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

III. The Synthesis of N-tertiary aminomethylacidamides

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Previously to this paper we had given an account on our synthetic pharmacological investigations carried out mainly on the field of N-tertiary aminoesters, thio ethers, unsaturated and saturated aminopropene derivaties. Since then we have prepared the various substituted derivatives of N-tertiary amino-methly-acid-amides and now we should like to review our syntehtic observations gained on this field.

In the N-tertiary amino-methyl-acid-amid group we could observe that the effect exerted on the central nervous system is mainly due to the structure.

From the N-tertiary amino acid amides, first of all, we prepared derivatives substituted by various halogens on phenyl radicals, and they showed significant differences in action intensity dipending on the position of the halogen substituent.

Besides the various halogen substituted derivatives we prepared benzoxy- and nitro-compounds too.

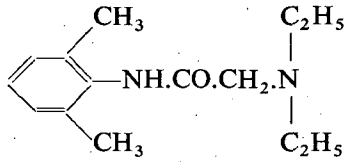
Among the acid amides the para-halophenyl derivatives showed the most intensive antinicotinic activity.

In our earlier works [1—5] we had given a detailed review on the synthesis and pharmacological investigation [2] regarding the different N-tertiary acetic acid (I) and propionic acid-esters [5].

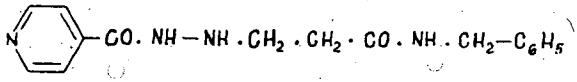
Eliminating the ester structure we examined the antinicotinic activity of the different ethers, thioethers and sulphones [4], as well as the similar effect of N-tertiary aminopropene and propane-derivatives [5].

After preparing and investigating the basic substance (N-piperidino-methyl-benzamide), we presumed that this compoundgroup conceals the synthesis of several substances with intense effect on the central nervous system *(C. N. S.)* [6].

Among the aromatic acid amides some localanestetics and drugs acting on the *C. N. S.* like xylocain, (I) (7) and *Nialamide (Niamide)* (II) (8) *(Chas. Pfizer and Co., Inc.)* had been detected previously to our findings.



(I.)



(II.)

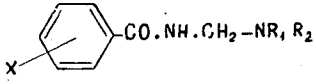
Therefore it was not surprising to detect a valuable sedative group in the acid amides.

In order to study this group more thoroughly we have carried out a series of synthetic investigations.

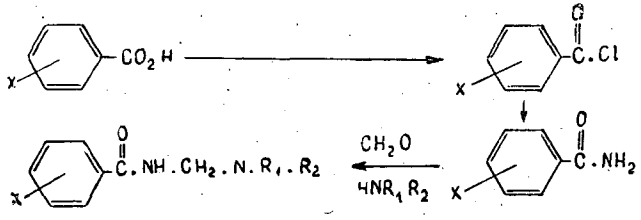
To obtain informations on the effect on the *C. N. S.* we used the examination of the antinicotinic activity [3].

Before discussing the studies on our synthetic work we should like to deal with the MANNICH-typed condensation of aromatic acid amides [9], our aromatic acid amide derivatives having been prepared by this method.

The general formulas of our acidic amides are to be seen below.



At the syntheses first we usually prepared the substituted benzoic acids, from these the adequate acid amides and with the obtained acid amides by MANNICH condensation the N-terciary-amoni-methyl-acidic amides.



Among our acid amides, but above all among the N-tertiary-amino-methyl acidic amides many unkown compounds could be detected [10].

In the following we should like to concern ourselves with the MANNICH-typed condensation of acid amides. The first investigation with acid amides were carried out by EINHORN, and in his first publication on this subject he described a number of aminomethylated products of acid amides. He illustrated the proceeding reac-

tion by the folloxing equation:

$$R_2 \cdot R_1 \cdot NH + CH_2O + H_2N{-}\overset{\overset{O}{\|}}{C}{-}R \rightarrow R_2R_1 \cdot N \cdot CH_2{-}NH \cdot \overset{\overset{O}{\|}}{C} \cdot R$$

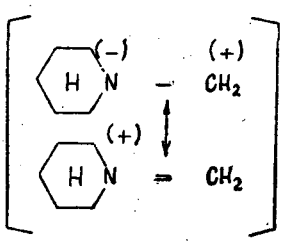
Later LIEBERMAN and WAGNER [12] as well as HELMANN and OPITZ [9] had been studying the mechanism of the MANNICH reaction [13], and they claimed that formaldehyde reacted first with resulting secundery amine components and oximethylamine losing water when propionated, and then transformed to a mezomer carbenium-imonium-ion.

