1-(4-CYCLOPENTYLPHENYL)ETHYLAMINE AND DERIVATIVES: SYNTHESIS AND PHARMACOLOGICAL SCREENING*

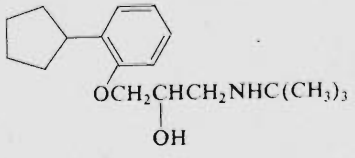
Zdeněk VEJDĚLEK, Jiří HOLUBEK, Marie BARTOŠOVÁ and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

Received January 13th, 1981

Reduction of 4-cyclopentylacetophenone oxime gave the title compound *II* which was transformed by a combination of acylation, alkylation, reduction and substitution reactions to compounds *III*—*XI*. 2-Benzylcyclopentanone oxime was reduced to 2-benzylcyclopentylamine (*XVI*) and converted by a reaction with methylmagnesium iodide and by the following Ritter reaction to the formamide derivative *XVIII* which was used as the starting material for preparing amines *XIX*—*XXI*. The local anaesthetic and spasmolytic activity were the most typical neurotropic effects of derivatives of compound *II*. 2-Benzyl-1-methylcyclopentylamine and derivatives *XIX*—*XXI* have some hypotensive activity.

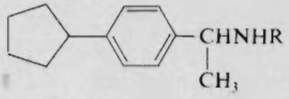
A correct balance between the lipophilic part, containing usually aromatic nuclei, and the hydrophilic fragment with the typical amino group is very important for molecules of neurotropic agents. A certain degree of lipophilicity is evidently indispensable since these agents have to penetrate through lipophilic membranes in the course of transport to the receptors. In molecules of most of the neurotropic and psychotropic agents we meet with the presence of two aromatic nuclei. A combination of an aromatic and an alicyclic nucleus is less common. An example of this type is the cyclopentylbenzene derivative penbutolol (*I*) which has the properties of an adrenergic β-blocker[1] and is used with favourable results in cardiac arrhythmia, angina pectoris and in long term treatment of moderate hypertension[2]. In the present communication we start with publishing our results with synthesis and pharmacology of some amines derived from cyclopentylbenzene and some related hydrocarbons which were prepared as potential neurotropic agents.



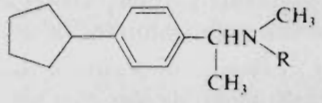
I

* Part CLVIII in the series Neurotropic and Psychotropic Agents; Part CLVII: This Journal *46*, 2222 (1981).

Starting compounds of our investigation, *i.e.* cyclopentylbenzene, 4-cyclopentylacetophenone and its oxime, were obtained by methods described in the literature[3,4]. 4-Cyclopentylacetophenone oxime[4] was reduced with sodium and ethanol to 1-(4-cyclopentylphenyl)ethylamine (*II*). Its formylation by heating with ethyl formate in an autoclave to 110–120°C resulted in the formamide derivative *III* which was reduced with lithium aluminium hydride in ether to give the methylamino derivative *IV*.



II, R = H
III, R = CHO



IV, R = H
V, R = CH_3
VI, R = $CH_2CH{=}CH_2$
VII, R = $CH_2C{\equiv}CH$
VIII, R = $COCH_2Cl$

IX, R = $COCH_2N$⟨⟩

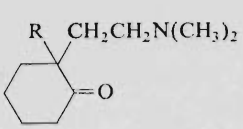
X, R = $COCH_2N$⟨O⟩

XI, R = $COCH_2N$⟨NCH_3⟩

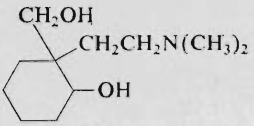
Methylation of the primary amine *II* with formaldehyde and formic acid gave the dimethylamino derivative *V*. Alkylation of the secondary amine *IV* with allyl bromide and propargyl bromide in 2-butanone in the presence of potassium carbonate afforded the tertiary amines *VI* and *VII*. A reaction of the methylamino derivative *IV* with chloroacetyl chloride gave the chloroacetamide derivative *VIII* which was subjected to substitution reactions with piperidine, morpholine and 1-methylpiperazine in 2-butanone in the presence of potassium carbonate leading to the substituted glycinamides *IX*–*XI*.

Via the basic keto ester *XII* (ref.[5–7]), the ketone *XIII* (ref.[5–7]) was obtained and further transformed to the tertiary alcohol *XV* (ref.[7,8]). For pharmacological tests, the bases *XIII* and *XV* were converted to the methiodides. Reduction of the ketoester *XII* with lithium aluminium hydride in ether resulted in the stereoisomeric mixture of diols *XIV* out of which one component was isolated in crystalline state.

