# N-SUBSTITUTED AMINOMETHYL 4-CYCLOPENTYLPHENYL KETONES AND 2-AMINO-1-(4-CYCLOPENTYLPHENYL)ETHANOLS; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

Zdeněk VEJDĚLEK and Miroslav PROTIVA

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

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The non-characterized bromo derivative *Ia*, obtained by bromination of 4-cyclopentylacetophenone, afforded by substitution reactions with diethylamine, benzylmethylamine, benzylisopropylamine, piperidine, morpholine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine the amino ketones *IIa*–*VIIIa* which were reduced with lithium aluminium hydride to the amino-alcohols *IIb*–*VIIIb*. Compounds *IIIb* and *IVb* were debenzylated by catalytic hydrogenation on palladium to the secondary amines *IXb* and *Xb*. The compounds prepared have central stimulant effects in higher doses which appears also in the rotarod test and in the evaluation of spontaneous motility. They have mostly a mild spasmolytic effect of the anticholinergic type, some of them bring about local anaesthetic and diuretic effects. The adrenolytic and hypotensive effects were found only with single compounds.

In connection with the two preceding communications of this series[1,2] we continued in the effort at finding neurotropically active amines derived from cyclopentylbenzene. We are now describing the synthesis and results of the pharmacological screening of a series of amino ketones *IIa*–*VIIIa* and amino alcohols *IIb*–*Xb* for which 4-cyclopentylacetophenone was the common starting compound[3,4].

Bromination of 4-cyclopentylacetophenone[3,4] with bromine in ether gave the oily bromoacetophenone derivative *Ia* which did not crystallize and was, therefore, used in the crude state for the substitution reactions with diethylamine, benzylmethylamine. benzylisopropylamine, piperidine, morpholine, 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine. These reactions were carried out in mixtures of ether and benzene at room temperature using an excess of about 100% of the corresponding amine (method *A*). The amino ketones *IIa*–*VIIIa* were reduced with lithium aluminium hydride in a mixture of ether and benzene (method *B*) to give the amino alcohols *IIb*–*VIIIb*. The N-benzylamino alcohols *IIIb* and *IVb* were debenzylated by catalytic hydrogenation on palladium in ethanol (method *C*) and the secondary amines *IXb* and *Xb* were obtained. Most of the compounds prepared could be isolated as crystalline bases which were transformed to the salts (mostly

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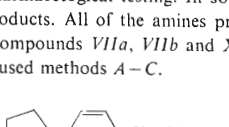
maleates) for pharmacological testing. In some cases only the salts were prepared as crystalline products. All of the amines prepared are assembled in Table I. The preparation of compounds *VIIa*, *VIIb* and *Xb* is described in the Experimental as examples of the used methods *A* – *C*.




