SYNTHESIS OF SUBSTANCES EFFECTING C. N. S. V

Synthesis of Some New Tertiary Amino-p-Alkyl-Aryl-Propene and -Propane Derivatives

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As a continuation of earlier synthetic investigations, several p-alkyl acetophenones were prepared by means of the FRIEDEL—CRAFTS reaction, which were converted into substituted N-piperidino-aralkylpropanones with the help of the MANNICH condensation. The aforesaid ketones were reduced to alcohols and dehydrated with perchloric acid to propenes. After repeated catalytic reduction propane-derivatives were obtained.

ISSEKUTZ, PÓRSZÁSZ and NÁDOR [1] were the first of deal comprehensively with the synthesis and pharmacological activities of arylketones [2, 3]. A considerable number of aminoketones belonging to this group had been known since MANNICH's [4] investigations, however, it was shown that not alone aminoketones exert CNS effects but other groups of MANNICH bases, too [7].

The authors had earlier devised a method to produce N-tertiary-amino-aralkyl-ketones [5] this method, however, proved to be too *involved* and complicated [6], consequently we continued to find an other way concerning the synthesis of amino-propane. Simultaneously, efforts were made to separate the stereoisomers (cis and trans) of amino propenes. The necessary aminoketones for the synthesis of

$$R.C_6H_4.CH=CH.CH_2-N.R_1R_2$$

have been made using MANNICH's condensation.

In the above mentioned general formula R is alkyl and $N.R_1R_2=N(C_2H_5)_2$ (diethylamino), $N.C_5H_{10}$ (piperidino), $N.C_4H_8$ (pyrrolidino) and $N.C_4H_8O$ (morpholino) radicals.

The aralkyl-compounds were synthetized with help of FRIEDEL—CRAFTS-reactions (8), using dry $AlCl_3$ as catalyst. As by-products di-, tri-, etc. alkyl-benzenes (I.) [9] were always obtained.

The same condensation was also used for the synthesis of p-aralkyl-acetophenones (II):

I.,
$$R.CH_2Cl + C_6H_6 \xrightarrow{AlCl_3} R.CH_2.C_6H_5 + HCl$$

II.,
$$R.CH_2.C_6H_5 + CH_3.\overset{\overset{O}{\|}}{C}.Cl \longrightarrow R.CH_2.C_6H_4.\overset{\overset{O}{\|}}{C}.CH_3 + HCl$$

R means here hydrogen or shorter p-alkyl groups.

The FRIEDEL—CRAFTS reactions were in general carried out in CS_2 or nitrobenzene solvents, sometimes, however, the excess of alkyl-benzene served as solvent.

The p-aralkylacetophenones were converted into aminoketones (MANNICH condensation). These reactions were catalysed by the presence of hydrochloric acid.

The rate of the MANNICH condensation depends on the reactivity of the hydrogen atoms of the methyl groups, whereas the reaction with p-nitro-acetophenone takes place momentarily, p-chloro-and p-hydroxy-acetophenones react very slowly and give a poor yield.

The first step of the MANNICH condensation of this type may proved into two directions, depending on reaction conditions, as to whether formaldehyde reacts first with the mobile methylene group (a) or with the amino group (b).

III.,
$$\begin{array}{lll} & R.\overset{\overset{O}{\|}}{C}.CH_3 + CH_2O & R_1R_2.NH + CH_2O \\ a) & \downarrow & b) \quad \downarrow \\ & R.\overset{\overset{O}{\|}}{C}.CH_2.CH_2OH & R_1.R_2N.CH_2OH \\ & \searrow \quad -H_2O \quad \swarrow & \\ & RC.CH_2.CH_2.N.R_1.R_2 & \\ & \| & \\ & O & \end{array}$$

R and N R_1R_2 mean the same as above.

The described reactions, however, indicate merely, the main direction of the reaction, however, on the basis of our experiments other side reactions are minimal.

When the acetophenone components are not sufficiently reactive and, as a consequence, the condensation would require a long time, the side reaction may

reappeare and the formation of a di-/-N-dialkyl/-methane can be expected:

$$R_2.R_1.N.CH_2.OH + NH.R_1.R_2$$
$$\downarrow$$
$$R_2.R_1.N.CH_2.N.R_1.R_2$$

In fact, we were able to isolate dipiperidino-methane-dihydrochloride (mp.: 246 °C), it could be separated from the main reaction product only by fractionate crystallization.

The reactivity of the p-aralkyl-acetophenone, synthetized by us, was only average consequently, the condensation required in general from 4—7 hours. The yield of the condensation, calculated for p-aralkly-acetophenone, ranged between 50—60%. We tried to apply FRY's [10] method in order to reduce the reaction time in several cases, however, without any result. Mostly, the above mentioned reaction path with piperidino hydrochloride failed, as piperidine-hidrochloride did not dissolve in the mixture of benzene-nitrobenzene, and heterogeneous conditions do not favor this type of condensation.

