

## N-(AMINOACYL) AND N-(AMINOALKYL) DERIVATIVES OF 4-CYCLOPENTYLANILINE AND N-ETHYL-4-CYCLOPENTYLANILINE; SYNTHESIS AND PHARMACOLOGICAL SCREENING\*

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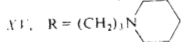
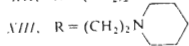
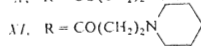
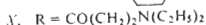
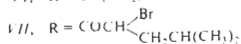
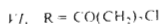
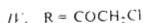
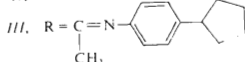
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Acylation of 4-cyclopentylaniline (*I*) with chloroacetyl chloride, 3-chloropropionyl chloride, 4-chlorobutyryl chloride and 2-bromo-4-methylvaleryl bromide gave the halogenoacyl derivatives *IV*–*VII* out of which the first two were subjected to substitution reactions with diethylamine and piperidine. The N-(aminoacyl) derivatives *VIII*–*XI* obtained were reduced with lithium aluminium hydride to the N-(aminoalkyl) derivatives *XII* and *XV*. N-Ethyl-4-cyclopentylaniline (*XVI*), prepared by reduction of N-(4-cyclopentylphenyl)acetamide (*II*), was similarly transformed via the chloroacetyl derivative *XVII* to the amide *XVIII* and the diamine *XIX*. Salts of the compounds prepared (amino amides and diamines) bring about in higher doses central excitation which is apparently in close connection with the found discoordinating effect of a part of products (*VIII*–*XI*, *XIII*) in the rotarod test, further with the antireserpine effects in the tests of antagonization of reserpine ptosis and hypothermia (*VIII*, *X*, *XII*, *XIII*) and finally with the anorectic effect of compound *X*. All substances showed a mild spasmolytic effect of the anticholinergic type. On the other hand, the expected local anaesthetic effect was found only with compounds *VIII*, *XVIII*, *XIX*.

In one of the preceding communications of this series<sup>1</sup> we have described one stage of our attempts at finding new neurotropic and psychotropic agents whose molecules would contain the lipophilic 4-cyclopentylphenyl fragment and have described a series of 1-(4-cyclopentylphenyl)ethylamine derivatives. In the present communication we used as the basis the known 4-cyclopentylaniline (*I*) which is accessible by the Beckmann rearrangement of 4-cyclopentylacetophenone oxime<sup>2</sup> with phosphorus pentachloride in ether and by the following acid hydrolysis of the N-(4-cyclopentylphenyl)acetamide (*II*) formed<sup>2</sup>. In reproducing this procedure we found that in the first stage a product is obtained in an almost theoretical yield which, however, is not homogeneous because its melting point is significantly lower than that of the pure acetamido derivative *II*. Its hydrolysis with aqueous-ethanolic hydrochloric acid affords the hydrochloride of the aniline derivative *I* which is soluble in water. Additionally we isolated in yields of 5–10% a water-insoluble substance which proved to be the hydrochloride of a further base. This base is crystalline and by means

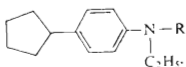
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of analysis and spectra it was identified as the amidine *III*. The formation of similar amidines by the Beckmann rearrangement of aromatic aliphatic ketoximes was described<sup>3,4</sup> in cases of the use of thionyl chloride (but also phosphorus pentachloride) as reagents; an attempt was made at the explanation of its mechanism<sup>4</sup>. The Beckmann rearrangement of 4-cyclopentylacetophenone oxime<sup>2</sup> has now been carried out also with boiling trifluoroacetic acid and the homogeneous acetamido derivative *II* was obtained in a high yield; the same compound was also prepared by acetylation of the aniline derivative *I*.



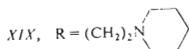
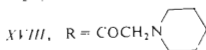
The aniline derivative *I* was acylated with chloroacetyl chloride, 3-chloropropionyl chloride<sup>5</sup>, 4-chlorobutyryl chloride and 2-bromo-4-methylvaleryl bromide<sup>6</sup> in boiling chloroform and in the presence of potassium carbonate (method *A*) (for a similar method of chloroacetylation of aniline, *cf.*<sup>7</sup>) and the halogenoacyl derivatives *IV*–*VII* were obtained. Substitution reactions of compounds *IV* and *V* with excessive diethylamine or piperidine in boiling benzene (method *B*) resulted in the aminoacyl derivatives *VIII*–*XI*, which are crystalline with the exception of compound *X* and all of them affording crystalline hydrochlorides. Reduction of these four amides with lithium aluminium hydride in ether (method *C*) gave the diamines *XII*–*XV* which were isolated as crystalline dihydrochlorides.

