SYNTHESIS OF SUBSTANCES EFFECTING ON C.N.S. IV*

Synthesis and Pharmacological Examination of Some Aminoethers

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Some $R{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}R_1{\cdot}R_2$ type of amino alkylethylether derivatives where the R-radical were phenyl or substituted phenyl or naphthoyl-radical, while the $N{\cdot}R_1{\cdot}R_2$ meant diethylamino-pirrolidino-, morpholino-, piperidino-radical were prepared with routine techniques. A few quaternary derivatives have been also prepared from this compounds. Examining the pharmacological activities the tertiary compounds showed antiadrenalitic activity, among the quaternary derivatives however, highly active ganglioplegic compound could be noted.

Previously the correlation of pharmacological effect and chemical structure was treated concerning the different substituted carbonic ester [1—3], tertiary aminoaryl-propene and propane [4], aryl-aminothioether and sufoxide [5], acidamides [6] etc. Some drugs had been selected from these groups and their pharmacological introduction is under way *(Gedeon Richter Pharmacological Works, Budapest)*. The antiadrenaline effect of the aminoethylphenylethers [7], "as well known" has been earlier examined. The aim of our earlier examinations was to see, the effect of the exchange in the ether oxygen to sulphur causes [5]. It was noted that the tertiary amino-ethyl-aryl-thioethers become adrenaline mobilisers and ganglion excitators. So this isoster exchange proves a significant change of pharmacological properties. The first effective and in the medical practice still used aminoether derivatives was produced by FOURNEAU [7]. Later investigating systematically this group numerous compounds were demonstrated possessing antihistamine and nicotine-like effect. [7, 8] Efforts were made to contribute to some new details to the problem.

The general formulae of the compounds synthetized:

$$XAr{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}R_1{\cdot}R_2$$

The synthesis of this group could be realized merely in several steps. The synthesis of halogen ethylaryl-ethers started from phenols was determined by WOHL and BERTHOLD [9] with dihalogenethane and the halogen-ethylarylether obtained could

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be connected with various secondary basis and so the above mentioned group can be reached.

$$ArOH + X.(CH_2)_2.X \xrightarrow{NaOH} Ar.O.(CH_2)_2.X$$

X = halogen atom

The disadvantage of this synthesis is that it may easily result diarylethylether.

However with PERKIN's [10] method the chlorethyl-group yields better results with alcohols and phenols. In this method β-chlorethyl-p-toluene-sulfonic acidesters are employed for the intake of the chlorethyl-group:

$$Ar.OH + H_3C.C_6H_4.SO_2.CH_2.CH_2.Cl$$
$$\downarrow NaOH$$
$$Ar.O.CH_2.CH_2.Cl + H_3C.C_6H_4.SO_2.OH$$

The method is mainly used to prepare naphthoyl ethers.

KIRNER [11] synthetized the β-chlorethyl-phenolethers in two steps. The phenyl-ethanol-ether is formed first at the reaction taking place between the phenol and ethylenechlorhydrine in alkalic solution:

$$ArOH + Cl.CH_2.CH_2.OH$$
$$\downarrow NaOH$$
$$Ar.O.CH_2.CH_2OH + HCl$$

which can be transformed into β-chlorethylphenyl-ether with thionyl-chloride:

$$Ar.O.CH_2.CH_2.OH$$
$$\downarrow SOCl_2$$
$$Ar.O.CH_2.CH_2.Cl$$

Aryl-thioether may be also obtained with this method [12].

