SYNTHESIS OF SEVERAL 1-(AMINOACYL)-4-CINNAMYLPIPERAZINES AS POTENTIAL ANALGETICS*

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A reaction of 1-cinnamylpiperazine (*III*) with chloroacetyl chloride gave the chloroacetyl derivative *IV* which was subjected to substitution reactions with aniline, 4-phenylpiperidin-4-ol (*XIa*), 4-(4-fluorophenyl)piperidin-4-ol (*XIb*) and 4-(4-chloro-3-trifluoromethylphenyl)piperidin-4-ol and afforded the title compounds *V* and *VII*–*IX*. Acylation reactions of compounds *V* and *VII* with propionyl chloride gave the propionanilide derivative *VI* and the 4-phenyl-4-propanoyloxypiperidine derivative *X*. With the exception of compound *VIII*, the new substances are analgetically less active than 1-butyryl-4-cinnamylpiperazine (*I*) and as antiinflammatory agents they are little active or inactive.

In connection with our systematic investigations in the field of neurotropically active piperazine derivatives[1], our attention was attracted by the reports on the analgetic activity of 1-butyryl-4-cinnamylpiperazine (*I*), known under the code number AP-237 (ref.[2]). This compound was described as being analgetically more active than aminophenazone (aminopyrine[3]) and its metabolism was carefully investigated[4–11]. For the purpose of comparison we prepared compound *I* by a modified procedure and synthesized several new 1-(aminoacyl)-4-cinnamylpiperazines *VI*–*X* in the belief that introduction of fragments, typical for strong analgesics[12], could enhance the activity.

For preparing compound *I*, 1-ethoxycarbonylpiperazine was treated with cinnamyl chloride[2] which afforded the carbamate *II* (cf. preparation by a different method[13]) which was hydrolyzed in the second step with ethanolic potassium hydroxide to 1-cinnamylpiperazine (*III*) (ref.[2]). The transformation of this compound to substance *I* by treatment with butyryl chloride proceeded according to the literature[2].

A reaction of 1-cinnamylpiperazine (*III*) with chloroacetyl chloride in chloroform at room temperature led to the hydrochloride of *IV*. Its decomposition with sodium hydrogen carbonate gave the base *IV* which was treated with aniline in boiling benzene. The obtained anilinoacetyl derivative *V* was acylated with propionyl chloride in a boiling mixture of chloroform and benzene. The product *VI* was isolated in the form

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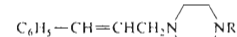
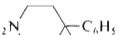
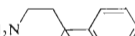


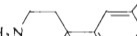
I, R = $CO(CH_2)_2CH_3$
II, R = $COOC_2H_5$
III, R = H
IV, R = $COCH_2Cl$
V, R = $COCH_2NH-C_6H_5$
VI, R = $COCH_2N(C_6H_5)COC_2H_5$



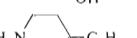
VII, R = $COCH_2N$(4-C_6H_5, 4-OH)



VIII, R = $COCH_2N$(4-OH, 3-(4-F-C_6H_4))



IX, R = $COCH_2N$(4-OH, 3-(2-CF_3, 4-Cl-C_6H_3))



X, R = $COCH_2N$(4-C_6H_5, 4-$OCOC_2H_5$)

of crystalline salts. Reactions of the chloroacetyl derivative *IV* with 4-phenylpiperidin-4-ol (*XIa*) (ref.[14–18]), 4-(4-fluorophenyl)piperidin-4-ol (*XIb*) (ref.[15–19]) and 4-(4-chloro-3-trifluoromethylphenyl)piperidin-4-ol[20] in boiling chloroform afforded compounds *VII*–*IX*. The starting amines *XIa* and *XIb* were obtained from 1-ethoxycarbonyl-4-piperidone[20] which was transformed by reactions with phenylmagnesium bromide and 4-fluorophenylmagnesium bromide to carbamates *XIIa* (for a different method of preparation, *cf.*[21]) and *XIIb*. In the following step the carbamates were hydrolyzed with potassium hydroxide in a small volume of boiling ethanol (for analogy, *cf.*[20]) to compounds *XIa* and *XIb*. The amino alcohol *VII* was treated with propionyl chloride in chloroform in the presence of triethylamine and gave the propionate *X*. The bases prepared were characterized as crystalline salts which likewise were used for pharmacological testing.

