ESTERS OF LUPININE AND N-(β -HYDROXYETHYL)ANABASINE WITH p-SUBSTITUTED BENZOIC ACIDS

UDC 542.91:547.94

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Among the local anesthetics the most widely used compounds are the aminoalkanol esters of p-aminobenzoic acid, containing various aminoalkanol moieties [1-5]. Lupinine, one of the principal alkaloids of <u>Anabasis aphylla</u> [6], has also been used for the same purpose. It was interesting to make a more extensive study of the possibility of synthesizing compounds which have a local anesthetic action among the alkaloidal derivatives of Anabasis aphylla, and primarily of lupinine and $N-(\beta-hydroxyethyl)$ anabasine.

For this purpose we synthesized the esters of the p-Cl, p-Br, p-NO₂, p-NH₂, and p-CH₃ derivatives of benzoic acid and the above-mentioned aminoalcohols. These compounds were obtained by reacting the aminoalcohols with the appropriate acid chlorides of the p-substituted benzoic acids in the presence of triethylamine (Tables 1 and 2)



 $R' = p - BrC_6H_4$; $p - CH_3C_6H_4$; $p - NO_2C_6H_1$; $p - NH_2C_6H_4$

Then all of the amino esters were converted to the corresponding hydrochlorides.

No.	-R'	Мр., °С	n_{D}^{20}		Yield	ield Found, % Empirica	Empi ri ca l	Calc.,%		
				R _f	%	С	н	formula	С	Ħ
I III III IV	$C_{5}H_{4}NO_{2}$ $C_{6}H_{4}Br$ $C_{6}H_{4}CH_{3}$ $C_{6}H_{4}NH_{2}$	87 * 33—34 52—53 159 †		$\begin{array}{c} 0,72 \\ 0,40 \\ 0,30 \\ 0,47 \end{array}$	70 71 80 50	64,1 57,6 74,8 70,5	7,0 6,3 8,7 8,1	$\begin{array}{c} C_{17}H_{22}N_2O_4\\ C_{17}H_{22}NO_2Br\\ C_{18}H_{25}NO_2\\ C_{17}H_{24}N_2O_2 \end{array}$	$64,1 \\ 57,9 \\ 75,2 \\ 70,8$	$^{6,9}_{6,2}_{8,7}_{8,3}$

TABLE 1. Esters of Lupinine ROCOR' ($_{R}$

*From [6]: mp 95°.

†From [6]: mp 162°.

Institute of Heteroorganic Compounds, Academy of Sciences of the USSR. V. I. Lenin Tashkent State University. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 952-953, April, 1972. Original article submitted May 10, 1971.

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L · HCl							A·HC1					
-R'	mp, °C	yield,%	empirical formula	found N, %	calc. N,	Т . тр, °С	yield, 🕼	empirical formula	found N,	calc. N,		
CsH4NO2	222-224 *	90	$\mathrm{C_{17}H_{23}N_2O_4Cl}$	7,7	7,8	204-205	Quantita-	$C_{19}H_{23}N_3O_4Cl_2$	9,7	9,8		
C_6H_4Br $C_6H_4CH_8$	203—205 191—193	90,5 89	C17H23 NO2 BrCl C19H26 NO2Cl	3,4 4,0	3,5 4,3	222-224 222-224	т т	$C_{19}H_{23}N_2O_2BrCl_2 \\ C_{20}H_{28}N_2O_2Cl_2$	5,9 6,9	6,0 7,0		

TABLE 2. Hydrochlorides of Esters of Lupinine (L \cdot HCl) and N-(β -Hydroxyethyl)anabasine (A \cdot HCl)

*From [6]: mp 229-231°.

TABLE 3. Esters of N-(β -Hydroxyethyl)anabasine

N-CH2-CH2OCOR'

······	·Mp, °C or Bp	· · ·	774 + 1 d	Foun	d, %	Empiric ol	Calc.,%	
$-\mathbf{R}'$	°C (p, mm of Hg)	Rſ	% %	с	н	formula	Calc. C 64,2 66,1 58,6	н
C ₈ H ₄ NO ₂ C ₆ H ₄ Cl C ₆ H ₄ Br C ₆ H ₄ CH ₃	49—50 208—209 (0,5)	$0,80 \\ 0,73 \\ 0,75 \\ 0,84$	66 40 40 55	63,9 65,8 58,4 73,7	5,8 6,3 5,5 7,4	$\begin{array}{c} C_{19}H_{21}N_{3}O_{4}\\ C_{19}H_{21}N_{2}O_{2}Cl\\ C_{19}H_{21}N_{2}O_{2}Br\\ C_{20}H_{24}N_{2}O_{2} \end{array}$	$64,2\\66,1\\58,6\\74,04$	$5,9 \\ 6,09 \\ 5,3 \\ 7,4$

EXPERIMENTAL

Anabasine, lupinine and N-(β -hydroxyethyl)anabasine were respectively obtained by the reported methods [7-9].

Esters of Lupinine. To a mixture of 0.017 mole of lupinine and 0.017 mole of triethylamine in 60 ml of absolute ether was added with stirring, at $0-2^{\circ}$ C, in 40 min, 0.017 mole of the acid chloride of the substituted benzoic acid in 40 ml of absolute ether. Then the stirring was continued for another 2 h, in which connection the temperature was gradually raised up to room temperature. The obtained triethylamine hydrochloride was filtered and washed with absolute ether. After distilling off the ether, (I), (II), and (III) were recrystallized from aqueous alcohol. An exception is (V), which was obtained from (I) as described in [6]. The purity of the obtained compounds was checked by TLC; the support was Al_2O_3 (II activity), and the eluant was the system: benzene-chloroform-methanol, 18:15:1 (see Table 1).

Hydrochlorides of Esters of Lupinine. To a stirred mixture of 0.017 Mof lupinine and 60 ml of absolute benzene at 0-2° was added in 40 min a solution of 0.017 mole of the chloride of the substituted benzoic acid in 40 ml of absolute benzene. The mixture was then stirred for another 2 h, with a gradual elevation of the temperature up to room temperature, and then it was heated for 1 h at 60-70°. The precipitate was filtered, washed with absolute benzene, and dried (see Table 2).

Esters of $N-(\beta-Hydroxyethyl)$ anabasine. To a stirred mixture of 0.0194 mole of $N-(\beta-hydroxyethyl)$ anabasine and 0.0194 mole of triethylamine in 100 ml of absolute benzene at 0-2° was added in 30 min a solution of 0.0194 mole of the acid chloride of the substituted benzoic acid in 50 ml of absolute benzene. Then the mixture was stirred for another 3 h, with a gradual elevation of the temperature up to room temperature, and then it was heated at 60-70° for 1 h. The precipitate of triethylamine hydrochloride was filtered and washed with absolute benzene. After distilling off the benzene the product was purified by passing its ether solution through a column filled with Al_2O_3 (II activity). The purity of the obtained compounds was checked by TLC; the support was Al_2O_3 , and the eluant was the system: benzene-acetone-methanol, 20:3:2 (Table 3).

Hydrochlorides of Esters of $N-(\beta-Hydroethyl)$ anabazine. A solution of 0.01 mole of the ester of $N-(\beta-Hydroxyethyl)$ anabasine in 100 ml of absolute ether was saturated with dry HCl until the hydrochloride was no longer formed. The precipitate was filtered, washed several times with absolute ether, and dried in a vacuum-desiccator (see Table 2).

CONCLUSIONS

Some new esters were synthesized by the reaction of lupinine and $N-(\beta-hydroxyethyl)$ anabasine with p-substituted benzoic acids.

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