The halogenethylphenyl-ether was reacted, with the excess of secondary amines (piperidine, pirrolidine, morpholine, ethylamine) in dry pyridine.

$$Ar.O.CH_2.CH_2.Cl + 2HN.R_1.R_2$$
$$\downarrow$$
$$Ar.O.CH_2.CH_2.N.R_1.R_2 + HCl.HN.R_1.R_2$$

After having the hydrochlorides of the above mentioned substances reacted with calculated amount of alcoholic hydrochloric acid and the methoiodides with methyl-iodide in ethanol.

$$Ar.O.CH_2.CH_2.N.R_1.R_2 \xrightarrow[CH_3J]{HCl} \begin{cases} Ar.O.CH_2.CH_2.N.R_1.R_2.HCl \\ Ar.O.CH_2.CH_2.\overset{(+)}{N}.R_1.R_2]\,J^{(-)} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\quad CH_3 \end{cases}$$

Experimental

β-hydroxyethylphenyl-ether (11)

17 gr of NaOH is solved in 20 ml of water and added to 30 gr of phenol. It is heated in water-bath and 24,4 gr ethylenechlorohydrine is added slowly stirring and constantly heating it for 10 minutes, than cool it. It results two phases, the water phase is separated from the oil and extracted with ether. Combine the upper phase and the ether extracts, washed 3—4 times with 20 ml of water and the etheric solution is dried (Na_2SO_4). After a while the solvent is distilled, the residue is fractionated.

Bp.: 128—130 °C/20 mm.

Yield: 84%.

β-chloroethyl-phenylether (11)

30 gr of pyridine is added to 35 gr of β-hydroxyethyl-phenylether and slowly dropwise 30 ml of fresh distilled thionylchloride added (in the caseof rapid reaction is cooled in ice), heat it in water bath for a short while thereafter cool it then pour it into ice cold water whereupon the product is crystallized. After filtering it is washed with water, diluted $NaHCO_3$ solution and is solved in ether. The ether is dried (Na_2SO_4), filtered and finally distilled. The oil-like residue is fractionated.

Bp.: 217—220 °C.

Bp.: 122—123 °C/26 mm.

Mp.: 27—28 °C.

Yield: 88%.

β-bromoethylphenyl-ether (9)

14 gr of phenol is mixed with 15 ml of dibromoethane and 50 ml of water is added to it. Refluxed for a time in oil-bath at 100—105 °C constantly stirring it. 4 ml (4 N) of NaOH solution is slowly dropped into it. Filtering it in hot condition and let it cool. Two layers are formed following the cooling. The oil-layer is separeted and the aqueous part is repeatedly extracted with ether. The oil-phase and the ether extract are combined washed with diluted NaOH. Drying (Na_2SO_4), the filtrate distilled and the residue is fractionated.

Bp.: 114—117 C/10 mm.

Yield: 59%.

β-chloroethylphenylether (10)

38 gr of phenol, 17 gr of NaOH solved in 30 ml of water adding to this 94 gr of β-chloroethyl-p-toluenesulfuric acidester is heated in water bath for 2—3 hours constantly stirring. Turning it into basic with potash following steam distillation it an agreeable smelling distillate is obtained. (During the steam-distillation 1—2 gr of diphenylethylen ether is formed in the cooler.) The oil has been separated, dried (Na_2SO_4) and fractionated.

Bp.: 217—220 °C.

Yield: 90%.

β-bromoethyl-naphthoylether (9)

4 gr of NaOH solved in 50 ml of water is added to 21,6 gr of β-naphthol and 28,2 gr of dibromethane. Stirring it for 24 hours and keeping it refluxed in

oil-bath at 100—110 °C. After cooling two layers are separated. The water phase is extracted as above. The oil phase and the ether extract are combined, dried (Na_2SO_4) and the ether evaporates, the residue is recrystallized from alcohol.

Mp.: 96 °C.

Yield: 40%.

N-piperidino-ethylphenyl-ether

17,03 gr (0,2 M) of piperidine is added to 15,66 gr (0,1 M) of β-chloroethyl-phenylether and reflux it in oil-bath at 150 °C for 30 minutes. Piperidine—HCl is precipitated then filter it, wash with dry benzene. The benzene as well as the unreacted piperidine are distilled and the residue is fractionated in vacuum. (Tabl. II and III show the bp., physical constants and analysis of compounds).

