

## 1-(4-CYCLOPENTYLPHENYL)PIPERAZINE AND ITS 4-SUBSTITUTED DERIVATIVES; SYNTHESIS AND BIOLOGICAL SCREENING

Zdeněk VEJDELEK and Miroslav PROTIVA

*Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3*

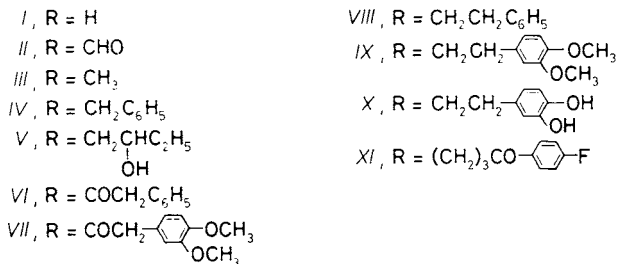
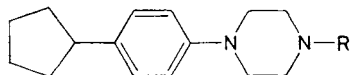
Received October 24th, 1986

Heating the hydrochlorides of 4-cyclopentylaniline and diethanolamine to 250°C gave 1-(4-cyclopentylphenyl)piperazine (*I*). Acylation of *I* with ethyl formate and the corresponding acyl chlorides gave the amides *II*, *VI*, and *VII* which were reduced with lithium aluminium hydride to the piperazines *III*, *VIII*, and *IX*. Treatment of *I* with benzyl chloride and with 4-chloro-1-(4-fluorophenyl)butan-1-one under different conditions led to compounds *IX* and *XI*. Addition reaction of *I* to 1,2-epoxybutane resulted in the amino alcohol *V*. The products showed marginal tranquillizing activity (especially compound *VIII*), some antimicrobial activity *in vitro* and some anthelmintic activity.

4-Substituted 1-arylpiperazines were found to exhibit pharmacodynamic properties and some of them were introduced as therapeutic agents. In the psychotropic field we meet them especially among the antidepressants (*e.g.* etoperidone<sup>1</sup>, trazodone<sup>2</sup>), tranquilizers (mepiprazole<sup>3</sup>, niaprazine<sup>4</sup>), and neuroleptics (fluanisone<sup>5</sup>). Continuing our efforts to find neurotropic and psychotropic agents within series of amines containing in their molecules the cyclopentylphenyl fragment as the lipophilic moiety (*cf.*<sup>6,7</sup>), we have now prepared several 4-substituted 1-(4-cyclopentylphenyl)piperazines and submitted them to biological screening (pharmacological, antimicrobial, and veterinary antiparasitic). In this communication we are describing the synthesis of these compounds and are mentioning the results of the screening.

The basic compound prepared, and at the same time the synthetic precursor of all compounds described here, was 1-(4-cyclopentylphenyl)piperazine (*I*) which was obtained by heating 4-cyclopentylaniline hydrochloride<sup>8</sup> with a slight excess of diethanolamine hydrochloride (method<sup>9</sup>) to 250°C. About 50% of the starting 4-cyclopentylaniline were recovered and the yield on compound *I*, calculated *per* conversion, was quite satisfactory. It was formylated by refluxing with ethyl formate to give the N-formyl derivative *II* in a high yield. The reduction of *II* with lithium aluminium hydride afforded 1-(4-cyclopentylphenyl)-4-methylpiperazine (*III*). Compounds *I–III* were characterized by <sup>1</sup>H NMR spectra and bases *I* and *III* were transformed to maleates for pharmacological testing. Treatment of compound *I* with benzyl chloride in 1-butanol in the presence of potassium carbonate at 110°C gave the N-benzyl compound *IV* which was isolated and characterized as the dihydro-

chloride. Reaction of *I* with 1,2-epoxybutane in methanol at 55–60°C resulted in the N-(2-hydroxybutyl) compound *V* whose structure was corroborated by spectra; its neutral maleate was prepared for the testing.



