SOME NEW AMINOALKYL ESTERS OF DIPHENYLACETIC AND BENZILIC ACIDS

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Continuing the search for active cholinolytics and the study of the relationship between their chemical structure and their physiological activity, we undertook the synthesis of the esters of diphenylacetic and benzilic acids with the aminoalcohols: N-methyl- and N-ethyl-N-tertiarybutylaminoethanol, cis- and trans-2-(N,N-dimethylamino)cyclopentanol. The esters of the first two aminoalcohols interested us from the point of view of the effect of the spatial factors in the region of the nitrogen on the cholinolytic activity of the substances, since it was previously shown that these factors played an important role [1-3]. The esters of the other two aminoalcohols could be of interest in elucidating the conformation in which the aminoalcohol esters interact with their biological substrate (cholinoreceptors).

The esters of diphenylacetic acid were prepared by the reaction of the acid chloride with the appropriate aminoalcohol. The aminoalcohol esters of benzilic acid were synthesized by the interesterification of the methyl ester with the aminoalcohol in the presence of a small amount of the sodium alcoholate of the latter. The hydrochlorides and methyl iodides of the aminoalcohols were prepared by the usual methods. Data about the synthesized compounds are given in Table 1.

The results of the preliminary pharmacological study of the synthesized compounds, carried out by S. I. Loktionov and E. P. Zatsepin, show that on changing from the N,N-dimethylaminoethyl esters of diphenylacetic and benzilic acids [R = $CH_2CH_2N(CH_3)_2$] to the corresponding N-methyl-N-tertiarybutylaminoethyl esters [R = $CH_2CH_2N(CH_3)$(tert. C_4H_9)] the central cholinolytic activity increases and the peripheral activity decreases. Transition from N,N-diethyl derivatives [R = $CH_2CH_2N(C_2H_5)_2$] to N-ethyl-N-tertiarybutyl derivatives [R = $CH_2CH_2N(C_2H_5)$ (tert · C_4H_9)] causes a decrease in cholinolytic activity both in the peripheral and in the central areas ot the nerve system, however the central cholinolytic activity decreases to a significantly lesser degree. The hydrochlorides of these aminoesters are of interest as selectively acting central cholinolytics.

As regards the derivatives of N,N-dimethylaminocyclopentanol, the cholinolytic activity is confined almost exclusively to the trans-derivative. It is possible that for compounds with an open chain, for example, derivatives of aminoethanol, the trans conformation is the more preferred for the interaction with the cholinoreceptor.

EXPERIMENTAL

N-Methyl-N-tert. butylaminoethanol. While cooling with ice, 5.07 g of methyltert. butylamine, 3.18 g of ethylene oxide and 10 ml of absolute methanol were mixed. The mixture was held at 0.5° for 5 h, then at room temperature for 18-20 h. The residue, after distilling off methanol and excess amine, was twice distilled in vacuo. Yield of the substituted aminoethanol, with bp 59° (8 mm), n_D^{16} 1.4499, was 4.75 g (66%). Found %: C 64.50, 64.62; H 12.68, 12.68; N 11.05, 11.07. $C_7H_{17}NO$. Calculated %: C 64.05; H 13.07; N 10.68.

N-Ethyl-N-tert.butylaminoethanol. This was prepared analogously to the above except that it was held at room temperature for 4 days. Yield of aminoethanol was 68% of theory, bp 75° (10 mm). Literature mp 75-76° (13 mm) [4]. The hydrochloride had mp 116-119°.

cis-2-(N,N-Dimethylamino)cyclopentanol. This was prepared from 2-chlorocyclopentanol [5]. trans-2-(N,N-Dimethylamino)cyclopentanol was prepared by the interaction of cyclopentene oxide with dimethylamine. The n_D^{20} was 1.4753 as compared with the n_D^{20} 1.4730 reported in the literature [6].

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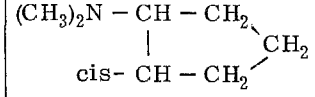
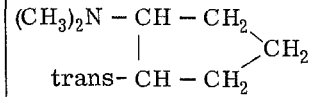
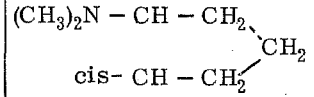
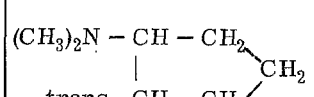
TABLE 1. Aminoalkyl Esters of Diphenylacetic and Benzilic Acids, $(C_6H_5)_2CXCOOR$