The next step was the reduction of the aminoketones. Initial experiments, carried out with Zn/Hg, were unsuccessful. A catalytic method, described by FODOR and KOVÁCS (12), proved to be the best. These authors obtained tyramine, respectively methyl-tyramine, from the ketone using the above method.

The reduction was made in acetic acid in the presence of perchloric acid with a Pd/(charcoal) catalyst. This reduction resultated in the expected alcohol but only at room temperature. The Pd/C-reduction was modified, according to the solubility of the substances, using dilute acetic acid, alcohol and, in many cases, water. Thus, the expected alcohol was obtained in quantitative yield.

The reduction proceeds as follows:

IV.,
$$R.\overset{\overset{O}{\|}}{C}.CH_2.CH_2.N.R_1R_2$$
$$\downarrow$$
$$R.CHOH.CH_2.CH_2.N.R_1.R_2$$

The formed racemic aminopropanol was and extracted with ether. A separation into the optically active alcohols has not been attempted.

The reduction was followed by dehydration for the sake of the formation of the unsaturated products:

V.,
$$R.CH.OH.CH_2.CH_2.N.R_1.R_2$$
$$\downarrow -H_2O$$
$$R.CH=CH.CH_2.N.R_1.R_2$$

Pyrolytic dehydration appeared too drastic in our case consequently milder dehydration conditions were applied [17, 18] and, finally perchloric acid-dehydration proved to be the most adequate [12]. At any rate, certain modifications had to be made.

To ensure the cis-isomers one has to start from the pure base because the presence of chloride ion traces favors according to our experiences the formation of trans-isomers.

Thus dehydration was carried out in methanol or benzene solution. The unsaturated compound was isolated as free bases.

The cis-isomer is very sensitive, leached with NaOH, it is transformed into 2-aminopropanol, hence neutralize the solution, $NaHCO_3$ was used. The cis-isomer is also sensitive to temperature and turns into the trans-isomer due to the chloride ion.

Having obtained propene-derivatives following dehydration in the presence of a Pd/C-catalyst, and upon hydrogenation at atmospheric pressure in acetic acid, we obtained the saturated propane derivatives.

VI. $R.CH=CH.CH_2.N.R_1.R_2$

$R.CH_2.CH_2.CH_2.N.R_1.R_2$

The thus synthetized compounds were pharmacologically active. Above all, they influence the CNS, they also show intensive antinicotinic activity, inhibit the counter extensor reflex, some of them produce prolonged muscle relaxation, very frequently, they prevent the spasms produced by electroshock.

Experimental

The m. p. are determinated by „Boëtius" apparatus and corrected.

3-piperidino-propiophenone HCl (I).

12,1 g of piperidine HCl, 12 g of acetophenone 1,5 g of 73% paraformaldehyde and 0,25 ml. of cc. HCl are dissolved, suspended in 50 ml of absolute ethanol and refluxed for 1,5 hour, 1,5 g of 73% paraformaldehyde is added and refluxed again for 1.5 hour. It is filtered hot and kept in an icebox for a few hours. A crystalline substance appears, which is then filtered and dried. The substance is recrystallized from a mixture (1:6) of alcohol-acetone. M. p.: 190—191 °C.
(Analytical data concerning the substances to be described and the substance I. are in Table I.)

1-phenyl-piperidino-propanol-1 (II).

20 g of I is solved in 100 ml of water and in 5 ml of acetic acid, 4 g of Pd/C catalyst is added and it is hydrogenated at atmospheric pressure as soon as the calculated amount of hydrogen is used up, the reaction is stopped and the catalyst filtered. The solution is rendered alkaline with 2 N NaOH and extracted with ether. The etheric solution is collected and dried on anhydrous Na_2SO_4 it is filtered and the ether distilled: there remains a pale yellow oil, which is distilled under completely anhydrous conditions a crystalline substance results. M. p.: 54—55 °C.
The hydrochloride of the mentioned substance was prepared (II) its. M. p. is = 151 °C.

1-phenyl-piperidino-propene 1-HCl (trans) III.

3 g of II-hydrochloride is dissolved in the mixture of 1 ml of $HClO_4$ in 15 ml of acetic acid and kept at 150 °C for 45 minutes: upon cooling, it is diluted with water and rendered slightly alkaline, it (pH 8) with NaOH. The base thus obtained in extracted with ether, and the ether solution evaporated. The remaining brownish solution is thrice dissolved in abs. ethanol and distilled to remove the water. The

weight of the thus obtained base is 2 g. It is dissolved, in an alcohol-acetone mixture (1:6) and a hydrochloride is separated with an absolute ether hydrochloric acid mixture. (2 g of hydrochloride). The latter is suspended in hot acetone and alcohol is added to it as long as it is not dissolved. Upon cooling white needles appear. M. p.: 213 °C.

