

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

Synthesis and Pharmacological Examination of Some Aminoethers

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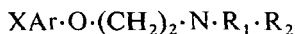
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Some $R \cdot O \cdot (CH_2)_2 \cdot N \cdot R_1 \cdot R_2$ type of amino alkylether derivatives where the R-radical were phenyl or substituted phenyl or naphthoyl-radical, while the $N \cdot R_1 \cdot R_2$ meant diethylamino-pyrrolidino-, morpholino-, 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 antiadrenalic 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.

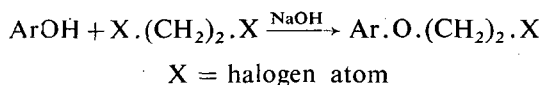
The general formulae of the compounds synthesized:



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

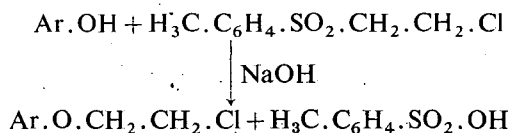
* Previously entitled: An Investigation of the Connection between Physiological Activity and Chemical Structure of New Drugs Acting on the Central Nervous System. (Central Nervous System = C. N. S.)

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



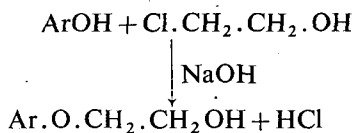
The disadvantage of this synthesis is that it may easily result diarylethylether.

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

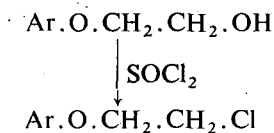


The method is mainly used to prepare naphthoyl ethers.

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

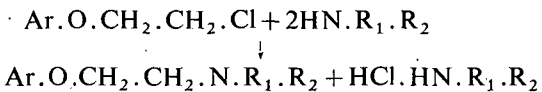


which can be transformed into β -chloroethylphenyl-ether with thionyl-chloride:

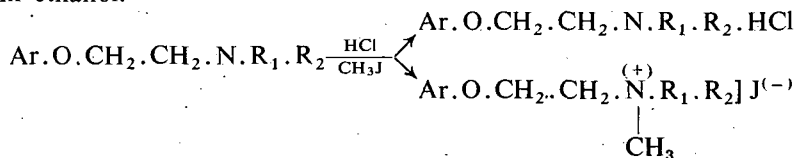


Aryl-thioether may be also obtained with this method [12].

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



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



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 case of 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 separated 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 dibromomethane. 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 -chloroethylphenylether 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-ethylphenylether

14,22 gr (0,2 M) of pirrolidine was added to 15,66 gr (0,1 M) of β -chloroethylphenyl-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 -chloroethylphenyl 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 -chloroethylphenylether. 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 -hydroxyphenylether 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 content. It is refluxed with constant stirring while 8 gr (2,1 M) of NaOH solution is being 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 separated 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 (Na₂SO₄). The solvent is distilled and the residue is fractionated.

(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 obtained, it is filtered and washed with benzene. The solvent is distilled and the residue is fractionated. (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 methiodides

The basis is solved in abs. ethanol and reacted with the calculated amount of methyl iodide.

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.

* * *

The authors wish to express their thanks to J. FÜLÖP, technician, for the analyses carried out in the Analytical Section of our Institute as well as to *Gedeon Richter Pharmaceutical Works, Budapest* for their kind support.

Table I (Pharmacological effect)

| Basis | Tertiary (HCl) | Quaternary methiodide |
|--|-------------------------------|-------------------------------|
| $C_6H_5 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10}$ | 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) | — |
| $\alpha\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10}$ | slight antiadrenalinic effect | slight ganglioplegic |
| $\alpha\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_4H_8$ | adrenaline mobilizer | slight ganglioplegic |
| $\beta\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10}$ | no effect on adrenaline | strong ganglioplegic (3×TEA) |
| $\beta\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_4H_8$ | no effect on adrenaline | ganglioplegic (1×TEA) |
| $C_6H_5 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10} \cdot J$ (+) (-) $CH_2C_6H_5$ | — | 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. | $\alpha\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10}$ | $C_{17}H_{21}ON$ | 255,35 | 120/2—3 | — | 52 |
| 8. | $\alpha\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_4H_8$ | $C_{16}H_{19}ON$ | 241,32 | 116/3 | — | 48 |
| 9. | $\beta\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_5H_{10}$ | $C_{17}H_{21}ON$ | 255,35 | 150—160/3—4 | — | 51 |
| 10. | $\beta\text{-}C_{10}H_7 \cdot O \cdot (CH_2)_2 \cdot N \cdot C_4H_{10}$ | $C_{16}H_{19}ON$ | 241,32 | 140—145/3 | — | 51 |

(continued)

| Number | Quaternary methiodide | | | | | | | | |
|--------|-----------------------|--------------|------|------|-------|---------|------|------|-------|
| | 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. Фельдеак, Й. Цомдош, Б. Маткович и Й. Порсас

Уже известными способами была изготовлена несколько $P \cdot O \cdot (CH_2)_2$, IP_1P_2 , производных типа аминовалкил — этилового эфира, где радикал P являлся замещённым фениловым нафтиловым радикалом. $IP_1P_2 =$ Диетиламино- пиперидино-, пи-пеолидино-, или морфолиновым основаниям.

Из этих соединений было изготовлено несколько квагернерных производных.

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

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