SYNTHESIS OF SUBSTANCES EFFECTING ON C.N.S. VII

The Synthesis of the Tertiary Aminoacetyl and Propionyl Derivatives of Aromatic and Homocyclic Amines

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(Received June 15, 1963)

It was known from our earlier publications that acidamide derivatives possess depressing effect on C.N.S. [1, 2].

Accordingly systematic examinations were carried out in the group of acidamides concerning the correlation between the effect and structure.

The present paper treats primarily the condensation of naphtylamines and homocyclic amines with chlorcarbonic acid chlorides (chlor-acetic acid chloride and chlor-propionic acid chloride) and the obtained aromatic or homocyclic amino-acid haloids were reacted with secondary amines. Having prepared series it became possible to determine the influence of the distance and the different bases on the C.N.S. effect.

Several local anaesthetic, antinicotine active compounds were found among synthetized series.

The compounds condensed with morpholine had in general neither C.N.S. nor local anaesthetic effect except in very high concentration.

In the III. part (1) of our publication was summarized the question what kind of structure in needed for an acidamide to exert an effect on CNS. At any rate numerous well known drugs have acidamide structure.

Having produced acid amides with MANNICH-condensation we looked for an other way to synthetize new acidamide derivatives.

Using in our experiments aromatic or homocyclic amines (I) we finally obtained chloroalkyl-acid amides (III) due to different reactivity of the two halogens of the chloro-carbonic acid chlorides (II) which we used for further reactions.

The reaction of chloro-carbonic acid chloride with primary amine occurs as follows:

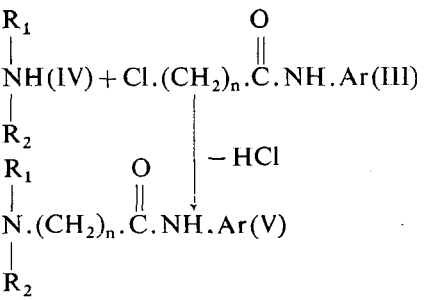
a)

$$\mathrm{Cl.(CH_2)_n.\overset{\overset{O}{\|}}{C}.Cl\,(II) + H_2N.Ar\,(I) \longrightarrow Cl.(CH_2)_n.\overset{\overset{O}{\|}}{C}.NH.Ar\,(III) + HCl}$$

This reaction was used to synthetize, among others, β-chloropropionic acid-N-anilide as starting material of hydro-carbostyrile (3).

The produced chloro-carbonic acid-aryl or homocyclic amines (III) could be reacted with different secondary amines (IV) and so the end product of the synthesis is reached (V)

b)



For the condensation of B were primarily employed piperidine, pirrolidine and morpholine.

The process of the synthesis first described in general α, β followed by five (1—5)-typical examples which clearly show the conditions under which the experiments were carried out.

The formulae, molecular weight, m. p. and the analytical data summarized in tables (1—3).

Experimental

1, 2, 3, 4-tetrahydronaphthylamine-1 (4) was prepared from α-tetralon-oxime. This was produced from α-tetralone and $NH_2OH \cdot HCl$ in the presence of KOH in MeOH by refluxing. The oxime is then reduced by Na in ethanol to give the amine.

Cyclohexylamine (5) was produced from cyclohexanonoxime reducing with Na in ethanol.

Cyclopentylamine (6) was obtained in the same way.

Chloro-acetic acid chloride was prepared from monochloracetic acid with PCl_3 and the end product distilled.

Chloro-propionic acid chloride (7) was prepared from acrylnitril with conc. HCl. First β-chloro-propionic acid was obtained then chlorinated with PCl_3 and the product distilled.

The preparation of chlorocarbonic acid amides (III).

(General description) (see reaction *a*) 0,1 mol of amine is dissolved in 200 ml dry benzene adding to it 0,1 mol of triethyl-amine constantly stirring it for about 30 minutes while dropping constantly 0,1 mol chlorocarbonic acid chloride dissolved in 100 ml of dry benzene. Thereafter the mixture is refluxed for 30 minutes, in water bath, then the crystals of the triethylamine-hydrochloride were filtered from the not wholly cooled mixture.

