AN INVESTIGATION OF THE CONNECTION BETWEEN PHYSIOLOGICAL ACTIVITY AND CHEMICAL STRUCTURE OF NEW DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

I. The Synthesis of Some Aminoacetates Containing Cyclic Tertiary Nitrogen Atom

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In the course of our work we have prepared some cyclic tertier-amino-acetic-acid-esters and the short series of their quaterner derivatives in order to subject them to pharmacological investigations.

Especially the effect of the mentioned ester-typed compounds on the central nervous system was examined.

This investigations made clear that from this group of compounds only the N-piperidino acetic acid benzyl-ester had, a slight antinicotinic effect that might be increased, to a little extent, by quaternerization.

The problems of the synthesis and pharmacology of β-amino ketones are recently often treated in literature. One of the authors [1]—[5], has devoted extensive studies to the pharmacology of this group of materials. Several of these compounds possess remarkable antinicotinic action, and some of them are known today as well established pharmaceuticals.

The main object of our investigations has been to find some connection between the physiological action and chemical structure. The possibility of such connection appeared to be all the more probable, since there are some other groups of compounds known besides β-amino ketones which have antinicotinic action. An example of such materials is Parpanit (diethylamino-ethyl ester of l-phenylcyclopentane-l-carboxylic acid), which is effective against spasms caused by nicotine, even when it is applied in very small doses, such as 5 mg/kg. Thus, in the course of our initial efforts, compounds having the general formula of $R\rangle N(CH_2)_nCOOR'$ were synthesized and their physiological action determined. At the same time also some of the „reversed esters", were prepared. (Fig. 1.)

$$R\rangle N(CH_2)_n \cdot COOR' \rightarrow R\rangle N(CH_2)_nO \cdot COR'$$

where R>N represents a piperidino, pyrrolidino or morpholino group, and R′ denotes methyl, ethyl, butyl, benzyl substituents, and n = 1, 2, 3.

A study was made of the influence of the number of methylene groups present on physiological activity, and the optimum methylene chain length was determined.

A short survey of the pharmaceutical use of similar N-piperidino and other secondary amine derivatives may be given as follows:

a) As it has been described earlier, different N-piperidino-β-amino ketones are known as compounds possessing antinicotinic action [1]—[6].

b) Some N-piperidino or other N-cyclic amino carboxylic esters or their amides are local anaesthetics or spasmolytic agents [7], [8], whereas some β-piperidino-benzoates have midriatic action [9].

c) Certain piperidine derivatives have been described as inhibitors of spirochetes.

d) Bis-(3-hydroxy dimethyl piperidinium) bromide ethers have been used as neuromuscular blocking agents [11].

e) Some dialkyl aminoalkyloxy-alkyl piperidines and pyrrolidines have been recommended as blood pressure lovering agents [12].

These few examples may show that a great number of various drugs have been derived from the chemical group of secondary cyclic amines.

During the course of the present investigations short series of cyclic N-substituted acetates have been prepared, and an attempt has been made to trace down the physiological properties of the products.

Our method of synthesis was the following:

The simplest way of preparing N-substituted acetates is the condensation of monochloroacetates with secondary amines [8]. In this way, a whole series of aminoacetic acid derivatives could be prepared:

$$2\,R{>}NH + Cl{\cdot}CH_2COOR' \rightarrow R{>}N{\cdot}CH_2COOR' + R{>}NH{\cdot}HCl$$

R>N = piperidino, pyrrolidino or morpholino groups,

R′ = methyl, ethyl, butyl or benzyl groups.

The experiments involved an investigation of the influence of the nature of the halogen substituent in the $X{\cdot}CH_2COOR'$ aliphatic halogen carboxylic esters on the yield of the final product. When X = I, or Br, or Cl, best yields could be obtained with bromoalkyl carboxylic esters [13]. Decrease of the yield may be explained by the polymerisation of by-products when iodoacetates were used, whereas the sluggish reaction of chloroacetates necessitated more severe reaction conditions producing the same detrimental result on the yield.

For the purpose of identification the picrates and the quaternary derivatives of the N-acetates were always prepared. On the other hand, hydrochlorides were best suitable for pharmacological tests, as a consequence of their solubility in water.