The acetamido derivative *II* was reduced with lithium aluminium hydride in ether to N-ethyl-4-cyclopentylaniline (*XVI*) which was converted by the use of the mentioned methods *A*–*C* via the chloroacetyl derivative *XVII* to the piperidinoacetyl derivative *XVIII* and the diamine *XIX*. Compounds prepared by methods *A*, *B* and *C* are assembled in Table I with the usual experimental data while the Experimental describes only examples of these preparations.



XVI, R = H

XVII, R = COCH<sub>2</sub>Cl



Compounds III, VIII–XV, XVIII and XIX were subjected to the general pharmacological screening in the form of salts, described in the Experimental and in Table I. In the first line, the medium lethal doses (LD<sub>50</sub>) in mice and the doses (D) which were used in the screening, are given, both in mg/kg and for *i.v.* administration: VIII, 50, 10; IX, 62.5, 12; X, 75, 15; XI, 62.5, 12; XII, 70, 14; XIII, 60, 12; XIV, 62.5, 12; XV, 50, 10; XVIII, 43.7, 8; XIX, 50, 10. All of these compounds in doses above D increase the activity and reactivity of mice, bring about ataxia, tremor and finally convulsions. Compound III was administered orally; a dose of 2 500 mg/kg is nontoxic and after doses of 300 mg/kg no pharmacological effects were observed. Discoordinating effect in the rotarod test in mice (doses bringing about ataxia in 50% animals): VIII, 1–5; IX, 5–12; X, 5–15; XI, 5; XIII, 10 (*i.v.* administration); the other compounds were inactive in doses D. Local anaesthetic effect in the test of infiltration anaesthesia (concentration in % bringing about a complete anaesthesia in 50% guinea-pigs; for procaine, ED = 1%): XVIII, 0.1–0.5; XIX, 0.1–0.5; in the test of corneal anaesthesia (concentration in % bringing about in 50% rabbits a complete anaesthesia of the eye cornea; for trimecaine, ED = 1%): VIII, 0.05–0.5; XVIII, 0.5, Spasmolytic (parasympatholytic) effect (concentrations in µg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50%; for atropine, ED = 0.05): VIII, 1–10; IX, 1–10; X, 10; XI, 10; XII, 1–10; XIII, 1–10; XIV, 10; XV, 10; XVIII, 1–10; XIX, 1–10. Spasmolytic (musculotropic) effect (similar arrangement, barium chloride contractions; for papaverine, ED = 5): VIII, 1–10; IX, 1–10; XII, 1–10; XIII, 1–10; XIX, 1–10. Effect on heart inotropy (concentration in µg/ml eliciting a decrease of inotropy of the isolated rabbit heart atrium by 25%): IX, 5–50; X, 5–50; XI, 25; XII, 50; XIII, 10–50; XIV, 50; XV, 50; XVIII, 25–50. Effect on heart frequency (similar arrangement): VIII, 50; XI, 25; XIII, 10–50; XV, 50, XIX, 25–50. Antireserpine activity: (a) Ptosis in mice (a dose *i.p.* antagonizing significantly the reserpine ptosis; for amphetamine, ED = 0.5 mg/kg): VIII, 10; X, 15 (oral doses of 20 and 40 mg/kg practically without effect); XII, 14; XIII, 12. (b) Hypothermia in mice (doses *i.p.* increasing the rectal temperature by 1°C in comparison with the reserpine control group; amphetamine, ED = 0.75 mg/kg): VIII, 10; X, 15; XII, 14; XIII, 12. Anorectic activity (dose in mg/kg orally decreasing the food consumption in mice by 50%;

for dexphenmetrazine, ED = 25): X, 75. Diuretic effect (oral dose in mg/kg increasing the diuresis in mice by 100% as compared with the control; for hydrochlorothiazide, ED = 100): X, 75.

Hyperglycaemic effect (oral dose in mg/kg increasing blood sugar in rats by 20%): XII, 70 XIII, 60; XIX, 25–50.

