可逆性胆碱酯酶抑制剂二甲氨基甲酸-[3-(烷氨基)烷氧基-4(5)-叔丁基]苯酯的合成

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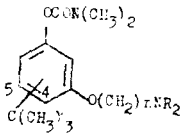
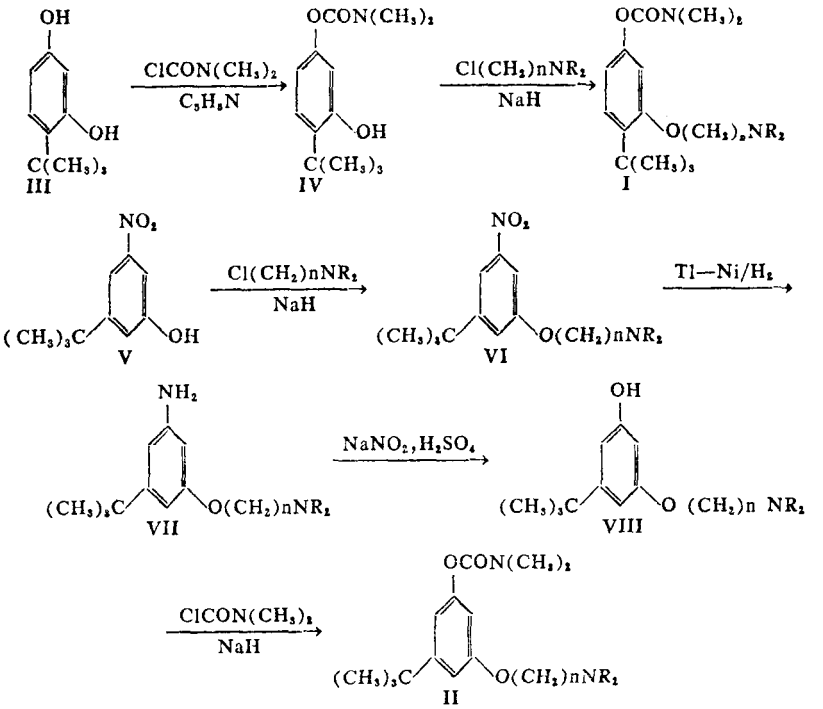
在催醒安的邻位和对位异构体及其同系物的苯环上引入烷基后，可以增强抑制胆碱酯酶的活性[1,2]，我们乃进一步在催醒安及其同系物的苯环不同位置上引入叔丁基，合成了一系列二甲氨基甲酸-[3-(烷氨基)烷氧基-4(5)-叔丁基]苯酯($I_{1\sim13}$和$II_{1\sim5}$)(表2)，以探索对活性的影响。



I=4-substituted
II=5-substituted

Structures of the compounds synthesized

化合物$I_{1\sim13}$和$II_{1\sim5}$均为未知化合物。其合成路线如下：



Scheme 1. Route of synthesis

中间体IV参照前报[1]方法制备，所得产物经元素分析和质谱测定，符合单酯化产品，但

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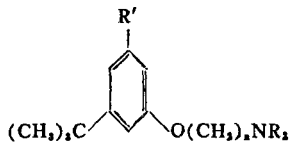
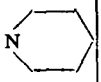
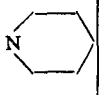
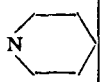
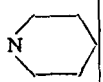
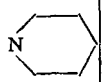
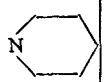
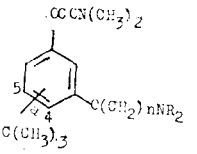
Tab 1. 3-(Alkylamino) alkoxy-5-t-butyl-1-substituted benzenes

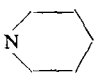
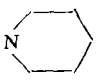
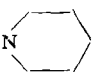
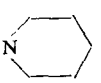