Table I

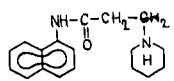
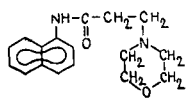
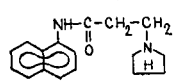
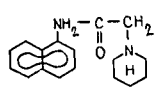
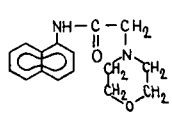
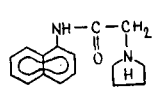
Names of substances	Summary form		M. w.	Physical data mp., bp., etc.	Calculated				Found			
					C%	H%	N%	Cl%	C%	H%	N%	Cl%
	Base	$C_{18}H_{22}N_2O$	282,37	90—91	—	—	—	—	—	—	—	—
	HCl	$C_{18}H_{23}N_2OCl$	318,84	208—209	67,80	7,27	8,78	11,12	67,78	7,20	8,80	11,30
	Base											
	HCl	$C_{17}H_{21}N_2O_2Cl$	320,83	230—231	63,64	6,59	8,73	11,05	64,30	6,82	8,78	9,34
	Base											
	HCl	$C_{17}H_{21}N_2OCl$	304,83	208—209	66,98	6,94	9,19	11,63	67,10	7,19	9,03	9,92
	Base	$C_{17}H_{20}N_2O$	268,35	118	76,08	7,51	10,44	—	75,13	7,87	10,31	
	HCl	$C_{17}H_{21}N_2OCl$	304,81	215	66,98	6,94	9,19	11,63	67,10	7,02	8,9	11,60
	Base	$C_{16}H_{18}N_2O_2$	270,32	106	71,08	6,71	10,36	—	71,33	6,98	9,67	
	HCl	$C_{16}H_{19}N_2O_2Cl$	306,64	235	62,63	6,24	9,13	12.10				
	Base	$C_{16}H_{18}N_2O$	254,32	108—109	75,55	7,13	11,01	- -	74,02	7,06	10,90	
	HCl	$C_{16}H_{19}N_2OCl$	290,79	219—221	66,08	6,58	9,63	12,19				

Table II.

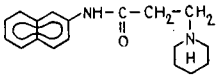
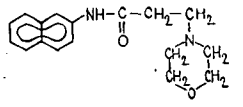
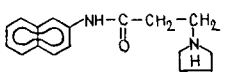
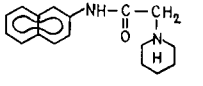
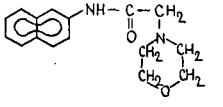
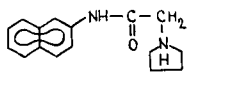
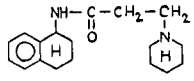
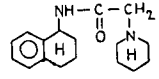
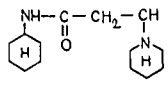
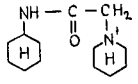
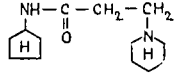
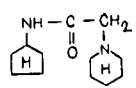
Names of substances	Summary form		M. w.	Physical data mp., bp., etc.	Analytical dates							
					Calculated				Found			
					C	H	N	Cl	C	H	N	Cl
	Base	$C_{18}H_{22}N_2O$	282,37	90—91°	—	—	—	—	—	—	—	—
	HCl	$C_{18}H_{23}N_2OCl$	318,84	219—220	67,90	7,27	8,78	11,12	67,77	7,54	8,73	10,86
	Base	$C_{17}H_{20}N_2O_2$	284,36	87—88	—	—	—	—	—	—	—	—
	HCl	$C_{17}H_{21}N_2O_2Cl$	320,83	255—256	63,64	6,59	8,73	11,05	63,56	6,96	8,42	10,91
	Base	$C_{17}H_{20}N_2O$	768,46	91—92	—	—	—	—	—	—	—	—
	HCl	$C_{17}H_{21}N_2OCl$	304,83	208—210	66,98	6,94	9,19	11,63	67,10	7,79	8,88	11,57
	Base	$C_{17}H_{20}N_2O$	268,46	89—90	—	—	—	—	—	—	—	—
	HCl	$C_{17}H_{21}N_2OCl$	304,83	242—244	66,98	6,94	9,19	11,63	67,63	7,07	9,08	11,30
	Base	$C_{16}H_{18}N_2O_2$	270,33	90—91	—	—	—	—	—	—	—	—
	HCl	$C_{16}H_{19}N_2O_2Cl$	306,80	235—237	62,63	6,24	9,13	12,10	62,72	6,45	8,91	11,51
	Base	$C_{16}H_{18}N_2O$	254,33	100—101	—	—	—	—	—	—	—	—
	HCl	$C_{16}H_{19}N_2OCl$	290,80	236—237	66,08	6,58	9,63	12,19	65,57	6,66	9,54	11,45