1-phenyl-3 piperidino-propene-1-HCl (cis) (IV).

3 g of base II is dissolved in 30 ml of abs. methanol and cooled in a salt-ice mixture. While constantly shaking it, 5 ml of cc. H_2SO_4 is dropwise added to the cooled solution. Then it is refluxed with 0,2 g of $CuSO_4$ for three hours. The boiling solution rendered alkaline with $NaHCO_3$ a little water is added, and the base extracted with ether. The ether solution is dried (anhydrous $MgSO_4$), filtered and the ether is evaporated *in vacuo*, the residue is dissolved in absolute ethanol and the solution in concentrated. The weight of the base is 1,8 g, it is dissolved in ether and a hydrochloride is prepared with the calculated amount of hydrochloric acid, it immediately precipitates (M. p.: 155—156 °C). The amorphous substance thus obtained is purified by recrystallization. M. p.: 174—176 °C.

p-methylacetophenone (V) (19).

A three-necked flask is supplied with a condenser and the top of it with a hydrochloric acid trap, stirrer and a dropping funnel, it is placed in an ice bath. 103,6 g of abs. toluene are poured in and 94,3 g of purified $AlCl_3$ is suspended in the solution while stirring, 29,4 g of glacial acetic acid is added within 30 minutes. Following dosaging it is kept in a water bath for an other hour, then the reaction mixture is poured in a mixture of 300 g of ice and 25 ml of cc. HCl. The organic phase is separated and washed with 50 ml of water, then dried (anhydrous $CaCl_2$). The residue of tolune is destilled and the substance is then fractionated in vacuo. The weight of the obtained material is 46,9 g. B. p.: 182 °C.

1-p-methyl-phenyl-3 dipiperidino-propanone-1-HCl (VI).

13,4 g of V is condensed as described with compound I. The weight of the crude product is 14 g, M. p. 180—181 °C. It is recrystallized from a mixture of alcohol and acetone. Yield: 10 g. B. p.: 182 °C.

1-p-methyl-phenyl-3-piperidino-propanol-1 (VII).

11 g of VI was prepared by a Pd/C reduction as described with compound II. The weight of the obtained base is 7,4 g. M. p. of the base: 79—81 °C. M. p. of hydrochloride: 148 °C.

1-p-methyl-phenyl-3-piperidino-propene-1 (trans) (VIII).

3 g of VII (hydrochloride) was made by using method III. 1,9 g of substance was obtained at m. p.: 237 °C. It was recrystallized from a hot acetone-alcohol mixture. With needles were separated. M. p.: 249 °C.

Using the method applied to the synthesis of IV it was attempted to prepare the cis-isomer, but here and in other cases the attempts failed. In every cases the trans-isomers were formed. The trans-isomer is the more stabile modification. Consequently, we shall not deal with this method any longer and describe merely the preparation of the trans-isomer.

Table I

Names of substances	Number of substances	M. w.	Summary forms
3-piperidino-propiophenone-HCl	I.	253,76	$C_{14}H_{20}NOCl$
1-phenyl-3-piperidino-propanol-1	II.	255,77	$C_{14}H_{22}NOCl$
1-phenyl-3-piperidino-propene-1-HCl (trans)	III.	237,76	$C_{14}H_{20}NCl$
1-phenyl-3-piperidino-propene-1-HCl (cis)	IV.	237,76	$C_{14}H_{20}NCl$
1-(p-methyl-)-phenyl-3-piperidino-propanone-1-HCl	VI.	267,79	$C_{15}H_{22}NOCl$
1-(p-methyl-)-phenyl-3-piperidino-propanol-1	VII.	269,8	$C_{15}H_{24}NOCl$
1-(-p-methyl-)-phenyl-3-piperidino-propene-1 (trans)	VIII.	251,78	$C_{15}H_{22}NCl$
1-(-p-ethyl)-phenyl-3-piperidino-propanone-1-HCl	X.	281	$C_{16}H_{24}NOCl$
1-(-p-ethyl)-phenyl-3-piperidino-propanol-1	XI.	223,34	$C_{14}H_{25}NO$
1-(-p-ethyl-)-phenyl-3-piperidino-propene-1 (trans)	XII.	205,33	$C_{14}H_{23}N$
1-(-p-i-propyl-)-phenyl-3-piperidino-propanone-1-HCl	XVII.	295,84	$C_{17}H_{26}NOCl$
1-(-p-i-propyl-)-phenyl-3-piperidino-propanol-1-HCl	XVIII.	261,34	$C_{17}H_{27}NO$
1-(-p-i-propyl)-phenyl-3-piperidino--propene-1-HCl (trans)	XIX.	245,37	$C_{17}H_{25}N$
1-(-p-t-butyl-)-phenyl-3-piperidino-propanol-1-HCl	XXIII.	309,87	$C_{18}H_{28}NOCl$
1-(-p-t-butyl-)-phenyl-3-piperidino-propanol-1-HCl	XXIV.	276,42	$C_{18}H_{30}NO$