*I*, R = Br

*II*, R = $N(C_2H_5)_2$

*III*, R = $N(CH_3)(CH_2C_6H_5)$

*IV*, R = $N(CH(CH_3)_2)(CH_2C_6H_5)$

*V*, R = N⟨ ⟩

*VI*, R = N⟨ ⟩O

*VII*, R = N⟨ ⟩N—$CH_3$

*VIII*, R = N⟨ ⟩N—$CH_2CH_2OH$

*IX*, R = $NHCH_3$

*X*, R = $NHCH(CH_3)_2$

The salts described in Table I were used for the general pharmacological screening. According to their solubility they were administered orally or parenterally (all doses in mg/kg). In the first line the values of acute toxicities in mice ($LD_{50}$) and the basic doses (D), which were used in the screening, are given: *IIa*, 62·5 and 12 *i.v.*; *IIIa*, 2 500 and 300 *p.o.*; *IVa*, 2 000 and 300 *p.o.*; *Va*, 50 and 10 *i.v.*; *VIa*, 150 and 30 *i.v.*; *VIIa*, 100 and 20 *i.v.*; *VIIIa*, 150 and 30 *i.v.*; *IIb*, 40 and 8 *i.v.*; *IIIb*, 2 500 and 300 *p.o.*; *IVb*, 2 000 and 300 *p.o.*; *Vb*, 30 and 6 *i.v.*; *VIb*, 138 and 25 *i.v.*; *VIIb*, 2 500 and 300 *p.o.*; *VIIIb*, 150 and 30 *i.v.*; *Xb*, 60 and 12 *i.v.* In doses higher than D all compounds tested bring about central excitation, ataxia, tremor and convulsions. The discoordinating effect on the rotarod is the result of this stimulating activity; doses bringing about ataxia in 50% mice (*i.v.* administration) are given: *IIa*, 5 – 12; *Va*, 5 – 10; *Vb*, 2·5 – 6; *Xb*, 12. The excitation is manifested also by the influence of the compounds on the spontaneous motility of mice (subcutaneous doses enhancing the motility by 50% in comparison with the control group are given): *IIa*, 12; *Vb*, 6; *VIIIb*, 30.

The compounds tested revealed some structurally less specific neurotropic effects. A mild spasmolytic action on the isolated rat duodenum towards the acetylcholine contractions is a very typical one (concentrations in μg/ml are given which reduce the contractions to 50%): *IIa*, 1 – 10; *Va*, 10; *IIb*, 1 – 10; *Vb*, 1 – 10; *VIb*, 10; *Xb*, 1 – 10.

Under similar conditions the spasmolytic effect towards barium chloride contractions was tested: *IIa*, 1–10; *Xb*, 10. In two cases a local anaesthetic effect in the test of infiltration anaesthesia was noted (concentrations bringing about complete anaesthesia in 50% guinea-pigs): *IIb*, 0·1–0·5%; *Xb*, 0·1–0·5%. In the test of corneal anaesthesia the effect was found only with one compound (concentration bringing about complete anaesthesia of the rabbit eye cornea in 50% animals): *Xb*, 0·1–0·5% With compound *VIIIa* the adrenolytic effect was observed: a dose of 30 mg/kg *i.v.* reduced the pressoric response to adrenaline in rats to 50%. The cardiovascular effects were not striking. In a single case (compound *VIIa*), a long-lasting drop of blood pressure in normotensive rats after a dose of 10 mg/kg *i.v.* was found. In several cases a negatively chronotropic effect on the isolated rabbit heart atria was observed (concentrations in μg/ml decreasing the frequency by 25%): *IIa*, 50; *Va*, 10; *Vb*, 50. In the same arrangement a negatively inotropic effect was also noted: *Vb*, 25–50; *VIIIb*, 50; *Xb*, 50. Several compounds proved a diuretic effect after oral administration in mice (doses enhancing the diuresis by 100% in comparison with the control group; for hydrochlorothiazide, ED = 100 mg/kg): *IIIa*, 50–100; *Va*, 50; *VIIIa*, 100.

The compounds prepared were also tested for antimicrobial activity in the tests *in vitro*; microorganisms and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *IIa* 100, *IIIa* 100, *IVa* 100, *Va* 100, *VIa* 100, *VIIa* 100, *VIIIa* 100, *IIb* 50, *IIIb* 100, *IVb* 25, *VIb* 100, *VIIb* 100, *VIIIb* 100; *Streptococcus faecalis*, *IVb* 100; *Staphylococcus pyogenes aureus*, *IIb* 100, *IVb* 50; *Pseudomonas aeruginosa*, *IVa* 100, *VIIa* 100, *VIIIa* 100, *IIIb* 100, *IVb* 100, *VIIIb* 100; *Proteus vulgaris*, *IIIa* 100, *IVa* 100, *VIIa* 100, *VIIIa* 100, *IIb* 100, *IVb* 100, *VIIb* 100; *Mycobacterium tuberculosis* H37Rv, *IIa* 100, *IIIa* 100, *IVa* 100, *VIIa* 100, *VIIIa* 100, *IIb* 25, *IIIb* 25, *IVb* 25, *Vb* 50, *VIb* 100, *VIIb* 100, *VIIIb* 100, *Xb* 25; *Saccharomyces pasterianus*, *IIa* 50, *Va* 50, *VIa* 50, *Vb* 50, *VIb* 50; *Trichophyton mentagrophytes*, *IIa* 50, *IIIa* 25, *IVa* 50, *VIa* 25, *VIIa* 25, *VIIIa* 50, *IIb* 50, *IIIb* 50, *IVb* 50, *Vb* 50, *VIb* 50, *VIIb* 50, *Xb* 50; *Candida albicans*, *VIa* 50; *Aspergillus niger*, *VIa* 50, *VIb* 50.