Table III.

Names of substances		Summary form	M. w.	Physical data mp., bp., etc.	Calculated				Found			
					C%	H%	N%	Hlg%	C%	H%	N%	Hlg%
	Base											
	HCl	$C_{18}H_{27}N_2OCl$	322,876	175	66,95	8,43	8,67	10,98	66,38	9,08	7,36	10,81
	Base											
	HCl	$C_{17}H_{25}N_2OCl$	308,846	182—183	66,11	8,15	9,07	11,74	65,93	8,04	9,08	11,17
	Base											
	HCl	$C_{14}H_{27}N_2OCl$	274,836	188	61,19	9,90	10,19	12,90	60,36	10,43	9,84	12,46
	Base											
	HCl	$C_{13}H_{25}N_2OCl$	260,806	166	59,86	9,66	10,74	13,59	59,80	9,80	10,90	13,75
	Base											
	HCl	$C_{13}H_{25}N_2OCl$	260,806	168—170	59,86	9,66	10,74	13,59	59,07	10,15	9,89	13,13
	Base											
	HCl	$C_{12}H_{23}N_2OCl$	246,776	164	58,40	9,39	11,35	14,37	58,30	9,75	11,20	14,12

The benzene filtrate was used for the next step, without isolation of III.

The further condensation of chlorocarbonic acid amide with piperidine or other secondary amines respectively. To obtain V.

(General description) (see reaction *b*)

The benzene solution obtained from step α was reduced in vacuum to 50 ml, then add 0,2 mol piperidine or other secondary bases to it.

The mixture as a rule was strongly warmed, few minutes after, crystals were separated. Refluxed it in water bath for 1 hour. After cooling the crystals were filtered, washed several times with water to remove the unchanged secondary base. Dried over anhydrous, evaporated, and the basic residue may be recrystallised from acetone if need be.

Dissolving the bases in acetone and acidified it by absolute alcoholic hydrochloride (about 20—25%) to acidic pH. Keep it in cold. Having filtered the crystals when needed recrystallized from absolute ethanol, aqueous ethanol, mixture of acetone-ethanol or only from acetone.

(It should be mentioned that the above generally described method refers to the substances listed in the tables. Only some typical examples will be emphasized.)

Example 1.

β-(1-piperidino)-propionic acid-α-naphtylamide-HCl.

28,6 g (0,2 mol of α-naphthyl-amine was dissolved in 200 ml of dry benezene in a 500 ml three necked round flash provided with stirrer, condenser and a dropping funnel. 20,2 g (0,2 mol) of triethylamine was added to it and dropping in 25,4 g (0,2 mol) β-chloro-propionic acid chloride dissolved in 50 ml of dry benezene, the solution stirred slowly and constantly (about 30 minutes). Following the dropping the reaction mixture is then refluxed for an other 30 minutes. Cooled it to about 40—50 °C and the triethylamine-HCl is filtered. The benzene filtrate is reduced to about 200 ml in vacuum and while skaking 34 g (0,4 mol) of piperidine was added in small portions. After the vigorous reactions, the mixture was refluxed for 30 minutes. Than it was cooled and the piperidine-HCl was filtered, then the filtrate diluted with benzene and washed several times with water to remove the unchanged piperidine. Having dried the benzene solution (anhydrous Na_2SO_4) the benzene was evaporated and the dense oily residue dissolved in about 10 ml acetone. After cooling it was rubbed as long as the crystallization was started. Keeped in a refrigerator at night then filtered and the precipitate was washed with a small amout of cold acetone.