The compounds were also tested for antimicrobial activity *in vitro* (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*, III 50, IX 50, X 100, XI 50, XII 50, XIII 50, XIV 50, XV 50, XIX 25; *Streptococcus faecalis* X 100, XIV 100; *Staphylococcus pyogenes aureus*, III 50, IX 100, XI 100, XIV 100, XIX 50; *Mycobacterium tuberculosis* H37Rv, VIII 12.5, IX 25, X 25, XI 25, XII 12.5, XIII 6.25, XIV 12.5, XV 3.1, XVI 50, XIX 6.25; *Saccharomyces pasteurianus*, III 25, VIII 100, IX 100, X 100, XI 100, XII 100, XIII 50, XIV 100, XV 100; *Trichophyton mentagrophytes*, III 25, VIII 50, IX 50, X 100, XI 100, XII 100, XIII 50, XIV 50, XV 50, XIX 25; *Candida albicans*, III 50, VIII 100, IX 100, X 100, XI 100, XII 100, XIV 100, XV 100; *Aspergillus niger*, III 50, VIII 100, IX 100, X 100, XI 100, XIV 100, XV 100.

## 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<sub>2</sub>O<sub>5</sub> at room temperature or at 77°C. The IR spectra (mostly in Nujol) were recorded with a Unicam SP 200G spectrophotometer, the UV spectrum (in methanol) with a Unicam SP 8000 spectrophotometer and the <sup>1</sup>H NMR spectra (in C<sup>2</sup>HCl<sub>3</sub>) with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel.

### N-(4-Cyclopentylphenyl)acetamide (II)

A) 4-Cyclopentylacetophenone oxime<sup>2</sup> (101.5 g) was rearranged by treatment with 155 g PCl<sub>5</sub> in 500 ml ether according to the literature<sup>2</sup> and 101 g (100%) crude II were obtained (m.p. 100–103°C) which were used without purification for the hydrolysis to I. Lit.<sup>2</sup>, m.p. 136°C.

B) 4-Cyclopentylacetophenone oxime<sup>2</sup> (50 g) was added over 30 min to 180 ml refluxing trifluoroacetic acid, the mixture was refluxed for 1.5 h, the acid was distilled off *in vacuo*, the residue was mixed with 150 ml water, the solid filtered, washed with water and dried *in vacuo*; 48 g (96%) crude II melting after a single crystallization from 70% aqueous ethanol at 133–134°C.

C) A mixture of 11.3 g I (ref.<sup>2</sup>), 100 ml chloroform and 11.6 g K<sub>2</sub>CO<sub>3</sub> was stirred and treated at room temperature over 30 min with a solution of 7.2 g acetyl chloride in 25 ml chloroform. The mixture was refluxed for 1.5 h, after cooling decomposed with 100 ml water, the organic layer was washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered with charcoal and evaporated. The solid residue (14.1 g) is the crude II which was crystallized from 70% aqueous ethanol, m.p. 133–134°C.

### 4-Cyclopentylaniline (I)

Crude II (101 g) obtained according to A) was hydrolyzed by refluxing for 3 h with a mixture of 500 ml ethanol and 150 ml hydrochloric acid. The volatile components were evaporated *in vacuo* and the residue was dissolved in 700 ml warm water. The undissolved solid was filtered

TABLE I  
 N-(Halogenoacyl), N-(aminoacyl) and N-(aminoalkyl) derivatives of 4-cyclopentylaniline