## 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 room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with a Unicam SP 200G spectrophotometer and $^1$H NMR spectra (in $C^2HCl_3$) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel.

### Bromomethyl 4-Cyclopentylphenyl Ketone (*Ia*)

A solution of 100 g 4-cyclopentylacetophenone[3,4] in 300 ml ether was stirred and treated over 30 min at 0–5°C with 87·3 g bromine. The mixture was stirred with cooling for another 30 min and then for 1 h without cooling. The solution was evaporated under reduced pressure (25–30°C), the residue was dissolved in a mixture of ether and benzene, the solution was washed with water,

TABLE I

N-Substituted aminomethyl-4-cyclopentylphenyl ketones, 2-amino-1-(4-cyclopentylphenyl)-ethanols and their salts

| Compound[a] | Method (yield, %) | M.p., °C (solvent) | Formula (mol.wt.) | Calculated/Found | | |
|---|---|---|---|---|---|---|
| | | | | % C | % H | % N |
| *IIa*-HM | *A* (72) | 108–109 (ethanol–ether) | $C_{21}H_{29}NO_5$ (375·5) | 67·17 66·99 | 7·79 7·88 | 3·73 3·78 |
| *IIIa*-HM | *A* (64) | 159–160 (ethanol) | $C_{25}H_{29}NO_5$ (423·5) | 70·90 70·72 | 6·90 7·01 | 3·31 3·21 |
| *IVa*-HM[b] | *A* (67) | 131–132 (ethanol–ether) | $C_{27}H_{33}NO_5 + H_2O$ (469·6) | 69·07 69·07 | 7·49 7·02 | 2·98 2·77 |
| *Va*-HM | *A* (75) | 144–145 (ethanol–ether) | $C_{22}H_{29}NO_5$ (387·5) | 68·19 67·76 | 7·55 7·62 | 3·61 3·85 |
| *VIa* | *A* (62) | 75–76[c] (hexane) | $C_{17}H_{23}NO_2$ (273·4) | 74·69 74·76 | 8·48 8·28 | 5·12 4·82 |
| *VIa*-HM | — | 150–151 (ethanol–ether) | $C_{21}H_{27}NO_6$ (389·4) | 64·76 64·68 | 6·99 6·79 | 3·59 3·53 |
| *VIIa* | *A*[d] (64) | 65–66 (benzene–hexane) | $C_{18}H_{26}N_2O$ (286·4) | 75·47 75·40 | 9·15 9·14 | 9·79 9·62 |
| *VIIa*-2 HM | — | 183–184 (aqueous ethanol) | $C_{26}H_{34}N_2O_9$ (518·6) | 60·23 60·14 | 6·63 6·91 | 5·40 5·13 |
| *VIIIa* | *A* (70) | 77–78[e] (benzene–hexane) | $C_{19}H_{28}N_2O_2$ (316·4) | 72·09 71·83 | 8·93 8·91 | 8·86 8·90 |
| *VIIIa*-2 HM | — | 159–160 (ethanol–ether) | $C_{27}H_{36}N_2O_{10}$ (548·6) | 59·08 58·75 | 6·64 7·03 | 5·11 5·13 |
| *IIb*-HCl | *B* (89) | 137–138 (ethanol–ether) | $C_{17}H_{28}ClNO$[f] (297·9) | 68·54 68·65 | 9·48 9·78 | 4·70 4·69 |
| *IIIb* | *B* (95) | 44–45[g] (hexane) | $C_{21}H_{27}NO$ (309·4) | 81·50 81·52 | 8·80 9·08 | 4·53 4·34 |
| *IIIb*-HM | — | 123–124 (ethanol–ether) | $C_{25}H_{31}NO_5$ (425·5) | 70·56 70·94 | 7·35 7·71 | 3·29 3·27 |
| *IVb*-HM[b] | *B* (98) | 131–132 (ethanol–ether) | $C_{27}H_{35}NO_5 + H_2O$ (471·6) | 68·75 68·94 | 7·90 7·59 | 2·99 3·27 |
| *Vb* | *B* (95) | 88–89[h] (hexane) | $C_{18}H_{27}NO$ (273·4) | 79·07 79·66 | 9·95 10·09 | 5·12 4·92 |