The amine *I* was acylated with phenylacetyl chloride and (3,4-dimethoxyphenyl)-acetyl chloride<sup>10</sup>. The resulting amides *VI* and *VII* were reduced with lithium aluminium hydride giving the amines *VIII* and *IX*. The dimethoxyphenyl compound *IX* was demethylated by refluxing with hydrobromic acid which led to the catecholamine-like product *X*. All the three amines *VIII*–*X* were characterized by spectra and were transformed to the maleates. Heating compound *I* with 4-chloro-1-(4-fluorophenyl)-butan-1-one<sup>11</sup> to 110–120°C for 50 h (method<sup>12</sup>) afforded the fluanisone analogue *XI* (characterized by spectra and the maleate).

Compounds *I*, *III*–*V*, and *VIII*–*X* were subjected to pharmacological screening in the form of salts, described in Experimental; due to the low water-solubility of the maleates, all compounds – with the exception of *V* – were administered orally. Their acute toxicity in mice is rather low, LD<sub>50</sub> (mg/kg): *I*, 1 250; *III*, 2 000; *IV*, > 2 500; *V*, 90 (*i.v.*); *VIII*, > 2 500; *IX*, 2 000; *X*, > 2 500. The doses used in the screening, D (mg/kg): *I*, 250; *III* and *IV*, 300; *V*, 17 (*i.v.*); *VIII*–*X*, 300. All compounds were inactive in the tests for incoordinating activity (rotarod in mice), analgetic activity (Haffner's test in mice), hypotensive activity (normotensive rats), antiarrhythmic activity (against aconitine in rats), antiinflammatory activity (kaolin oedema in rats), antihistamine activity (detoxication of histamine in guinea-pigs), and they did not influence the hemocoagulation (bleeding time in mice). Most of the compounds showed some hypothermic effects in rats, ED (mg/kg): *I*, 100–250; *III*, 100–300; *IV*, 50–100; *VIII*, 100 (doses decreasing the rectal temperature by 1°C). Exceptional were the following effects: prolongation of the thiopental sleeping time in mice, *VIII*, 50–100 mg/kg (the dose prolonging to 200% of the control); anticonvulsant effects in mice, *IX*, towards pentetrazole 100–300 mg/kg (significant

effect), towards electroshock 300 mg/kg (protection of 50% animals); hypoglycaemic effect in rats, IX, 300 mg/kg (decreasing the blood sugar concentration by 20%); diuretic effect in mice, IX, 100 mg/kg (increasing diuresis by 100%); spasmolytic effect towards acetylcholine contractions of the isolated rat duodenum, V, 10 µg/ml (concentration reducing the contractions by 50%); negative inotropic effect on the isolated rabbit heart atrium, V, 25–50 µg/ml (concentration decreasing the inotropy by 25%); influence on the locomotor activity of mice, VIII, 300 mg/kg (significant inhibition of the activity). By its combination of central depressant, thiopental potentiating and hypothermic effects, only compound VIII has the profile of a mild tranquillizer. Complete inactivity of the catecholamine-like compound X is surprising.

Due to its structural relation to fluanisone<sup>5</sup>, compound XI was tested as a potential neuroleptic agent. Its acute toxicity in mice, LD<sub>50</sub> is higher than 1 000 mg/kg (*p.o.*) (30% lethality after this dose). Discoordinating activity in the rotarod test in mice, ED<sub>50</sub> = 30 mg/kg *p.o.* For estimating the cataleptic activity in rats, the compound was administered in doses of 2.5, 5.0, 10, 25, 50, and 100 mg/kg *p.o.* There was no relation between the dose and the effect. Lower doses were seemingly more active (catalepsy with 40% of rats) than the highest dose used. Compound XI cannot thus be classified as a neuroleptic.

Antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in µg/ml are given unless they exceed 100 µg/ml): *Streptococcus β-haemolyticus*, I 50, X 50; *Streptococcus faecalis*, X 50; *Staphylococcus pyogenes aureus*, I 100, X 25; *Pseudomonas aeruginosa*, X 100; *Proteus vulgaris*, X 100; *Mycobacterium tuberculosis* H37Rv, I 12.5, III 50, IV 12.5, V 25, VIII 100, IX 50, X 100, XI 50; *Saccharomyces pasterianus*, IV 50, VIII 25, IX 12.5, X 50, XI 25; *Trichophyton mentagrophytes*, I 50, III 50, IV 12.5, VIII 12.5, IX 12.5, X 12.5, XI 25; *Candida albicans*, VIII 50, IX 25, X 50, XI 50; *Aspergillus niger*, IX 50, XI 50.