Experimental

A general method of preparing the picrates, quaternary derivatives and hydrochlorides is given as follows:

Picrates were obtained by adding a 5 % picric acid solution in anhydrous ethanol to the material or to its anhydrous alcoholic solution.

Quaternary methiodides were prepared by reacting the materials with the calculated amount of methyl iodide. In several cases the formation of the methiodides failed to occur, mainly due to solubility factors.

The preparation of hydrochlorides was carried out by means of a calculated amount of hydrogen chloride in dry ether solution.

The crystalline products obtained were filtered in all the three cases, they were washed with the appropriate solvent and dried for analysis.

A general description of the preparation of N-cyclic aminoacetic esters is the following: 1 mol. of a chloroacetate was reacted with 2 mol. of the cyclic secondary amine in dry benzene solution, and the formed secondary amine hydrochloride was filtered. If the reaction was too slow, as it was the case especially with morpholino-derivatives, the mixture was refluxed for several hours on the steam bath. The secondary amine hydrochloride was washed with hot anhydrous benzene, the filtrates were combined, and the solvent was evaporated. Finally, the residue was distilled under reduced pressure.

Below are given the empirical formulae, molecular weights, some physical constants and analyses of the compounds prepared.

N-(piperidino) acetic acid methyl ester

$C_8H_{15}O_2N$ · MW: 143,1 · B. p. 69°C at 5 mm.
Calculated C 61,50; H 9,68; N 8,97 %
Found C 61,75; H 9,19; N 8,37 %.
Picrate: $C_{14}H_{18}O_9N_4$. MW: 386,31. M. p. 115°C.
Calculated N 14,51 %. Found N 15,22 %.

N-(piperidinium) acetic acid methyl ester methiodide

$C_9H_{18}O_2NI$ · MW: 285,15 · M. p. 163—164°C.
Calculated C 36,13; H 6,06; N 4,68; I 42,42 %
Found C 36,33; H 6,10; N 4,72; I 42,90 %.
Hydrochloride: $C_8H_{16}O_2NCl$ · MW: 193,66 · M. p. 214°C.

N-(piperidino) acetic acid ethyl ester

$C_9H_{17}O_2N$ · MW: 171,14 · B. p. 68°C at 1 mm.
Calculated C 63,13; H 10,01; N 8,18 %
Found C 63,10; H 10,15; N 8,60 %.
Picrate: $C_{15}H_{20}O_9N_4$ · MW: 400,34 · M. p. 122°C.
Calculated N 13,99 %. Found N 14,30 %.

N-(piperidinium) acetic acid ethyl ester methiodide

$C_{10}H_{20}O_2NI$ · MW: 313,08 · M. p. 160—161°C.
Calculated C 38,35; H 6,44; N 4,47; I 40,53 %
Found C 38,02; H 6,85; N 4,50; I 40,70 %.

Hydrochloride: $C_9H_{18}O_2NCl$ · MW: 207,63 · M. p. 117—117,5°C.

N-(piperidino) acetic acid butyl ester

$C_{11}H_{21}O_2N$ · MW: 185,15 · B. p. 100—101°C at 4 mm.
Calculated C 66,29; H 10,62; N 7,03 %
Found C 66,50; H 9,98; N 6,79 %.

Picrate: $C_{17}H_{24}O_9N_4$ · MW: 428,39 · M. p. 85°C.
Calculated N 13,08 %. Found 13,20 %.

N-(piperidinium) acetic acid butyl ester methiodide

$C_{12}H_{24}O_2NI$ · MW: 341,18 · M. p. 178°C.
Calculated C 42,23; H 7,09; N 4,11; I 37,19 %
Found C 42,51; H 7,49; N 4,20; I 36,38 %.

Hydrocloride: $C_{11}H_{22}O_2NCl$ · MW: 235,74 · M. p. 118°C.

N-(piperidine) acetic acid benzyl ester

$C_{14}H_{19}O_2N$ · MW: 220,14 · B. p. 134—135°C at 1 mm.
Calculated C 72,06; H 8,21; N 6,00 %
Found C 72,15; H 8,30; N 6,25 %.