The weight of the product: 28,3 g (yield 50,2% calculated on α-naphthylamine). Mp.: 87—89 °C.

By recrytallization from about 10 ml acetone the substance weight: 22,6., mp.: 90—91 °C.

The recrystallized pure base (22,6 g) was dissolved in 500 ml of hot acetone thereafter the calculated amount of absolute alcoholic HCl (about 20—30%) was dropped meanwhile shaking the solution. Keeping it in refrigerator. The praecipitate was filtered and washed with absolute alcohol. Weight: 25,2 g. Yield: 92,2%; mp.: 208—209 °C (decomp.). Recrystallized again from 85% ethanol the m. p. is

unchanged. The weight will be: 22,0 g. (It is to be noted, that the bases were mostly obtained as HCl salt without isolation of the free base.)

Example 2.

1-(piperidino) acetic acid-α-naphthylamide-HCl.

14,3 g (0,1 mol) of α-naphthylamine was dissolved in 500 ml dry benzene in a 1000 ml round-bottom three-necked flask supplied with stirrer, condenser and with a dropping-funnel. Adding 10,1 g (0,1 mol) triethylamine, then 11,3 g (0,1 mol) chloroacetic acid chloride dissolved in 200 ml of dry benzene being dropped (about 30 minutes) while constantly stirring the mixture.

The mixture was refluxed for 30 minutes after having dropped the acid chloride the triethylamine-HCl was separated from the solution. The benzene solution was evaporated to about 40—80 ml and 17 g of piperidine solution were added. The mixture was heated for 30 minutes after the intensive reaction. Thereafter the piperidine-HCl was filtered and the solution was diluted with water and washed in order to remove the piperidine HCl residue. (The coloured solution was always successfully purified with 20% of HCl. The basis were released with Na_2CO_3 from the acidic solution. The base was extracted from the basic solution with benzene. It was dried (anhydrous Na_2SO_4). The benzene solution was filtered, evaporated and the residue was recrystallized from acetone. The weight of the base: 16,5 g (Yield: 61,5% calculated on naphthylamide-1) m. p.: 118 °C. The hydrochloride was prepared from the acetone solution of the base with the calculated amout of alcoholic HCl. Kept in a refrigerator for a night. The obtained crystals were filtered, washed with absolute ethanol. Weight: 17,5 g (Yield: 96,4%). It could be recrystallized from 85% ethanol. M. p.: 215 °C.

Example 3.

β-(1-piperidino)-propionic acid-α-1, 2, 3, 4-tetrahydronaphthyl-amine-HCl.

14,7 g (0,1 mol) of 1, 2, 3, 4-tetrahydro-α-naphthylamine was dissolved in 100 ml of dry benzene in a 500 ml round bottomed three-necked flask provided with a stirrer condenser and a dropping-funnel. 10,1 g (0,1 mol) triethylamine, then 12,6 g (0,1 mol) β-chloro-propionic acid chlorides dissolved in 100 ml of dry benzene for 30 minutes. Refluxed it for about 30 minutes, filter the triethylamine-HCl crystals while hot. The benzene solution was then evaporated to about 50 ml in vacuum. 17 g of piperidine was added and refluxed after the strong reaction for about 30 minutes. The piperidine-HCl was filtered and the solution washed in the same way as described above. It was dried (anhydrous Na_2SO_4). Filtered and the solution evaporated in vacuum. The residue was dissolved in acetone and the calculated amount of alcoholic HCl was added, kept in a refrigerator for the night. The crystals were filtered and washed with absolute ethanol. Weight: 30,2 g (Yield: 93% calculated of 1, 2, 3, 4-tetrahydro-α-naphthylamine.). It can be recrystallized from absolute ethanol if needed. Mp.: 175 °C.