Compounds I, III, IV, and IX showed some activity in the primary screening for coccidiostatic activity (*Eimeria tenella*). The screening for anthelmintic effects reveals the inactivity of compounds I, III–VI, and VIII–X against *Hymenolepis nana* and *Nippostrongylus brasiliensis*. On the other hand, III was active towards *Trichocephalus muris* and *Aspicularis tetraptera*, and V was active towards *Fasciola hepatica*. The activities found did not warrant, however, more detailed investigations.

## EXPERIMENTAL

The melting points of analytical samples were determined in Kofler block and they are not corrected; the samples were dried *in vacuo* of about 60 Pa over P<sub>2</sub>O<sub>5</sub> at room temperature or at 77°C. The UV spectrum (in ethanol) was recorded with a Unicam SP 8000 spectrophotometer,

the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer, and the  $^1\text{H}$  NMR spectra (in  $\text{C}^2\text{HCl}_3$  unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were mostly dried with  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure on a rotating evaporator.

#### 1-(4-Cyclopentylphenyl)piperazine (*I*)

A mixture of 52.2 g 4-cyclopentylaniline, 15<sup>8</sup> ml ethanol, 37.2 g diethanolamine, and 50 ml water was treated with 60 ml hydrochloric acid, and the volatile components were distilled off on bath whose temperature was slowly raised until 230–250°C. After standing overnight, the melt was warmed, dissolved in 500 ml water, the solution was made alkaline with 20% NaOH, and extracted with a 3 : 7 mixture of benzene and ether. The extract was dried with KOH and processed by distillation. The first fraction (12.5 g), b.p. 120–130°C/0.2 kPa, was the recovered 4-cyclopentylaniline. The base *I* distilled at 175–184°C/0.2 kPa; 49.0 g (86% *per conversion*). The product crystallized from hexane, m.p. 79–80°C.  $^1\text{H}$  NMR spectrum:  $\delta$  7.10 (d,  $J = 8.0$  Hz, 3 H, 3,5- $\text{H}_2$  of phenyl), 6.80 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), 3.00 (s, 8 H, 4  $\text{CH}_2\text{N}$  of piperazine), c. 2.90 (m, 1 H, ArCH of cyclopentyl), 2.00 (s, 1 H, NH), 1.40–2.20 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{15}\text{H}_{22}\text{N}_2$  (230.3) calculated: 78.20% C, 9.63% H, 12.17% N; found: 78.21% C, 9.50% H, 12.16% N.

*Maleate*, m.p. 166–167°C (ethanol). For  $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4$  (346.4) calculated: 65.86% C, 7.57% H, 8.09% N; found: 65.98% C, 7.54% H, 8.14% N.

#### 1-(4-Cyclopentylphenyl)-4-formylpiperazine (*II*)

A mixture of 10.0 g *I* and 25 ml ethyl formate was refluxed for 6 h and evaporated. The residue crystallized from 30 ml hexane; 9.60 g (86%), m.p. 119–121°C. Analytical sample, m.p. 123 to 124°C (benzene–hexane). IR spectrum: 810 (2 adjacent Ar–H), 1 445, 1 520 (Ar), 1 642  $\text{cm}^{-1}$  ( $\text{>NCHO}$ ).  $^1\text{H}$  NMR spectrum:  $\delta$  8.02 (s, 1 H, N–CHO), 7.12 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$  of phenyl), 6.82 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), c. 3.50 (m, 4 H,  $\text{CH}_2\text{N}^4\text{CH}_2$  of piperazine), 3.12 (m, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), 2.85 (m, 1 H, ArCH of cyclopentyl), 1.40–2.20 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$  (258.4) calculated: 74.37% C, 8.58% H, 10.85% N; found: 74.36% C, 8.83% H, 10.95% N.