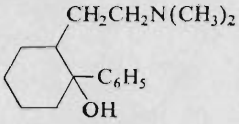
The last part of this communication deals with amines derived from benzylcyclopentane. The starting 2-benzylcyclopentanone[9,10] was obtained by the ketone cleavage of the corresponding β-ketoester. 2-Benzylcyclopentanone oxime[11] was reduced



XII, R = $COOC_2H_5$
XIII, R = H

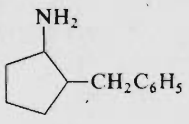


XIV

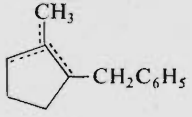


XV

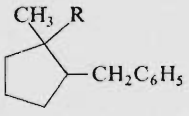
with sodium in ethanol to a mixture of stereoisomers from which the major component was isolated in the form of the hydrochloride. In accordance with the analogy[12,13] and with the Skita' rule[14], this product is considered to be the *trans*-isomer. The base released from the hydrochloride was characterized by gas chromatography as completely homogeneous. Processing of the mother liquor gave a lower melting hydrochloride which was also converted to the base and characterized by gas chromatography: It is a *cis-trans* mixture in the ratio of about 4: 1. The tertiary alcohol, obtained by reaction of 2-benzylcyclopentanone[9-11] with methylmagnesium iodide, was dehydrated during distillation and the resulting inhomogeneous olefinic product *XVII* was subjected to the Ritter' reaction with sodium cyanide in a mixture of acetic and sulfuric acid. N-(2-Benzyl-1-methylcyclopentyl)-formamide (*XVIII*) was obtained and its identity confirmed by the ^{1}H-NMR spectra of amines prepared from it. Alkaline hydrolysis gave the primary amine *XIX*, reduc-



XVI



XVII



XVIII, R = NHCHO
XIX, R = NH_2
XX, R = $NHCH_3$
XXI, R = $N(CH_3)_2$

tion of the amide *XVIII* with lithium aluminium hydride resulted in the secondary amine *XX* and methylation of a mixture of amines *XIX* and *XX* with formaldehyde and formic acid afforded the dimethylamino derivative *XXI*. ^{1}H-NMR spectra of the amines *XIX*–*XXI* show a singlet corresponding to the C-methyl group being a proof of the structure.

Most of the compounds prepared were evaluated in the form of salts (described in the Experimental) by methods of the general pharmacological screening with special emphasis on the neurotropic effects. Some of the results are presented in Table I showing in the first line the acute toxicities in mice (groups by 5 animals observed for 3 days) and the basic doses used in the *in vivo* tests. Compounds *III*, *VI* and *X* were more potent in the test of infiltration anaesthesia than procaine and compounds *III* and *XI* were equipotent with trimecaine in the test of corneal anaesthesia.

TABLE I

Pharmacological screening of substances *II*–*XI* and *XVIII*–*XXI* (intravenous administration)

Compound	Acute toxicity LD_{50}, mg/kg	Basic dose D, mg/kg	Local anaesthetic		Spasmolytic effect	
			inf.[a]	corneal[b]	ACh[c]	$BaCl_2$[d]
II	50	10	0·25	0·5	—	—
IV	50	10	—	—	5	5
V	50	10	—	—	5	10
VI	37·5	7	0·25	—	5	5
VII	75	15	—	—	—	10
IX	50	10	—	—	5	—
X	87·5	17	0·25	—	—	—
XI	100	20	—	1	10	10
XVIII[e]	1 000	200	—	—	—	—
XIX	35	7	>1	—	—	—
XX	25	5	>1	—	—	—
XXI	15	3	—	—	—	—
Procaine	—	—	1	—	—	—
Trimecaine	—	—	—	1	—	—
Atropine	—	—	—	—	0·05	—
Papaverine	—	—	—	—	—	5

[a] A concentration in per cent bringing about a complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia. [b] A concentration in per cent bringing about in 50% rabbits a complete anaesthesia of the eye cornea. [c] A concentration in μg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50%. [d] A concentration in μg/ml effecting a reduction of barium chloride contractions of the isolated rat duodenum by 50%. [e] Oral administration.

Some of the compounds have moderate spasmolytic (anticholinergic) activity (1% of the atropine activity) and a rather high myotropic spasmolytic activity (equaling that of papaverine).

Compounds *II*, *IV* and *V* in doses > D enhance the reactivity of mice (a moderate excitating effect). Compound *XVIII* brings about ataxia in the rotarod test in mice after the oral administration of the dose D. Compound *IV* has an anticonvulsant effect; an oral dose of 25 mg/kg prolongs significantly the latency of clonic convulsions in mice elicited by pentetrazole (for phenytoine as a standard, ED = = 100 mg/kg *p.o.*). Compound *XVIII* has a similar effect in an oral dose of 200 mg/kg; the activity was found also in the electro-shock test in mice. Compounds *VI* and *VII*, being structurally related to pargyline, were tested for the antireserpine effects in mice (antagonization of the reserpine hypothermia and the reserpine ptosis); they were found inactive.

