4-AMINO-1-(4-CYCLOPENTYLPHENYL)BUTAN-1-ONES; SYNTHESIS AND BIOLOGICAL SCREENING

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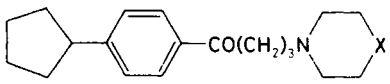
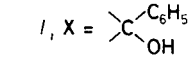
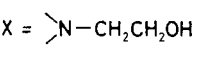
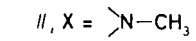
4-Chloro-1-(4-cyclopentylphenyl)butan-1-one (*IX*), obtained by Friedel–Crafts reaction of cyclopentylbenzene with 4-chlorobutanoyl chloride, was subjected to substitution reactions with 4-phenylpiperidin-4-ol and a series of N-monosubstituted piperazines, and gave the title compounds *I*– *VIII*. Their salts underwent biological screening in various lines. Only compounds *I*, *V* and *VII* showed clear indications of tranquillizing activity (ataxia, thiopental potentiation, hypothermic effect, inhibition of locomotor activity, antiamphetamine effect).

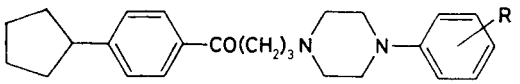
The present communication is devoted to continuation of our effort to find useful neurotropic agents within series of amines containing in their molecules the cyclopentylphenyl fragment as the lipophilic moiety[1-3]. The analgetic, neuroleptic and tranquillizing activity of 4-amino-1-(4-fluorophenyl)butan-1-ones is well known[4,5]. We have now tried to enhance the lipophilic character of such compounds by substituting the fluorine atom by the cyclopentyl residue. The result was the series of the title compounds *I*– *VIII*.



I, X = 

III, X = 

II, X = 



IV, R = H

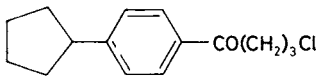
V, R = 2 - CH_3

VI, R = 3 - CF_3

VII, R = 3 - Cl

VIII, R = 4 - OCH_3

For preparing compounds *I*–*VIII*, 4-chloro-1-(4-cyclopentylphenyl)butan-1-one (*IX*) was needed as the intermediate. It was obtained by the Friedel–Crafts reaction of cyclopentylbenzenene[6] with 4-chlorobutanoyl chloride and aluminium chloride in benzene in a good yield. Compounds *I*–*VIII* were prepared by a general method consisting in substitution reactions of the chloro compound *IX* with 4-phenylpiperidin-4-ol[7], 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-phenylpiperazine[8], 1-(2-tolyl)piperazine[9], 1-(3-trifluoromethylphenyl)piperazine[10], 1-(3-chlorophenyl)-piperazine[9] and 1-(4-methoxyphenyl)piperazine[11]. The reactions were carried out in dimethyl sulfoxide at 120°C in the presence of potassium carbonate; the chloro compound *IX* and the amines were used in approximately equimolecular quantities. With the exception of compounds *I* and *II*, the bases were crystalline and were used for recording the UV, IR and ^{1}H NMR spectra which confirmed the expected structures in all cases. All of the bases were transformed to hydrochlorides; compound *VII* gave a mixture of the mono- and dihydrochloride and, therefore, the maleate was prepared for characterization and biological testing. Compounds *I*–*VIII*, prepared by this general method, are assembled in Table I with the usual experimental data. The Experimental presents in addition to the description of synthesis of compound *IX*, only the preparation of compound *V* as the example of carrying out the preparation according to the general method.