Compd	R′	n	NR_2	BP °C/kP$_a$(mm) and/or MP °C(Solvent)	Yield (%)	Formula[a]	MS m/z(M^+)
VI_1	NO_2	2	$N(CH_3)_2$	135～140/0.07(0.5) 182～183(EtOH)[b]	73.3	$C_{14}H_{22}N_2O_3 \cdot HCl$	266[d]
VI_2	NO_2	2		152～155/0.005(0.04)	75.7	$C_{16}H_{24}N_2O_3$	292
VI_3	NO_2	2		178～184/0.07(0.5)	83.3	$C_{17}H_{26}N_2O_3$	306
VI_4	NO_2	3		129/0.009(0.07)	75.2	$C_{17}H_{26}N_2O_3$	306
VI_5	NO_2	3		148～151/0.0004(0.003)	96.3	$C_{18}H_{28}N_2O_3$	320
VII_1	NH_2	2	$N(CH_3)_2$	246(EtOH)[b]	84.0[c]	$C_{14}H_{24}N_2O \cdot 2HCl$	236[d]
VII_2	NH_2	2		130～136/0.009(0.07) 66.5～68.5(petr ether 30～60°)	53.2	$C_{16}H_{26}N_2O$	262
VII_3	NH_2	2		160～162/0.01(0.08) (90～91, petr ether 30～60°)	62.1	$C_{17}H_{28}N_2O$	276
VII_4	NH_2	3		129～132/0.0001(0.001) 236～239(EtOH-Et_2O)[b]	81.2	$C_{17}H_{28}N_2O \cdot 2HCl$	276[d]
VII_5	NH_2	3		165～167/0.007(0.05) 236～238(EtOH)[b]	68.4	$C_{18}H_{30}N_2O \cdot 2HCl \cdot \frac{1}{2}H_2O$	290[d]
$VIII_1$	OH	2	$N(CH_3)_2$	116～117, EtOH-petr ether 30～60°	61.4	$C_{14}H_{23}NO_2$	237
$VIII_2$	OH	2		104～105, Me_2CO	65.7	$C_{16}H_{25}NO_2$	263
$VIII_3$	OH	2		132～133.5, Et_2O	72.0	$C_{17}H_{27}NO_2$	277
$VIII_4$	OH	3		122～124, Me_2CO	52.8	$C_{17}H_{27}NO_2$	277
$VIII_5$	OH	3		107～108, petr ether 60～90°	48.5	$C_{18}H_{29}NO_2$	291

a. Analytical results for C, H, and N are within ±0.4% of the calculated values; b. Melting point of hydrochloride salt; c. The yield of compound VII_1 is based on hydrochloride salt, others of VII are based on the correspounding free bases; d. M^+ of free base.

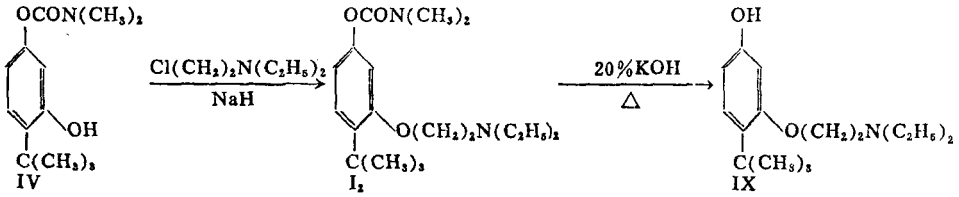
Tab 2. 3-(Alkylamino)alkoxy-4(5)-t-butylphenyl N,N-dimethylcarbamates