#### 1-(4-Cyclopentylphenyl)-4-methylpiperazine (*III*)

A solution of 14.0 g *II* in 150 ml benzene was added dropwise to a stirred solution of 6.2 g  $\text{LiAlH}_4$  in 110 ml ether and the mixture was refluxed for 5 h. After cooling it was decomposed under stirring by a slow addition of 25 ml 20% NaOH, the mixture was stirred for 30 min, the solid was filtered off, washed with benzene, and the filtrate was evaporated; 13.2 g (100%) *III* which crystallized by standing, m.p. 78–79°C (benzene–pentane).  $^1\text{H}$  NMR spectrum:  $\delta$  7.15 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$  of phenyl), 6.85 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), 3.15 (t, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), 2.90 (m, 1 H, Ar–CH of cyclopentyl), 2.58 (t, 4 H,  $\text{CH}_2\text{N}^4\text{CH}_2$  of piperazine), 2.30 (s, 3 H,  $\text{NCH}_3$ ), 1.40–2.20 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{16}\text{H}_{24}\text{N}_2$  (244.4) calculated: 78.63% C, 9.90% H, 11.47% N; found: 78.94% C, 9.97% H, 11.40% N.

*Maleate*, m.p. 180–181°C (ethanol). For  $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4$  (360.4) calculated: 66.64% C, 7.83% H, 7.77% N; found: 66.94% C, 8.15% H, 7.79% N.

## 1-Benzyl-4-(4-cyclopentylphenyl)piperazine (IV)

A solution of 6.8 g *I* in 50 ml warm 1-butanol was stirred and treated with 5.0 g  $K_2CO_3$  and 4.4 g benzyl chloride, and the mixture was stirred and heated for 6 h to 110°C. The solid was filtered off, washed with benzene and ethanol, the filtrate was evaporated *in vacuo*, and the oily residue was shaken with a solution of 20 ml hydrochloric acid in 80 ml water. The separated solid dihydrochloride was filtered, washed with water and benzene, and dried *in vacuo*; 8.0 g (76%), m.p. 225–226°C (Kofler block) or 235–237°C (capillary) (aqueous ethanol). For  $C_{22}H_{30}Cl_2N_2$  (393.4) calculated: 67.16% C, 7.69% H, 18.03% Cl, 7.12% N; found: 67.02% C, 7.79% H, 18.07% Cl, 6.99% N.

## 1-(4-Cyclopentylphenyl)-4-(2-hydroxybutyl)piperazine (V)

A stirred solution of 6.1 g *I* in 15 ml methanol was treated over 20 min with 4.0 g 1,2-epoxybutane, added dropwise, and the mixture was heated for 3 h to 55–60°C. Volatile components were evaporated *in vacuo*, the solid residue was treated with 25 ml hexane, filtered, washed with hexane, and dried *in vacuo*; 6.1 g (76%), m.p. 111–112°C (hexane). IR spectrum: 809, 825 (2 adjacent Ar—H), 990, 1 152, 1 238 (CHOH), 1 455, 1 522, 1 565 (Ar), 3 290, 3 340  $cm^{-1}$  (OH).  $^1H$  NMR spectrum:  $\delta$  7.12 (d,  $J = 8.0$  Hz, 2 H, 3,5- $H_2$  of phenyl), 6.82 (d,  $J = 8.0$  Hz, 2 H, 2,6- $H_2$  of phenyl), 3.60 (m, 1 H, CH—O), 3.40 (bs, 1 H, OH), 3.15 (t, 4 H,  $CH_2N^1CH_2$  of piperazine), 2.20–3.00 (m, 7 H, remaining 3  $CH_2N$  and ArCH of cyclopentyl), 1.40–2.20 (m, 8 H, 4  $CH_2$  of cyclopentyl), c. 1.40 (m, 2 H, 3- $CH_2$  of butyl), 0.97 (t, 3 H,  $CH_3$ ). For  $C_{19}H_{30}N_2O$  (302.5) calculated: 75.44% C, 10.00% H, 9.27% N; found: 75.69% C, 10.15% H, 9.22% N.

*Maleate*, m.p. 159–160°C (ethanol-ether). For  $C_{23}H_{34}N_2O_5$  (418.5) calculated: 66.00% C, 8.19% H, 6.79% N; found: 66.16% C, 8.24% H, 6.63% N.