TABLE I
(*Continued*)

| Compound[a] | Method (yield, %) | M.p., °C (solvent) | Formula (mol.wt.) | Calculated/Found | | |
|---|---|---|---|---|---|---|
| | | | | % C | % H | % N |
| *Vb*-HM | — | 113—114 (2-propanol–ether) | $C_{22}H_{31}NO_5$ (389·6) | 67·84 67·43 | 8·03 8·12 | 3·59 3·74 |
| *VIb* | *B* (95) | 99—100[i] (hexane–benzene) | $C_{17}H_{25}NO_2$ (275·4) | 74·14 74·42 | 9·15 8·96 | 5·09 4·95 |
| *VIb*-HM | — | 138—139 (ethanol–ether) | $C_{21}H_{29}NO_6$ (391·5) | 64·42 64·55 | 7·47 7·50 | 3·58 3·55 |
| *VIIb* | *B*[d] (100) | 117—118 (cyclohexane) | $C_{18}H_{28}N_2O$ (288·4) | 74·95 74·60 | 9·79 10·05 | 9·71 9·58 |
| *VIIb*-2 HM | — | 192—193 (aqueous ethanol) | $C_{26}H_{36}N_2O_9$ (520·6) | 59·99 60·14 | 6·97 7·29 | 5·38 5·58 |
| *VIIIb* | *B* (82) | 138—139[j] (cyclohexane–ethanol) | $C_{19}H_{30}N_2O_2$ (318·5) | 71·66 71·64 | 9·50 9·69 | 8·80 8·86 |
| *VIIIb*-2 HM | — | 182—183 (aqueous ethanol) | $C_{27}H_{38}N_2O_{10}$ (550·6) | 58·89 58·95 | 6·96 6·96 | 5·09 5·16 |
| *IXb* | *C* (95) | 78—79[k] (hexane–pentane) | $C_{14}H_{21}NO$ (219·3) | 76·66 76·99 | 9·65 9·79 | 6·39 6·04 |
| *IXb*-HM | — | 125—126 (ethanol–ether) | $C_{18}H_{25}NO_5$ (335·4) | 64·46 65·10 | 7·51 7·81 | 4·18 4·22 |
| *Xb* | *C*[d] (95) | 108—109 (hexane) | $C_{16}H_{25}NO$ (247·4) | 77·68 77·99 | 10·19 10·35 | 5·66 5·46 |
| *Xb*-HM | | 127—128 (ethanol–ether) | $C_{20}H_{29}NO_5$ (363·4) | 66·10 66·25 | 8·04 8·35 | 3·85 3·71 |