XI, R = H
XII, R = $COOC_2H_5$
a, R^1 = H
b, R^1 = F

In comparison with compound *I* (hydrochloride, AP-237) the substances *II* and *VI*–*X* were tested using oral administration for the acute toxicity in mice, for analgetic activity in mice with mechanical (pressure) and chemical stimulation (intraperitoneal administration of acetic acid), and finally for antiinflammatory activity in the test of carrageenan edema of the rat paw. The results are summarized in Table I.

In conclusion, the new compounds are little toxic, with the exception of compound *VIII* they are less analgetically active than compound *I* and they are little active or inactive as antiinflammatory agents.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa at 77°C or at room temperature. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200 G spectrophotometer and the ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the reaction mixtures were checked by chromatography on thin layers of silica gel (Silufol). Preparative chromatography was done with neutral Al_2O_3 (activity II).

1-Cinnamyl-4-(ethoxycarbonyl)piperazine (*II*)

A) A stirred suspension of 18·5 g $NaHCO_3$ in a solution of 90·6 g 1-ethoxycarbonylpiperazine in 190 ml ethanol was treated dropwise over 5 min with 31·0 g cinnamyl chloride[2]. The mixture was stirred for 30 min at room temperature, refluxed for 7 h and allowed to stand for 48 h at room temperature. The salts were filtered off, the filtrate was evaporated and the residue distilled; 28·8 g (52%), b.p. 171—174°C/70 Pa. Treatment of the base with maleic acid in ethanol gave the hydrogen maleate, m.p. 152°C (ethanol). For $C_{20}H_{26}N_2O_6$ (390·4) calculated: 61·52% C, 6·71% H, 7·17% N; found: 61·46% C, 7·00% H, 7·07% N.

TABLE I

Toxicity, analgetic and antiinflammatory activity of 1-cinnamylpiperazines (oral administration)

Compound[a]	Acute toxicity LD_{50} g/kg	Analgesia, mechanical stimulation ED_{50} mg/kg	Analgesia, chemical stimulation ED_{50} mg/kg	Carrageenan edema, dose mg/kg; % of inhibition[b]
I	>1·0	91	69	50; 25 +
II	>1·0	134	84	60; 16 +
VI	*c.* 1·0	183	74	100; 0
VII	*c.* 0·6	205	113	100; 0
VIII	<0·5	[c]	62	100; 21 +
IX	>1·0	[d]	[d]	[d]
X	>0·5	[c]	153	100; 0
Aminophenazone	0·8	94	104	50; 28 +

[a] Tested in the form of salts described in the Experimental; [b] + indicates statistical significance; [c] was not tested; [d] difficulties with the preparation of suspensions.

B) A mixture of 57·7 g 1-ethoxycarbonylpiperazine and 27·7 g cinnamyl chloride[2] was stirred for 30 min without heating and then heated for 3 h to 90°C. After cooling it was decomposed with 120 ml 10% NaOH and extracted with ether. The extract was washed with saturated solution of K_2CO_3, dried with K_2CO_3 and distilled; 31·0 g (62%), b.p. 165–169°C/80 Pa. The product is identical with that obtained under *A*.

1-Cinnamylpiperazine (*III*)

A mixture of 15·6 g *II*, 7·75 g KOH and 16 ml ethanol was refluxed for 3·5 h in a bath of 120 to 125°C. After cooling the mixture was diluted with 100 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and distilled; 8·1 g (75%), b.p. 112–114°C/ /13 Pa. Dipicrate, m.p. 245–248°C with decomposition (ethanol). Lit[2], m.p. 247°C.

1-Butyryl-4-cinnamylpiperazine (*I*)

A reaction of *III* with butyryl chloride in benzene in the presence of $NaHCO_3$ according to Irikura and coworkers[2] gave 65% base, b.p. 184–185°C/25 Pa. Hydrochloride, m.p. 200–202°C (acetonitrile). Lit.[2], b.p. 194–196°C/14 Pa (base) and m.p. 207–209°C (hydrochloride).

1-(Chloroacetyl)-4-cinnamylpiperazine (*IV*)

A solution of 14·3 g *III* in 90 ml chloroform was treated under stirring at 5–10°C over 20 min with 8·0 g chloroacetyl chloride, added dropwise. The mixture was stirred for 3 h at room temperature and allowed to stand for 2 days. The precipitated hydrochloride of the product (17·0 g, 78%) was filtered and crystallized from chloroform, m.p. 174–177°C (with softening at 111°C and resolidification to needles). UV spectrum: λ_{max} 248 nm (log ε 4·34). IR spectrum (KBr): 699, 750, (C_6H_5), 960 (*trans*-CH=CH), 1 668 (CON), 2 395 cm^{-1} (NH^+). For $C_{15}H_{20}Cl_2N_2O$ (315·2) calculated: 57·15% C, 6·40% H, 22·49% Cl, 8·89% N; found: 57·13% C, 6·44% H, 22·54% Cl, 8·81% N.