## 1-(4-Cyclopentylphenyl)-4-(phenylacetyl)piperazine (VI)

$K_2CO_3$  (4.4 g) was added to a solution of 6.0 g *I* in 25 ml chloroform, the stirred mixture was treated over 25 min with a solution of 4.8 g phenylacetyl chloride in 20 ml chloroform, added dropwise, and refluxed for 90 min. After cooling it was decomposed by addition of 40 ml water and 10 ml 6%  $NaHCO_3$ , after dissolution of the inorganic salts the organic layer was separated, washed with 100 ml 6%  $NaHCO_3$ , dried, and evaporated. The residue was treated with 50 ml hexane, the mixture was shaken and cooled which induced crystallization; 6.5 g (72%), m.p. 92–93°C (cyclohexane). IR spectrum: 706, 729, 820 (5 and 2 adjacent Ar—H), 1 455, 1 520, 1 606 (Ar), 1 633  $cm^{-1}$  ( $>NCO$ ). For  $C_{23}H_{28}N_2O$  (348.5) calculated: 79.27% C, 8.10% H, 8.04% N; found: 79.46% C, 8.21% H, 7.83% N.

## 1-(4-Cyclopentylphenyl)-4-(3,4-dimethoxyphenylacetyl)piperazine (VII)

A similar reaction of 11.5 g *I* with 12.0 g (3,4-dimethoxyphenyl)acetyl chloride<sup>10</sup> in 90 ml chloroform and in the presence of 9.2 g  $K_2CO_3$  (2 h refluxing) gave 18.0 g (89%) *VII*, mp. 121–122°C (ethanol). IR spectrum: 805, 820, 840, 909 (2 adjacent and solitary Ar—H), 1 025, 1 145, 1 175, 1 240, 1 280, 1 370, 1 450 (Ar—O— $CH_3$ ), 1 470, 1 520, 1 590 (Ar), 1 635 (NCO), 2 824  $cm^{-1}$  (ArO $CH_3$ ). For  $C_{25}H_{32}N_2O_3$  (408.5) calculated: 73.49% C, 7.90% H, 6.86% N; found: 73.88% C, 8.08% H, 6.74% N.

## 1-(4-Cyclopentylphenyl)-4-(2-phenylethyl)piperazine (VIII)

A solution of 6.1 g *VI* in 50 ml benzene was slowly added to a stirred solution of 2.5 g  $LiAlH_4$  in 50 ml ether and the mixture was refluxed for 5 h. After cooling it was decomposed by the slow

addition of 10 ml 20% NaOH, the mixture was stirred for 30 min, the solid was filtered off and the filtrate evaporated. The solid residue (5.9 g, 100%) was purified by crystallization from hexane, m.p. 104–105°C.  $^1\text{H NMR}$  spectrum,  $\delta$  7.20 (s, 5 H,  $\text{C}_6\text{H}_5$ ), 7.15 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$  of phenyl), 6.85 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), 3.15 (t, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), c. 2.70 (m, 9 H,  $\begin{matrix} \text{CH}_2 \\ \text{CH}_2 \end{matrix} \text{NCH}_2\text{CH}_2\text{Ar}$  and ArCH of cyclopentyl), 1.40–2.20 (8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{23}\text{H}_{30}\text{N}_2$  (334.5) calculated: 82.58% C, 9.04% H, 8.38% N; found: 82.72% C, 9.36% H, 8.14% N.

*Maleate*, m.p. 177–178°C (ethanol). For  $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_4$  (450.6) calculated: 71.96% C, 7.61% H, 6.22% N; found: 72.22% C, 8.00% H, 6.32% N.

#### 1-(4-Cyclopentylphenyl)-4-(2-(3,4-dimethoxyphenyl)ethyl)piperazine (IX)

A similar reduction of 17.5 g VIII with 6.0 g  $\text{LiAlH}_4$  in a mixture of 100 ml benzene and 60 ml ether gave theoretical yield (16.8 g) of the solid base IX, m.p. 105–106°C (benzene-hexane).  $^1\text{H NMR}$  spectrum:  $\delta$  7.15 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$  of phenyl), 6.85 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), 6.75 (s, 3 H, 3 ArH of dimethoxyphenyl), 3.86 and 3.85 (2 s, 3 + 3 H, 2  $\text{OCH}_3$ ), 3.15 (t, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), c. 2.70 (m, 9 H,  $\begin{matrix} \text{CH}_2 \\ \text{CH}_2 \end{matrix} \text{NCH}_2\text{CH}_2\text{Ar}$  and ArCH of cyclopentyl), 1.40–2.20 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_2$  (394.5) calculated: 76.10% C, 8.69% H, 7.10% N; found: 75.96% C, 8.71% H, 6.78% N.