IX

Compounds *I*–*VIII* were tested in the form of salts in the first line in a general screening programme oriented especially to the expected central neurotropic activities. The acute toxicities in mice (LD_{50} in mg/kg), the screened doses (D in mg/kg) and the way of administration are given: *I*, 500, 100, *p.o.*; *II*, 62·5, 12, *i.v.*; *III*, 100, 20, *i.v.*, and 1 500, 300, *p.o.*; *IV*, >2 500, 300, *p.o.*; *V*, 750, 150, *p.o.*; *VI*, 300, 60, *p.o.*; *VII*, 1 500, 300, *p.o.*; *VIII*, >2 500, 300, *p.o.* Ataxia in the rotarod test in mice was brought about only by two of the compounds (ED in mg/kg given): *I* 50; *VII*, 100 to 300. Some of the compounds showed hypothermic effect in high doses in rats (ED in mg/kg is the dose decreasing the rectal temperature by 1·0°C): *I*, 50–100; *IV*, 300; *VII*, 100–300 (for chlorpromazine, ED = 5–10 mg/kg *p.o.*). Several compounds potentiated the thiopental action in mice (ED in mg/kg is the dose prolonging the duration of the sleeping time to 200% of the control value): *I*, 100; *IV*, 100–300; *VI*, 25–60; *VII*, 10–50 (for chlorpromazine, ED = 1 mg/kg *p.o.*). Some of the compounds inhibited the motility of mice on the basis of central depressant effect (ED in mg/kg is the dose inhibiting the motility with statistical significance): *V*, 150; *VII*, 300; *VIII*, 300. Antiamphetamine effect was shown only by compound *V* in the dose

of 50 mg/kg *p.o.* (the dose protecting 100% mice from the lethal effect of a standard dose of amphetamine; for chlorpromazine, ED = 1·5 mg/kg *p.o.*). Antiapomorphine effect was noted only with compound *VI* which significantly inhibited the apomorphine stereotypies in rats in the dose of 30 mg/kg *p.o.* None of the compounds showed cataleptic activity in rats in the doses D. Two compounds had some anticonvulsant activity in mice (ED is the dose prolonging significantly the latency of clonic convulsions elicited by pentetrazole): *V*, 100–150; *VIII*, 300; both compounds were inactive in the electroshock test. In conclusion, the compounds prepared showed only low degree of CNS activity; only *I*, *V* and *VII* can be designated as mild tranquillizers.

The compounds were also tested for antimicrobial activity *in vitro* (minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *I* 25, *II* 50; *Streptococcus faecalis*, *I* 25; *Staphylococcus pyogenes aureus*, *I* 25, *II* 100; *Escherichia coli*, *I* 12·5; *Mycobacterium tuberculosis* H37Rv, *I* 3·12, *II* 25; *Saccharomyces pasterianus*, *V* 50; *Trichophyton mentagrophytes*, *I* 25, *III* 50, *V* 25, *VII* 50, *VIII* 50.

The anthelmintic screening showed some activity of two compounds against *Nippostrongylus brasiliensis* (*VI*, *VIII*), *Hymenolepis nana* (*VI*, *VIII*) and *Trichocephalus muris* (*VI*).

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_2O_5 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 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 mixtures were checked by thin-layer chromatography on silica gel (Silufol).

4-Chloro-1-(4-cyclopentylphenyl)butan-1-one (*IX*)

A solution of 14·0 g cyclopentylbenzene[6] and 14·0 g 4-chlorobutanoyl chloride in 100 ml benzene was stirred and treated at 0–5°C with 14·0 g $AlCl_3$, added in portions. The mixture was stirred for 1 h under cooling and for 2 h at room temperature, it was then poured into a stirred mixture of 100 g ice and 20 ml hydrochloric acid, and extracted with benzene. The extract was washed with 1 : 10 dilute hydrochloric acid and with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated. The residue was distilled; 19·0 g (79%) *IX*, b.p. 190–195°C/0·4–0·5 kPa. The distillate crystallized by cooling and a sample was recrystallized from a mixture of benzene and hexane. m.p. 40–41°C. UV spectrum: λ_{max} 255 nm (log ε 4·27). IR spectrum (KBr): 826 (2 adjacent Ar—H), 1 572, 1 609, 3 065 (Ar), 1 680 cm^{-1} (ArCO). ^{1}H NMR spectrum: δ 7·90 (d, J = 8·0 Hz, 2 H, 2,6-H_2 of phenyl), 7·30 (d, J = 8·0 Hz, 2 H, 3,5-H_2 of phenyl), 3·68 (t, J = 6·0 Hz, 2 H, CH_2Cl), 3·15 (t, J = 7·0 Hz, 2 H, CH_2CO), 3·00 (m, 1 H, Ar—CH of cyclopentyl), 2·20 (m, 2 H, CH_2 in position 3 of butanone), 1·50–2·20 (m, 8 H, 4 CH_2 of cyclopentyl). For $C_{15}H_{19}ClO$ (250·8) calculated: 71·84% C, 7·64% H, 14·14% Cl; found: 72·36% C, 7·56% H, 13·78% Cl.

