NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. LII.*
N-(1-BENZYLCYCLOPENTYL)AMIDES AND SULFONAMIDES

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After demonstrating the anticonvulsant activity of N-(1-benzylcyclopentyl)formamide (*II*) a number of similar amides (*III*—*XV*, *XXIII*, *XXIV*) and sulfonamides (*XVI*—*XX*) were prepared. None of them shows greater anticonvulsant activity than compound *II*. The N-(1-benzylcyclopentyl)glycinamides *XI*—*XV* are characterized by peripheral neurotropic effects (local anaesthetic, spasmolytic, mydriatic).

We have described[1] the preparation of 1-benzylcyclopentylamine (*I*) and 1-benzylcyclohexylamine (*XXI*), as well as of a number of their N-substitution derivatives, for which a central stimulant activity was predicted and partly confirmed experimentally. Of special interest was the finding of the substantial anticonvulsant effect of formamide derivatives *II* and *XXII*. In an attempt to obtain other compounds with this effect we prepared now a series of amides and sulfonamides, derived from 1-benzylcyclopentylamine (*I*) and two similar compounds, derived from amine *XXI*.

Amides *III*, *V* - *VII* and *XXIII* were prepared by a reaction of amines *I* and *XXI* with the appropriate acyl chlorides (*i.e.* acetyl chloride, capronyl chloride[2], benzoyl chloride and *o*-chlorobenzoyl chloride[2,3]) in the presence of pyridine (method A). The acetamide derivative *III* was obtained also by heating amine *I* with acetic anhydride; the propionamide derivative *IV* was prepared analogously (method B). The acetamide *III* resulted further in a low yield as the product of reaction of amine *I* with acetylsalicyloyl chloride[4] in pyridine. The carbamates *VIII* and *XXIV* were prepared by a reaction of amines *I* and *XXI* with ethyl chloroformate in boiling benzene in the presence of pyridine (method C). In an analogous reaction of amine *I* with dimethylcarbamyl chloride[5] the only product obtained was the symmetrical derivative of urea *IX*.**

Reaction of amine *I* with chloroacetyl chloride in benzene in the presence of sodium carbonate yielded the chloroacetamido derivative *X* which was condensed in boiling toluene with isobutylamine, piperidine, morpholine, 1-methylpiperazine and 2-diethylaminoethylamine (method D); in this way the substituted glycinamides *XI*—*XV* were obtained. Reaction of amine *I* with methanesulfonyl chloride, *o*-toluenesulfonyl

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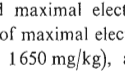
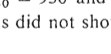
** Compounds *III*, *VIII*, *IX*, *XXIII* and *XXIV* were prepared in this laboratory by Dr E. Adlerová.

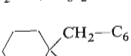
chloride, *p*-toluene sulfonyl chloride and *p*-acetamidobenzenesulfonyl chloride[6] in pyridine at room temperature (method E) yielded the sulfonamides *XVI* – *XIX*. Alkaline hydrolysis of compound *XIX* resulted in the sulfanilamide derivative *XX*. All the compounds prepared are summarized in Table I.

Compounds *III* – *VI* and *VIII* were tested pharmacologically as potential antiepileptics, in comparison with compound *II*. In view of the low solubility of the compounds in water all the tests were carried out with oral administration. The compounds were found to possess low toxicity (acute toxicity for mice: LD_{50} for *II* 1·2 g/kg, for *III* 3·1 g/kg, for *IV* 4·5 g/kg, for *V*, *VI* and *VIII* more than 5·0 g/kg). It is possible that the low toxicity is partly due to incomplete resorption. The toxic symptoms that were found were a general depression, sleepiness and inhibition of respiration. The anticonvulsant effect was estimated with the aid of pentetrazol seizures, strychnine seizures and maximal electro-shock in mice[7,8]. A protective effect was found only in the test of maximal electro-shock in the case of *II* (PD_{50} = = 240 mg/kg) and *IV* (PD_{50} = 1 650 mg/kg), a slight effect having been found with *III*. The standard used ("sulthiam", Ospolot)[9,10] did not display under the present experimental arrangement a significant effect in the test of the maximal electro-shock but it did show an anticonvulsant effect in the pentetrazol and strychnine seizures test (PD_{50} = 930 and 920 mg/kg, respectively). In the last two tests the present compounds did not show any effect when applied in doses of 1·0 – 2·0 g/kg.