Compound	X	R	Derivative	Yield (in %)	mp (in °C), in brackets – solvent for crystallization	Found (in %) N	Found (in %) halogen	Empirical formula	Found (in %) N	Found (in %) halogen
I	H	$CH_2CH_2N(CH_3)(tert.\text{-}C_4H_9)$	Base		Liquid					
			Hydrochloride	64	148-9 (alcohol-ether)		9.50; 9.47;	$C_{21}H_{27}NO_2 \cdot HCl$		9.80
			Methyl iodide	84	155.5-156.5 (dichlorethane-ether)		26.61; 26.58	$C_{22}H_{30}INO_2$		27.15
II	H	$CH_2CH_2N(C_2H_5)(tert.\text{-}C_4H_9)$	Base		Liquid					
			Hydrochloride	58	158-9 (alcohol-ether)		9.24, 9.30	$C_{22}H_{29}NO_2 \cdot HCl$		9.43
			Methyl iodide	65	158 (methanol)		26.60, 26.58	$C_{23}H_{32}INO_2$		26.36
III	H		Base		Liquid, bp 127-130° (0.01 mm), n_D^{20} 1.5525	4.12		$C_{21}H_{25}NO_2$	4.33	
			Hydrochloride	82	205-6 (alcohol-ether)	3.61	9.84	$C_{21}H_{25}NO_2 \cdot HCl$	3.89	9.85
			Methyl iodide	71	155-6 (alcohol-ether)		27.59	$C_{22}H_{28}INO_2$		27.27
IV	H		Base		Liquid, bp 143-147° (0.05 mm), n_D^{20} 1.5514	4.39		$C_{21}H_{25}NO_2$	4.33	
			Hydrochloride	75	154-5 (alcohol-ether)		9.86	$C_{21}H_{25}NO_2 \cdot HCl$	3.89	9.85
			Methyl iodide	41	177-8 (alcohol-ether)		27.62	$C_{22}H_{28}INO_2$		27.27
V	OH	$CH_2CH_2N(CH_3)(tert.\text{-}C_4H_9)$	Base		91-2 (n-pentane)	4.52, 4.49		$C_{21}H_{27}NO_3$	4.10	
			Hydrochloride	53	180-1 (alcohol)		9.14, 9.18	$C_{21}H_{27}NO_3 \cdot HCl$		9.39
			Methyl iodide	65	169-70 (alcohol-ether)		26.77, 26.65	$C_{22}H_{30}INO_3$		26.25
VI	OH	$CH_2CH_2N(C_2H_6)(tert.\text{-}C_4H_9)$	Base		Liquid					
			Hydrochloride	41	168-9 (alcohol)		8.95, 8.92	$C_{22}H_{29}NO_3 \cdot HCl$		9.05
			Methyl iodide	24	140-1 (dichlorethane)		25.78, 25.81	$C_{23}H_{32}INO_3$		25.51
VII	OH		Base		83-9 (n-pentane)	4.20, 4.13		$C_{21}H_{25}NO_3$	4.13	
			Hydrochloride	51	190-1 (alcohol-ether)		9.23	$C_{21}H_{25}NO_3 \cdot HCl$		9.43
			Methyl iodide	72	129-30 (alcohol-ether)		25.68	$C_{22}H_{28}INO_3$		26.36
VIII	OH		Base		92-3 (n-pentane)	4.33, 4.41		$C_{21}H_{25}NO_3$	4.13	
			Hydrochloride	48	174-6 (alcohol-ether)		9.65	$C_{21}H_{25}NO_3 \cdot HCl$		9.43
			Methyl iodide	70	200-2 (alcohol-ether)		25.70	$C_{22}H_{28}INO_3$		26.36

Hydrochlorides of the Aminoalkyl Esters of Diphenylacetic Acid (Ib, IIb, IIIb, and IVb). To a solution of 0.028 mole of diphenylacetyl chloride in 7 ml of chloroform at 15-20° 0.03 mole of the aminoalcohol in 5 ml of chloroform was added dropwise. The mixture was boiled for 1 h and the chloroform was distilled off. The residue was shaken with 30 ml of a 20% solution of sodium carbonate. The aminoester base which separated was extracted with ether. The small amount of unreacted aminoalcohol was removed by washing the extract three times with water, and then the aminoester base extracted with 10% hydrochloric acid (3 × 10 ml). The aqueous acidic extract was made alkaline with potassium carbonate, the aminoester base was extracted with ether, the ether extract was dried with anhydrous potassium carbonate and acidified with an alcoholic solution of hydrogen chloride. The precipitate of the aminoester hydrochloric was filtered off, washed with ether, and recrystallized from a suitable solvent.

Hydrochlorides of the Aminoalkyl Esters of Benzilic Acid (Vb, VIb, VIIb, and VIIIb). These were prepared from the methyl ester of benzilic acid and the appropriate aminoalcohol by a method previously described by one of us (method B) [7].

The free aminoester bases were obtained from their hydrochlorides by the usual method. The methyl iodides were prepared by the action of a 3-4 times excess of methyl iodide on the aminoester base in one or other solvent at room or at higher temperature. Compounds IIIb, IVc, VIIc, and VIIIc were prepared by the reaction of the reagents in ether at room temperature for 2 days, compounds Ic and Vc – in acetone at boiling points for 6 h, compounds IIc and VIc – in dimethylformamide at 50° (in a sealed tube) for 20 h.

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