5-[β-(β'-ALKYLAMINOETHOXY)ETHOXY]-1, 4-BENZODIOXANES

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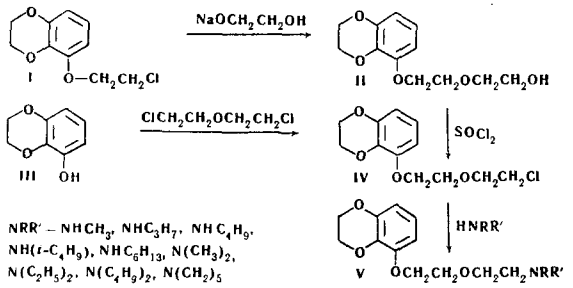
Pharmacologically interesting new aminoethers of the 1, 4-benzodioxane series are synthesized.

We previously synthesized aminoalkyl ethers of 5-hydroxy-1, 4-benzodioxane possessing multiple biological activities [1–6]. Continuing that work, we have prepared new aminoethers: 5-[β-(β'-alkylaminoethoxy)ethoxy]-1, 4-benzodioxanes (V) by reacting 5-[β-(β'-chloroethoxy)ethoxy]-1, 4-benzodioxanes (IV) with primary or secondary amines.



The starting chloroether IV was prepared by two independent routes: by the action of thionyl chloride on 5-[β-(β'-hydroxyethoxy)ethoxy]-1, 4-benzodioxane (II) obtained by reacting 5-(β-chloroethoxy)-1, 4-benzodioxane (I) with sodium glycolate (method a), or by reacting 5-hydroxy-1, 4-benzodioxane (III) with β, β'-dichloroethyl ether in a solution of potassium hydroxide in methanol (method b). All the compounds synthesized (I–V) give UV spectra with an absorption maximum at 268–270 mμ, characteristic of 1, 2, 3-trialkoxybenzenes [7].

The biological activity of aminoethers V was investigated in the pharmacology department of Vil'nyus University, under the supervision of G. Polukordas. The butylamino derivative (V, R = H, R' = C_4H_9) was found to have local anesthetic activity, and to depress the central nervous system. Many of the V compounds stimulate the central nervous system.

EXPERIMENTAL

5-[β-(β'-Hydroxyethoxy)ethoxy]-1, 4-benzodioxane (II). 8 g I [1, 3] was added to a solution of 0.9 g Na in 50 ml dry glycol, the whole heated for 24 hr at 170° C, the products cooled, made acid with HCl, the glycol vacuum-distilled off, the residue dissolved in dichloroethane (NaCl filtered off), and the solution distilled. Yield of II 5.4 g (61%), bp 227°–228° C (10 mm), mp 65°–66° (ex CCl_4). Found: C 60.20; 60.27; H 6.89; 6.75%. Calculated for $C_{12}H_{16}O_5$: C 59.99; H 6.71%.

5-Hydroxy-1, 4-benzodioxane (III). 378 g pyrogallol, 415 g dry K_2CO_3, and 350 ml glycerol were stirred together under N at 150° C for 2 hr, and 565 g dibromomethane added over 3 hr, the whole stirred for 3 hr more, the products cooled, 1000 ml water added, then made acid with HCl. The aqueous layer was separated from the tar, then extracted twice with toluene; the tar was boiled twice with toluene. The toluene extracts were bulked, dried, and distilled to give 132 g (29%) III, bp 145°–147° C (15 mm) [8]; n_D^{20} 1.5719; d_4^{20} 1.2931. Benzoate mp 108°–109° C (ex EtOH) [9].

5-[β-(β'-Chloroethoxy)ethoxy]-1, 4-benzodioxane (IV). a) 18 g $SOCl_2$ was dropped into a mixture of 21 g II, 7.2 g pyridine, and 200 ml dichloroethane held at 0°, the products left for 24 hr at 30°, washed with dil HCl, then with water, dried, and distilled. Yield of IV 17 g (79%), bp 165°–168° C (0.7 mm), mp 55°–56° (ex MeOH).

b) A solution of 21.8 g KOH in 450 ml MeOH was added, over a period of 3 hr, to a stirred mixture of 66 g III and 170 g β, β'-dichloroethyl ether heated on a water-bath. Then heating and stirring were continued for 30 hr longer, the MeOH distilled off, 200 ml water added, the mixture extracted with ether, the extract washed a few times with 10% NaOH, then dried and distilled to give 55 g (52%) IV, bp 161°–162° C (0.13 mm), mp 55.5°–56° (ex MeOH). Found: C 59.95; 56.01; H 6.93; 6.20; Cl 13.53; 14.00%. Calculated for $C_{12}H_{15}ClO_4$: C 55.70; H 5.84; Cl 13.70%.