N-pirrolidino-ethylpenylether

14,22 gr (0,2 M) of pirrolidine was added to 15,66 gr (0,1 M) of β-chloroethyl-phenyl-ether. It was refluxed in oil bath at 140 °C for 1 hour. It results a jelly-like precipitate of pirrolidine-HCl. The pirrolidine-HCl and the unreacted pirrolidine is washed with water as well as diluted potash. The fluid is three times extracted with ether, dried (Na_2SO_4), then the solvent is evaporated. The residue is fractionated. (Tabl. II and III).

N-morpholinoethylphenyl-ether

17,43 gr (0,2 M) of morpholine is added to 15,66 gr (0,1 M) of β-chloroethyl-phenyl ether. Keeping refluxed in oil-bath at 170—175 °C for 1 hour. After cooling morpholine-HCl crystals are precipitated filter it and washed with dry benzene. The residue after evaporation is fractionated. (Tabl. II and III).

N-diethylaminoethyl-phenylether

21,74 gr (0,3 M) of diethylamine is added to 15,66 gr (0,1 M) of β-chloroethyl-phenylether. It is refluxed in oil-bath at 150 °C for 3—4 hours. The rest of the procedure is followed as above (Tabl. II and III).

2,4-dichlorophenyl-β-hydroxy-ethylether

82 gr of 2,4-dichlorophenol is solved in 200 gr 10% of NaOH and add 47 gr of ethylenechlorohydrine refluxed it for 12 hours. After cooling it is extracted with ether and the extract is washed with 5% NaOH solution. The ether is evaporated and the oil like residue is fractionated.

Bp.: 158—160 °C/11 mm.

Mp.: 57—58 °C.

Yield: 42,8%.

2,4-dichlorophenyl-β-chloroethylether

46 gr of PCl_5 is added to 44,5 gr of 2,4-dichlorophenyl-β-hydroxyphenyl-ether and heated over asbestos. The reaction rapidly occurs. The by-product is distilled and oil-like residue is fractionated.

Bp.: 126—127 °C/8 mm.

Yield: 63,58%.

2,4-dichlorophenyl-β-bromo-ethylether. (13)

326 gr (2 M) of 2,4-dichlorophenol, 470 gr of dibromoethane and 1 l of distilled water are put in a 3-necked flask of 3 l contant. It is refluxed with constant stirring while 8 gr (2,1 M) of NaOH solution is beeing added for 1 hour. After cooling the two phases are separated and the upper one is washed, dried (Na_2SO_4), filtered and fractionated.

Bp.: 157—159 °C/10 mm.
Yield: 69%.

N-piperidino-ethyl-2,4-dichlorophenylether

10 gr of β-bromoethyl-2,4-dichlorophenylether is added to 6,7 gr of piperidine solved in 20 ml of dry benzene and refluxed 50 minutes. After cooling is filtered and washed with benzene. The solvent is distilled and the oily residue is fractionated. (Tabl. II and III).

N-diethylaminoethyl-2,4-dichlorophenylether

9,5 gr of diethylamine is added to 15 gr of β-bromoethyl-2,4-dichlorophenylether and refluxed at 150 °C for 3 hours. After cooling it is filtered, the precipitate is washed with benzene. The solvent is distilled and from the residue results in hydrochloride with alcoholic HCl.

p-toluene sulfonic acid chloride is prepared with the method described by VOGEL. [14].

β-chloroethyl-p-toluene sulfonic acidester (10)

95 gr of *p*-toluenesulfonic acidchloride with 100 gr of ethylenechlorohydrine is refluxed 155—160 °C (HCl gas is formed) for about 2—3 hours. The excess of ethylenechlorohydrine is distilled (over 60 gr) in vacuum. The residue is alkalized with diluted excess of NaOH and extracted with benzene. The combined extract is dried (K_2CO_3), filtered and distilled. The residue is fractionated.

Bp.: 210 °C/21 mm.
Bp.: 155—157 °C/3 mm.
Yield: 87%.