Compounds *XIX*–*XXI* exhibit hypotensive effect in normotensive rats at doses D. The drops of blood pressure are moderate and brief (*XX*) or relatively long-lasting (*XIX*, *XXI*). These effects are probably in connection with the ganglionic blockade (structural relation to the polymethylcycloalkylamines described previously[15,16]). Compound *XXI* was tested also on oral administration: a dose of 30 mg/kg reduced the blood pressure of rats in the interval of 3–24 h by 5–15%. Compounds *II*, *IV*, *V*, *VI*, *IX*, *X* and *XX* had negative inotropic effects (concentrations of 10–50 μg/ml elicited a decrease of inotropy of the isolated rabbit heart atrium by 25%); compounds *II*, *IV*, *V* and *VI* had also a negative chronotropic effect (concentrations of 25–50 μg/ml decreased the frequency by 25%). Only compound *XXI* revealed a positive effect on the heart inotropy (concentration of 50 μg/ml). A diuretic effect could be shown for compounds *XI* (100 mg/kg) and *XVIII* (200 mg/kg) (oral doses increasing diuresis in mice by 100% as compared with the control; for hydrochlorothiazide as a standard, ED = 100 mg/kg). The methiodides of compounds *XIII* and *XV* were tested for spasmolytic and hypotensive effects; significant activity was not observed.

The products were also evaluated for the antimicrobial activity in the *in vitro* tests (Dr J. Turinová, bacteriological department of this institute). Microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *II* 50, *VI* 100, *IX* 50, *XI* 50; *Streptococcus faecalis*, *VI* 100, *XI* 100; *Staphylococcus pyogenes aureus*, *VI* 100, *XI* 100; *Escherichia coli*, *VI* 100; *Mycobacterium tuberculosis* H37Rv, *II* 25, *IV* 25, *V* 25, *VI* 6·25, *VII* 12·5, *IX* 25, *X* 50, *XI* 25; *Saccharomyces pasterianus*, *IV* 50; *Trichophyton mentagrophytes*, *II* 50, *IV* 50, *V* 50, *VI* 50, *VII* 25, *IX* 50, *X* 25, *XI* 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 over P_2O_5 at room temperature or at 77°C. The IR spectra (in Nujol) were recorded with a Unicam SP 200G spectrophotometer and

^{1}H-NMR spectra (in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer (a small part with a ZKR 60, Zeiss-Jena, spectrometer). The homogeneity of the compounds was checked by thin layer chromatography on silica gel.

1-(4-Cyclopentylphenyl)ethylamine (*II*)

A solution of 64 g 4-cyclopentylacetophenone oxime[4] in 400 ml ethanol was added dropwise to 195 g Na and the refluxing mixture was then slowly treated with 1 400 ml ethanol which effected the complete dissolution of Na. The mixture was allowed to stand overnight, decomposed by a slow addition of 300 ml water, ethanol was evaporated under reduced pressure, the residue diluted with further 500 ml water and extracted with a mixture of benzene and ether. Processing of the extract gave 58·5 g (98%) oily base *II*, a sample of which was distilled, b.p. 130–132°C/ /0·33 kPa, n_D^{19} 1·5322. ^{1}H-NMR spectrum: δ 7·18 (s, 4 H, Ar—H), 4·05 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 2·95 (m, 1 H, Ar—CH in cyclopentyl), 2·48 (bs, 2 H, NH_2), 1·20–2·20 (m, 8 H, 4 CH_2 of cyclopentyl), 1·35 (d, J = 7·0 Hz, 3 H, CH_3). For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H, 7·40% N; found: 82·24% C, 10·44% H, 7·24% N.

Hydrochloride, m.p. 225–226°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 69·17% C, 8·77% H, 15·55% Cl, 5·94% N.

N-[1-(4-Cyclopentylphenyl)ethyl]formamide (*III*)

A mixture of 42·8 g *II* and 75 ml ethyl formate was heated for 6 h in an autoclave to 110–120°C. After cooling, the mixture was diluted with benzene, the solution washed with 1 : 4 dilute hydrochloric acid and with 8% $NaHCO_3$, dried with Na_2SO_4 and evaporated; 47·0 g (96%), m.p. 78–80°C. Analytical sample, m.p. 100–101°C (benzene–hexane). IR spectrum: 829 (2 adjacent Ar—H), 1 249, 1 269, 1 555, 1 662, 1 699, 3 053 (CONH), 1 492, 1 555 (Ar), 3 225 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 8·08 (bs, 1 H, N—CHO), 7·20 (s, 4 H, Ar—H), 6·18 (bs, 1 H, NHCO), 5·15 (q, 1 H, Ar—CH—N), 2·90 (m, 1 H, Ar—CH in cyclopentyl), 1·20–2·20 (m, 8 H, 4 CH_2 of cyclopentyl), 1·48 (d, 3 H, CH_3). For $C_{14}H_{19}NO$ (217·3) calculated: 77·38% C, 8·81% H, 6·45% N; found: 77·54% C, 8·81% H, 6·22% N.

