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

Synthesis of cyclic tertiary aminopropionic esters and "reversed" esters

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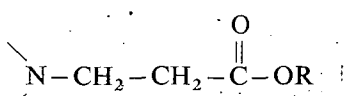
The methly, ethyl, butyl and benzyl esters of piperidine, pyrrolidine and morpholine and their methoiodides have been prepared. The action of these compounds on the central nervous system was examined, and from the results some conclusions were drawn concerning the connection between pharmaceutical effect and chemical structure.

In our previous publication on similar subject (1) we had stated that in experiments with animals tertiary aminoacetates showed nicotin-like action, except for the benzyl ester, which produced in large doses slight anti-nicotinic effects. In our experiments described in the present paper we studied whether anti-nicotinic activity could be increased by lengthening the alkyl chain connecting the carboxyl groups with the tertiary amine.

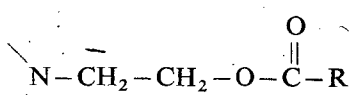
To this end cyclic tertiary aminopropionic esters and so-called "reversed" esters were prepared. By this latter name we mean the esters of tertiary aminoalcohols with aliphatic or aromatic carboxylic acids. Their structure is the following:



R ester of tertiary aminopropionic acid

= piperidine, pyrrolidine morpholine

R = methyl, ethyl, butyl, benzyl

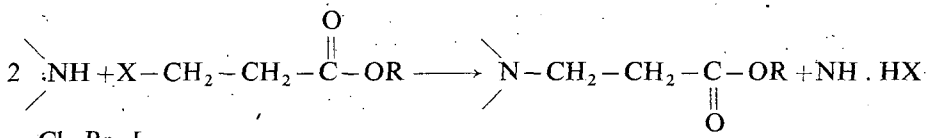


„reversed" ester

= piperidine, pyrrolidine

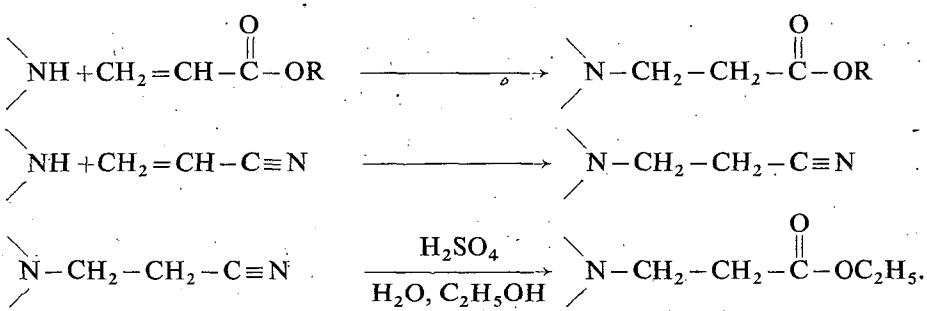
R = phenyl, methyl

For the synthesis of tertiary aminopropionates, first WEDEKIND's (2)method was applied, viz. β-iodopropionates were reacted with the secondary amine in the molar ratio 1:2, in a medium of anhydrous benzene. In our case this method did not give satisfactory yields of the required products. According to our experiments, best yields were obtained by carrying out the condensation with chloro- or bromopropionic esters (3). The reaction scheme is:



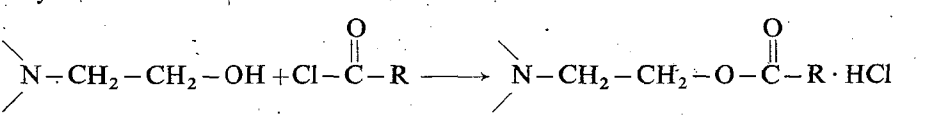
X = Cl, Br, I.

The β-chloropropionates were prepared from chloropropionic acid and the corresponding alcohol (4,5) in the presence of sulphuric acid. This method could not be applied for the preparation of benzyl ester; this synthesis can be achieved by starting with β-chloropropionyl chloride (6). Tertiarisation with acrylates is more limited in scope, however, it gives very good results here: *E. g.*, the reaction of a secondary amine with methyl acrylate in the molar ratio of 1:1, gave an almost quantitative yield of the corresponding tertiary methyl aminopropionate (7). Carrying out this reaction by using acrylonitrile, subsequent saponification gave also very high yields of the tertiary amino-carboxylic acid or, when alcohol and sulphuric acid were used, of the corresponding ester:



Methyl pyrrolidino, piperidino and morpholidinopropionates were prepared by this method, too.

