement of the benzene ring by a naphthalene ring (VIh), increases local anesthetic activity and has little effect on acute toxicity, but somewhat intensifies the local irritant action of the amino esters. The structural analogs VIa and VII are significantly weaker in anesthetic activity than compound VIb, whereas compounds VIb, e h are no less effective than the local anesthetics employed in medicine. Moreover, their local anesthetic action is of considerable duration.

The tests undertaken indicate the search for new medicinal agents among the compounds of the type under examination holds considerable promise.

EXPERIMENTAL

UV-spectra were recorded on a Specord UV-VIS (GDR) instrument and the PMR-spectra were recorded on a Tesla BS 487C (Czechoslovakia) instrument with a working frequency of 80 MHz in CCl_4. TMS was the internal standard.

The found values for the new compounds' element analyses corresponded to the calculated ones. The characteristics and yields of the compounds are given in Table 1.

2-Arylmethoxy-1,3-dihalogen propanes (Ih, IId-g) and 1,4-Di[(1-bromo-3-chloro-2-propyloxy)methyl]benzene (VII). A mixture of 23.1 g (250 mmole) of epichlorohydrin, 200 mmole of the corresponding halogen methylarene (or 100 mmole of 1,4-di(bromomethyl)benzene) and 2 mmole of copper dibromide or dichloride was heated for 10 h at 150°C and vacuum-distilled. Compound VII was recrystallized from hexane.

2-Arylmethoxy-1,3-di(dialkylamino)propanes (IVb, Vb, VId-h) and 1,4-Di[(1,3-dipiperidino-2-propyloxy]benzene (VIII). A mixture of 50 mmole of the halogen esters Ib, h, IId-g and 200 mmole of the corresponding secondary amine (or 50 mmole of the halogen ester VII and 400 mmole of piperidine) was heated for 50 h at 100°C, then cooled and dissolved in diluted HCl. After extraction with ether, the aqueous layer was made alkaline with NaOH, then extracted with ether. The extract was dried over KOH and concentrated. The hydrochlorides were obtained by passing anhydrous HCl gas into acetone solutions of the bases and recrystallized from a 1:2 mixture of 2-propanol and ethyl acetate.

EXPERIMENTAL (PHARMACOLOGICAL)

All of the tested compounds were administered subcutaneously in the form of a 1% aqueous solution. The tests were performed on non-pedigree white mice weighing 18-25 g and white rats weighing 150-230 g. Animals of both sexes were used. Acute toxicity for the mice was measured by the Litchfield—Wilcoxon method as modified by Roth [1]. Infiltration anesthesia was tested on guinea pigs by method [7]. Conduction anesthesia was tested on mice by recording motor paralysis [13]. The local irritant action was tested on rats by method [12] as modified by [14].

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SYNTHESIS AND VASCULAR ACTIVITY EXAMINATION OF 3-DIMETHOXYPHOSPHORYL PROPYL ESTERS OF N-ACYL DERIVATIVES OF NEUROACTIVE MONOCARBOXYLIC AMINO ACIDS

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Neuroactive monocarboxylic amino acids, particularly γ-amino butyric, β-alanine and glycine, acting as inhibitory mediators in the CNS, participate in the central regulation of blood circulation. However, these substances' low penetrability of the blood-brain barrier (BBB) constitutes a considerable limitation to the use of these amino acids for clinical purposes [6]. A number of structural analogs of the neuroactive inhibitor amino acids have been synthesized that are capable of penetrating the BBB and that can reproduce various effects of inhibitory mediators [4]. We know, for example, that the phosphorylated analogs of γ-aminobutyric acid are effective anticonvulsants [9].

For the purpose of finding new prototype drugs based on the inhibitory amino acids that can easily gain entry into the brain and that exhibit cardiovascular activity, we synthesized 3-dimethoxyphosphorylated esters of N-acyl derivatives of glycine (VII), β-alanine (VIII), and γ-aminobutyric acid (IX), and investigated their vascular activity. The indicated compounds were synthesized by alkylating the sodium or potassium salts of N-benzolglycine (I), N-acetyl-β-analine (II) and N-acetyl-γ-aminobutyric acid (III) with allyl bromide in an aqueous acetonitrile medium in the presence of interphase transfer catalysts followed by the homolytic phosphorylation of the resultant allyl esters by dimethylphosphite in the presence of a peroxide initiator:

$$\underset{\text{I—III}}{RCONH(CH_2)_nCOONa} \xrightarrow{CH_2=CHCH_2Br,\ \text{Crown ether}} \underset{\text{IV—VI}}{RCONH(CH_2)_nCOOCH_2CH=CH_2} \xrightarrow{HP(O)(OCH_3)_2,\ \text{peroxide}} RCONH(CH_2)_nCOOCH_2CH_2CH_2PO(OCH_3)_2\ (\text{VII—IX})$$

R = C_6H_5 (I, IV, VII), CH_3 (II, III, V, VI, VIII, IX); n = 1 (I, IV, VII), 2 (II, V, VIII), 3 (III, VI, IX).

Crown ethers are widely used in organic synthesis, including the synthesis of complex carboxylic acid esters [8]. However, the existing methods require the use of anhydrous salts and absolute solvents. We have devised a convenient preparatory method of obtaining the allyl ethers of N-acylated amino acids by alkylating the corresponding sodium or potassium salts with allyl bromide in the presence of crown ethers (15-crown-5, 18-crown-6, dibenzo-18-crown-6) at a molar ratio of acylamino acid salt:allyl bromide:crown ether corresponding to 1:(1-1.25):(0.02-0.05) at a temperature range of 20°C-80°C. The process takes place in an aqueous acetonitrile medium with an allowable water content of up to 20 wt. %. In accordance with this method an aqueous solution of a sodium or potassium salt of the N-acylated amino acid is added to the crown ether solution in acetonitrile and the resultant emulsion is treated with allyl bromide. This obviates the preparation of anhydrous salts and the use of absolute solvents. The highest yield of the allyl ester is observed in the case of N-benzolglycine (92.6%). However, when N-acetyl-β-alanine and N-acetyl-γ-aminobutyric acid are used as the substrates, the yield of the allyl esters is reduced to 43.8 and 34.6% respectively. This is probably due to the lower solubility of the indicated N-acyl amino acid salt complexes with the crown ethers

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