N-Methyl-1-(4-cyclopentylphenyl)ethylamine (*IV*)

A solution of 46 g *III* in 250 ml benzene was added dropwise to a stirred suspension of 16 g $LiAlH_4$ in 200 ml ether and the mixture was refluxed for 5 h. After cooling it was decomposed by a slow addition of 65 ml 20% NaOH, the mixture was stirred for 30 min, the solid filtered off, washed with benzene, and the filtrate was distilled; 41 g (95%), b.p. 133°C/0·4 kPa, n_D^{20} 1·5232. ^{1}H-NMR spectrum: δ 7·18 (s, 4 H, Ar—H), 3·58 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 2·90 (m, 1 H, Ar—H, Ar—CH of cyclopentyl), 2·25 (s, 3 H, NCH_3), 1·20–2·20 (m, 9 H, 4 CH_2 of cyclopentyl and NH), 1·31 (d, J = 7·0 Hz, 3 H, remaining CH_3). For $C_{14}H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 82·84% C, 10·70% H, 6·39% N.

Hydrochloride, m.p. 161–162°C (ethanol–ether). For $C_{14}H_{22}ClN$ (239·8) calculated: 70·12% C, 9·25% H, 14·79% Cl, 5·84% N; found: 70·43% C, 9·45% H, 14·63% Cl, 5·60% N.

N,N-Dimethyl-1-(4-cyclopentylphenyl)ethylamine (*V*)

A mixture of 7·5 g crude *II*, 10 ml water, 8 ml 85% formic acid and 15 ml 28% aqueous formaldehyde was refluxed for 8 h. After cooling the mixture was treated with 25 ml hydrochloric

acid and evaporated *in vacuo*. The residue was dissolved in 60 ml water under the addition of 2 ml hydrochloric acid, the solution washed with ether, made alkaline with 20% NaOH and extracted with ether. Processing of the extract and distillation of the residue gave 7·9 g (92%) base, b.p. 136—138°C/0·4 kPa, n_D^{20} 1·5154. For $C_{15}H_{23}N$ (217·3) calculated: 6·45% N; found: 5·80% N.

Hydrochloride, m.p. 243—244°C (ethanol–ether). For $C_{15}H_{24}ClN$ (253·8) calculated: 70·98% C, 9·53% H, 13·97% Cl, 5·52% N; found: 71·17% C, 9·95% H, 13·70% Cl, 5·26% N.

N-Allyl-N-methyl-1-(4-cyclopentylphenyl)ethylamine (*VI*)

A mixture of 6·5 g *IV*, 5·8 g allyl bromide, 6·6 g K_2CO_3 and 60 ml 2-butanone was stirred and heated to 60—70°C for 8 h. After cooling the salts were filtered off, washed with acetone and the filtrate evaporated. The residue was dissolved in a mixture 1 : 1 of benzene and ether and the base was extracted into a solution of 15 ml hydrochloric acid in 65 ml water. The aqueous layer was washed with ether, made alkaline with 20% NaOH and extracted with a mixture of benzene and ether. Processing of the extract gave 6·80 g (88%) crude oily *VI*. It was dissolved in 70 ml ether and transformed by treatment with a solution of HCl in ether into the hydrochloride (6·7 g), m.p. 145—146°C (ethanol–ether). For $C_{17}H_{26}ClN$ (279·8) calculated: 72·96% C, 9·37% H, 12·67% Cl, 5·00% N; found: 72·68% C, 9·59% H, 12·51% Cl, 4·94% N.