Physical data (mp., bp.,, n_D^{20})	Calculated				Found				Yield %
	C%	H%	N%	Hlg%	C%	H%	N%	Hlg%	
190 – 191°C	66,4	7,97	5,53	14,17	66,29	7,87	5,41	14,30	63
54 – 55°C	65,67	8,60	5,49	13,72	65,75	8,65	5,69	13,85	81
213°C	70,88	8,43	5,9	15,12	70,67	8,65	5,75	15,20	68
174 – 176°C	70,88	8,43	5,88	15,12	70,76	8,35	5,90	15,35	62
182°C	67,21	8,36	5,24	13,1	67,30	8,40	5,20	13,05	37
148°C	66,91	8,92	5,18	13,01	66,95	8,88	5,30	12,93	85
249°C	75,47	10,37	5,55	7,58	75,32	9,92	5,60	7,62	38
183 – 184°C	68,32	8,54	4,98	12,45	68,40	8,56	4,79	12,30	52
140°C	67,84	9,18	6,26	–	67,92	9,21	6,40	–	54,4
240°C	81,81	11,21	5,28	13,20	81,75	11,20	5,22	13,15	96
178 – 180°C	69,01	8,85	4,73	11,98	68,93	9,0	4,68	11,73	72,5
186°C	68,54	9,47	4,70	11,91	78,05	10,29	4,90	12,10	50
237°C	72,95	9,53	5,95	12,6	73,02	9,42	6,05	12,7	74,2
164 – 165°C	67,82	9,68	4,51	12,11	67,91	9,45	4,60	12,07	54,2
196°C	69,45	9,64	5,06	11,25	69,31	9,72	5,15	11,34	80,7

Table I (contd.)

Names of substances	Number of substances	M. w.	Summary forms
1-(-p-t-butyl)-phenyl-3-piperidino-propanone-1 (trans)	XXV.	258,41	$C_{18}H_{28}N$
1-piperidino-3-(-p-cyclohexyl-phenyl-)-propanone--3-HCl	XXVII.	335,83	$C_{20}H_{30}NOCl$
1-piperidino-3-(-p-cyclohexyl-phenyl-)-propanol--3-HCl	XXVIII.	337,85	$C_{20}H_{32}NOCl$
1-piperidino-3-(-p-cyclohexyl-phenyl-)-propene-3-HCl	XXIX.	319,83	$C_{20}H_{30}NCl$
1-piperidino-3-(-p-cyclohexylphenyl-)-propene-HCl	XXX.	321,85	$C_{20}H_{32}NCl$
1-piperidino-3-(-p-methyl-phenyl-)-2-methylpropanol--3-HCl	XXXI.	283,75	$C_{16}H_{26}NOCl$
1-piperidino-3-(-p-methylphenyl-)-2-methyl-propene--3-HCl	XXXII.	266,75	$C_{16}H_{25}NCl$
1-piperidino-3-(-2-naphtyl-tetrahydro-5, 6, 7, 8-)--propenon-3-HCl	XXXIII.	307,65	$C_{18}H_{26}NOCl$
1-piperidino-3-(-2-naphtyl-tetrahydro-5, 6, 7, 8-)--propanol-3-HCl	XXXIV.	309,67	$C_{18}H_{28}NOCl$
1-piperidino-3-(-2-naphtyl-tetrahydro-5, 6, 7, 8-)--propene-3-HCl	XXXV.	291,65	$C_{18}H_{26}NCl$
1-(-β-oxyethylaminomethyl-)-3-phenyl-propene-3-HCl	XXXVI.	227,58	$C_{12}H_{18}NOCl$
1-(-β-chloromethylamino-methyl-)-3-phenyl-propene--3-HCl	XXXVII.	246,03	$C_{12}H_{17}NCl_2$
1-(-β-piperidino-ethylamino-methyl-)-3--phenylpropene-3-2-HCl	XXXVIII.	311,12	$C_{17}H_{28}N_2Cl_2$
1-(-p-i-propyl-)-phenyl-3-piperidino-propane-HCl	XXXIX.	281,86	$C_{17}H_{27}NCl$