I, R = H
II, R = COH
III, R = $COCH_3$
IV, R = COC_2H_5
V, R = $CO(CH_2)_4CH_3$
VI, R = COC_6H_5
VII, R = 2-COC_6H_4Cl
VIII, R = $COOC_2H_5$
IX, R = 
X, R = $COCH_2Cl$
XI, R = $COCH_2NHCH_2CH(CH_3)_2$

XII, R = 
XIII, R = 
XIV, R =
XV, R = $COCH_2NH(CH_2)_2N(C_2H_5)_2$
XVI, R = SO_2CH_3
XVII, R = 2-$SO_2C_6H_4CH_3$
XVIII, R = 4-$SO_2C_6H_4CH_3$
XIX, R = 4-$SO_2C_6H_4NHCOCH_3$
XX, R = 4-$SO_2C_6H_4NH_2$



XXI, R = H
XXII, R = COH

XXIII, R = $COCH_3$
XXIV, R = $COOC_2H_5$

The other compounds were evaluated pharmacologically in a wider spectrum of tests by methods of general screening (the mode of application, the value of acute toxicity for mice LD_{50}

in mg/kg and finally the dose in mg/kg, used in most of the *in vivo* tests): *VII* (*p.o.*, 3500, 300), *X* (*p.o.*, > 2500, 300), *XI*-HCl (*i.v.*, 42·5, 9·0), *XII*-HCl (*i.v.*, 30, 6), *XIII*-HCl (*i.v.*, 135, 25), *XIV*·2 HCl (*i.v.*, 87, 18), *XV*·2 HCl (*i.v.*, 62·5. 12·0), *XVI* (*p.o.*, > 2500, 300), *XVII* (*p. o.*, > 2500, 300), *XVIII* (*p.o.*, 2500, 300), *XIX* (*p.o.*, > 2500, 300), *XX* (*p.o.*, > 2500, 300), *XXIII* (*p.o.*, > 2500, 300), *XXIV* (*p.o.*, > 2500, 300).

The anticonvulsant activity toward pentetrazol seizures in mice is shown slightly by *X*–*XV*, *XVII* and *XX*, more significantly only by *XVI* and especially *XXIII*. In the case of *XVI*, high doses produced signs of central depression, with some compounds a slight potentiation of thiopental sleep was observed (*VII*, *XVIII*, *XIX*), in the case of *XVIII* also a slight hypothermic activity in rats. Compound *XIX* prolongs the survival of the asphyctic mouse myocard. The group of substituted glycinamides shows pharmacodynamic properties different from those of the other compounds. All the substances (*XI*–*XV*) cause a slight and short-term drop of the blood pressure and some of them show a slight vasodilatory activity (*XIII*–*XV*). They have a clear local anaesthetic effect on rabbit cornea (*XI*, *XII*) and a slight antiarrhythmic effect in the test of chloroform arrhythmia in mice (*XI*, *XIV*). In high doses they bring about a short-term central excitation (*XIII*–*XV*) and show parasympatholytic activity, displayed by a spasmolytic effect on isolated rat duodenum toward acetylcholine contractions (*XII*–*XV*, compound *XIV* to a similar extent as adiphenine) and further by mydriatic effect (*XIII* quite clearly, *XIV* pronouncedly). In no case, however, were the effects of such magnitude as to warrant more detailed tests.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block. The samples were dried in the usual way. The IR spectra (in Nujol) were recorded in a Unicam SP 200 G spectrophotometer, the NMR spectrum (in deuteriochloroform) was recorded in a ZKR 60 (Zeiss, Jena) spectrometer.