TABLE I

4-Amino-1-(4-cyclopentylphenyl)butan-1-ones and their salts

Compound (yield %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found			
			% C	% H	% Cl	% N
I-HCl[a] (54)	237–238[b] (aqueous ethanol)	$C_{26}H_{34}ClNO + H_2O$ (430·1)	72·66 73·07	8·40 8·07	8·24 8·32	3·26 3·32
II-2 HCl[c] (50)	223–224 (aqueous ethanol–ether)	$C_{20}H_{32}Cl_2N_2O + 0{\cdot}5\ H_2O$ (396·4)	60·61 61·11	8·38 8·24	17·89 17·69	7·07 6·97
III (31)	73–74[d] (cyclohexane)	$C_{21}H_{32}N_2O_2$ (344·5)	73·21 73·12	9·37 9·50	— —	8·13 7·82
III-2 HCl	226–227 (aqueous ethanol–ether)	$C_{21}H_{34}Cl_2N_2O_2$ (417·4)	60·42 60·18	8·21 8·46	16·99 16·91	6·71 6·94
IV (67)	123–124[e] (cyclohexane)	$C_{25}H_{32}N_2O$ (376·5)	79·74 79·47	8·57 8·60	— —	7·44 7·23
IV-2 HCl	193–194 (aqueous ethanol–ether)	$C_{25}H_{34}Cl_2N_2O$ (449·5)	66·82 67·21	7·62 7·86	15·74 15·28	6·24 6·24
V[f] (47)	76–77 (cyclohexane)	$C_{26}H_{34}N_2O$ (390·6)	79·95 80·15	8·78 8·83	— —	7·17 7·19
V-HCl	212–213 (ethanol)	$C_{26}H_{35}ClN_2O$ (427·0)	73·12 72·83	8·27 8·35	8·30 8·22	6·56 6·32
VI (78)	66–67[g] (cyclohexane–benzene)	$C_{26}H_{31}F_3N_2O$[h] (444·5)	70·25 69·83	7·03 6·80	— —	6·30 6·25
VI-HCl	188–189 (ethanol–ether)	$C_{26}H_{32}ClF_3N_2O$[i] (481·0)	64·92 64·94	6·71 6·93	7·37 7·59	5·82 5·63
VII (33)	87–88[j] (hexane)	$C_{25}H_{31}ClN_2O$ (411·0)	73·05 73·45	7·61 7·83	8·63 8·66	6·82 7·05
VII-M[k]	157–158 (ethanol–ether)	$C_{29}H_{35}ClN_2O_5$ (527·0)	66·08 65·53	6·69 6·85	6·73 6·70	5·32 5·26
VIII (57)	125–126[l] (benzene–hexane)	$C_{26}H_{34}N_2O_2$ (406·6)	76·81 77·36	8·43 8·63	— —	6·89 6·79
VIII-2 HCl	202–203 (aqueous ethanol)	$C_{26}H_{36}Cl_2N_2O_2$ (479·5)	65·12 65·18	7·58 7·96	14·79 14·88	5·84 6·03