This transformation was expected to be the primary agent of the MANNICH reaction, forming a nucleophyl reaction with an electrophyl condensating partner. $R_2R_1NH + CH_2O \rightleftharpoons R_2R_1NCH_2OH + H^{(+)}$

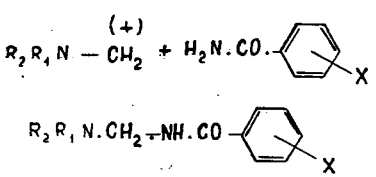
$$\left[\begin{array}{l} R_1 \quad (-) \quad (+) \\ \quad\diagdown \\ \quad\quad N \cdot CH_2 \\ \quad\diagup \\ R_2 \end{array} \right] \leftrightarrow \left[\begin{array}{l} R_1 \\ \quad\diagdown \\ \quad\quad N = CH_2 \\ \quad\diagup \\ R_2 \end{array} \right] + H_2O.$$

The carbenium — imonium ions formed in this way, are acting however in acidic medium only, and this N-oximethylamine was formed again in watery medium at pH 7.

In the case of piperidine the following carbenium-imonium iones are formed:



This ion-form will then react with the substituted acid amides,



and the N-piperidino-methyl-acid amides will be forming. Whereas the mentioned mechanism explains the phenomenon of the Mannich condensation, the reaction in alcalic medium cannot be so clearly elucidated.

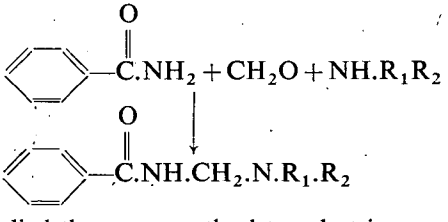
As already mentioned, the halogen substituted tertiary amino methyl-acid amides possess an intense antinicotinic activity (6), while the p-hydroxy-substitution leads to a new central spasmodic effect, and this may account for the 5—10-times stronger efficacity in the case of p-oxy-benzamido-methyl-piperidine-HCl compared with Metrazol (14).

With our later investigations we tried to throw light on the relation of effect and structure in the case of o-, p-, m-, oxy-benzamides.

The nitro substituent eliminated both effects of the above structures. Finally we should like to mention the possibility of rearrangement, which may take place parallel to the Mannich condensation of different oxibenzamides, but above all of the o-oxy-benzamides and possibly may account for the rather contrasting pharmacological effect of the oxy-benzamide-derivatives. When reacting o-oxybenzamides to Mannich condensation in acidic medium we could equally gain the expected o-oxy-benz-amido-methyl-piperidine and the o-oxy-2-benzamido-4-methyl-piperidine, and this latter structure may be rearranged to substituted di-oxy-diphenyl-methane upon the effect of heat (15). The effect divergent from pharmacological effect of the halogen-derivatives arising from the substitution of oxy may point to this phenomenon. The investigation of this problem is in progress.

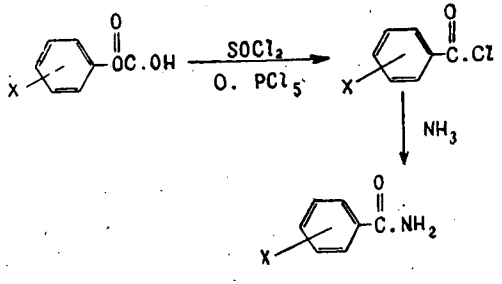
Experimental

As mentioned before, it was EINHORN (11) who first studied the Mannich condensation of the acid amides. The essential point of his method is that acid amides are reacted in methanol or ethanol with aqueous formaldehyde and piperidine.



Fundamentally we applied the some method too, but in some cases it has been modified, as described later.

Further we shall discuss the preparation of substituted acid amides as well. As a rule acid chloride was prepared from substituted acid and it was aminated with NH_4OH.



N-piperidino methylbenzamide was prepared from benzamide with EINHORN [11] method.

p-bromtoluene was prepered from p-toluidine with cuprobromide and sulphuric acid [16], while *p-brombezoic* acid was prepared from p-bromtoluene by oxidation with aqueous $KMnO_4$ [17].

p-brombenzoilchloride was prepared from p-brombenzoic acid with $SOCl_2$ [18, 19].

p-brombenzamide, on the other hand, was prepared from p-brom-benzoilchloride in abs. ether at constant cooling introducing NH_3-gas.