Picrate: $C_{20}H_{22}O_9N_4$ · MW: 426,41 · M. p. 138°C.
Calculated N 12,12 %. Found 12,81 %.

N-(piperidinium) acetic acid butyl ester methiodide

$C_{15}H_{22}O_2NI$ · MW: 375,20 · M. p. 93°C.
Calculated C 48,10; H 5,87; N 3,73; I 33,59 %
Found C 48,20; H 6,00; N 3,95; I 33,9 %.

Hydrochloride: $C_{14}H_{20}O_2NCl$ · MW: 269,77 · M. p. 133°C.

N-(morpholino) acetic acid methyl ester

$C_7H_{13}O_3N$ · MW: 159,1 · B. p. 77°C at 2 mm.
Calculated C 52,81; H 8,23; N 8,80 %
Found C 59,90; H 8,40; N 9,10 %.

Picrate: $C_{13}H_{16}O_{10}N_4$ · MW: 372,16 · M. p. 143°C.
Calculated N 14,43 %. Found 14,50 %.

N-(morpholinium) acetic acid methyl ester methiodide

$C_8H_{16}O_3NI$ · MW: 301,13 · M. p. 147,5°C.
Calculated C 31,89; H 5,32; N 4,65; I 42,19 %
Found C 32,05; H 5,63; N 5,03; I 42,10 %.
Hydrochloride: $C_7H_{14}O_3NCl$ · MW: 194,63 · M. p. 150,5°C.

N-(morpholino) acetic acid ethyl ester

$C_8H_{15}O_3N$ · MW: 173,12 · B. p. 86—87°C at 4 mm.
Calculated C 55,47; H 8,73; N 7,72
Found C 55,40; H 8,95; N 7,90 %.
Picrate: $C_{14}H_{18}O_{10}N_4$ · MW: 402,14 · M. p. 163°C.
Calculated 13,93 %. Found 14,29 %.

N-(morpholinum) acetic acid ethyl ester methiodide

$C_9H_{18}O_3NI$ MW: 315,07 · M. p. 132—133°C.
Calculated C 36,47; H 6,08; N 4,26; I 38,60 %
Found C 36,70; H 6,20; N 4,55; I 39,10 %.

N-(morpholino) acetic acid butyl ester

$C_{10}H_{19}O_3N$ · MW: 201,15 · B. p. 105,5—106°C at 3 mm.
Calculated C 59,67; H 9,52; N 6,96 %
Found C 59,80; H 9,40; N 6,60 %.
Picrate: $C_{16}H_{21}O_{10}N_4$ · MW: 429,36 · M. p. 118°C.
Calculated N 13,02 %. Found 13,15 %.

N-(morpholinium) acetic acid butyl ester methiodide

$C_{11}H_{22}O_3NI$ · MW: 343,10 · M. p. 95—96°C.
Calculated C 38,48; H 6,46; N 4,08; I 37,00 %
Found C 38,56; H 6,60; N 4,15; I 36,76 %.
Hydrochloride: $C_{10}H_{20}O_3NCl$ · MW: 237,61 · M. p. 128°C.

N-(morpholino) acetic acid benzyl ester

$C_{13}H_{17}O_3N$ · MW: 236,14 · B. p. 164—165°C at 5 mm.
Calculated C 67,74; H 7,68; N 5,62 %
Found C 67,10; H 7,70; N 5,80 %.
Picrate: $C_{19}H_{20}O_{10}N_4$ · MW: 450,14 · M. p. 144°C.
Calculated N 12,12 %. Found 12,73 %.

N-(morpholinium) acetic acid benzyl ester methiodide

$C_{14}H_{20}O_3NI$ · MW: 376,22.

This compound was not formed.

Hydrochloride: $C_{13}H_{18}O_3NCl$ · MW: 268,60 · M. p. 149°C.

N-(pyrrolidino) acetic acid methyl ester

$C_7H_{13}O_2N$ · MW: 157,12 · B. p. 72°C at 8 mm.
Calculated C 53,50; H 8,46; N 8,89 %
Found C 53,70; H 8,50; N 9,05 %.
Picrate: $C_{13}H_{16}O_9N_4$ · MW: 372,29 · M. p. 104°C.
Calculated N 15,05 %. Found N 15,20 %.