[a] Monohydrate. [b] UV spectrum: λ_{max} 256 nm (log ε 4·30); IR spectrum: 704, 761 (C_6H_5), 977, 1 140, 1 188, 1 301, 3 385 (OH), 1 500, 1 609 (Ar), 1 683 (ArCO), 2 600, 2 680 cm^{-1} (NH^+). [c] Hemihydrate. [d] UV spectrum: λ_{max} 255 nm (log ε 4·32); IR spectrum (KBr): 820 (2 adjacent Ar—H), 1 061 (CH_2OH), 1 165, 1 286, 3 150 (OH), 1 610 (Ar), 1 680 cm^{-1} (ArCO); ^1H NMR

1-(4-Cyclopentylphenyl)-4-(4-(2-tolyl)piperazino)butan-1-one (*V*)

A mixture of 4·6 g 1-(2-tolyl)piperazine[9], 15 ml dimethyl sulfoxide and 4·0 g K_2CO_3 was stirred and treated with 7·5 g *IX*; the mixture was then heated to 120°C for 16 h. After cooling it was diluted with 250 ml water and extracted with a mixture of benzene and ether. The extract was shaken with 150 ml 1 : 10 dilute hydrochloric acid, the precipitated hydrochloride (2·0 g, m.p. 208–210°C) was filtered off, the acid aqueous layer was made alkaline with NH_4OH, and the base *V* was isolated by extraction with ether; 2·80 g, m.p. 76–77°C (cyclohexane). UV spectrum: λ_{max} 252·5 nm (log ε 4·40). IR spectrum: 768, 832 (4 and 2 adjacent Ar—H), 1 495, 1 572, 1 605, 3 000, 3 025 (Ar), 1 680 cm^{-1} (ArCO). ^1H NMR spectrum: δ 7·78 (d, *J* = 8·5 Hz, 2 H, 2,6-H_2 of 1,4-phenylene), 7·25 (d, *J* = 8·5 Hz, 2 H, 3,5-H_2 of 1,4-phenylene), c. 7·00 (m, 4 H, 3,4,5,6-H_4 of 2-tolyl), 2·95 (t, *J* = 6·0 Hz, 2 H, CH_2CO), 2·85 (m, 5 H, $CH_2N^4CH_2$ of piperazine and Ar—CH of cyclopentyl), 2·52 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·42 (t, *J* = 7·0 Hz, 2 H, CH_2N in the chain), 2·21 (s, 3 H, CH_3Ar), 1·95 (m, 2 H, CH_2 in position 3 of butanone), 1·30–2·10 (m, 8 H, 4 CH_2 of cyclopentyl).