Compound	Method (yield. %)	M., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
				% C	% H	% N	% Cl
IV	A <sup>a</sup> (93)	151—152 (benzene-hexane)	C <sub>13</sub> H <sub>16</sub> ClNO (237.7)	65.68	6.78	5.89	14.92
				65.86	6.91	5.72	15.14
V	A (95)	138—139 <sup>b</sup> (benzene-hexane)	C <sub>14</sub> H <sub>18</sub> ClNO (251.7)	66.79	7.21	5.56	14.08
				67.12	7.36	5.71	13.93
VI	A (92)	104—105 <sup>c</sup> (benzene-hexane)	C <sub>15</sub> H <sub>20</sub> ClNO (265.8)	67.78	7.59	5.27	13.34
VII	A (98)	88—89 <sup>d</sup> (hexane-benzene)	C <sub>17</sub> H <sub>24</sub> BrNO (338.3)	60.35	7.15	4.14	23.63 <sup>e</sup>
				59.62	7.15	3.95	23.86
VIII	B <sup>a</sup> (100)	47—48 (hexane)	C <sub>17</sub> H <sub>26</sub> N <sub>2</sub> O (274.4)	74.41	9.55	10.21	—
				74.43	9.46	10.18	—
VIII-HCl	—	187—188 (ethanol)	C <sub>17</sub> H <sub>27</sub> ClN <sub>2</sub> O (310.9)	65.66	8.76	9.02	11.41
IX	B (100)	79—80 (hexane)	C <sub>18</sub> H <sub>26</sub> N <sub>2</sub> O (286.4)	65.74	8.54	8.87	11.41
				75.48	9.15	9.78	—
IX-HCl	—	219—220 (ethanol)	C <sub>18</sub> H <sub>27</sub> ClN <sub>2</sub> O (322.9)	66.95	8.43	8.68	10.98
				67.25	8.40	8.70	11.13
X-HCl	B (100)	180—181 (ethanol-ether)	C <sub>18</sub> H <sub>29</sub> ClN <sub>2</sub> O (324.9)	66.54	9.00	8.62	10.92
XI	B (96)	66—67 <sup>f</sup> (hexane)	C <sub>19</sub> H <sub>28</sub> N <sub>2</sub> O (300.4)	66.41	9.11	8.51	10.89
				75.95	9.39	9.33	—
XI-HCl	—	223—224 (ethanol)	C <sub>19</sub> H <sub>29</sub> ClN <sub>2</sub> O (336.9)	75.96	9.23	9.22	—
				67.72	8.68	8.32	10.53
XII-2 HCl	C <sup>a</sup> (100)	116—117 (acetone-ethyl acetate)	C <sub>17</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> (333.3)	67.52	8.49	8.23	10.66
				61.24	9.07	8.41	21.28
XIII-2 HCl	C (100)	252—253 (ethanol containing HCl)	C <sub>18</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> (345.4)	61.01	9.12	8.35	21.20
				62.59	8.76	8.11	20.54
XIV-2 HCl	C (96)	157—158 (ethanol-ether containing HCl)	C <sub>18</sub> H <sub>32</sub> Cl <sub>2</sub> N <sub>2</sub> (347.4)	62.70	8.60	8.06	20.75
				62.22	9.29	8.07	20.42
XV-2 HCl <sup>g</sup>	C (98)	208—210 (ethanol-ether containing HCl)	C <sub>19</sub> H <sub>32</sub> Cl <sub>2</sub> N <sub>2</sub> + 0.5 H <sub>2</sub> O (368.4)	62.05	9.19	7.88	20.25
				61.92	9.03	7.61	19.26
XVII	A (100)	<sup>h</sup> (265.8)	C <sub>15</sub> H <sub>20</sub> ClNO (265.8)	62.13	8.99	7.53	19.36
				—	—	5.27	—
XVIII-M <sup>i</sup>	B (83)	116—117 (ethanol-ether)	C <sub>24</sub> H <sub>34</sub> N <sub>2</sub> O <sub>5</sub> (430.5)	—	—	5.48	—
				66.95	7.96	6.51	—
XIX-2 HCl	C (99)	226—227 (ethanol-ether containing HCl)	C <sub>20</sub> H <sub>34</sub> Cl <sub>2</sub> N <sub>2</sub> (373.4)	66.96	8.05	6.38	—
				64.33	9.18	7.50	18.99
				64.14	8.96	7.55	18.79

off and the filtrate was made alkaline with 20% NaOH. The base *I* was isolated by extraction with benzene and distillation; 60.0 g (75%), b.p. 118–120°C/0.2 kPa. Lit<sup>2</sup>, b.p. 165–167°C/3.0 kPa.

The undissolved solid by-product was obtained in a yield of 4.0 g (5%) (in another experiment there were obtained from 305 g 4-cyclopentylacetophenone oxime 24.0 g, i.e. 9% of the same product), m.p. 220–225°C, and was characterized as the hydrochloride of a base. Its suspension in water was made alkaline at 60°C with 20% NaOH and the base was extracted with benzene. Processing of the extract gave a product which was crystallized from hexane and melted at 116 to 117°C (needles). It was identified as N,N'-bis(4-cyclopentylphenyl)acetamidine (*III*). UV spectrum:  $\lambda_{\max}$  263 nm (log  $\epsilon$  4.23). IR spectrum: 822, 831 (2 adjacent Ar—H), 1 219, 1 379 (Ar—N), 1 506, 1 516, 1 539 (Ar), 1 635 (Ar—N=C), 3 210, 3 290 cm<sup>-1</sup> (NH). <sup>1</sup>H NMR spectrum:  $\delta$  c. 7.00 (m, 8 H, Ar—H), 6.08 (bs, 1 H, NH), 2.90 (m, 2 H, 2 Ar—CH of the cyclopentyls), 1.90 (s, 3 H, C—CH<sub>3</sub>), 1.00–2.20 (m, 16 H, 8 CH<sub>2</sub> of the cyclopentyls). For C<sub>24</sub>H<sub>30</sub>N<sub>2</sub> (346.5) calculated: 83.19% C, 8.73% H, 8.09% N; found: 83.21% C, 8.86% H, 8.11% N.