Decomposition of the hydrochloride with a saturated $NaHCO_3$ solution and extraction with benzene gave the crude solid base, m.p. 98–104°C, which was used without further purification.

1-(Anilinoacetyl)-4-cinnamylpiperazine (*V*)

A mixture of 2·5 g *IV*, 3·5 ml aniline and 5 ml benzene was stirred and refluxed for 2 h and allowed to stand overnight. The precipitated hydrochloride was filtered, decomposed with 50 ml 10% NaOH and the base extracted with benzene. Processing of the extract gave 2·2 g (73%) product melting at 142–144°C. Analytical sample. m.p. 144–146°C (benzene). UV spectrum: λ_{max} 246·5 nm (log ε 4·51), 282 nm (3·60), 291·5 nm (3·53). IR spectrum: 699, 702, 746, 755 (C_6H_5), 979 (*trans*-CH=CH), 1 519, 1 585, 1 610 (Ar), 1 645 (CON), 3 010, 3 033, 3 060 (Ar), 3 380 cm^{-1} (NH). ^1H NMR spectrum: δ 6·00–7·50 (m, 12 H, 2 C_6H_5 and CH=CH), 4·95 (bt, disappears after ^2H_2O, 1 H, NH), 3·84 (d, J = 4·0 Hz, 2 H, s after ^2H_2O, $COCH_2N$), 3·70 and 3·41 (2 t, 4 H, $CH_2N^1CH_2$ of piperazine), 3·15 (*d*, J = 6·0 Hz, 2 H, CH_2 of cinnamyl), 2·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine). For $C_{21}H_{25}N_3O$ (335·4) calculated: 75·19% C, 7·51% H, 12·53% N; found: 75·67% C, 7·40% H, 12·41% N.

1-Cinnamyl-4-[(N-propionanilido)acetyl]piperazine (*VI*)

A solution of 6·2 g *V* in a mixture of 100 ml benzene and 10 ml chloroform was stirred and treated at 30°C with a solution of 1·75 g propionyl chloride in 10 ml benzene, added dropwise. The mix-

ture was refluxed for 2 h. After cooling, the precipitated hydrochloride was filtered, decomposed with NH_4OH and the base isolated by extraction with benzene. It was purified by chromatography on 130 g Al_2O_3; 5·7 g (79%) homogeneous oily base. Neutralization of a solution of the base in acetone with a solution of HCl in ether gave the hydrochloride, m.p. 210—215°C with decomposition (ethanol). For $C_{24}H_{30}ClN_3O_2$ (428·0) calculated: 67·35% C, 7·07% H, 8·28% Cl, 9·82% N; found: 67·39% C, 7·06% H, 8·18% Cl, 10·03% N. Neutralization of the base with maleic acid in ethanol gave the hydrogen maleate, m.p. 146—148°C (ethanol). For $C_{28}H_{33}N_3O_6$ (507·6) calculated: 66·25% C, 6·55% H, 8·28% N; found: 66·05% C, 6·64% H, 8·49% N. Decomposition of a sample of the pure hydrochloride with NH_4OH and extraction with ether gave the pure oily base used for recording the ^1H NMR spectrum: δ 7·30 (m, 10 H, 2 C_6H_5), 6·00 to 6·70 (m, 2 H, CH=CH), 4·41 (s, 2 H, $COCH_2N$), 3·50 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 3·12 (d, J = 6·5 Hz, 2 H, CH_2 of cinnamyl), 2·48 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·13 (q, J = 7·0 Hz, 2 H, CH_2 of propionyl), 1·08 (t, J = 7·0 Hz, 3 H, CH_3).

1-(Ethoxycarbonyl)-4-phenylpiperidin-4-ol (*XIIa*)

The Grignard reagent was prepared from 5·84 g Mg and 37 g bromobenzene in 180 ml ether. Under stirring it was treated over 50 min with a solution of 28 g 1-ethoxycarbonyl-4-piperidone[20] in 320 ml ether, the mixture was stirred for 1 h at room temperature and refluxed for 1 h. After standing overnight it was decomposed with 200 ml 20% NH_4Cl, the organic layer was separated, the undissolved solid was extracted with chloroform, the solutions were combined, dried and evaporated; 29·6 g (73%), m.p. 152—154°C. Recrystallization from benzene gave a product melting at 156—158°C. Lit.[21], m.p. 154°C (prepared differently).