Mention should be made here of the general procedure of synthesizing reversed esters, which were prepared by reacting the corresponding acid chloride with the tertiary aminoethanol:



From among the reversed esters, the piperidino-β-ethyl esters of benzoic acid and of acetic acid have been prepared so far.

The hydrochlorides, picrates — and with a few exceptions — the methoiodides of all the bases have been prepared.

In view of the experimental results obtained so far, the relationship between chemical structure and action exerted on the central nervous system can be summarized as follows:

1. It is known that certain tertiary aminocarbonic esters, besides other advantagoeus therapeutic properties, can hinder nicotinic convulsions even in very small doses. Parpanit (diethylaminoethyl ester of 1-phenylcyclopentane-1-carboxylic acid) belongs to this group. This observation turned our attention to the group of amino esters. In connection with the classes of compounds synthesized by us, the following observations were derived:

a) The methyl, ethyl and butyl esters of piperidinoacetic acid show nicotin-like effect, while benzyl esters have antinicotinic action, when administered in large doses.

b) The same holds true for derivatives of pyrrolidinoacetic acid but their nicotin-like activity is more pronounced.

c) Esters of morpholinoacetic acid have no antinicotinic action. A similar grouping of propionic esters reveal the following observations:

a) With piperidinopropionic esters, nicotin-like effect is decreased when the number of the carbon atoms of the esterifying alcohol is increased a weak antinicotinic action appears in the butyl ester, while the benzyl ester definitely hinders the spasms caused by nicotine.

b) Pyrrolidino derivatives show even stronger nicotin-like activity except for the benzyl ester which even in this series possess antinicotinic action. Preparation of the methoiodides from pyrrolidinoacetic and propionic esters having nicotin-like action increases this effect.

c) In the series of morpholinopropionic esters both effects are practically suspended.

It follows generally from the above mentioned facts that esters containing aliphatic substituents with smaller radical-weight have nicotin-like action while homologous esters with a higher number of carbon atoms and those which contain aromatic substituents show antinicotinic activity. The nature of the tertiary base modifies the effect only partly, while in the case of morpholine the activity in both directions is considerably decreased.

2. In the series of "reversed esters", *e. g.*, with piperidino-β-ethyl benzate, where the "carbonyl" function is in reversed position in comparison with the previous type, of esters, increased antinicotinic action is revealed.

3. Quaternary derivatives of tertiary aminopropionic esters show ganglion-blocking effect running parallel with the appearance of the antinicotinic effect of the bases.

Experimental

β-chloropropionic acid was prepared by the addition of hydrogen chloride to acrylonitrile; the hydrolysis of the product gave β-chloropropionic acid (7, 8). B. p. 150—160° C at 40 mm; M. p. 41° C.

The esters of β-chloropropionic acid were prepared in the usual way of esterification with the corresponding alcohol in the presence of sulphuric acid (4, 5).

For the preparation of the methyl ester, HROMATKA's method (7) was found to be the best: 0,27 mol methyl acrylate was reacted with 0,27 mol piperidine under

cooling and stirring (the time of the addition of piperidine was 25 to 30 min). After complete addition, stirring was continued for 3 hours and the mixture was refluxed on a water-bath over a period of 8 hours. B. p.: 72° C, at 2 mm.

β-chloroethyl benzoate was obtained from ethylene chlorohydrin and benzoylchloride (8). Freshly distilled β-chloroethyl benzoate was added to piperidine in anhydrous benzoene. The reaction was very slow, therefore the mixture had to be refluxed for 2 or 3 hours on a water-bath. After cooling benzene was distilled off and the viscous residual oil was fractionated. B. p.: 141° C, at 2 mm. The hydrochloride was separated from the product in ether solution by a calculated amount of hydrogen chloride dissolved in ether. M. p. 184° C.