N-piperidinomethyl-p-brombenzamide may be prepared from p-brom-benzamide with MANNICH condensation. The exact way of preparation will be discussed later. The various o-, m-, p-halo-benzamides can be prepared through similar steps from adequate toluidimes [16].

p-iodotoluene was likewise made from p-toluidine [16], then oxidized with $KMnO_4$ and thus the proper carbonic acid was gained.

p-iodobenzoic acidchloride was made from p-iodobenzoic acid with $POCl_3$ or $SOCl_2$ [19] and acid chloride was converted into acid amide with the aqueous solution of NH_4OH [19]. The halobenzamides won in this way were then carried into the MANNICH condensation.

p-tertiary-buthyltoluene was made with the method of BIALOBZENSKI [20], and was transformed into p-tertiary-buthylbenzoic acid by $KMnO_4$ oxidation [21].

While preparing β-indolylacetic acid [22] we obtained β-indolylacetamide as by-product. Recrystallizing the *β-indolacetic-acid amide* we came to the starting material used at the MANNICH condensation.

p-nitrobenzoicacidamide was obtained from p-nitrotoluene with aqueous $KMnO_4$ [23]; the starting material was then chlorinated and aminated.

Nicotinic acidamide was made from nicotinic acidchloride hydrochloride [25] with NH_4OH solution in aqueous methanol. This was furthered to MANNICH condensation [26].

The preparation of *4-methoxibenzioc acidamide started* from 4-methoxibenzoic acid and carriedout with the previously mentioned method [27].

α-, and β-naphtoic acidamides were prepared from α-and β-naphtonitril refluxed in ethanol in an alcalic solution [29].

Phenylacetic acidamides [30] were prepared from benzyl cyanide.

3,4-dimethoxyphenylacetic acidamides were made from 3,4-dimethoxy phenylacetonitril with alcalic saponification [31].

Raceme mandelic acidamide was prepared from mandelic acid heated with PCl_5 and hydrolized with NH_4OH [32].

When preparing *diphenylacetic acidamide* we started out from diphenylacetic acid [33] from which diphenylacetic acidchloride [34], further diphenylacetic acidamide was formed [35].

2,4-phenoxiacetic acidchloride was made starting out from 2,4-phenoxiacetic acid, then aminating with NH_4OH.

The synthesis and the MANNICH condensation of this material will be discussed later.

α-and β-naphthaleneacetic acidamide was prepared from α-and β-naphthalene-

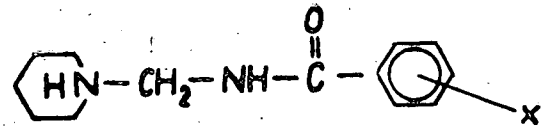


Table I.

X=	Summary form	M. W.	M. p.° C		Calculated %			Found %			Rel. antinicotinic activity	Notes
			basis	hydrochloride	C	H	N	C	H	N		
H	$C_{13}H_{18}ON_2$	218,1	138 — 39	181	70,06	8,29	12,83	70,30	8,15	12 – 63	1	
(o-OH)	$C_{13}H_{18}O_2N_2$	234	95	171 — 72	66,67	7,69	11,69	66,59	7,65	11,90		spasmodic
o-Cl	$C_{13}H_{17}ON_2Cl$	252,5	186	165	61,80	6,77	11,07	61,93	7,10	11,30	0,5	
p-Cl	$C_{13}H_{17}ON_2Cl$	252,5	149,50	177	61,80	6,77	11,07	62,10	6,80	10,91	0,5	
o-Br	$C_{13}H_{17}ON_2Br$	297	200	180 — 81	52,51	5,77	9,42	52,40	5,70	9,63	0,25	
m-Br	$C_{13}H_{17}ON_2Br$	297	—	173 — 74	51,52	5,77	9,42	52,63	5,80	9,92	0,5	
p-Br	$C_{13}H_{17}ON_2Br$	297	153	184	52,51	5,77	9,42	52,21	5,40	9,45	0,4	
p-J	$C_{13}H_{17}ON_2J$	344	148	178	45,04	4,94	8,14	45,1	4,80	8,12	0,4	
p-terc. but.	$C_{17}H_{26}ON_2$	274,2	160,61	184	73,25	9,56	10,02	73,10	9,45	10,30	2	
p-NO_2	$C_{13}H_{17}O_3N_3$	263,1	205	215	59,40	6,50	15,95	59,60	6,35	16,24	0,5	

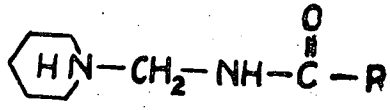
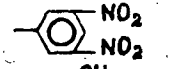
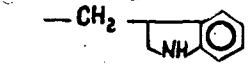
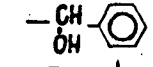
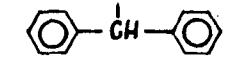
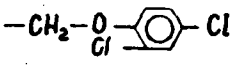
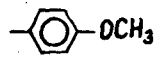
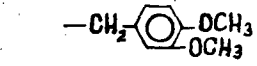
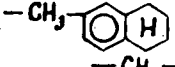
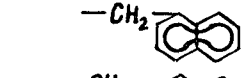
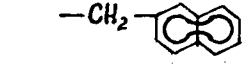


Table II.