1-(Ethoxycarbonyl)-4-(4-fluorophenyl)piperidin-4-ol (*XIIb*)

Was prepared similarly from 4-fluorophenylmagnesium bromide (7·0 g Mg, 52·6 g 4-bromofluorobenzene, 180 ml ether) and 42·6 g 1-ethoxycarbonyl-4-piperidone[20] in 250 ml ether; 60 g (90%) oily product which slowly crystallized by cooling and a sample was recrystallized from a large excess of hexane; m.p. 80—82°C. For $C_{14}H_{18}FNO_3$ (267·3) calculated: 62·90% C, 6·79% H, 5·24% N; found: 62·74% C, 7·01% H, 5·55% N.

4-Phenylpiperidin-4-ol (*XIa*)

A mixture of 14·5 g *XIIa*, 16·5 g KOH and 24 ml ethanol was refluxed for 2 h in a bath of 120°C. After cooling the mixture was diluted with water and extracted with dichloromethane. Processing of the extract gave 9·3 g (90%) product melting at 154—156°C. Washing with hexane increased the m.p. to 161—162°C. Lit.[15], m.p. 159—160°C (different method of preparation).

4-(4-Fluorophenyl)piperidin-4-ol (*XIb*)

A similar treatment of a mixture of 46 g *XIIb*, 50 g KOH and 70 ml ethanol gave 29 g (87%) crude product which crystallized from hexane and was recrystallized from a mixture of acetone and hexane, m.p. 114—117·5°C. Lit[15], m.p. 116·4—117·6°C (different method of preparation).

1-Cinnamyl-4-[(4-hydroxy-4-phenylpiperidino)acetyl]piperazine (*VII*)

A solution of 4·9 g *XIa* in 50 ml chloroform was stirred and treated over 30 min with a solution of 7·2 g *IV* in 30 ml chloroform. The mixture was refluxed for 4 h, evaporated, the residue de-

composed with 100 ml 10% NaOH and extracted with chloroform. Processing of the extract gave 7·2 g (67%) product melting at 135–140°C. Analytical sample, m.p. 137·5–139·5°C (ethanol–ether). UV spectrum: λ_{max} 250 nm (log ε 4·34), 282·5 nm (3·23), 291·5 nm (3·09). IR spectrum: 706, 752, 770 (C_6H_5), 962 (*trans*-CH=CH), 1 130 (R_3C—OH), 1 472, 1 600 (Ar), 1 649 (CON), 3 140 cm^{-1} (OH). ^1H NMR spectrum: δ 7·10–7·60 (m, 10 H, 2 C_6H_5), 6·00–6·70 (m, 2 H, CH=CH), 3·65 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 3·20 (s, 2 H, $COCH_2N$), 3·15 (d, 2 H, CH_2 of cinnamyl), 1·50–3·00 (m, remaining 6 CH_2). For $C_{26}H_{33}N_3O_2$ (419·6) calculated: 74·43% C, 7·93% H, 10·02% N; found: 74·38% C, 7·88% H, 9·87% N.

Monohydrochloride, m.p. 225·5–227°C with decomposition (ethanol–ether). For $C_{26}H_{34}Cl.N_3O_2$ (456·0) calculated: 68·47% C, 7·52% H, 7·78% Cl, 9·21% N; found: 67·81% C, 7·43% H, 7·55% Cl, 9·44% N.

Dihydrochloride monohydrate, m.p. 254–255°C with decomposition (97% ethanol–ether). For $C_{26}H_{35}Cl_2N_3O_2 + H_2O$ (510·5) calculated: 61·17% C, 7·31% H, 13·89% Cl, 8·23% N; found: 61·50% C, 7·27% H, 13·92% Cl, 8·31% N.

1-Cinnamyl-4-[4-(4-fluorophenyl)-4-hydroxypiperidino]acetylpiperazine (*VIII*)

A solution of 5·45 g *XIb* in 50 ml chloroform was treated with a solution of 7·7 g *IV* in 45 ml chloroform and the mixture processed similarly like in the preceding case; 9·1 g (75%) base, m.p. 142–147°C. Analytical sample, m.p. 145·5–147°C (acetone). IR spectrum: 698, 750, 840 (5 and 2 adjacent Ar–H), 960 (*trans*-CH=CH), 1 130 (R_3C—OH), 1 512, 1 600, 3 045, 3 070 (Ar), 1 646 (CON), 3 140 cm^{-1} (OH). For $C_{26}H_{32}FN_3O_2$ (437·5) calculated: 71·37% C, 7·37% H, 4·34% F, 9·61% N; found: 71·31% C, 7·68% H, 4·30% F, 9·44% N.

