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Synthesis and analgesic activity of *N*-aryl/arylalkyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]propanamides[1]

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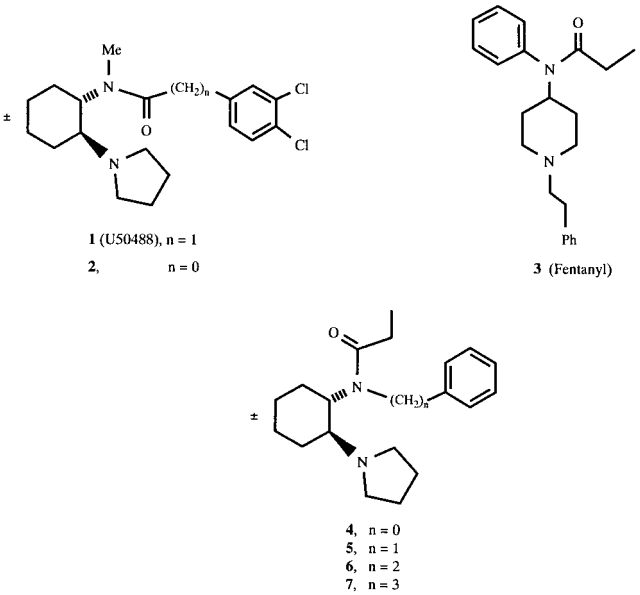
The synthesis and *in vivo* analgesic activity (hot-plate test) of *N*-benzyl, *N*-(2-phenylethyl) and *N*-(3-phenylpropyl) derivatives of *trans*-(±)-*N*-[2-(1-pyrrolidinyl)cyclohexyl]propanamide (**5**–**7**, respectively) are discussed. Attempts to synthesize the *N*-phenyl derivative **4** are also discussed. The lack of significant analgesic activity of **5**–**7** indicated the stringent structural requirement for the *N*-methyl-*N*-arylacetamido group of the κ-selective opioid *trans*-(±)-2-(3,4-dichlorophenyl)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]acetamide (U50488) (**1**).

1. Introduction

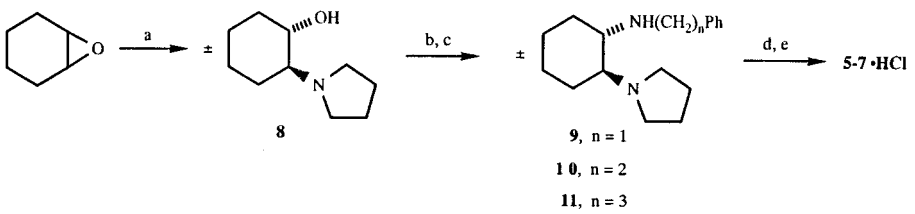
Opioid ligands exert their pharmacological effects by binding to different types of opioid receptors (μ, κ, δ) [1]. Although highly selective ligands have been identified, structural and steric requirements for each receptor type are not yet clearly defined. Furthermore, subtle structural modification can result in a pronounced effect on the binding and pharmacological profile of an opioid ligand. For example, compound **1** (U50488) is a selective κ agonist [2]. However, its benzamide derivative **2** showed considerable μ or morphine-like behavioral effects in animals [2]. Likewise, replacement of the pyrrolidino moiety of **1** by an *N*-methyl-*N*-phenethyl group is reported to increase its μ-receptor affinity [3]. A phenethyl *N*-substituent is known to be crucial for the activity of the μ-selective fentanyl (**3**) [4–6]. The objective of this study was to further investigate the presence of structural or functional analogies between the arylacetamide U50488 (**1**) and fentanyl (**3**). For that purpose, it was desired to synthesize compounds **4**–**7**, and to investigate whether they have analgesic effect against noxious thermal stimulus in mice [7]. In compounds **4**–**7**, the arylacetamido moiety of U50488 is replaced by the *N*-arylpropanamido group of the fentanyl series. The distance between the amidic nitrogen and the aromatic residue (which appears to be critical for opioid selectivity) is varied using methylene units.