Compd[a]	a	n	NR_2	BP °C/kPa(mm) or MP°C	Yield (%)	HCl Salt MP°C[b]	HCl Salt Yield (%)	Formula[c]	Pharmacological results LD_{50} mg/kg(ip)	Pharmacological results pI_{50}
I_1	4	2	$N(CH_3)_2$	145～150/0.007(0.05)	68.0	198～200	95.0	$C_{17}H_{28}N_2O_3 \cdot HCl$	266	<4
I_2	4	2	$N(C_2H_5)_2$	142～145/0.0004(0.003)	81.8	185～187	84.0	$C_{19}H_{32}N_2O_3 \cdot HCl$	147	<4
I_3	4	2	$N(nC_3H_7)_2$	148～150/0.003(0.02)	73.4	170～171	72.6	$C_{21}H_{36}N_2O_3 \cdot HCl$	147	<4
I_4	4	2	$N(iC_3H_7)_2$	134～138/0.005(0.04)	87.7	181～183	56.6	$C_{21}H_{36}N_2O_3 \cdot HCl$	178	6.19
I_5	4	2	$N(nC_4H_9)_2$			123～124	45.6	$C_{25}H_{40}N_2O_3 \cdot HCl$	300	>9
I_6	4	2		78～80[d]	88.7	171～174	57.6	$C_{19}H_{30}N_2O_3 \cdot HCl$	147	<4
I_7	4	2		142～143/0.005(0.04)	74.2	171.5～172	87.9	$C_{20}H_{32}N_2O_3 \cdot HCl$	46.4	4.51
I_8	4	2				205	68.0	$C_{27}H_{44}N_2O_3 \cdot HCl$		
I_9	4	3	$N(CH_3)_2$	167～168/0.007(0.05)	60.3	161.5～163	84.6	$C_{18}H_{30}N_2O_3 \cdot HCl$	147	6.7
I_{10}	4	3		178～179/0.01(0.08)	71.4	155.5～156.5	74.5	$C_{20}H_{32}N_2O_3 \cdot HCl$	147	7.0
I_{11}	4	3		162～166/0.008(0.06)	82.4	183～185	79.1	$C_{21}H_{34}N_2O_3 \cdot HCl$	147	4
I_{12}	4	3	$N(C_2H_5)_2$	176～183/0.004(0.03)	83.1	152～153.5	77.2	$C_{20}H_{34}N_2O_3 \cdot HCl$	147	<4
I_{13}	4	3	$N(nC_3H_7)_2$	168～170/0.007(0.05)	60.2	119.5～120	65.5	$C_{22}H_{38}N_2O_3 \cdot HCl$	82.5	4.24
II_1	5	2	$N(CH_3)_2$			190～192	70.8	$C_{17}H_{28}N_2O_3 \cdot HCl$	215	4.9
II_2	5	2				176～178	66.2	$C_{19}H_{30}N_2O_3 \cdot HCl$	82.5	5.3
II_3	5	2				179～181	75.3	$C_{20}H_{32}N_2O_3 \cdot HCl$	56.2	5.4
II_4	5	3				167～168	50.4	$C_{20}H_{32}N_2O_3 \cdot HCl$	68.1	5.2
II_5	5	3				173～175	54.4	$C_{21}H_{34}N_2O_3 \cdot HCl$	68.1	6.05
3-(2-dimethylamino) ethoxyphenyl N, N-dimethylcarbamate									48	6.82

a. MS, IR and ^{1}HNMR of all compounds are consistent with the assigned structures. b. Recryst from EtOH-Et_2O c. Analytical results for C, H and N are within ±0.4% of the calculated values, except C of I_{11} which was found to be 62.76%. d. Recryst from 95% EtOH

核磁共振谱不能确定其结构为中间体 IV。我们乃将所得单酯化合物先与二乙氨基氯乙烷进行醚化生成化合物 I_2，再经水解，所得产物 IX 的熔点为 106.5～107.5℃（60～90℃石油醚重结晶）与文献[3]定位合成的完全一致，从而确定了单酯化合物即为中间体 IV。



所有化合物分别经孙长荣和马秀英等进行了初步药理评选。发现引入叔丁基后多数化合物的毒性和抑酶活性均有所下降；大多数化合物 I 经口服给药预防小鼠有机磷化合物中毒的效价明显增强。

