Of course, the above recommended method of increasing the activity is not the only possible one. In some cases the ABA is more important and in others the PR is more important. Depending on this, the means of increasing the activity may change, although the general picture will remain the same.

LITERATURE CITED

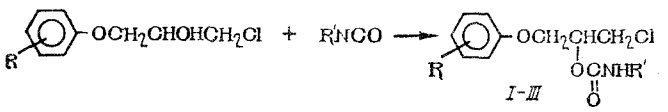
1. S. M. Free and W. Wilson, J. Med. Chem., 7, 395 (1964).
2. C. Silipo and C. Hansch, J. Med. Chem., 19, 62 (1976).
3. A. Camarata et al., J. Pharm. Sci., 59, 1496 (1970).
4. A. L. Mndzhoyan, V. E. Badalyan, Yu. Z. Ter-Zakharyan, et al., Arm. Khim. Zh., No. 8, 720 (1969).
5. A. L. Mndzhoyan, M. G. Tsinker, É. S. Mkrtchyan, et al., Khim. Farm. Zh., No. 5, 15 (1970).
6. A. L. Mndzhoyan, M. G. Tsinker, S. Z. Bil'bulyan, et al., Khim. Farm., Zh., No. 9, 3 (1974).
7. Sh. L. Mndzhoyan, M. G. Tsinker, L. O. Tevosyan, et al., Khim. Farm. Zh., No. 8, 43 (1976).
8. C. Hansch et al., J. Med. Chem., 16, 1207 (1973).
9. S. H. Unger and C. Hansch, J. Med. Chem., 16, 745 (1973).

SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF SOME CARBAMIC ACID DERIVATIVES

S. S. Kukalenko, A. G. Tsybulevskii, A. S. Saratikov, V. K. Gorshkova, and G. Ya. Voronina

UDC 615.213:547.495.1

It is known that monocarbamates of 1,2-dihydroxy-3-aryloxypropane have neurotropic activity [1, 2]. For the purpose of searching for biologically active compounds among the derivatives of 1-chloro-3-aryloxy-2-propanol, we have synthesized a series of substituted 1-chloro-3-aryloxy-2-propyl carbamates (I-III) using the following reaction scheme:



The resulting carbamates (I-III) (Table 1) are white crystalline substances with an aromatic odor. Their yields ranged from 80 to 90%.

The IR spectra of the products have bands in the 1710- to 1715-cm^{-1} region, characteristic of the stretching vibrations of carbamate carbonyl groups, and bands in the 3330- to 3340-cm^{-1} region, which correspond to the N–H bond.

Bearing in mind that carbamates include compounds with sedative, tranquilizing, and spasmolytic properties [3-5], we investigated the neurotropic activity of the products and determined their acute toxicity (Table 2). The carbamates studied have relatively low toxicities, with LD_{50} values of more than 1 g/kg. In contrast to compound I, compounds II and III depress long-term activity at the indicated dose. At a dose of 1/8 LD_{50}, compound II and, to a lesser extent, compound I have a spasmolytic action (maximum electroshock test), and both compounds give a significant decrease in rectal temperature in mice. Compound III is inactive in this respect.

On the basis of a comparison of the structures of the compounds in question, we can

All-Union Scientific-Research Institute for Chemical Plant-Protection Agents, Moscow. Tomsk Medical Institute.

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 6, pp. 41-43, June, 1977. Original article submitted July 19, 1976.

0091-150X/77/1106-0769$07.50

TABLE 1. 1-Chloro-3-aryloxy-2-propyl Carbamates

Compound	R	R'	Yield, %	Melting point, deg*	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
I	H	C_2H_5	90	51—2	55,81	6,18	5,29	$C_{12}H_{16}ClNO_3$	55,80	6,21	5,43
II	H	C_4H_9	84	61—2	58,46	7,10	6,01	$C_{14}H_{20}ClNO$	58,90	7,00	4,90
III	3-Cl	C_6H_5	83	93—4	56,52	4,35	3,99	$C_{16}H_{15}Cl_2NO_3$	56,50	4,42	4,12

*Compound I was crystallized from hexane, and II and II from ether.

TABLE 2. Pharmacological Activity of 1-Chloro-3-aryloxy-2-propyl Carbamates (average of six experiments)

Index	I	II	III
LD_{50}, mg/kg (sc, mouse)	>1000	1240 (1042÷1476)	>1000
Dose, mg/kg (sc)	125	155	125
Depression of coordination, %:			
initial background	0	0	0
30 min	0	16,7	0
60 "	16,7	16,7	0
120 "	66,7	33,3	33,3
Rectal temperature, deg:			
initial background	37,5±0,3	36,2±0,6	36,7±0,7
30 min	36,9±0,5 (0,073)	35,8±0,3 (0,165)	36,9±0,5 (0,698)
60 "	36,0±0,5 (0,013)	35,8±0,4 (0,389)	36,9±0,5 (0,698)
120 "	35,5±0,6 (0,006)	33,9±0,8 (0,016)	35,8±0,7 (0,258)
Electroshock pain threshold, V:			
initial background	4,5±0,7	4,3±0,5	3,6±0,4
30 min	3,4±0,6 (0,102)	4,8±0,5 (0,389)	4,2±0,2 (0,022)
60 "	3,7±0,5 (0,120)	4,4±1,2 (0,922)	2,9±0,5 (0,192)
120 "	4,2±0,5 (0,562)	4,0±0,7 (0,698)	4,2±0,5 (0,258)
Maximum electroshock:			
% inhibition of spasms	50,0	100	33,3
% survival	83,3	100	66,7
Chloral hydrate sleep:			
latent period, min:			
control	18,5±3,1	14,3±3,1	18,5±3,1
expt.	17,2±1,8 (0,770)	14,2±1,8 (1,000)	19,3±3,6 (0,845)
sleep duration, min:			
control	88,0±19,9	99,6±37,4	88,0±19,9
expt.	59,0±12,3 (0,258)	102,2±26,8 (0,500)	52,3±14,0 (0,165)