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spectrum: δ 7·84 (d, *J* = 8·5 Hz, 2 H, 2,6-H_2 of phenylene), 7·13 (d, *J* = 8·5 Hz, 2 H, 3,5-H_2 of phenylene), 3·58 (t, *J* = 6·0 Hz, 2 H, CH_2O), 3·02 (s, 1 H, OH), 2·95 (t, *J* = 6·0 Hz, 2 H, CH_2CO), c. 3·00 (m, 1 H, Ar—CH of cyclopentyl), 2·44 (s, 8 H, 4 CH_2N of piperazine), 2·41 (t, 4 H, 2 CH_2N in the chains), 1·95 (m, 2 H, CH_2 in position 3 of butanone), 1·30–2·10 (m, 8 H, 4 CH_2 of cyclopentyl). [e] UV spectrum: λ_{max} 252·5 nm (log ε 4·47); IR spectrum: 684, 751 (C_6H_5), 1 604 (Ar), 1 679 cm^{-1} (ArCO); ^1H NMR spectrum: δ 7·89 (d, *J* = 8·5 Hz, 2 H, 2,6-H_2 of phenylene), 7·28 (d, *J* = 8·5 Hz, 2 H, 3,5-H_2 of phenylene), 7·20 (m, 2 H, 2,6-H_2 of phenyl), 6·82 (m, 3 H, remaining ArH), 3·10 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·99 (t, *J* = 7·0 Hz, 2 H, CH_2CO), 3·00 (m, 1 H, Ar—CH of cyclopentyl), 2·55 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, *J* = 7·0 Hz, 2 H, CH_2N in the chain), 1·40–2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [f] See Experimental. [g] UV spectrum: λ_{max} 255 nm (log ε 4·51) infl. 302 nm (3·36); IR spectrum: 700, 790, 821, 861 (3 and 2 adjacent, and solitary Ar—H), 1 138, 1 170, 1 322 ($ArCF_3$), 1 500, 1 608, 3 067 (Ar), 1 682 cm^{-1} (ArCO); ^1H NMR spectrum: δ 7·89 (d, *J* = 8·0 Hz, 2 H, 2,6-H_2 of 1,4-phenylene), 7·27 (d, *J* = 8·0 Hz, 2 H, 3,5-H_2 of 1,4-phenylene), 6·90–7·40 (m, 4 H, remaining ArH), 3·16 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·99 (t, *J* = 6·0 Hz, 2 H, CH_2CO), 3·00 (m, 1 H, Ar—CH of cyclopentyl), 2·55 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, *J* = 6·0 Hz, 2 H, CH_2N in the chain), 2·00 (m, 2 H, CH_2 in position 3 of butanone), 1·50–2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [h] Calculated: 12·82% F; found: 12·86% F. — [i] Calculated: 11·80% F; found: 11·75% F. [j] UV spectrum: λ_{max} 255·5 nm (log ε 4·52); IR spectrum: 680, 768, 832, 869 (3 and 2 adjacent, and solitary Ar—H), 1 561, 1 594, 1 604 (Ar), 1 683 (ArCO), 2 696, 2 745, 2 770 cm^{-1} (CH_2—N); ^1H NMR spectrum: δ 7·88 (d, *J* = 8·5 Hz, 2 H, 2,6-H_2 of 1,4-phenylene), 7·28 (d, *J* = 8·5 Hz, 2 H, 3,5-H_2 of 1,4-phenylene), 6·60–7·20 (m, 4 H, remaining ArH), 3·12 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·98 (t, *J* = 7·0 Hz, 2 H, CH_2CO), 2·80 (m, 1 H, Ar—CH of cyclopentyl), 2·52 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·42 (t, *J* = 7·0 Hz, 2 H, CH_2N in the chain), 2·00 (m, 2 H, CH_2 in position 3 of butanone), 1·40–2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [k] Maleate. [l] UV spectrum: λ_{max} 250 nm (log ε 4·53); IR spectrum: 821 (2 adjacent Ar—H), 1 151, 1 268 ($ArOCH_3$), 1 518, 1 609, 3 035 (Ar), 1 685 cm^{-1} (ArCO); ^1H NMR spectrum: δ 7·78 (d, *J* = 8·5 Hz, 2 H, 2,6-H_2 of benzoyl), 7·25 (d, *J* = 8·5 Hz, 2 H, 3,5-H_2 of benzoyl), 6·80 (s, 4 H, remaining ArH), 3·80 (s, 3 H, OCH_3), c. 3·00 (m, 5 H, CH_2N^4. .CH_2 of piperazine and Ar—CH of cyclopentyl), 2·95 (t, *J* = 6·0 Hz, 2 H, CH_2CO), 2·55 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·42 (t, *J* = 7·0 Hz, 2 H, CH_2N in the chain), 1·95 (m, 2 H, CH_2 in position 3 of butanone), 1·30–2·10 (m, 8 H, 4 CH_2 of cyclopentyl).

Hydrochloride, m.p. 212—213°C (ethanol). The total yield (base and hydrochloride) was 47%. The analyses of the base and of the hydrochloride are included in Table I.

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