*Maleate*, m.p. 176–177°C (ethanol). For  $\text{C}_{29}\text{H}_{38}\text{N}_2\text{O}_6$  (510.6) calculated: 68.21% C, 7.50% H, 5.49% N; found: 68.40% C, 7.36% H, 5.46% N.

#### 1-(4-Cyclopentylphenyl)-4-(2-(3,4-dihydroxyphenyl)ethyl)piperazine (X)

A mixture of 9.0 g IX and 120 g 46% hydrobromic acid ( $d$  1.49) was refluxed for 11 h (bath of 150–160°C) and evaporated *in vacuo*. The residue was diluted with 100 ml water, treated with an excess of  $\text{NH}_4\text{OH}$ , and the crude solid base X was filtered. It was dissolved in 210 ml chloroform, the solution was filtered, evaporated, the residue was treated with 100 ml boiling ethanol, and the solution was evaporated *in vacuo*; 6.70 g (81%), m.p. 181–182°C (ethanol). IR spectrum: 820, 866 (2 adjacent and solitary Ar–H), 1 240, 1 289, 3 550 (ArOH), 1 450, 1 518, 1 612  $\text{cm}^{-1}$  (Ar).  $^1\text{H NMR}$  spectrum ( $\text{C}^2\text{H}_5\text{SOC}^2\text{H}_3$ ):  $\delta$  7.04 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$  of phenyl), 6.78, (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of phenyl), 6.60 (m, 3 H, 3 ArH of dihydroxyphenyl), 6.00 (bs, 2 H, 2 OH), 3.00 (bs, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), 2.70 (m, 1 H, ArCH of cyclopentyl), c. 2.50 (m, 8 H,  $\begin{matrix} \text{CH}_2 \\ \text{CH}_2 \end{matrix} \text{NCH}_2\text{CH}_2\text{Ar}$ ), 1.00–2.50 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_2$  (366.5) calculated: 75.37% C, 8.25% H, 7.65% N; found: 75.22% C, 8.03% H, 7.46% N.

*Maleate*, m.p. 203–205°C (aqueous ethanol). For  $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_6$  (482.6) calculated: 67.20% C, 7.10% H, 5.80% N, found: 66.77% C, 7.26% H, 5.48% N.

#### 4-(4-(4-Cyclopentylphenyl)-1-piperazinyl)-1-(4-fluorophenyl)butan-1-one (XI)

A mixture of 13.8 g I and 6.0 g 4-chloro-1-(4-fluorophenyl)butan-1-one<sup>11</sup> was heated for 50 h to 110–120°C (air condenser with KOH trap). After cooling, the melt was treated with 80 ml boiling benzene, the mixture was cooled and the hydrochloride of the recovered I (7.7 g) was filtered off. The filtrate was washed with water and shaken with 100 ml 1 : 9 dilute hydrochloric acid. Three layers were obtained; the oily layer was combined with the aqueous layer, the mixture