1-Benzylcyclopentylamine (*I*)

This compound was prepared by a modification of an earlier method[1]. A mixture of 106 g N-(1-benzylcyclopentyl)formamide (*II*) (ref.[1]), 155 ml ethanol and 145 g potassium hydroxide was heated for 2 h in 100–110°C bath. After cooling it was diluted with 150 ml water and extracted with ether. Treatment of the extract yielded 80·0 g (91%) base *I*, boiling at 128–130°C/12 Torr. The earlier[1] value of the b.p. was 136–140°C/20 Torr.

3,4-*Dimethoxyphenylacetate* was obtained in an attempt at preparing the appropriate amide by heating an equimolecular mixture of base *I* and of homoveratric acid to 190°C; m.p. 134–136°C (benzene). For $C_{22}H_{29}NO_4$ (371·5) calculated: 71·13% C, 7·87% H, 3·77% N; found: 71·19% C, 7·89% H, 3·54% N.

N-(1-Benzylcyclopentyl)acetamide (*III*)

A. *From acetyl chloride* (method A): 8·0 g acetyl chloride was added dropwise to a solution of 17·5 g amine *I* in 50 ml benzene and 50 ml pyridine and the mixture was refluxed for 20 min on a boiling-water bath. The volatile fractions were then evaporated at reduced pressure and the

TABLE I
N(1-Benzylcycloalkyl)amides and Sulfonamides

Compound	Method[a] (yield, %)	M.p., °C (ethanol)	Formula (M.w.)	Calculated/Found % C	% H	% N	% Cl(S)
III	A, B (91, 89)	133 – 134.5[b]	$C_{14}H_{19}NO$ (217·3)	77·38 / 77·35	8·81 / 8·66	6·45 / 6·57	—
IV	B (56)	95·5 – 96·5[b]	$C_{15}H_{21}NO$ (231·3)	77·88 / 78·04	9·15 / 9·30	6·05 / 6·15	—
V	A (65)	71·5 – 72·5[b]	$C_{18}H_{27}NO$ (273·4)	79·07 / 79·15	9·95 / 10·05	5·12 / 5·36	—
VI	A (52)	123·5 – 125[b,c]	$C_{19}H_{21}NO$ (279·4)	81·68 / 82·11	7·58 / 7·59	—	—
VII	A (43)	125·5 – 127·5[b]	$C_{19}H_{20}ClNO$ (313·8)	72·72 / 72·64	6·42 / 6·40	4·46 / 4·41	11·30 / 11·31
VIII	C[a] (50)	43 – 44[b]	$C_{15}H_{21}NO_2$ (247·3)	72·84 / 73·02	8·56 / 8·52	5·66 / 5·87	—
IX	[a]	225 – 227	$C_{25}H_{32}N_2O$ (376·5)	79·74 / 79·96	8·57 / 8·85	7·44 / 6·94	—
X	[a]	98 – 100[b]	$C_{14}H_{18}ClNO$ (251·7)	66·79 / 67·04	7·20 / 7·27	5·60 / 5·68	14·07 / 14·14
XI HCl	D	170 – 176[d]	$C_{18}H_{29}ClN_2O$ (324·9)	66·54 / 66·41	9·00 / 8·94	8·62 / 8·42	—
XII HCl	D (77)	170 – 171·5[d]	$C_{19}H_{29}ClN_2O$ (336·9)	67·74 / 67·96	8·67 / 8·84	8·32 / 8·34	10·52 / 10·80
XIII HCl	D (74)	168 – 170[d]	$C_{18}H_{27}ClN_2O_2$ (338·9)	63·79 / 63·30	8·03 / 8·14	8·27 / 8·24	10·46 / 10·37
XIV 2 HCl[e]	D[a] (80)	173 – 176[d]	$C_{19}H_{31}Cl_2N_3O.$ $\frac{1}{2}H_2O$ (397·4)	57·42 / 57·12	8·11 / 8·29	10·57 / 10·89	17·84 / 17·76
XV 2 HCl	D (54)	186 – 189[d]	$C_{20}H_{35}Cl_2N_3O$ (404·4)	59·39 / 59·44	8·72 / 8·78	10·39 / 10·38	17·54 / 17·64
XVI	E[a] (58)	131·5[b]	$C_{13}H_{19}NO_2S$ (253·4)	61·62 / 61·52	7·59 / 7·60	5·53 / 5·55	12·65 / 12·45
XVII	E (56)	91 – 94[b]	$C_{19}H_{23}NO_2S$ (329·4)	69·27 / 69·30	7·04 / 7·01	4·25 / 4·28	9·73 / 9·75
XVIII	E (54)	161 – 162·5	$C_{19}H_{23}NO_2S$ (329·4)	69·27 / 69·42	7·04 / 7·05	4·25 / 4·31	9·73 / 9·52
XIX	E (50)	184 – 185	$C_{20}H_{24}N_2O_3S$ (372·5)	64·49 / 64·65	6·49 / 6·61	7·52 / 7·53	8·61 / 8·80
XX	[a] (52)	161·5 – 163	$C_{18}H_{22}N_2O_2S$ (330·4)	65·42 / 65·47	6·71 / 6·59	8·48 / 8·64	9·71 / 9·70
XXIII	A (95)	123 – 124[b]	$C_{15}H_{21}NO$ (231·3)	77·88 / 77·93	9·15 / 9·36	6·05 / 6·04	—
XXIV	C (52)	65 – 67[b,f]	$C_{16}H_{23}NO_2$ (261·4)	73·53 / 73·88	8·87 / 8·82	5·36 / 5·38	—