*Hydrochloride*, m.p. 238–239°C (ethanol-ether). For C<sub>24</sub>H<sub>31</sub>ClN<sub>2</sub> (383.9) calculated: 75.27% C, 8.16% H, 9.26% Cl, 7.32% N; found: 75.31% C, 8.24% H, 9.43% Cl, 7.32% N.

#### N-(4-Cyclopentylphenyl)chloroacetamide (*II'*) (Method A)

K<sub>2</sub>CO<sub>3</sub> (16.6 g) was added to a solution of 16.1 g *I* in 50 ml chloroform and the stirred mixture was treated at room temperature over 45 min with a solution of 15 g chloroacetyl chloride in 50 ml chloroform, added dropwise. It was then refluxed for 1.5 h, cooled and diluted with 150 ml chloroform (to dissolve the precipitated *II'*), the chloroform solution was washed with water, dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated *in vacuo*. The residue was mixed with 50 ml hexane, filtered, washed with hexane and dried *in vacuo*; 22.1 g (93%), m.p. 145–147°C. Analytical sample, m.p. 151–152°C (benzene-hexane). IR spectrum: 824, 838 (2 adjacent Ar—H), 1 252, 1 515, 1 559, 1 614, 1 670 (Ar—NH—CO), 3 135, 3 203, 3 270 cm<sup>-1</sup> (NH). The analysis, cf. Table I.

←  
<sup>a</sup> See Experimental. <sup>b</sup> IR spectrum: 835 (2 adjacent Ar—H), 1 518, 1 540, 1 660 (NHCO), 1 610 (Ar), 3 140, 3 210, 3 315 cm<sup>-1</sup> (NH). <sup>c</sup> IR spectrum: 822 (2 adjacent Ar—H), 1 529, 1 595, 1 665 (Ar—NHCO), 3 335 cm<sup>-1</sup> (NH). <sup>d</sup> IR spectrum: 824 (2 adjacent Ar—H), 1 367, 1 384 [CH(CH<sub>3</sub>)<sub>2</sub>], 1 530, 1 600, 1 664 (Ar—NHCO), 3 320 cm<sup>-1</sup> (NH); <sup>1</sup>H NMR spectrum:  $\delta$  8.12 (bs, 1 H, NH), 7.40 (d,  $J$  = 8.0 Hz, 2 H, 2,6-H<sub>2</sub>), 7.10 (d,  $J$  = 8.0 Hz, 2 H, 3,5-H<sub>2</sub>), 4.42 (t,  $J$  = 7.0 Hz, 1 H, COCHBr), 2.90 (m, 1 H, Ar—CH of cyclopentyl), 1.98 (d,  $J$  = 7.0 Hz, 2 H, CH<sub>2</sub> in the acyl residue), 1.30–2.20 (m, 9 H, 4 CH<sub>2</sub> of cyclopentyl and CH of isopropyl), 0.98 and 0.88 (2 d,  $J$  = 6.0 Hz, 6 H, 2 CH<sub>3</sub> of isopropyl). <sup>e</sup> % Br. <sup>f</sup> IR spectrum (KBr): 826 (2 adjacent Ar—H), 1 520, 1 595, 1 650 cm<sup>-1</sup> (Ar—NHCO); <sup>1</sup>H NMR spectrum:  $\delta$  11.15 (bs, 1 H, NH), 7.40 (d,  $J$  = 8.0 Hz, 2 H, 2,6-H<sub>2</sub>), 7.10 (d,  $J$  = 8.0 Hz, 2 H, 3,5-H<sub>2</sub>), 2.30–3.00 (m, 9 H, ArCH of cyclopentyl, COCH<sub>2</sub> and 3 NCH<sub>2</sub>), 1.30–2.20 (m, 14 H, 4 CH<sub>2</sub> of cyclopentyl and remaining 3 CH<sub>2</sub> of piperidine). <sup>g</sup> Hemihydrate. <sup>h</sup> Homogeneous oily substance obtained by chromatography of the crude base on neutral Al<sub>2</sub>O<sub>3</sub> (activity II) and elution with hexane;  $n_D^{22}$  1.5356; <sup>1</sup>H NMR spectrum:  $\delta$  7.28 (d,  $J$  = 8.0 Hz, 2 H, 3,5-H<sub>2</sub>), 7.04 (d,  $J$  = 8.0 Hz, 2 H, 2,6-H<sub>2</sub>), 3.78 (s, 2 H, COCH<sub>2</sub>Cl), 3.71 (q,  $J$  = 7.0 Hz, 2 H, NCH<sub>2</sub>), 2.90 (m, 1 H, Ar—CH of cyclopentyl), 1.20–2.20 (m, 8 H, 4 CH<sub>2</sub> of cyclopentyl), 1.12 (t,  $J$  = 7.0 Hz, 3 H, CH<sub>3</sub> of ethyl). <sup>i</sup> Maleate.