Note: M ± m values given with p in brackets.

conclude that the alkyl radical is of considerable importance with respect to their neurotropic properties: The activity increases on passing from the ethyl to the butyl residue.

EXPERIMENTAL

Chemistry

The IR spectra were recorded with a UR-20 spectrophotometer with a lithium fluoride prism using potassium bromide pellets containing 3300 mg of the compound.

1-Chloro-3-phenoxy-2-propyl-N-butylcarbamate (II). A solution of 18.7 g (0.1 mole) of 1-chloro-3-phenoxy-2-propanol in 20 ml of hexane was treated with 9.9 g (0.1 mole) of butyl isocyanate. Dibutyltin dilaurate (2-3 drops) was added as catalyst. The reaction mixture was stirred at 25-30°C for 1 h and the precipitate filtered off to give 24 g (84%) of II, mp 61-62°C (from ether). Found, %: C 58.46; H 7.10; N 5.01. $C_{14}H_{20}ClNO_3$. Calculated, %:

C 58.90; H 7.00; N 4.90.

Compounds I and III were prepared analogously.

Pharmacology

To evaluate the neurotropic activity spectrum, we determined the following forms of activity in experiments on white mice: spasmolytic, on the basis of the ability to inhibit spasms during maximum electroshock [6]; muscle relaxant, using the rotating rod test [7]; analgesic, on the basis of the change in electroshock pain threshold; and hypnosedative, from the change in rectal temperature and potentiation of the hypnotic action of chloral hydrate [8]. The results of the experiments were processed statistically by the method of direct and indirect differences [9]. The acute daily toxicity was determined as in [10], and the LD_{50} was calculated as in [11].

LITERATURE CITED

1. M. Baizer, R. Clark, and L. Swidinsky, J. Org. Chem., 22, 1995 (1957).
2. H. L. Yale, E. J. Pribyl, W. Braker, et al., J. Am. Chem. Soc., 72, 3710 (1960).
3. P. May and G. M. Dyson, Chemistry of Synthetic Drugs, Wiley, New York (1959) [Russian translation: Moscow (1964), p. 109].
4. J. W. Bastian and G. R. Clements, Dis. Nerv. Syst., 22, No. 9, Suppl., 9 (1961).
5. M. P. Latwon and B. Cahn, J. Psychol. 54, 131 (1962).
6. E. A. Swinyard, W. C. Brown, and L. S. Goodman, J. Pharmacol. Exp. Ther., 106, 319 (1952).
7. N. W. Dunham and T. S. Miya, J. Am. Pharm. Assoc. Sci. Ed., 46, 208 (1957).
8. L. A. Krandl and R. K. Lim, in: Modern Physiology [in Russian], Leningrad (1959), pp. 235-241.
9. E. V. Montsevichyute-Eringene, Patol. Fiziol., No. 4, 71 (1964).
10. S. R. Buchby, in: Experimental Chemotherapy (ed. by R. J. Schnitzer and J. Hawking), Vol. 1, Academic Press, New York (1963), pp 25-53.
11. M. L. Belenkii, Quantitative Evaluation of Pharmacological Effects [in Russian], Leningrad (1963), pp. 81-117.

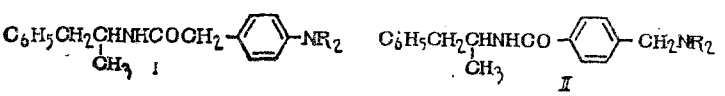
DRUGS DERIVED FROM β-PHENYLISOPROPYLAMINE.

VII. PHENYLISOPROPYLAMIDES OF p-AMINOMETHYL- AND p-DIALKYLAMINOMETHYLBENZOIC ACIDS

N. I. Kudryashova and N. V. Khromov-Borisov

UDC 615.214.22.012.1

As has been shown in [1], the β-phenylisopropylamides of p-amino- and p-dialkylaminophenylacetic acids (I) produce a pronounced sedative effect. In the present work, we will describe the synthesis of a series of new β-phenylisopropylamine derivatives, viz. the β-phenylisopropylamides of p-aminomethyl- and p-dialkylaminomethylbenzoic acids (II).



As can be seen, the new compounds (II), while having the same composition, differ from the previously prepared compounds I in having a more basic amino group. Compounds II (see Table 1) were synthesized according to the following reaction scheme:

Scientific-Research Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, Leningrad. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 6, pp. 44-46, June, 1977. Original article submitted December 30, 1976.

0091-150X/77/-1106-0771$07.50