[a] See Experimental; [b] from aqueous ethanol; [c] ref.[11] gives m.p. 123·5 – 124°C; [d] from ethanol–ether; [e] hemihydrate; [f] b.p. 141°C/0·82 Torr. IR spectrum: 698 and 771 (C_6H_5), 1 104 and 1 257 (COOR), 1 539 (CONH), 1 720 (NHCOOR), 3 326 cm^{-1} (NH).

residue was diluted with water. After standing overnight, the precipitated solid was isolated by filtration: 19·8 g (91%), m.p. 132—133·5°C (aqueous ethanol).

B. *From acetic anhydride* (method B): 3·4 g acetic anhydride was added to a solution of 5·25 g amine *I* in 5 ml acetic acid and the mixture was refluxed for 2 h in a 120°C bath. It was then diluted with 500 ml water and, after several hours of standing, the precipitated product was filtered and recrystallized from aqueous ethanol; 5·8 g (89%), m.p. 133—134·5°C.

C. *From acetylsalicyloyl chloride*: 17·8 g acetylsalicyloyl chloride[4] was added in parts and under stirring to a solution of 15·0 g amine *I* in 30 ml pyridine and the mixture was stirred for 90 min at 40°C. After cooling, it was diluted with 500 ml water and the separated oil was extracted with chloroform. The extract was washed with 2·5M-HCl and water, dried with magnesium sulfate and evaporated. The residue was dissolved in a small amount of benzene and light petroleum was added. On longer standing, 3·0 g compound melting at 138°C precipitated (aqueous ethanol). IR spectrum: 706 and 740 (C_6H_5), 1307, 1543 and 1645 (CONH), 3120 and 3300 cm^{-1} (amide NH). For $C_{14}H_{19}NO$ (217·3) calculated: 77·38% C, 8·81% H, 6·45% N; found: 76·99% C, 9·00% H, 6·31% N.

Ethyl N-(1-benzylcyclopentyl)carbamate (*VIII*) (Method C)

11·0 g ethyl chloroformate in 10 ml benzene were added dropwise to a solution of 17·5 g amine *I* in 50 ml benzene and 25 ml pyridine and the mixture was refluxed for 2 h. The solvents were then evaporated at reduced pressure, the residue was diluted with water and the mixture was extracted with benzene. Treatment of the extract and distillation of the residue yielded 12·5 g (50%) product boiling at 149°C/2 Torr which crystallized upon standing; m.p. 43—44°C (aqueous ethanol).