β-chloroethyl-β-naphthylether (10)

8 gr of NaOH and 47 gr of β-chloroethyl p-toluene sulfonic acid ester sold in 14 ml of water are added to 30 gr of β-naphthol. It is stirred and heated in steam-bath for 1 hour. The product is solidified while cooled, then ground and dried in an exsiccator over potash. The by- product β-naphthylether can be spearated by petroleum ether extraction. Having concentrated the petroleum ether extract the expected material is crystallized in plate forms.

Mp.: 83 °C.
Yield: 75%.

β-chloroethyl α-naphthyl-ether. (10)

It is produced like the β-chloroethyl-β-naphthylether.
Mp.: 28 °C.
Bp.: 202 °C/16 mm.
Bp.: 172—175 °C/3 mm.
Yield: 51%.

β-piperidinoethyl-α-naphthylether

17,03 gr (0,2 M) of piperidine is added to 20,67 gr (0,1 M) of β-chloroethyl-α-naphthylether. It is kept at 150—160 °C for 1 hour. The precipitate is filtered, washed with benzene and dried (Na_2SO_4). The solvent is distilled and the residue is fractioneted.
(Tabl. II and III).

β-pirrolidinoethyl-α-naphthylether

14,22 gr (0,2 M) of pirrolidine is added to 20,67 gr (0,1 M) of β-chloroethyl-α naphthylether. Refluxed at 140 °C for 2 hours. After cooling the precipitate is filtered, washed with benzene and the solvent evaporated and the residue is fractionated (Tabl. II and III).

β-piperidinoethyl-β-naphthylether

20,67 gr (0,1 M) of β-chloroethyl-β-naphthylether is solved in 17,03 gr (0,2 M) of piperidine. The solution is kept in oil bath at 150 °C for 0,5 hour. After cooling a praecipitate is obtanied, it is filtered and washed with benzene. The solvent is distilled and the residue is fractioned. (Tabl. II and III).

β-pirrolidino-ethyl-β-naphthylether

It was produced similarly to the afore said method.

Preparation of hydrochlorides

The basis is solved in absolute ethanol or ether and reacted with calculated amount of ethanolic and etheric hydrochloric acid.

Preparation of methoiodides

The basis is solved in abs. ethanol and reacted with the calculated amount of methyliodide.
Keeping it for a couple of days at room temperature the quaterner compounds are precipitated. Filtered it and recrystallized from dry ethanol.
They are light sensitive.

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Table I (Pharmacological effect)

Basis	Tertiary (HCl)	Quaternary methoiodide
$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	antiadrenalinic effect (100)	slight ganglion excitator
$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8$	antiadrenalinic effect (50)	—
$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8{\cdot}O$	antiadrenalinic effect (10)	somewhat nicotine-like effect
$C_6H_3Cl_2{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	antiadrenalinic effect (20)	slight ganglioplegic
$C_6H_3{\cdot}Cl_2{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_{10}$	antiadrenalinic effect (30)	—
$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_{10}$	antiadrenalinic effect (100)	—
α-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	slight antiadrenalinic effect	slight ganglioplegic
α-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8$	adrenaline mobilizer	slight ganglioplegic
β-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	no effect on adrenaline	strong ganglioplegic (3×TEA)
β-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8$	no effect on adrenaline	ganglioplegic (1×TEA)
$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}\overset{(+)}{N}{\cdot}C_5H_{10}{\cdot}\overset{(-)}{J}$ $CH_2C_6H_5$	—	strong ganglioplegic (3×TEA)

Table III

Number	Tertiary hydrochloride								
	Mp. °C	Calculated %				Found %			
		C	H	N	$Cl^{(-)}$	C	H	N	$Cl^{(-)}$
1	175	64,67	8,38	5,79	14,67	64,75	8,32	5,67	14,49
2	154	50,27	7,97	6,15	15,57	50,13	7,88	5,94	15,39
3	189	59,13	7,03	5,75	14,55	59,27	7,20	5,62	14,47
4	145	62,72	8,82	6,10	15,43	62,50	8,77	6,05	15,30
5	172	50,04	5,85	4,51	11,32	50,25	5,93	4,70	11,20
6	134	48,40	6,07	4,96	12,00	48,72	6,21	4,79	12,31
7	175	61,60	7,62	4,79	12,12	61,45	7,63	4,77	12,10
8	152	69,17	7,26	5,04	12,76	69,38	7,20	5,03	12,65
9	209	61,60	7,62	4,79	12,12	61,62	7,55	4,81	12,02
10	208	69,17	7,26	5,04	12,76	69,40	7,15	5,00	12,70