N-Methyl-N-propargyl-1-(4-cyclopentylphenyl)ethylamine (*VII*)

A mixture of 7·3 g *IV*, 6·4 g propargyl bromide, 7·4 g K_2CO_3 and 60 ml 2-butanone was stirred and heated to 60—70°C for 8 h. Similar processing of the mixture like in the preceding case gave 6·8 g crude base which was distilled; 5·90 g (68%), b.p. 158°C/0·4 kPa, n_D^{22} 1·5302. ^{1}H-NMR spectrum: δ 7·18 (s, 4 H, Ar—H), 3·50 (q, J = 7·0 Hz, 1 H, Ar—CH—N), 3·48 and 3·12 (2 mcd, J = 17·0; 2·5 Hz, 2 H, NCH_2), 2·90 (m, 1 H, Ar—CH of cyclopentyl), 2·28 (s, 3 H, NCH_3), 2·18 (t, J = 2·5 Hz, 1 H, C≡CH), 1·20—2·20 (m, 8 H, 4 CH_2 of cyclopentyl), 1·35 (d, J = 7·0 Hz, 3 H, C—CH_3). For $C_{17}H_{23}N$ (241·4) calculated: 84·58% C, 9·61% H, 5·81% N; found: 84·42% C, 10·02% H, 5·56% N.

Hydrochloride, m.p. 191—192°C (ethanol–ether). For $C_{17}H_{24}ClN$ (277·8) calculated: 73·47% C, 8·72% H, 12·77% Cl, 5·04% N; found: 73·42% C, 8·82% H, 12·67% Cl, 5·06% N.

N-[1-(4-Cyclopentylphenyl)ethyl]-N-methylchloracetamide (*VIII*)

A solution of 20·3 g *IV* in 100 ml chloroform was treated with 16·6 g K_2CO_3, the mixture was stirred and treated over 40 min with a solution of 15 g chloroacetyl chloride in 50 ml chloroform and then refluxed for 2 h. After cooling it was decomposed by addition of 150 ml water, stirred for 10 min, the organic layer was separated, dried with Na_2SO_4 and evaporated under reduced pressure; 28 g (100%) crude product which did not crystallize. A sample (1·0 g) was chromatographed on a column of 30 g neutral Al_2O_3 (activity II) with elution with hexane. The product obtained by evaporation of the eluate *in vacuo* remained oily, n_D^{19}1 ·5402. For $C_{16}H_{22}ClNO$ (279·8) calculated: 68·67% C, 7·94% H, 12·67% Cl, 5·00% N; found: 69·02% C, 8·45% H, 12·09% Cl, 4·60% N.

N-[1-(4-Cyclopentylphenyl)ethyl]-N-methyl-piperidinoacetamide (*IX*)

A mixture of 6·0 g *VIII*, 1·9 g piperidine, 3·0 g K_2CO_3 and 60 ml 2-butanone was stirred and refluxed for 8 h. After cooling the salts were filtered off, washed with acetone, the filtrate was

evaporated *in vacuo* and the residue dissolved in a mixture of benzene and ether. The base was extracted into a solution of 15 ml hydrochloric acid in 70 ml water, the aqueous layer was made alkaline with 20% NaOH and the released based extracted with a mixture of benzene and ether. The extract was washed with water, dried with Na_2SO_4 and evaporated under reduced pressure; 5·2 g (74%) crude base. It was dissolved in 70 ml ether and the solution neutralized with a solution of 1·9 g maleic acid in 4 ml 95% ethanol; 5·8 g hydrogen maleate hemihydrate, m.p. 126 to 127°C (95% ethanol–ether). For $C_{25}H_{36}N_2O_5 + 0{\cdot}5\ H_2O$ (453·6) calculated: 66·22% C, 8·22% H, 6·18% N; found: 66·69% C, 8·21% H, 6·27% N.

N-[1-(4-Cyclopentylphenyl)ethyl]-N-methyl-morpholinoacetamide (*X*)

A mixture of 6·0 g *VIII*, 1·9 g morpholine, 3·0 g K_2CO_3 and 60 ml 2-butanone was processed similarly like in the preceding case; 5·60 g (80%) crude oily base. *Hydrogen maleate*, m.p. 116 to 117°C (ethanol–ether). IR spectrum: 1 660 (CONRR′), 2 570 cm^{-1} (NH^+). For $C_{24}H_{34}N_2O_6$ (446·5) calculated: 64·54% C, 7·68% H, 6·27% N; found: 64·28% C, 7·50% H, 6·13% N.

N-[1-(4-Cyclopentylphenyl)ethyl]-N-methyl-(4-methylpiperazino)acetamide (*XI*)

A mixture of 6·0 g *VIII*, 2·2 g 1-methylpiperazine, 3·0 g K_2CO_3 and 60 ml chloroform was stirred and heated to 60°C for 7 h. After cooling the solid was filtered off, the filtrate washed with water and the base extracted into a solution of 15 ml hydrochloric acid in 70 ml water. The aqueous solution of the hydrochloride was processed like in the preceding cases; 5·0 g (68%) crude oily base. It was transformed by neutralization with a solution of HCl in ether to a dihydrochloride (5·8 g) which crystallized from a mixture of 95% ethanol and ether as a monohydrate, m.p. 186—187°C. For $C_{21}H_{35}Cl_2N_3O + H_2O$ (434·5) calculated: 58·08% C, 8·58% H, 16·32% Cl, 9·67% N; found: 58·49% C, 8·64% H, 15·97% Cl, 9·85% N.