N,N'-Bis(1-benzylcyclopentyl)urea (*IX*)

A solution of 11·0 g dimethylcarbamyl chloride[5] in 10 ml benzene was added to a solution of 17·5 g amine *I* in 50 ml benzene and 25 ml pyridine and the mixture was refluxed for 8 h. After evaporation of the solvents at reduced pressure the residue was mixed with water and the mixture was extracted with ether. After drying and evaporation of the extract a total of 7·9 g residue was obtained, m.p. 225—227°C (ethanol). IR spectrum: 704 and 758 (C_6H_5), 1556 and 1629 (CONH), 3335 and 3370 cm^{-1} (NH).

N-(1-Benzylcyclopentyl)chloracetamide (*X*)

A solution of 25 g chloracetyl chloride in 50 ml benzene was added under stirring dropwise over a period of 1 h at 0°C to a mixture of 35 g amine *I*, 12·1 g anhydrous sodium carbonate and 120 ml benzene. The mixture was diluted with 200 ml benzene and heated for 1 h to 40°C. After standing overnight, another 300 ml benzene were added and the mixture was thoroughly washed with water. By drying and evaporation of the benzene solution a total of 39 g (75%) product was obtained, this having been purified by crystallization from aqueous ethanol: m.p. 98—100°C. NMR spectrum: δ 7·15 (multiplet, 5 H of phenyl), 6·02 (wide singlet, 1 H of the NH group), 3·86 (singlet, 2 H of CH_2Cl), 3·06 (singlet, 2 H of $ArCH_2$), 1·74 (multiplet, 8 H of CH_2 groups of cyclopentane).

N-(1-Benzylcyclopentyl)-4-methylpiperazinoacetamide (*XIV*) (Method D)

A mixture of 3·5 g *X*, 3·6 g 1-methylpiperazine and 24 ml toluene was refluxed under stirring for 5 h in a bath at 110°C. After cooling, filtration was applied to remove the precipitated methylpiperazine hydrochloride and the filtrate was evaporated at reduced pressure. The residue was dissolved in 100 ml 2·5M-HCl, the solution was washed with benzene, filtered with charcoal and then made alkaline with 10% sodium hydroxide. The precipitated product was isolated by extraction with benzene. 3·0 g of an oily base were obtained. The base was converted to the hydrochloride with anhydrous hydrogen chloride in a mixture of ethanol and ether; 3·9 g (80%), m.p. 173–176°C (ethanol–ether). The analysis (Table I) showed it to be a dihydrochloride hemihydrate.

N-(1-Benzylcyclopentyl)methanesulfonamide (*XVI*) (Method E)

9·5 g methanesulfonylchloride were added dropwise over 30 min at 0–5°C to a solution of 13·2 g amine *I* in 20 ml pyridine. The mixture was stirred for further 30 min at room temperature and then poured into 500 ml ice-cold water. The precipitated solid product was filtered (11·0 g, 58%) and recrystallized from aqueous ethanol with charcoal; m.p. 131·5°C.

N^1-(1-Benzylcyclopentyl)sulfanilamide (*XX*)

A mixture of 5·0 g N^1-(1-benzylcyclopentyl)-N^4-acetylsulfanilamide (*XIX*) and 50 ml 5M-NaOH was refluxed for 10 h, cooled, approximately neutralized with acetic acid and the precipitated product was filtered; 4·0 g, m.p. 161·5–163°C (ethanol).

The anticonvulsant activity of the compounds was evaluated by Dr I. Podvalová (Pharmacological department of this Institute). The pharmacological screening of the compounds was done by Dr J. Němec at the unit of this institute, Rosice n/L. All the compounds were tested by Dr J. Turinová (Bacteriological department of this institute) (headed by Dr A. Šimek) as to their antimicrobial activity in vitro *toward several typical microorganisms. The IR and NMR spectra were recorded and interpreted by Dr E. Svátek and Dr J. Holubek in the physico-chemical laboratories of this institute. The analytical determinations were done at the analytical department of this Institute (headed by Dr J. Körbl) by Mr K. Havel, Mr M. Čech, Mrs V. Šmídová, Mrs J. Komancová and Mrs A. Slavíková.*

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