Example 4.

β-(1-piperidino)-propionic acid cyclohexylamine-HCl.

9,9 (0,1 mol) of cyclohexylamine was dissolved in 100 ml of dry benzene and 10,1 g (0,1 mol) of triethylamine was added in a 250 ml three necked flask provided as described above. Dropping into the flask 12,6 g (6,1 mol) of β-chloro-propionic acid chloride dissolved in 50 ml of dry benzene. The procedure is exactly the same as described in example 3.

The obtained weight of HCl was 18,5 g (Yield: 67,5% calculated for cyclohexylamine).

Recrystallized from absolute ethanol, m. p.: 188 °C.

Example 5.

(1-piperidino)-acetic acid-cyclopenthylamine-HCl.

8,5 g (0,1 mol) of cyclopentylamine was solved in 100 ml of dry benzene and 10,1 g (0,1 mol) of triethylamine was added in a 250 ml three necked flask provided as described above. Dropping 11,2 g (0,1 mol) of chloroacetic acid chloride for 30 minutes.

The procedure is alike that described in the other examples.

The benzene solution was extracted with dilute HCl and the benzene phase containing contaminations was separated. The acidic solution alcalized with Na_2CO_3 and extracted again with benzene. The dried benzene solution (anhydrous Na_2SO_4) evaporated and the basic residue was dissolved in acetone and the HCl salt formed with the calculated amount of alcoholic HCl. Keeping in refrigerator at night. The obtained crystals were filtered and washed with acetone. Weight: 12,6 g (Yield: 51,2% calculated for cyclopentylamine). Recrystallized from a mixture of absolute alcohol and acetone.

M. p.: 164 °C.

* * *

We wish to express our thanks to Mr. J. FÜLÖP and Dr. J. FISZTER for their valuable assistance and our indebtedness for the analysis to our Analytical Laboratory and to „*Gedeon Richter Pharmaceutical Works, Budapest*" for their kind support.

The detailed pharmacological examinations will be published elsewhere.

ИЗУЧЕНИЯ ДЕЙСТВИЯ МЕЖДУ ФИЗИОЛОГИЧЕСКИМИ И ХИМИЧЕСКИМИ СТРОЕНИЯМИ ВЕЩЕСТВ, ДЕЙСТВУЮЩИХ НА ЦЕНТРАЛЬНЫЙ НЕРВНЫЙ МОЗГ. VII

Синтез ароматических и гомоциклических терциер-аминоацетилов и пропионил-производных

Й. Лазар, Б. Маткович, Ш. Фельдеак, Й. Порсас

Уже перед рассмотрениями было известно, что аминокислоты в центральной нервной системе вызывают депрессию. Поэтому были произведены рассмотрения в группе аминокислот для взаимной зависимости действия и строения.

Публикация занимается конденсацией нафтиламинов и разных гомоциклических аминов, возникшей при действии клоралкилклорангидрида

$$(Cl{\cdot}CH_2COCl,\ Cl{\cdot}CH_2{\cdot}CH_2COCl)$$

и разных вторичных аминов. Для полученных соединениях изучалась роль дальности метилена и разных оснований на фармагологическое действие. Между рассмотренными соединениями нашлись многочисленные соединения антиникотинного действия местного анестетика.

References

[1] *Földeák, S., B. Matkovics, J. Pórszász:* Acta Phys. et Chem. Szeged, **8**, 88, (1962).
[2] *Földeák, S., B. Matkovics, J. Pórszász:* Acta Physiol. Hung., Suppl. **18**, 87, (1961).
[3] *Mayer, F. L. von Zutphen, H. Philipps:* Ber. **60**, 858, (1927).
[4] *Green, A. G., F. M. Rowe:* J. Chem. Soc., **113**, 955, (1918).
[5] *Baeyer A.:* Ann., **278**, 103 (1894).
[6] *Wislicenus, J. W. Hentschel:* Ann., **275**, 325, (1893).
[7] *Henry, L..:* J. prakt. Chem., **31**, 127, (1885).