2-Hydroxymethyl-2-(2-dimethylaminoethyl)cyclohexanol (*XIV*)

A solution of 10·0 g ethyl 1-(2-dimethylaminoethyl)-2-oxocyclohexanecarboxylate (*XII*) (ref.[5–7]) in 30 ml ether was added to a stirred suspension of 2·0 g $LiAlH_4$ in 50 ml ether and the mixture was refluxed for 15 min. After cooling it was decomposed by a slow addition of 2 ml water, 2 ml 20% NaOH and 6 ml water, the precipitated solid was filtered off, washed with ether, the filtrate was dried and processed by distillation; 7·1 g (86%), b.p. 119—122°C/53 Pa, mixture of stereoisomeric *XIV*. A sample for analysis was redistilled, b.p. 114·5°C/40 Pa. For $C_{11}H_{23}NO_2$ (201·3) calculated: 65·63% C, 11·52% H, 6·96% N; found: 65·40% C, 11·46% H, 6·99% N. After a longer contact with light petroleum the product partly crystallized which resulted in isolation of one homogeneous stereoisomer, m.p. 68·5—69·5°C (ether–light petroleum). For $C_{11}H_{23}NO_2$ (201·3) calculated: 65·63% C, 11·52% H, 6·96% N; found: 65·70% C, 11·75% H, 7·19% N.

Hydrochloride, m.p. 136°C (ethanol–ether). For $C_{11}H_{24}ClNO_2$ (237·8) calculated: 55·58% C, 10·17% H, 14·91% Cl, 5·89% N; found: 55·69% C, 10·35% H, 15·11% Cl, 6·15% N.

2-(2-Dimethylaminoethyl)cyclohexanone (*XIII*)

It was obtained in a yield of 40% by refluxing crude *XII* (ref.[5]) with hydrochloric acid for 8 h, b.p. 114—115°C/2·0 kPa (*cf.*[5,6]). Treatment of 6·0 g base in 6 ml acetone with 2·7 ml methyl iodide gave 6·3 g methiodide, m.p. 153°C (methanol–ether). For $C_{11}H_{22}INO$ (311·2) calculated: 42·45% C, 7·12% H, 40·79% I, 4·50% N; found: 42·19% C, 7·00% H, 40·44% I, 4·70% N.

2-(2-Dimethylaminoethyl)-1-phenylcyclohexanol (*XV*)

The crude product (mixture of stereoisomers contaminated probably with products of dehydration), boiling unsharply at 100—133°C/80 Pa, was obtained by treatment of *XIII* with phenylmagnesium bromide in ether[7,8]. Longer standing of this product led to separation of a component, melting constantly at 65—68°C (light petroleum). The product is probably identical with the homogeneous stereoisomer of *XV* described by MacElvain and Clampitt[8] but we were not able to reproduce their m.p. 71—72°C. For $C_{16}H_{25}NO$ (247·4) calculated: 77·68% C, 10·19% H, 5·66% N; found: 77·71% C, 10·58% H, 5·90% N.

Methiodide, m.p. 156—160°C (methanol). For $C_{17}H_{28}INO$ (389·3) calculated: 52·44% C, 7·24% H, 32·60% I, 3·60% N; found: 52·19% C, 7·43% H, 32·67% I, 3·49% N.

2-Benzylcyclopentylamine (*XVI*)

A solution of 60 g 2-benzylcyclopentanone oxime[11] in 400 ml ethanol was dropped over 25 min to 195 g Na and the refluxing mixture was then slowly treated over 7 h with 950 ml ethanol. After complete dissolution of Na, the mixture was decomposed by a slow addition of 450 ml water and the base was distilled with steam into a solution of 90 ml hydrochloric acid in 400 ml water. The distillate (6 l) was evaporated under reduced pressure to a volume of 100 ml. This solution deposited on standing 41·2 g (62%) hydrochloride A, m.p. 191—195°C. The mother liquor was evaporated *in vacuo*, the residue was treated with a small quantity of a mixture of ethanol and ether and filtered giving 10·0 g (15%) hydrochloride B, m.p. 132—134°C. The hydrochloride A gave by two crystallizations from ethanol 21·0 g homogeneous stereoisomer A considered to be the *trans*-isomer, m.p. 209·5—210°C. For $C_{12}H_{18}ClN$ (211·7) calculated: 68·08% C, 8·57% H, 16·74% Cl, 6·61% N; found: 68·24% C, 8·69% H, 16·85% Cl, 6·47% N. This hydrochloride was decomposed with a solution of NaOH and the base isolated by extraction with ether, b.p. 98—99°C/67 Pa. It was characterized by gas chromatography as completely homogeneous. For $C_{12}H_{17}N$ (175·3) calculated: 82·23% C, 9·78% H, 7·99% N; found: 82·50% C, 9·94% H, 8·13% N. The hydrochloride B was also decomposed with a solution of NaOH and the base isolated by extraction with ether, b.p. 160—162°C/2·7 kPa. According to gas chromatography, this product consisted of some 20% *trans-XVI* and some 80% of a second component, presumably *cis-XVI*.