After IV had distilled over, there remained in the flask 4 g β, β'-di(1, 4-benzodioxan-5-yloxy)diethyl ether, mp 131.5°–132.5° C (ex EtOH). Found: C 63.95; 64.12; H 6.03; 6.10%. Calculated for $C_{20}H_{22}O_7$: C 64.18; H 5.29%.

5-[β-(β'-Alkylaminoethoxy)ethoxy]-1, 4-benzodioxane (V). A solution of 0.05 mole IV plus 0.1 mole of the primary or secondary amine in 50 ml EtOH was refluxed (in the case of gaseous amines they were put in a sealed tube and heated on a water-bath) for 60 hr, the EtOH distilled off, the residue dissolved in dil HCl, the solution extracted with ether, the aqueous layer made alkaline and extracted with toluene, the toluene extract dried and distilled to give V. V hydrochlorides were prepared by passing dry HCl gas into an ether solution of the base, while the reineckates were obtained by adding an aqueous solution of ammonium reineckate to an aqueous solution of V hydrochloride, followed by precipitation from acetone with water. Data for V are given in the table.

5-[β-(β'-Alkylaminoethoxy)ethoxy]-1, 4-benzodioxanes (V)

NRR'		Bp °C (pressure mm)	Mp, °C (solvent)	n_D^{20}	Formula	Found, %		Calculated, %		Yield, %
						Cl	N	Cl	N	
$NHCH_3$	Base	178—179 (8)	—	1.5352	$C_{13}H_{19}NO_4$	—	5.56; 5.65	—	5.52	31
	Hydrochloride	—	146.5—147.5 ($CHCl_3$)	—	$C_{13}H_{19}NO_4 \cdot HCl$	12.23; 12.49	4.85; 4.78	12.23	4.82	—
NHC_3H_7	Base	168—169 (0.05)	—	1.5206	$C_{15}H_{23}NO_4$	—	4.88; 4.95	—	4.98	67
	Hydrochloride	—	84.5—86 (acetone)	—	$C_{15}H_{23}NO_4 \cdot HCl$	11.09; 11.03	4.22; 4.29	11.15	4.41	—
NHC_4H_9	Base	178—180 (2)	—	1.5213	$C_{16}H_{25}NO_4$	—	4.93; 5.02	—	4.74	48
	Hydrochloride	—	77.5—78 (EtOH-ether)	—	$C_{16}H_{25}NO_4 \cdot HCl$	10.90; 10.99	4.47; 4.50	10.69	4.22	—
$NH(i\text{-}C_4H_9)$	Base	171—172 (0.05)	—	1.5161	$C_{16}H_{25}NO_4$	—	4.62; 4.71	—	4.74	53
	Hydrochloride	—	119—120 (acetone)	—	$C_{16}H_{25}NO_4 \cdot HCl$	10.88; 10.94	4.13; 4.29	10.68	4.22	—
NHC_6H_{13}	Base	196—198 (0.1)	—	1.5185	$C_{18}H_{29}NO_4$	—	4.23; 4.28	—	4.33	29
	Reineckate*	—	110—112	—	$C_{18}H_{29}NO_4 \cdot \cdot C_4H_7CrN_6S_4$	—	15.20; 15.27	—	15.25	—
$N(CH_3)_2$	Base	163—164 (0.05)	—	1.5234	$C_{14}H_{21}NO_4$	—	5.14; 5.22	—	5.24	88
	Hydrochloride	—	134.5—135.5 (dioxane)	—	$C_{14}H_{21}NO_4 \cdot HCl$	11.91; 12.00	4.57; 4.67	11.67	4.61	—
$N(C_2H_5)_2$	Base	229—230 (10)	—	1.5220	$C_{16}H_{25}NO_4$	—	4.51; 4.55	—	4.74	53
	Reineckate*	—	96.5—97	—	$C_{16}H_{25}NO_4 \cdot \cdot C_4H_7CrN_6S_4$	—	15.81; 16.14	—	15.95	—
$N(C_4H_9)_2$	Base	189—190 (0.15)	—	1.5091	$C_{20}H_{33}NO_4$	—	3.68; 3.81	—	3.98	62
	Reineckate*	—	42.5—44	—	$C_{20}H_{33}NO_4 \cdot \cdot C_4H_7CrN_6S_4$	—	14.83; 14.90	—	14.70	—
$N(CH_2)_5$	Base	237—240 (10)	—	1.5375	$C_{17}H_{25}NO_4$	—	4.33; 4.42	—	4.55	60
	Reineckate*	—	120.5—121	—	$C_{17}H_{25}NO_4 \cdot \cdot C_4H_7CrN_6S_4$	—	15.46; 15.64	—	15.65	—

*Very hygroscopic hydrochloride.

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