was made alkaline with 20% NaOH and the crude oily base *XI* was isolated by extraction with a mixture of benzene and ether; 7.7 g (65%). Purification was carried out by chromatography on a column of 200 g neutral  $\text{Al}_2\text{O}_3$  (activity II). Elution with benzene gave first 0.34 g of a less polar component which was discarded. It was followed by crystalline *XI*, m.p. 112–113°C (hexane–benzene). UV spectrum:  $\lambda_{\text{max}}$  243 nm ( $\log \epsilon$  4.46), infl. 290 nm. IR spectrum (KBr): 823, 837 (2 adjacent Ar—H), 1 147, 1 159, 1 242 (CO), 1 512, 1 520, 1 604, 1 619 (Ar), 1 686 (ArCO), 2 810, 2 845  $\text{cm}^{-1}$  ( $\text{CH}_2\text{N}$ ).  $^1\text{H}$  NMR spectrum:  $\delta$  7.95 (dd,  $J = 8.0$ ; 7.0 Hz, 2 H, 2,6- $\text{H}_2$  of fluorophenyl), 7.10 (d,  $J = 8.0$  Hz, 4 H, 3,5- $\text{H}_2$  of fluorophenyl and 3,5- $\text{H}_2$  of cyclopentylphenyl), 6.80 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$  of cyclopentylphenyl), 3.10 (m, 5 H,  $\text{CH}_2\text{N}^4\text{CH}_2$  of piperazine and ArCH of cyclopentyl), 2.98 (t, 2 H,  $\text{CH}_2\text{CO}$ ), 2.52 (def. t, 4 H,  $\text{CH}_2\text{N}^1\text{CH}_2$  of piperazine), 2.45 (t, 2 H,  $\text{NCH}_2$  in the chain), 2.00 (m, 2 H, 3- $\text{CH}_2$  in butanone), 1.40–2.20 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl). For  $\text{C}_{25}\text{H}_{31}\text{FN}_2\text{O}$  (394.5) calculated: 76.10% C, 7.92% H, 7.10% N; found: 76.17% C, 8.07% H, 7.00% N.

*Maleate*, m.p. 164–165°C (ethanol). For  $\text{C}_{29}\text{H}_{35}\text{FN}_2\text{O}_5$  (510.6) calculated: 68.21% C 6.91% H, 3.72% F, 5.49% N; found: 68.20% C, 6.94% H, 3.74% F, 5.36% N.

*The authors wish to thank their colleagues at this Institute and in other laboratories for their contributions: Drs J. Holubek and E. Svátek (recording and interpretation of spectra), Mr L. Tůma (synthesis of the starting compounds), Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech (elemental analyses), Dr J. Metyšová (psychopharmacological testing), Dr M. Bartošová (general pharmacological screening), (†) Dr J. Vintika (microbiological screening), Drs J. Daněk and P. Bedrník (Research Institute of Feed Supplements and Veterinary Drugs, Jilové near Prague), and Dr R. Špaldonová (Helminthological Institute, Slovak Academy of Sciences, Košice) (screening for coccidiostatic and anthelmintic activity).*

#### REFERENCES

1. Lisciani R., Baldini A., Feo G. de, Silvestrini B.: *Arzneim.-Forsch.* 28, 417 (1978).
2. Brogden R. N., Heel R. C., Speight Z. M., Avery G. S.: *Drugs* 21, 401 (1981).
3. Koppe V., Poetsch E., Schulte K.: *Eur. J. Med. Chem.* 10, 154 (1975).
4. Hache J., Tachon J.: *J. Pharmacol.* 7, 469 (1976); *Chem. Abstr.* 86, 65566 (1977).
5. Fregnan G. B., Porta R.: *Arzneim.-Forsch.* 31, 70 (1981).
6. Vejdělek Z., Protiva M.: *Collect. Czech. Chem. Commun.* 51, 1494 (1986).
7. Vejdělek Z., Protiva M.: *Collect. Czech. Chem. Commun.* 52, 1073 (1987).
8. Vejdělek Z., Bartošová M., Protiva M.: *Collect. Czech. Chem. Commun.* 48, 156 (1983).
9. Pollard C. B., Mac Dowell L. G.: *J. Am. Chem. Soc.* 56, 2199 (1934).
10. Lindenmann A.: *Helv. Chim. Acta* 32, 69 (1949).
11. Janssen P. A. J., Van de Westeringh C., Jageneau A. H. M., Demoen P. J. A., Hermans H. K. F., Van Daele G. H. P., Schellekens K. H. L., Van der Eycken C. A. M., Niemegeers C. J. E.: *J. Med. Pharm. Chem.* 1, 281 (1959).
12. Janssen P. A. J.: *U.S.* 2,979,508 (11.04.61); *Chem. Abstr.* 55, 18785 (1961).

Translated by the author (M.P.).