实 验 部 分

物理常数均未校正。红外光谱仪用岛津 IR-408 型，KBr 压片。核磁共振仪用 JEOL-JNM-PMX 60 S_1 型，$CDCl_3$为溶剂，TMS为内标。质谱仪用 MAT-711型。

二甲氨基甲酸-(3-羟基-4-叔丁基)苯酯(IV)

取-4-叔丁基间苯二酚溶于苯中，在吡啶为去酸剂条件下与二甲胺基甲酰氯反应制备[1]。mp 191～193℃，产率 40.2%。MS m/z 237 (M^+)。IRcm^{-1} 3320，1690，1395，1370。元素分析 $C_{13}H_{19}NO_3$，计算值%C 65.80，H 8.07，N 5.90；实测值 %C 65.91，H 8.16，N 5.88。

5-硝基-3-(烷氨基)烷氧基叔丁基苯(VI)

取 5-硝基-3-叔丁基苯酚 (V)[4,5]溶于甲苯中，加入等摩尔的 80%NaH，搅拌回流1.5h后，滴加烷氨基氯代烷(与 V 的摩尔比为 1.3:1)，继续回流 2～5 h。用 10% 盐酸溶液提取，以浓氨水碱化酸提取液，乙醚提取，无水 $MgSO_4$干燥，减压蒸馏即得中间体 VI。结果见表 1。

3-(烷氨基)烷氧基-5-叔丁基苯胺(VII)

取中间体 VI 溶于无水乙醇中，加入 Tl-Ni 于常压下室温催化氢化至吸氢量接近于理论值，然后按常法处理即得。结果见表 1。

3-(烷氨基)烷氧基-5-叔丁基苯酚(VIII)

参照文献[5]，将中间体 VII 经重氮化水解制备。结果见表 1。

二甲氨基甲酸-[3-(烷氨基)烷氧基-4-叔丁基]苯酯(I)

以中间体 IV 为原料，仿制备中间体 VI 的方法制取。结果见表 2。

二甲氨基甲酸-[3-(烷氨基)烷氧基-5-叔丁基]苯酯(II)

取相应的中间体 VIII 溶于甲苯中，先与等摩尔的 80%NaH反应 1.5 h，再与过量的二甲氨基甲酰氯反应 2 h。所得游离碱未经蒸馏，直接做成盐酸盐。结果见表 2。

关键词 胆碱酯酶抑制剂；二甲氨基甲酸-[3-(烷氨基)烷氧基-4-叔丁基]苯酯；二甲氨基甲酸-[3-(烷氨基)烷氧基-5-叔丁基]苯酯

致谢 光谱和元素分析由本所金素琴、王好山及本院仪器中心王小琴、金人慈、缪振春、魏同太、贾进山和武力民等同志测定；氢化实验由苏俊和李荣立两位同志帮助完成。

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SYNTHESIS OF 3-(ALKYLAMINO) ALKOXY-4(5)-t-BUTYLPHENYL N, N-DIMETHYLCARBAMATES AS REVERSIBLE CHOLINESTERASE INHIBITORS

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ABSTRACT A series of 3-(dialkylamino) alkoxy-4(5)-t-butylphenyl N, N-dimethylcarbamates(I and II), which are the nuclear alkylated derivatives of 3-(2-dimethylamino) ethoxyphenyl N, N-dimethylcarbamate (CUI XING AN) was prepared as potential anticholinesterase agents. Preliminary screening tests showed that the introduction of t-butyl group in CUI XING AN and its homologs decreased the toxicity and anticholinesterase activity. Compounds of type I have increased protective activity against organophosphorus poisoning.

Key words Cholinesterase inhibitor; 3-(Alkylamino)alkoxy-4-t-butylphenyl N,N-dimethylcarbamates; 3-(Alkylamino)alkoxy-5-t-butylphenyl N,N-dimethylcarbamates