Bis(hydrogen maleate) monohydrate, m.p. 94–97°C (ethanol–ether). For $C_{34}H_{40}FN_3O_{10} + H_2O$ (687·7) calculated: 59·38% C, 6·16% H, 2·76% F, 6·11% N; found: 59·84% C, 6·05% H, 2·44% F, 5·86% N.

Dihydrochloride monohydrate, m.p. 243–245·5°C with decomposition (95% ethanol). For $C_{26}H_{34}Cl_2FN_3O_2 + H_2O$ (528·5) calculated: 59·08% C, 6·87% H, 13·43% Cl, 3·60% F, 7·94% N; found: 58·89% C, 7·08% H, 13·54% Cl, 3·25% F, 7·74% N.

1-Cinnamyl-4-[4-(4-chloro-3-trifluoromethylphenyl)-4-hydroxypiperidino]acetyl-piperazine (*IX*)

A reaction of 2·3 g 4-(4-chloro-3-trifluoromethylphenyl)piperidin-4-ol[20] with 2·4 g *IV* in 25 ml boiling chloroform gave similarly like in the preceding cases 2·6 g (54%) crude base, m.p. 151 to 157°C. Analytical sample, m.p. 156–158°C (benzene). IR spectrum: 677, 748 (C_6H_5), 967 (*trans*-CH=CH), 1 149 (R_3C—OH), 1 168, 1 320 ($ArCF_3$), 1 487, 3 000, 3 070, 3 100 (Ar), 1 634 (CON), 3 403 cm^{-1} (OH). ^1H NMR spectrum: δ 7·00–8·00 (m, 8 H, Ar—H), 6·52 and 6·12 (d and dt, J = 14·0 and 14·0; 6·0 Hz, 2 H, CH=CH), 3·58 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 3·18 (s, 2 H, $COCH_2N$), 3·14 (d, J = 6;0 Hz, 2 H, CH_2 of cinnamyl), 2·48 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 1·20–3·00 (m, 4 CH_2). For $C_{27}H_{31}ClF_3N_3O_2$ (522·0) calculated: 62·12% C, 5·99% H, 6·79% Cl, 10·92% F, 8·05% N; found: 62·12% C, 6·11% H, 6·89% Cl, 10·76% F, 7·84% N.

Bis(hydrogen maleate), m.p. 151–154°C (acetone–ether). For $C_{35}H_{39}ClF_3N_3O_{10}$ (754·1) calculated: 55·74% C, 5·21% H, 4·70% Cl, 7·56% F, 5·57% N; found: 55·45% C, 5·16% H, 4·83% Cl, 7·63% F, 5·46% N.

1-Cinnamyl-4-[(4-phenyl-4-propionoxypiperidino)acetyl]-piperazine (*X*)

A solution of 5·2 g *VII* and 1·0 g triethylamine in 25 ml chloroform was stirred and treated (under cooling with water) with 2·5 g propionyl chloride, added dropwise. The mixture was stirred for 6 h at room temperature, allowed to stand overnight, shaken with 150 ml saturated K_2CO_3 solution and extracted with chloroform. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue was chromatographed on 250 g Al_2O_3. Elution with benzene, containing 25% chloroform, gave 2·8 g (48%) homogeneous oily base. Neutralization with maleic acid in acetone gave the bis(hydrogen maleate), m.p. 184—186°C (95% ethanol). For $C_{37}H_{45}.N_3O_{11}$ (707·8) calculated: 62·79% C, 6·41% H, 5·93% N; found: 62·74% C, 6·63% H, 5·89% N. A sample of the salt was decomposed with NH_4OH and the pure base isolated by extraction with ether; it was used for recording the IR spectrum (CS_2): 702, 747, 767 (C_6H_5), 971 (*trans*-CH=CH), 1 652 (CON), 1 742 cm^{-1} (RCOOR').

The spectra were recorded and interpreted by Drs E. Svátek and J. Holubek (physico-chemical department of this institute). Compounds I—III, XIab *and* XIIab *were prepared by Dr Z. Vejdělek and Mr J. Pomykáček in this laboratory. The analyses were carried out by Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech (analytical department of this institute).*

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