– R =	Summary form	M. W.	M. p. °C		Calculated			Found %			Rel. antinicotinic activity	Notes
			basis	hydrochloride	C	H	N	C	H	N		
	$C_{13}H_{16}O_5N_4$	308,1	151,5	202	50,62	5,19	18,18	50,45	9,36	18,26	0,3	
	$C_{16}H_{21}ON_3$	279,16	169	170	70,90	7,77	15,52	71,13	7,91	15,30	0,4	
	$C_{14}H_{20}O_2N_2$	248,16	141	190	67,80	8,11	11,29	67,73	8,25	11,43	0,5	
	$C_{20}H_{24}ON_2$	326,16	157	174	73,60	7,39	8,59	73,81	7,24	8,43	0,4	
	$C_{14}H_{18}O_2N_2Cl_2$	316,94	110	195	53,05	5,72	8,83	52,80	5,93	8,95	–	local anaesthetic
	$C_{14}H_{20}O_2N_2$	248,16	137	162	67,80	8,11	11,28	67,50	8,43	10,97	—	
	$C_{16}H_{24}O_3N_2$	292,16	oil	163	65,80	8,27	9,59	65,40	8,35	9,71	—	
	$C_{18}H_{26}ON_2$	286,2	—	160	75,60	9,16	9,78	75,40	9,12	9,85	1	
	$C_{18}H_{22}ON_2$	282,17	169	178	76,75	7,83	9,93	76,77	7,99	9,81	0,3	
	$C_{18}H_{22}ON_2$	282,17	140	169 – 71	76,75	7,83	9,93	76,45	7,91	10,12	1	
	$C_{17}H_{20}ON_2$	268,16	—	173	76,17	7,47	10,04	76,05	7,53	10,23	0,2	

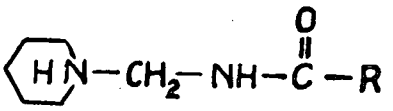
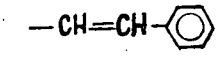
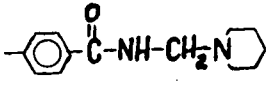
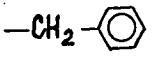
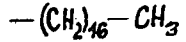


Table III.

– R =	Summary form	M. W.	M. p.° C		Caloulated %			Found %			Rel. antini-cotinic activity	Notes
			basis	hydro-chloride	C	H	N	C	H	N		
	$C_{17}H_{20}ON_2$	268,16	—	173	76,17	7,47	10,04	76,25	7,60	10,12	—	—
	$C_{14}H_{18}ON_2$	230,14	—	241	73,13	7,88	12,16	76,34	7,73	12,24	—	nicotine like activity
	$C_{20}H_{30}O_2N_4$	358,24	oil	227	67,05	8,39	15,62	67,20	8,40	15,65	—	curare like activity
	$C_{14}H_{20}ON_2$	232,16	118–19	185	72,35	8,66	12,02	72,20	8,84	12,21	0,2	—
	$C_{24}H_{48}ON_2$	380,38	—	128	75,02	12,57	7,30	75,10	12,63	7,20	0,3	—
	$C_{12}H_{17}ON_3$	219,13	—	165	66,00	7,92	19,32	66,28	8,11	19,20		

acetic acid; first we made acidchloride with PCl_5, then acidamide with concentrated NH_4OH solution in the case of β-naphthaleneacetic acidamide [36]; naphthalene acetonitril, however, was transformed to acidamide with cc. HCl at 40° C.

The 5,6,7,8-tetrahydro-β-naphthaleneacetic acidamide was made from 5,6,7,8-tetrahydro-β-acetonitril with cc. HCl at 25° C. [38].

Terephtalic acidamide was made from terephtalic acid; it was first chlorinated at 40° C with PCl_5 [39], then converted to acidamide with aqueous ammonia [40].

Cinnamic acidamide was made from cinnamic acid with NH_3, then refluxed for 3 hours at 150° C [41].