Physical data (mp., bp., n_D^{20})	Calculated				Found				Yield %
	C%	H%	N%	Hlg%	C%	H%	N%	Hlg%	
220°C	73,72	9,55	5,41	11,94	73,65	9,40	5,60	11,80	87,9
188°C	71,52	8,96	4,18	10,71	71,60	8,99	4,23	11,10	69
217°C	71,32	9,56	4,14	10,50	71,54	9,81	4,30	10,78	56
234 – 235°C	74,50	8,92	4,36	12,12	74,56	9,22	4,50	12,19	70,5
199 – 200°C	74,75	9,95	4,34	11,02	74,53	9,58	4,45	11,38	60,5
130 – 131°C	67,40	9,12	4,93	12,42	67,40	9,13	4,90	12,49	51,6
200°C	72,01	9,47	5,23	13,28	72,00	8,98	5,35	13,43	42,7
178,5°C	68,80	8,47	4,55	12,42	68,94	8,32	4,70	12,24	85
160°C	65,02	9,13	4,52	11,32	64,92	9,00	4,65	11,25	73
224 – 225°C	74,50	8,95	4,80	12,12	74,56	9,15	5,00	12,19	64
121°C	63,45	7,49	6,15	15,61	63,24	8,07	6,25	15,47	68,3
147°C	58,76	6,95	5,69	28,90	58,35	7,24	5,75	29,00	70,5
248 – 250°C	65,52	9,08	4,51	22,68	65,34	9,24	4,65	22,43	47,6
203 – 204°C	72,43	10,02	4,97	12,58	72,40	10,12	5,05	12,72	98

p-ethyl-acetophenone (IX) (20).

A mixture of 12 g of ethylbenzene, 15 g of acetyl-chloride and 50 ml of petroleum ether is placed in a three-necked flask supplied with a refluxing condenser and stirrer, in one of the necks a dry stoppered test tube is fixed. It is strongly cooled and 15 g of $AlCl_3$ is added in small doses, at constant stirring, for about half an hour. It is refluxed on the water bath for some time and the complex is poured into ice water and treated in the usual way. Yield: 9,53 g. B. p.: 132—136 °C/40 mm. $n_D = 1{,}5275$.

1-(-p-ethyl-)-phenyl-piperidino-propanone-1-HCl (X).

14,8 g of IX is condensed according to method I. Yield: 14,62 g. M. p.: 183—184 °C.

1-(-p-ethyl-)-phenyl-3-piperidino-propanol-1-HCl (XI).

8,62 g of the hydrochloride of X is reduced and thus 7,95 g of base is obtained. M. p. of the hydrochloride: 140 °C.

1-(-p-ethyl-)-phenyl-3-piperidino-propene-1-HCl (trans) (XII).

3 g of XI was dehydrated using method III. Yield: 2,27 g base. M. p. of the hydrochloride: 240 °C.

n-propyl bromide (XIII) (21).

A mixture of 500 g of 48% HBr, 150 g of cc. H_2SO_4 and 144 g of n-propanol is warmed on a water bath and 120 g of cc. H_2SO_4 is slowly added dropwise. The simultaneously, propyl bromide is distilled. The cooler and the receiver are cooled with ice water. The substance formed is washed with the equivalent of cc. HCl, water, 5% $NaHCO_3$ and then again with water. It is dried (anhydrous $CaCl_2$), filtered and distilled. Yield: 134 g. B. p.: 70—73 °C. Product: 45% $n_D = 1{,}4321$.

Isopropyl chloride (XIV).

1,5 l of cc. HCl (36%) is placed in a 2,5 l round-bottomed flask provided with a cooler and with a dropping funnel and heated to 60 °C. 500 ml of isopropanol is added dropwise. It is kept in a hot water bath for 8—10 hours. The isopropyl chloride formed is distilled under ice cooling. Yield: 180 g. B. p. 34,5 °C. Product: 35,3%.

Isopropyl benzene (XV) (21).

A two liter, three-necked flask, provided with stirrer, cooler and with a dropping funnel, is placed in a salt-ice bath. An acid trap is fixed to the end of the cooler. 16 g of $AlCl_3$ is suspended in 611 ml of benzene in the flask and the mixture of 262 ml of benzene and 120 g of n-propyl bromide or of isopropyl chloride is added to it. The mixture is heated to 80 °C for two hours.

The upper phase is then removed, washed with diluted NaOH, and with water, and dried (anhydrous $MgSO_4$). Yield: 114,75 g. B. p.: 82—85 °C/43 mm. Product: 96% $n_D = 1{,}4975$.

The isopropyl compound (XV) may be prepared, using another method, namely a modification of that published by MAZONSKI and his coworker (22).

675,5 g of dried benzene and 266 g of $AlCl_3$ are poured in a round-bottomed flask, provided with a 2-liter stirrer, reflux condenser and a thermometer. The reaction

mixture is cooled to 0 °C (with a salt-ice mixture, containing very little salt.) 120.2 g of isopropyl alcohol is added dropwise to it, stirring very intensively for about an hour. The inner temperature during the reaction must be constantly kept between 0° and 5 °C. Following the addition of isopropyl alcohol, the stirring is continued for about 2 hours until elimination of the hydrochloric acid, raising the temperature to 18—20 °C. Then the solution is poured over the mixture of 200 ml of cc. HCl and 600 g of ice. The benzene phase is gradually separated, dried (anhydrous $CaCl_2$), filtered, and the excess of benzene driven off the isopropyl benzene is the distilled at atmospheric pressure. B. p.: 151—153 °C. Yield: 116 g $n_D = 1{,}4935$.

p-isopropyl-acetophenone (XVI) (23).