Table II

Number	Basis	Summary form	Mol. wt.	Bp. °C/Hgmm	n_D^t	Yield
1.	$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	$C_{13}H_{19}ON$	205,29	131/1	$1{,}5280^{25}$	75
2.	$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8$	$C_{12}H_{17}ON$	191,27	114/1	$1{,}5270^{25}$	68
3.	$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8{\cdot}O$	$C_{12}H_{17}O_2N$	207,26	146/4	$1{,}5320^{25}$	73
4.	$C_6H_5{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_{10}$	$C_{12}H_{19}ON$	193,29	131/5	—	32
5.	$C_6H_3{\cdot}Cl_2{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	$C_{13}H_{17}ONCl_2$	274,14	146/2,5	—	62
6.	$C_6H_3{\cdot}Cl_2{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_{10}$	$C_{12}H_{17}ONCl_2$	262,19	—	—	—
7.	α-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	$C_{17}H_{21}ON$	255,35	120/2—3	—	52
8.	α-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_8$	$C_{16}H_{19}ON$	241,32	116/3	—	48
9.	β-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_5H_{10}$	$C_{17}H_{21}ON$	255,35	150—160/3—4	—	51
10.	β-$C_{10}H_7{\cdot}O{\cdot}(CH_2)_2{\cdot}N{\cdot}C_4H_{10}$	$C_{16}H_{19}ON$	241,32	140—145/3	—	51

(continued)

Number	Quaternary methoiodide								
	Mp. °C	Calculated %				Found %			
		C	H	N	J(−)	C	H	N	J(−)
1	130	48,45	6,39	4,03	36,54	48,72	6,25	4.02	36,17
2	—	—	—	—	—	—	—	—	—
3	105	44,70	5,80	4,01	36,33	44,87	5,85	4,22	36,01
4	—	—	—	—	—	—	—	—	—
5	165	—	—	—	31,92	—	—	—	31,40
6	—	—	—	—	—	—	—	—	—
7	132	54,42	6,09	3,53	31,95	54,70	6,00	3,39	31,62
8	125	53,27	5,79	3,66	33,11	53,22	5,77	3,58	32,89
9	152	54,42	6,09	3,58	31,95	54,67	6,23	3,47	31,55
10	124	53,27	5,79	3,66	33,11	53,22	5,66	3,62	32,97

ИЗУЧЕНИЕ ДЕЙСТВИЯ МЕЖДУ ФИЗИОЛОГИЧЕСКИМИ И ХИМИЧЕСКИМИ СТРОЕНИЯМИ ВЕЩЕСТВ, ДЕЙСТВУЮЩИХ НА ЦЕНТРАЛЬНЫЙ НЕРВНЫЙ МОЗГ. IV

Синтез терциераминовых ациламидов

Ш. Фёльдеак, Й. Цомдош, Б. Маткович и Й. Порсас

Уже известными способами была изготовлена несколько $P \cdot O \cdot (CH_2)_2$, $ИР_1P_2$, производных типа аминоалкил — этилового эфира, где радикал P являлся замещённым фениловым нафтиловым радикалом. $ИР_1P_2$ = Диетиламино- пиперидино-, пипеолидино-, или морфолиновым основаниям.

Из этих соединений было изготовлено несколько кватернерных производных.

Рассматривая их фармакологическую активиость, установилось, что терциерные соединения обладали активностью антиадреналина. Между кватернических производными же встречались очень активные блокирующие ганглиона.

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