N-(2-Benzyl-1-methylcyclopentyl)formamide (*XVIII*)

2-Benzylcyclopentanone[9-11] (80 g) was dissolved in 160 ml ether and the solution was added over 80 min to a stirred and refluxing solution of methylmagnesium iodide, prepared from 75 g methyl iodide and 12·15 g Mg in 140 ml ether. The mixture was refluxed for 3 h, allowed to stand overnight at room temperature, decomposed by a slow addition of a solution of 50 g NH_4Cl in 250 ml water, the organic layer was separated, dried with $MgSO_4$ and distilled; 58 g, b.p. 103—107°C/0·13 kPa. This product, which is a mixture of some 80% olefins *XVII* and 20% 2-benzyl-1-methylcyclopentanol, was used for the following Ritter reaction. Repeated distillation of a sample gave an oxygen-free product with a b.p. of 80°C/67 Pa, n_D^{20} 1·5340, considered to be a mixture of olefins *XVII*. For $C_{13}H_{16}$ (172·3) calculated: 90·64% C, 9·36% H; found: 90·45% C, 9·35% H.

Crude product (52 g) was dissolved in a cold mixture of 180 ml acetic acid and 22 ml H_2SO_4, the mixture was cooled to 5°C, stirred and treated over 70 min with 48 g powdered NaCN (temperature max. 8°C). The mixture was stirred for 10 min and treated over 50 min at max. 10°C with a mixture of 37 ml acetic acid and 48 ml H_2SO_4. The stirring was continued for 3 h with cooling

and the mixture was then allowed to stand for 48 h at room temperature. It was poured into a mixture of 800 g ice and 250 ml water, neutralized with 20% NaOH under cooling (pH 7—8), diluted with water to dissolve the precipitated Na_2SO_4 and extracted with ether. The extract was dried with $MgSO_4$ and evaporated; 54 g oil which was dissolved in 50 ml light petroleum and the solution allowed to crystallize in a refrigerator. There separated 17·6 g (27%) crystalline product which is probably one homogeneous racemate of structure *XVIII*. Analytical sample, m.p. 77—78°C (benzene–hexane). For $C_{14}H_{19}NO$ (217·3) calculated: 77·37% C, 8·81% H, 6·45% N; found: 77·56% C, 9·01% H, 6·14% N.

2-Benzyl-1-methylcyclopentylamine (*XIX*)

A solution of 15·0 g *XVIII* in 55 ml ethanol was treated with a solution of 5·0 g NaOH in 45 ml water and the mixture was refluxed for 48 h. After the addition of 50 ml 20% NaOH, the mixture was distilled with steam into a solution of 15 ml hydrochloric acid in 80 ml water. The distillate (2 l) was evaporated under reduced pressure to a volume of 35 ml and the hydrochloride allowed to crystallize on standing overnight in a refrigerator; 15·5 g (100%), m.p. 226—227°C (ethanol–ether). For $C_{13}H_{20}ClN$ (225·8) calculated: 69·16% C, 8·93% H, 15·71% Cl, 6·20% N; found: 68·94% C, 8·90% H, 15·53% Cl, 6·24% N. Decomposition of the hydrochloride with a solution of NaOH and extraction with ether gave the oily base *XIX*, b.p. 94°C/67 Pa, n_D^{18} 1·5295. ^{1}H-NMR spectrum (ZKR 60): δ 7·28 (s, 5 H, C_6H_5), 1·23 (s, 3 H, C—CH_3), 1·17 (s, disappears after D_2O, 2 H, NH_2). For $C_{13}H_{19}N$ (189·3) calculated: 82·48% C, 10·12% H, 7·40% N; found: 82·57% C, 10·29% H, 7·43% N.