Analysis ($C_{14}H_{20}O_2NCl$)	Calculated:	C 62,31	H 7,47	Cl 13,15
	Found:	C 62,21	H 7,53	Cl 13,40%.

Preparation of cyclic amino-propionic esters. All the cyclic aminopropionic esters have been prepared under similar conditions by condensing halocarboxylic esters with secondary amines, therefore the method of preparing all these products is given in the general description below. Data for the products are to be found in Table I (on page 64).

A three-necked flask with ground-glass joints, immersed into ice-water, was equipped with a mechanical stirrer, reflux condenser, carrying a calciumchloride tube and with a dropping funnel. 2 X mol of the freshly distilled anhydrous amine was dissolved in 2,5 mol of anhydrous benzene, and introduced into the flask and 1 X mol halocarboxylic acid dissolved in 2,5 mol of anhydrous benzene was added dropwise through the funnel under constant stirring. After having completed the addition of the halocarboxylic acid solution, stirring was continued for half an hour, meanwhile the temperature was raised by heating the water-bath to attain 70—80° C. Then the mixture was allowed to stand 2 or 3 hours. The precipitate was filtered, washed with some benzene, the combined benzene solutions were dried over anhydrous sodium sulphate, the solvent was evaporated, and the residual oil fractionated. Amine ester hydrochlorides were prepared from the produced tertiary aminoesters in ether solution with the calculated amount of hydrogen chloride dissolved in ether, while quaternary salts were precipitated in anhydrous ethanol solution by means of methyl iodide.

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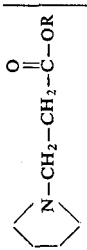
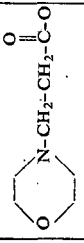
Table I

	R =	Empirical formula	b. p., °C / m. Hg.	Analysis Nitrogen % Calc.	Analysis Nitrogen % Found	Picrate M. p. °C	Picrate Nitrogen % Calc.	Picrate Nitrogen % Found	Metoiodide M. p. °C	Metoiodide Iodine Calc.	Metoiodide Iodine Found	Hydrochloride M. p. °C
	methyl	$C_9H_{17}O_2N$	72/2	8,19	8,30	164	14,00	13,98	147—148	40,07	40,70	189
	ethyl	$C_{10}H_{19}O_2N$	102—103/5	7,56	7,43	131,5	13,52	14,20	—	—	—	169
	butyl	$C_{12}H_{24}O_2N$	124—125/6	6,51	6,76	108—109	12,26	12,10	110	42,43	41,70	164,7
	benzyl	$C_{15}H_{21}O_2N$	149—150/1	5,66	5,89	113	11,49	11,95	—	—	—	193,5
	methyl	$C_8H_{15}O_2N$	76/5	8,91	8,72	147	14,51	14,55	166	42,47	43,10	125
	ethyl	$C_9H_{17}O_2N$	85/6	8,19	8,30	114	14,00	14,30	—	—	—	146
	butyl	$C_{11}H_{21}O_2N$	106—108/5	7,02	7,12	97	13,08	13,38	—	—	—	74—75
	benzyl	$C_{14}H_{19}O_2N$	138—139/1	6,00	5,88	102	12,12	12,54	154	33,96	34,28	152
	methyl	$C_8H_{15}O_3N$	82/2	8,13	8,23	129	13,93	14,12	151	40,32	39,65	203
	ethyl	$C_9H_{17}O_3N$	108/6	7,87	7,94	108	13,52	14,01	—	—	—	188—189
	butyl	$C_{11}H_{21}O_3N$	131—132/6	6,51	6,81	150	12,67	13,05	115	35,57	35,66	173
	benzyl	$C_{14}H_{19}O_3N$	154/1	5,62	5,83	125	11,68	11,73	—	—	—	189—190

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

Б. Маткович, Ш. Фельдеак и И. Порсас

Бензиловые, метильные, этильные и бутильные эфиры и метойодиды приперидино, пирролидино и морфолино — пропионной кислоты были приготовлены. Эффект этих примесей на центральную нервную систему был также исследован. Из результатов авторы делали выводы на связь между химической структурной и фармакологическим эффектом.