[a] HM hydrogen maleate. [b] Monohydrate. [c] UV spectrum: $\lambda_{max}$ 256 nm (log $\varepsilon$ 4·36); IR spectrum (KBr): 830 (2 adjacent Ar—H), 1 223 (ROR), 1 605 (Ar), 1 688 $cm^{-1}$ (ArCO). [d] See Experimental. [e] UV spectrum: $\lambda_{max}$ 257 nm (log $\varepsilon$ 4·23); IR spectrum (KBr): 825 (2 adjacent Ar—H), 1 054 ($CH_2OH$), 1 603 (Ar), 1 685 (ArCO), 3 190, 3 390 $cm^{-1}$ (OH); $^1H$ NMR spectrum: $\delta$ 7·88 (d, $J$ = 8·0 Hz, 2 H, 2,6-$H_2$ of benzoyl), 7·25 (d, $J$ = 8·0 Hz, 2 H, 3,5-$H_2$ of benzoyl), 3·78 (s, 2 H, $COCH_2N$), 3·60 (t, $J$ = 7·0 Hz, 2 H, $CH_2O$), 3·10 (bs, disappears after $^2H_2O$, 1 H, OH), 3·00 (m, 1 H, Ar—CH of cyclopentyl), 2·60 (s, 8 H, 4 $NCH_2$ of piperazine), 2·52 (t, $J$ = 7·0 Hz, 2 H, $NCH_2$ of hydroxyethylamino), 1·40—2·20 (m, 8 H, 4 $CH_2$ of cyclopentyl). [f] Calculated: 11·91% Cl; found: 12·11% Cl. [g] IR spectrum: 699, 730, 823 (5 and 2 adjacent Ar—H), 1 087 (CHOH), 1 500, 1 515, 1 587, 1 604 (Ar), 3 400, 3 670 $cm^{-1}$ (OH). [h] IR spectrum: 828 (2 adjacent Ar—H), 1 098, 1 117, 1 130 (CHOH), 1 513, 1 600 (Ar), 2 760, 2 770 (C—H of $NCH_2$), 3 130 $cm^{-1}$ (OH . . N). [i] IR spectrum (KBr): 823 (2 adjacent Ar—H), 1 110 (CHOH), 1 507, 1 611 (Ar), 3 140 $cm^{-1}$ (OH); $^1H$ NMR spectrum: $\delta$ 7·22 (s, 4 H, ArH), 4·70 (t, 1 H, Ar—CH—O), 3·70 (t, 4 H, $CH_2OCH_2$ of morpholine), 2·20—3·00 (m, 8 H, 3 $NCH_2$, OH and

$NaHCO_3$ solution and water, dried with $Na_2SO_4$ and evaporated under reduced pressure (30°C). The residue (148 g, 100%) is an oil which could not be induced to crystallize and which was used in this state for reactions with the amines. The compound *Ia* was not characterized.

4-Cyclopentylphenyl 4'-Methylpiperazinomethyl Ketone (*VIIa*)
(Method *A*)

A solution of 11·5 g 1-methylpiperazine in 50 ml ether was stirred and treated over 15 min with a solution of 15·0 g crude *Ia* in 60 ml benzene. The mixture was stirred for 5 h at room temperature and allowed to stand for 48 h. The precipitated solid was filtered off, the filtrate was washed with water, 20% NaOH and saturated NaCl solution. The basic product was extracted by shaking into a solution of 20 ml hydrochloric acid in 150 ml water, the obtained solution of the hydrochloride was filtered with charcoal, the filtrate was made alkaline with 20% NaOH and the base was extracted with a mixture of ether and benzene. The extract was dried with $Na_2SO_4$ and evaporated; 10·2 g (64%). A sample was recrystallized from a mixture of benzene and hexane, m.p. 65–66°C. Bis(hydrogen maleate), m.p. 183–184°C (aqueous ethanol). The analyses are to be found in Table I.