135 g of $AlCl_3$ is solved in 135 ml of CS_2 and cooled to −5 °C. The mixture of isopropyl benzene and 87,02 g of acetyl chloride, under cooling and constant stirring, is dropped into the system at such a rate as not to allow the temperature to rise over +5 °C. The solution is heated to 15 °C, and it is poured into a mixture of 143 ml of cc. HCl and 600 g of ice. The organic phase is separated and the aqueous part is extracted 3 times with 150 ml of ether. The phase formerly separated and the etheric phase are combined and dried (anhydrous K_2CO_3). Yield: 115 g. B. p.: 155—158 °C/42 mm. B. p.: 122—124 °C/10 mm $n_D = 1{,}5193$.

1-(-p-i-propyl-)-phenyl-3-piperidino-propenone-1-HCl (XVII).

18,2 g of XVI is condensed into XVII using method. I. Yield: 21,34 g. M. p.: 176—178 °C.

i-(-p-i-propyl-)-phenyl-3-piperidino-propanol-1-HCl (XVIII).

29,5 g of XVII is reduced by method II. Yield: 14,75 g base. M. p. of the hydrochloride: 155 °C.

i-(-p-i-propyl-)-phenyl-3-piperidino-propene-1-HCl (trans) (XIX).

3 g of the hydrochloride of XVIII are dehydrated by method III. Yield: 2,1 g hydrochloride. M. p.: 237 °C.

Preparation of t-butylchloride (XX) (21).

25 g of absolute t-butanol and 85 ml of cc. HCl are placed in a 250 ml separatory funnel and constantly shaken for 20 minutes. The two phases are separated. The t-butylchloride formed is washed with 20 ml of 5% $NaHCO_3$ and with water, dried (anhydrous $CaCl_2$) and distilled. Yield: 16 g. B. p.: 49—52 °C. $n_D = 1{,}3859$

t-butylbenzene (XXI) (24).

In a well cooled mixture of 150 g of benzene and 50 g of $AlCl_3$, 44 g of t-butylchloride is slowly dropped in for 48 hours. It is stirred at room temperature for two hours and poured into ice water and washed with distilled water, then warmed on a water bath with dilute NaOH for half an hour. The two phases are separated. It is washed with water, and dried (anhydrous $NaSO_4$), filtered, and distilled. Yield: 20 g of t-butylbenzene $n_D = 1{,}502$. The yield of the product, treated with abs. benzene, and the mixture well cooled, may be increased to 50%.

p-t-butyl-acetophenone (XXII) (25).

81 g of $AlCl_3$ is solved in 81 ml of SC_2 and cooled to −5 °C. A mixture of 80 g of t-butylbenzene and 51,6 g of acetyl chloride is dropwise added to at constant cooling and stirring in such a way as not to allow the temperature to rise above −5 °C. Then the mixture is heated to 15 °C, thereafter poured into a mixture of 400 g of ice and 100 ml of cc. HCl. The solution is extracted with 4 ×200 ml of ether. The combined etheric extracts are dried (anhydrous K_2CO_3), the solvent is evaporated and the residue is distilled. Yield: 50,5 g. B. p.: 134—135/11 mm. $n_D^{20} = 1{,}5179$.

1-(-p-t butyl-)-phenyl-3-piperidino-propanone-1-HCl (XXIII).

39,2 g of XXII is continued, using method I. Yield: 33,4 g. M. p.: 164—165 °C.

1-(-p-t butyl-)-phenyl-3-piperidino-propanol-1-HCl (XXIV).

33,4 g of XXIII compound is reduced to the alcohol by method II. Yield: 24,9 base. M. p. of the hydrochloride: 196 °C.

1-(p-t-butyl-)-phenyl-3-piperidino-propane-1-HCl (trans) (XXV).

Water is eliminated with $HClO_3$ from 3 g of XXIV hydrochloride. Yield: 2,18 g base. M. p. of hydrochloride: 220 °C.

p-cyclohexylacetophenone (XXVI) was obtained by the method, described by LUTZ *et al.* (26).

1-piperidino-3-p cyclohexylacetophenyl-propanone-3-HCl (XXVII).

20 g of piperidino NCl, 32 g of XXVI, 9 g of paraformaldehyde is refluxed in 80 ml of absolute ethanol for two hours, thereafter 9 g of more paraformaldehyde is added to the mixture and it is continued to reflux for 3 hours. It is filtered warm, the solution is evaporated to half and 50 ml of acetone is added to it the amino-ketone is crystallized, filtered, washed with acetone. M. p.: 183—184 °C. Yield: 37 g. Crystallized from acetone-ethanol, M. p.: 188 °C.

1-piperidino-3-(-p ciclohexylphenyl-)propanol-3-HCl (XXVIII).