N-(pyrrolidinium) acetic acid methyl ester methiodide

$C_8H_{16}O_2NI$ · MW: 285,12 · M. p. 153°C.
Calculated C 33,68; H 5,65; N 4,91; I 44,44 %
Found C 33,80; H 5,70; N 5,10; I 44,60 %.
Hydrochloride: $C_7H_{14}O_2NCl$ · MW: 193,58 it is very hydroscopic.

N-(pyrrolidino) acetic acid ethyl ester

$C_8H_{15}O_2N$ · MW: 157,12 · B. p. 59—60°C at 2 mm.
Calculated C 61,10; H 9,63; N 8,91 %
Found C 61,20; H 9,71; N 9,10 %.
Picrate: $C_{14}H_{18}O_9N_4$ · MW: 386,31 · M. p. 119,5°C.
Calculated N 14,50; Found 14,98 %.

N-(pyrrolidinium) acetic acid ethyl ester methiodide

$C_9H_{18}O_2NI$ · MW: 299,15.

This compound was not formed.

Hydrochloride: $C_8H_{16}O_2NCl$ · MW: 197,59 · M. p. 133°C.

N-(pyrrolidino) acetic acid butyl ester

$C_{10}H_{19}O_2N$ · MW: 185,25 · B. p. 81—82°C/3 mm.
Calculated C 51,07; H 7,9; N 21,54 %
Found C 51,20; H 7,95; N 21,60 %.
Picrate: $C_{16}H_{22}O_9N_4$ · MW: 414,36 · M. p. 109,5°C.
Calculated N 13,52 %. Found 13,88 %.

N-(pyrrolidinium) acetic acid butyl ester methiodide

$C_{11}H_{22}O_2NI$ · MW: 327,20 · M. p. 104°C.
Calculated C 38,08; H 6,98; N 4,44; I 40,31 %
Found C 39,10; H 7,04; N 4,60; I 39,90 %.
Hydrochloride: $C_{10}H_{20}O_2NCl$ · MW: 235,63 it is very hydroscopic.

N-(pyrrolidino) acetic acid benzyl ester

$C_{13}H_{17}O_2N$ · MW: 219,13 · B. p. 134—135°C at 1 mm.
Calculated C 71,22; H 7,94; N 6,31 %
Found C 71,16; H 8,13; N 6,42 %.
Picrate: $C_{19}H_{20}O_9N_4$ · MW: 488,38 · M. p. 159—160°C.
Calculated N 12,21 %. Found 12,50 %.

N-(pyrrolidinium) acetic acid benzyl ester methiodide

$C_{14}H_{20}O_2NI$ · MW: 361,22 · M. p. 156°C.
Calculated C 43,53; H 5,54; N 3,87; I 35,18 %
Found C 43,60; H 5,60; N 3,95; I 35,42 %.
Hydrochloride: $C_{13}H_{18}O_2NCl$ · MW: 270,62 · M. p. 139°C.

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ИССЛЕДОВАНИЕ СВЯЗИ ФАРМАКОЛОГИЧЕСКОГО ЭФФЕКТА И ХИМИЧЕСКОЙ СТРУКТУРЫ В СЛУЧАЕ НОВЫХ ЛЕКАРСТВ, ВЛИЯЮЩИХ ЦЕНТРАЛЬНУЮ НЕРВНУЮ СИСТЕМУ

Б. Матковиц, Ш. Фельдеак и Й. Порсас

В результате работы был получен краткий ряд различных циклических секундерно-аминовых эфиров уксусной кислоты а также их кватернеров, с целью подвергнуть их фармакологическому исследованию.

Цель исследований состоял в первую очередь в наблюдении действия упомянутых соединений типа эфира на центральную нервную систему.

В результате исследований было установлено, что лишь бензиловый эфир пиперидиноо- и пирролидино-уксусной кислоты обладает небольшой антиникотинной активностью. В упомянутых двух случаях действие было повышено б небольшой степени кватернированием.