1-(4-Cyclopentylphenyl)-2-(4-methylpiperazino)ethanol (*VIIb*)
(Method *B*)

A solution of 5·3 g *VIIa* in 50 ml benzene was added dropwise to a stirred suspension of 3·0 g $LiAlH_4$ in 50 ml ether and the mixture was refluxed for 3 h. After cooling it was decomposed by a slow addition of 12 ml 20% NaOH, after stirring for 30 min the solid was filtered off and washed with benzene. The filtrate was evaporated under reduced pressure and the solid residue (5·3 g, almost 100%) was recrystallized from a mixture of benzene and hexane or from cyclohexane, m.p. 117–118°C. IR spectrum (KBr): 830, 856 (2 adjacent Ar—H), 1 163 (CHOH), 1 515, 1 613, 3 015, 3 055 (Ar), 2 765, 2 800 (N—$CH_3$), 3 150 $cm^{-1}$ (OH). Bis(hydrogen maleate), m.p. 192–193°C (aqueous ethanol). The analyses are included in Table I.

1-(4-Cyclopentylphenyl)-2-(isopropylamino)ethanol (*Xb*)
(Method *C*)

A solution of 7·6 g *IVb* in 180 ml ethanol was hydrogenated under normal conditions over 2·5 g 10% palladium on carbon. The theoretical consumption of hydrogen was attained after 8 h shaking. The mixture was filtered and the filtrate was evaporated under reduced pressure; 5·3 g (95%), m.p. 97–101°C. Analytical sample, m.p. 108–109°C (hexane). IR spectrum: 826 (2 adjacent Ar—H), 1 071, 1 088 (CHOH), 1 598 (Ar), 3 120 (OH), 3 300 $cm^{-1}$ (NH). $^1H$ NMR spec-

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Ar—CH of cyclopentyl), 1·50–2·20 (m, 8 H, 4 $CH_2$ of cyclopentyl). [j] IR spectrum: 828 (2 adjacent Ar—H), 1 050 ($CH_2OH$), 1 118 (CHOH), 1 511, 1 611 (Ar), 3 140, 3 495 $cm^{-1}$ (OH); $^1H$ NMR spectrum: $\delta$ 7·22 (s, 4 H, ArH), 4·68 (t, $J$ = 7·0 Hz, 1 H, Ar—CH—O), 3·60 (t, $J$ = 6·0 Hz, 2 H, $CH_2O$), 3·00 (m, 3 H, 2 OH and Ar—CH of cyclopentyl), 2·30–2·80 (m, 12 H, 6 $NCH_2$). 1·40–2·20 (m, 8 H, 4 $CH_2$ of cyclopentyl). [k] IR spectrum: 831 (2 adjacent Ar—H), 1 071 (CHOH), 1 519, 1 580, 1 598 (Ar), 3 160 (OH), 3 320 $cm^{-1}$ (NH); $^1H$ NMR spectrum: $\delta$ 7·20 (s, 4 H, ArH), 4·68 (t, $J$ = 6·0 Hz, 1 H, Ar—CH—O), 3·10 (bs, disappears after $^2H_2O$, 2 H, OH and NH), 2·90 (m, 1 H, Ar—CH of cyclopentyl), 2·68 (d, $J$ = 6·0 Hz, 2 H, $CH_2N$), 2·30 (s, 3 H, $NCH_3$), 1·20–2·20 (m, 8 H, 4 $CH_2$ of cyclopentyl).

trum: $\delta$ 7·20 (s, 4 H, ArH), 4·62 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—O), *c.* 2·90 (bs, disappears after $^2H_2O$, 2 H, OH and NH), *c.* 2·80 (m, 2 H, N—CH and ArCH of cyclopentyl), 2·70 (m, 2 H, $NCH_2$), 1·20—2·20 (m, 8 H, 4 $CH_2$ of cyclopentyl), 1·00 (d, $J$ = 6·0 Hz, 6 H, 2 $CH_3$ of isopropyl). Hydrogen maleate, m.p. 127—128°C (ethanol–ether). The analyses are in Table I.

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