## N-(4-Cyclopentylphenyl)diethylaminoacetamide (VIII) (Method B)

A mixture of 11.0 g IV, 70 ml benzene and 8.5 g diethylamine was refluxed for 6 h and allowed to stand overnight. The precipitated diethylamine hydrochloride was filtered off, the filtrate was washed with water, dried with  $\text{Na}_2\text{SO}_4$  and evaporated *in vacuo*; 12.6 g (100%) oil crystallizing from hexane and melting at 47–48°C. IR spectrum: 830 (2 adjacent Ar—H), 1 530, 1 695 (NHCO), 1 506, 1 590, 1 615 (Ar), 3 290  $\text{cm}^{-1}$  (NH).  $^1\text{H}$  NMR spectrum:  $\delta$  9.25 (bs, 1 H, ArNHCO), 7.45 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$ ), 7.10 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$ ), 3.10 (s, 2 H,  $\text{COCH}_2\text{N}$ ), c. 2.90 (m, 1 H, Ar—CH of cyclopentyl), 2.58 (q,  $J = 7.0$  Hz, 4 H,  $\text{CH}_2\text{NCH}_2$  of diethylamino), 1.40–2.10 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl), 1.08 (t,  $J = 7.0$  Hz, 6 H, 2  $\text{CH}_3$  of diethylamino). Hydrochloride, m.p. 187–188°C (ethanol). Analyses, cf. Table I.

## N-(2-Diethylaminoethyl)-4-cyclopentylaniline (XII) (Method C)

A solution of 6.3 g VIII in 50 ml benzene was slowly added to a stirred suspension of 2.5 g  $\text{LiAlH}_4$  in 50 ml ether and the mixture was refluxed for 5 h. After standing overnight it was decomposed under stirring by a slow addition of 10 ml 20% NaOH, the mixture was stirred for 30 min, the solid was filtered off and washed with benzene. The filtrate was evaporated and gave 6.0 g (100%) crude oily XII. It was dissolved in 60 ml ether and the solution was neutralized with ethanolic solution of HCl. The mixture was evaporated *in vacuo*, the residue was dissolved in 50 ml acetone and the solution was treated slowly with 70 ml ethyl acetate. After standing overnight 6.2 g dihydrochloride were filtered, m.p. 114–117°C. Analytical sample, m.p. 116 to 117°C (acetone–ethyl acetate). Analysis, cf. Table I.

## N-Ethyl-4-cyclopentylaniline (XVI)

A solution of 22 g II in 140 ml benzene was slowly added to a suspension of 8.0 g  $\text{LiAlH}_4$  in 80 ml ether and the mixture was refluxed for 5 h. After cooling it was decomposed with 32 ml 20% NaOH, added dropwise, the salt was filtered off and the filtrate evaporated. The crude product was distilled; 19.8 g (97%), b.p. 125°C/0.13 kPa,  $n_D^{21}$  1.5545.  $^1\text{H}$  NMR spectrum:  $\delta$  7.00 (d,  $J = 8.0$  Hz, 2 H, 3,5- $\text{H}_2$ ), 6.50 (d,  $J = 8.0$  Hz, 2 H, 2,6- $\text{H}_2$ ), 3.25 (bs, 1 H, NH), 3.10 (q,  $J = 7.0$  Hz, 2 H,  $\text{NCH}_2$ ), c. 2.85 (m, 1 H, Ar—CH of cyclopentyl), 1.40–2.10 (m, 8 H, 4  $\text{CH}_2$  of cyclopentyl), 1.18 (t,  $J = 7.0$  Hz, 3 H,  $\text{CH}_3$ ). For  $\text{C}_{13}\text{H}_{19}\text{N}$  (189.3) calculated: 82.48% C, 10.12% H, 7.40% N; found: 82.25% C, 10.08% H, 7.35% N.

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