Stearic acidamide was prepared by forming stearic acid chloride with PCl_5 from stearic acid [42], then transformed with NH_4OH into amide [43].

In the following we wish to give some typical examples on the MANNICH condensation made with acidamides, but the physical data and analysis of the basis and hydrochlorides are given in table I—III.

In connection with the condensations first we should like to describe one or two typical instances, further we want to speak about the cases in which the condensation was not performed with the usual method of the MANNICH condensation, either pH of the medium or the applied circumstances being different.

The next example is a very typical one:

N-piperidinomethyl-p-brombenzamide. 5,7 gr p-brombenzamide [19] and 2,29 gr piperidine was dissolved in 15 ml abs. ethanol and the solution of 2,45 gr 38% aqueous formaldehyde. Refluxed for 4 hrs. at 145° C. The hot solution was filtered and evaporated in vacuo (5,8 gr). The gained crystallic residue was twice recrystallized from ethanol, HCl in abs. ethanol M. p.: 153° C. The hydrochloride of the basis was prepared, with m. p.: 184° C. (The data of the analysis are shown in table I.)

N-piperidino-methyl-p-iodobenzamide. Warm 6,8 gr. p-iodobenzamide (16) and 2,38 gr piperidine was dissolved in 30 ml dioxane, then 3 ml 5% NaOH solution and 2,4 gr 38% formaldehyde was added. The mixture was refluxed on water bath for 20 minutes, the hot solution filtered and distilled water added until opalescense began. For some hours it was left at room temperature and the crystals filtered. M. p.: 148° C.

Hydrochloride was made from the basis gained with abs. etheric HCl. M. p.: 178° C (Table I.)

2,4-dichlorophenxoiacetic acidchloride. 40 ml freshly distilled $SOCl_2$ was added to 20 gr 2,4-dichorophenoxiacetic acid. The won solution was heated for 2 hours on water bath. After cooling, the collected precipitate was filtered, the exess of $SOCl_2$ distilled at decreased pressure and the residue fractionately distilled. The b. p. of 2,4-dichlorophenoxiacetic acidchloride is 122° C. (2 mm of mercury.)

2,4-dichlorophenoxiacetic acidamide. 70 ml cc. NH_3 solution was added to 2,4-dichlorophenoxiacetic acidchloride at constant stirring and cooling. The formed acetic acidamide segregated as a precipitate. The precipitate was filtered, made ion-free by washing with distilled water, and the obtained raw product was many times recrystallized from ethanol. M. p. 159° C. Calculated: N: 6,3 found: N: 6,25.

N-piperidionomethyl-2,4-dichlorophenoxiacetic acidamide. On heating 1,95 gr piperidine 5 gr. 2,4-dichlorophenoxiacetic acidamide was dissolved in 40 ml abs.

ethanol and 1,9 gr 38% formaldehyde added to the warm solution, then refluxed for 10 hrs on water bath, filtered and kept in an ice box for 24 hrs. The crystals were filtered out. M. p.: 110° C. (Table II.) The bases dissolved in abs. ethanol and the hydrochloride was obtained when treated with the calculated amount of HCl in abs. ethanol. M. p.: 195° C. (Table II).

N,N'-dipiperidinomethylterphtalic acidamide. The mixture of 5 gr terephtalic acidamide (40), 5,2 gr piperidine, 5 gr 38% formaldehyde and 30 ml abs. ethanol was refluxed on water bath for 3 hours. The solution was filtered, then the solvent distilled at decreased pressure. A viscous substance remained, which was then transformed into hydrochloride in abs. etheric hydrochloric acid, isolated, recrystallized from acetone. M. p.: 270° C. (Table II).

* * *

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

III. СИНТЕЗ ТЕРЦИЕРАМИНОВЫХ-АЦИЛАМИДОВ

Ш. Фельдеак, Б. Маткович и Й. Порсас

После синтетических и фармакологических изучений терциераминеэфиров, тиоэфиров, насыщенных и ненасыщенных аминопропенов, были синтезированы различные замещенные производные терциераминовых-ациламидоз. И в настоящих исследованиях наблюдалось, что действие на центральный нервный мозг, в большом размере, зависит от строения. Из терциераминевых-ациламидов были сделаны, главный образом, на фенилной группе, различные, замещенные производные галогеном. Зависимости от положения галогена, изученные вещества показывали большую разницу в интевсивности. Кроме того были сделаны бензокси- и нитро-соединения. Из ациламидов Р-галофениловые производные показывали самое интевсивное антиникотиновое действие.