8 g of XXVII is hydrogenated at room temperature in 20 ml of a methanol solution in the presence of 0,1 g of Pt-oxide catalyst, (at atmospheric pressure). To take up the calculated amount of hydrogen about four hours are needed. After filtering when turbidity commences, absolute ether is added and it is kept standing for some hours in refrigerator 4,5 g of substance crystallizes. M. p.: 212 °C. Recrystallized from an acetone-methanol mixture the m. p. is 217 °C.

1-piperidino-3-(p-cyclohexylphenyl-)propene-3-HCl (XXIX).

1,5 g of XXVIII is dissolved in 10 ml of acetic acid and, it is refluxed in the presence of 0,4 ml of 9,4 N $HClO_3$ for 50 minutes. Upon cooling, the perchlorate of the unsturated compound in precipitated in lamellated crystals, it is filtered and dried. (M. p. 166 °C). It is dissolved in 10 ml of acetone and rendered alkaline with aqueous sodium carbonate. The base is crystallized from the solution, it is filtered and washed with water. M. p.: 67—68 °C (1 g). It is dissolved in ethanol and the hydrochloride prepared with ethanol hydrochloric acid. M. p. 232°C. Recrystallized from ethanol-acetone. M. p.: 234—235 °C.

1-piperidino-3-(p-cyclohexylphenyl)propane-HCl (XXX).

5 g of XXIX is hydrogenated in 30 ml of acetic acid in the presence of 1,6 g of Pd/C, at room temperature and at atmospheric pressure. The calculated amount of hydrogen is taken up in about 5 hours, if not, 1,3 ml of 9,8 N $HClO_3$ is added to the solution and the hydrogenation is continued at 85 °C for further 5 hours. After cooling, it is filtered, potassium acetate is added to the filtrate to remove the perchlorate residue. It is filtered again and the solvent is distilled in vacuo. The oily residue is dissolved in 20 ml of water and rendered alkaline by 10% NaOH it is extracted with ether. The ether extract is washed with water and dried (anhydrous Na_2SO_4). Upon distillation the ether, the residue is dissolved in 5 ml of abs. ethanol and hydrochloric ether is added to it up to a slightly acidic pH. While kept standing it is crystallized, then filtered, and it is recrystallized from an acetone ethanol mixture (lamellated crystals). Yield: 3,2 g. M. p.: 199—200 °C.

1-piperidino-3-(p-methylphenyl-)2-methyl-propanol-3-HCl (XXXI).

10 g of 1-piperidino-3(p-methylphenyl-)-methyl-propanone-3-HCl (Mydeton) is hydrogenated in 40 ml of abs. ethanol, in the presence of 1,5 g of Pd/C, at room temperature and atmospheric pressure. About 8 hours are needed to take up the calculated amount of hydrogen. It is filtered, concentrated to half, and kept in refrigerator. It is filtered, and washed with abs. acetone. Yield: 5,2 g. M. p.: 130—131 °C.

1-piperidino-3-(-p-methylphenyl-)-2-methyl-propene-3-HCl (XXXII).

3 g of hydroxy compound XXX is dissolved in 10 ml of acetic acid and it is refluxed in the presence of 1 ml of 9,4 N $HClO_3$ for 50 minutes. After cooling, another ml of $HClO_3$ is added and it is diluted until turbidity begins. The perchlorate of the unsaturated compound is crystallized while standing. Yield: 2,5 g. M. p.: 162 °C. The perchlorate is solved in 5 ml of acetone and alkalized with 2 N NaOH, then diluted with 10 ml of water and extracted with ether. The ether solution is washed with water, dried anhydrous (Na_2SO_4) and evaporeted. The oily residue after distillation, is dissolved in 5 ml of absolute acetone and ether-hydrochloric acid is added until a slightly acidic pH. While standing, the hydrochloride of the propene derivative crystallizes. Yield: 1,2 g. M. p.: 200 °C.

1-piperidino-3-(2-tetrahydro-(5, 6, 7, 8)-naphthyl-)propanone-3-HCl (XXXIII).

50 g of 2-acetyl-tetrahydro-(5, 6, 7, 8)-naphthalene (27), 34,8 g piperidine HCl and 15 g of paraformaldehyde are suspended in 150 ml of abs. ethanol and refluxed for 6 hours. The warm solution is filtered and evaporated to half at reduced pressure. 200 ml of abs. acetone is added to the residue and it is kept in a refrigerator. The next day it is filtered, washed with acetone and dried. Yield: 75 g. M. p.: 172—174 °C. Recrystallized from acetone-ethanole mixture, M. p.: 178,5 °C.

1-piperidino-3-(-2-tetrahydro-(5, 6, 7, 8) naphthyl-)propanol-3-HCl (XXXIV).