2-Benzyl-N,1-dimethylcyclopentylamine (*XX*)

A solution of 17·0 g *XVIII* in 50 ml tetrahydrofuran was added to a stirred suspension of 5·0 g $LiAlH_4$ in 70 ml ether and the mixture was refluxed for 3 h. After cooling it was decomposed by addition of 25 ml 20% NaOH, the precipitated solid was filtered off, washed with ether and the filtrate distilled; 13·0 g (82%), b.p. 108°C/0·13 kPa, n_D^{21} 1·5249. ^{1}H-NMR spectrum (ZKR 60): δ 7·22 (s, 5 H, C_6H_5), 2·34 (s, 3 H, NCH_3), 1·16 (s, 3 H, C—CH_3), 1·13 (s, 1 H, NH). For C_{14}·$H_{21}N$ (203·3) calculated: 82·70% C, 10·41% H, 6·89% N; found: 83·06% C, 10·38% H, 6·92% N.

Hydrochloride, m.p. 208°C (ethanol–ether). For $C_{14}H_{22}ClN$ (239·8) calculated: 70·12% C, 9·25% H, 14·79% Cl, 5·84% N; found: 69·62% C, 9·24% H, 14·63% Cl, 5·84% N.

2-Benzyl-N,N,1-trimethylcyclopentylamine (*XXI*)

A mixture of 8·5 g *XIX*, 5·2 g *XX*, 20 ml water, 15 ml 85% formic acid and 20 ml 36% aqueous formaldehyde was refluxed for 5 h in a bath of 120—130°C. After the addition of 50 ml hydrochloric acid, the mixture was evaporated under reduced pressure. The residue was dissolved in 75 ml water, the solution made alkaline with 20% NaOH and the base extracted with ether. The extract was dried with solid KOH and processed by distillation; 14·6 g (93%), b.p. 122°C/0·27 kPa, n_D^{21} 1·5258. ^{1}H-NMR spectrum (ZKR 60): δ 7·23 (m, 5 H, C_6H_5), 2·31 (s, 6 H, CH_3NCH_3), 0·95 (s, 3 H, C—CH_3). For $C_{15}H_{23}N$ (217·3) calculated: 82·88% C, 10·67% H, 6·45% N; found: 82·71% C, 10·70% H, 6·39% N.

Hydrochloride, m.p. 214—215°C (ethanol–ether). For $C_{15}H_{24}ClN$ (253·8) calculated: 70·98% C, 9·53% H, 13·97% Cl, 5·52% N; found: 70·48% C, 9·61% H, 13·81% Cl, 5·59% N.

The authors are indebted to Dr E. Svátek (department of physical chemistry of this institute) for recording and interpretation of the IR *spectra, to Mr L. Tůma for the assistance with the synthesis*

of intermediates and to Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, Mr M. Čech, Mr K. Havel, Mrs M. Aixnerová and Mrs J. Schmidtová (analytical department of this institute) for carrying out the analyses. The synthesis of compounds XII—XV *was carried out by Dr V. Seidlová, Dr E. Adlerová and Mrs P. Vejdělková in our laboratory.*

REFERENCES

1. Härtfelder G., Lessenich H., Schmitt K.: Arzneim.-Forsch. *22*, 930 (1972).
2. Castaňer J., Weetman D. F.: Drugs of the Future *1*, 494 (1976); *2*, 706 (1977).
3. Kleene R. D.: J. Amer. Chem. Soc. *71*, 1893 (1949).
4. Hai P. V., Buu-Hoi N. P., Xuong N. D.: J. Org. Chem. *23*, 39 (1958).
5. Grewe R.: Ber. Deut. Chem. Ges. *76*, 1072 (1943).
6. Doering W. v. E., Rhoads S. J.: J. Amer. Chem. Soc. *73*, 3082 (1951).
7. Takahashi T., Hori M., Tsuruha H.: Yakugaku Zasshi *76*, 56 (1956); Chem. Abstr. *50*, 12 849 (1956).
8. McElvain S. M., Clampitt R. B.: J. Amer. Chem. Soc. *81*, 5590 (1959).
9. Baker W., Leeds W. G.: J. Chem. Soc. *1948*, 974.
10. Treibs W., Mayer R., Madejski M.: Chem. Ber. *87*, 356 (1954).
11. Cornubert R., Anziani P., Morelle G.: Bull. Soc. Chim. Fr. *11*, 299 (1944); Chem. Abstr. *40*, 1792 (1946).
12. Hückel W., Kupka R.: Chem. Ber. *89*, 1694 (1956).
13. Hückel W., Thomas K.-D.: Chem. Ber. *96*, 2514 (1963).
14. Zymalkowski F. in the book: *Katalytische Hydrierungen im Organisch-Chemischen Laboratorium*, p. 64. Enke, Stuttgart 1965.
15. Vejdělek Z. J., Rajšner M., Protiva M.: This Journal *25*, 245 (1960).
16. Protiva M., Novák L., Vejdělek Z. J., Ernest I.: Česk. Farm. *14*, 346 (1965).

Translated by the author (M. P.).