45 g of hydrochloride of XXXIII is dissolved in a mixture of 250 ml of water and 50 ml of ethanol. It is acidified with a few drops of HCl and reduced in the presence of 11 g of a Pd/C catalyst at atmospheric pressure. The calculated amount of hydrogen is taken up in about 18 hours. It is filtered and the filtrate is evaporated to 1/4 the volume at reduced pressure. The residue is rendered alkaline with 5% NaOH,

it is extracted with 4 ×60 ml of ether. The combined ether extracts are washed with water and dried with anhydrous Na_2SO_4. After evaporation of the ether 26 g of viscous oil remains, which is converted into the hydrochloride (in acetone solution with hydrochloric ether). The filtered crystalline substance is recrystallized from acetone. Yield: 33 g. M. p.: 168 °C.

1-piperidino-3-(-2-teirahydro (5, 6, 7, 8) naphthyl-)propene-3-HCl (XXXV).

5 g of XXXIV is dissolved in 15 ml of acetic acid and refluxed in the presence of 0,6 ml of 9,4 $HClO_3$ for one hour. After cooling an other ml of $HClO_3$ is added to the solution and diluted with water until the appearance of turbidity. The perchlorate of the base crystallizes while standing. Yield: 3,4 g. M. p.: 165—166 °C. Dissolved in acetone, it is rendered alkaline with 5% KOH, and it is extracted with ether. The ether solution is washed with water and dried (anhydrous Na_2SO_4). The dense oily residue is distilled and dissolved in 5 ml of absolute ethanol, it is acidified with hydrochloric ethanol, and ether is added until turbidity begins. While left standing lamellated crystals are precipitated from the solution, it is filtered and washed with little absolute acetone. M. p.: 224—225 °C.

1-(-beta-hydroxyethyl-aminomethyl-)-3-phenyl-propene-3-HCl (XXXVI).

5 g of cinnamic alcohol is added dropwise to 5,3 g of methylamino-ethanol in 10 minutes under constant. It is heated on a water bath for 40 minutes after the addition and kept standing for two hours at room temperature, it is diluted with 30 ml of water, then extracted with ether. The ether extract is washed with water and dried (anhydrous Na_2SO_4).

Evaporating the solvent, the oily residue is fractionated. The b. p. of the main fraction is 140 °C/4 mm. Yield: 5.1 g.
The HCl was obtained with alcoholic hydrochloric acid at 15—20 °C. M. p. of HCl: 121 °C.

1-(-beta-chlorethylaminomethyl-)-3-phenyl-propene-3-HCl (XXXVII).

9 g of thionylchloride is added to 5 g of XXXVI—HCl under cooling. Thereafter, it is heated, and refluxed for 1/2 hour.

The residue of the thionyl chloride is distilled *in vacuo*. The remaining brown, crystalline substance is solved in 30 ml of absolute acetone. On cooling, slightly brown crystals are precipitated.

It is filtered and recrystallized, m. p.: 147 °C. Yield: 3,8 g. (Special caution is advised because the substance induces inflammation of the skin.)

1-(-beta-piperidino-ethylamino-ethyl-)-3-phenyl-propene-3-2.HCl (XXXVIII).

10 g of piperidine is slowly dropped to 5 g of XXXVII—HCl, then refluxed for 2 hours, and kept at room temperature for one day, it is diluted with water and extracted with ether. The collected etheric extract was washed with water to remove the residue of piperidine and piperidine-HCl. It is dried (anhydrous Na_2SO_4), the ether evaporated and the residue dissolved in 30 ml of an acetone:ethanol mixture (1:1), it is acidified with HCl in dry ethanol to a slightly aceadic pH.

It is crystallized while kept standing. Small lamellae of mother-of- pearl color are obtained (3 g). M. p. of HCl is 248—250 °C.

1-(-p-i-propyl-)-phenyl-3-piperidino-propane-HCl (XXXIX).

27,9 g XIX is dissolved in 200 ml of absolute methanol and acidified with a small amount of HCl in dry ethanol and hydrogenated in the presence of 3 gr of Pd/C at atmospheric pressure. The hydrogenation is stopped after taking up the calculated amount of hydrogen. Having filtered the catalyst and evaporated the solvent in vacuo, about 70 ml, 23,6 g of white substance was filtered. M. p.: 203—204 °C. Further crystallized substance can be obtained from the mother liquor.

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

Синтез некоторых новых производных 1-(р-алкиларий)-3-трет.-амино-1-пропена и пропана

Щ. Фельдеак, Б. Маткович, И. Добо, Я. Порсас

Продолжая наши раннше синтетические исследования в области депрессантов центральной нервной системы (ц. н. с.), были получены при помощи реакции Фриделя—Крефца некоторые п-алкилацетофеноны и переведены реакцией Манниха в И-ниперидиноалкил-п-алкилфенилкетоны. Они восстановлены до спиртов и дегидратированы хлорной кислатой до пропенов, а после повторного каталитического восстановления были получены производные пропанов.

Фармакологически установлено, что многие из синтезированных соединений являются активными депрессантами ц. н. с.

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