2. Investigations and results

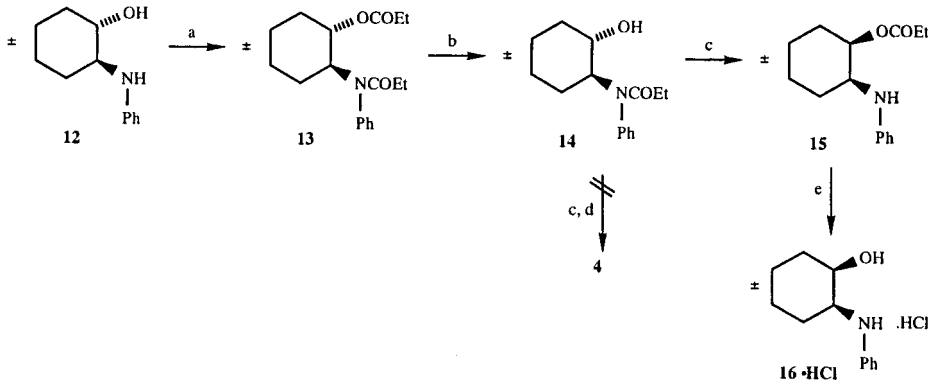
Compounds **5**–**7** were prepared as outlined in Scheme 1. Ring opening of cyclohexene oxide with pyrrolidine gave the racemic *trans*-pyrrolidinocyclohexanol **8** [8]. Compound **8** was reacted with methanesulfonyl chloride (MsCl)/TEA, followed by treatment of the sulfonate ester with excess (2 mol) of the appropriate arylalkylamine to give diamines **9**–**11**. These diamines were not separated, but their crude mixture (containing excess arylalkylamines) was acylated with propionyl chloride. The target compounds **5**–**7** were separated and purified by crystallization as their hydrochloride salts. In the above displacement reaction, the *trans* stereochemistry was retained by neighbouring group mechanism, possibly via a bicyclic aziridinium intermediate [8]. This was verified from ^{1}H NMR analyses (first order approximation) of **5**–**7** as HCl salts in $CDCl_3$ which showed the H-1 and H-2 methine signals at δ 4.5 and 3.8 ppm, respectively, as triplets of doublets ($J_{ax\text{-}ax} = 12$, and $J_{ax\text{-}eq} = 4$ Hz) or as unresolved multiplets of width at half height (W_H) of 20 to 24 Hz which is consistent with their axial dispositions [9]. Benzylic protons of **5** showed an AB pattern as two doublets ($J_{gem} = 17.6$ Hz) at δ 5.39 and 4.43 ppm. ^{13}C NMR analysis of **6** showed one carbonyl carbon absorption at δ 176.5 ppm and a single set of aromatic car-

Scheme 1



(a) Pyrrolidine, Me_2CHOH; (b) MsCl, TEA, CH_2Cl_2; (c) $Ph(CH_2)_{1-3}NH_2$, THF; (d) EtCOCl, TEA, CH_2Cl_2; (e) $(Et)_2O$/HCl

Scheme 2



(a) EtCOCl, TEA, PhH; (b) K_2CO_3, MeOH; (c) MsCl, TEA, CH_2Cl_2; (d) Pyrrolidine, THF; (e) HCl/MeOH

bons (see experimental section). The above synthetic route, however, failed to afford anilide **4** in a readily purified form possibly due to steric bulk or weak nucleophilicity of the used amine (aniline) (TLC analysis of the reaction of aniline with mesylate ester of **8** showed the formation of several components). Therefore, an alternative route (Scheme 2) in which the anilino group was introduced earlier in the synthesis was attempted. Accordingly, cyclohexene oxide was reacted with aniline to give anilinocyclohexanol **12**. Acylation of **12** with EtCOCl gave the diacyl derivative **13**, which was hydrolyzed in K_2CO_3/MeOH to give the anilidocyclohexanol **14**. Compound **14** showed its H-1 and H-2 resonances at δ 3.36 and 4.74 ppm, respectively, as triplets of doublets of $J_{ax\text{-}ax} = 11.5$ and $J_{ax\text{-}eq} = 4.4$ Hz which ascertains its *trans* configuration. It was expected that subsequent mesylation of **14**, followed by the addition of pyrrolidine should give **4**, possibly in *trans* configuration due to anchemeric assistance from the anilide oxygen. However, it was found that treatment of **14** with MsCl/TEA resulted in N → O acyl migration with inversion of configuration at C-1 to give *cis*-anilinocyclohexyl propionate **15** (Scheme 3). Conceivably, this rearrangement occurred via internal S_N2 reaction by the anilide oxygen at C-1 to form a resonance-stabilized oxazolidinium intermediate which was rapidly hydrolyzed to **15**. Since reaction of pyrrolidine with this presumed intermediate should give **4**, attempts were made to perform the mesylation reaction under anhydrous conditions, followed by immediate pyrrolidine addition. However, these attempts did not significantly alter the reaction outcome. Significantly, no acyl exchange occurred upon heating of **14** in methylene chloride for 2 h. Mild acidic hydrolysis of **15** gave **16**; the *cis* isomer of compound **12**. ^{1}H NMR of *cis* compounds **15** · HCl and **16** · HCl (in $CDCl_3$) showed their H-1 signals at 4.85 and 4.68 ppm of $W_H = 10.28$ and 12.1 Hz, respectively, which indicated their equatorial dispositions. The H-2 signals appeared as doublets of doublets at 3.36 ($J_{ax\text{-}ax} = 11.6$ and $J_{ax\text{-}eq} = 3.3$ Hz) and 3.39 ($J_{ax\text{-}ax} = 10.2$ and $J_{ax\text{-}eq} = 3.8$ Hz) ppm, respectively. These values clearly reflect the preferred equatorial disposition of the anilino (anilinium) group in both compounds and hence the axial orientations of OCOEt and OH groups. Significantly, a greater population of the flip conformer of **16** than in the case of **15** is suggested by its smaller C-2 diaxial proton coupling and somewhat larger $J_{ax\text{-}eq}$ than that of **15**. An alternative synthesis for **4** is being sought.

Compounds **5**–**7** were tested for antinociception using the 55 °C mouse hot-plate test [7, 10]. Selected data are shown in the Table. The *N*-benzyl compound **5** did not show any significant analgesic activity up to 40 mg/kg. At this dose, animals exhibited occasional tremors and con-

Scheme 3

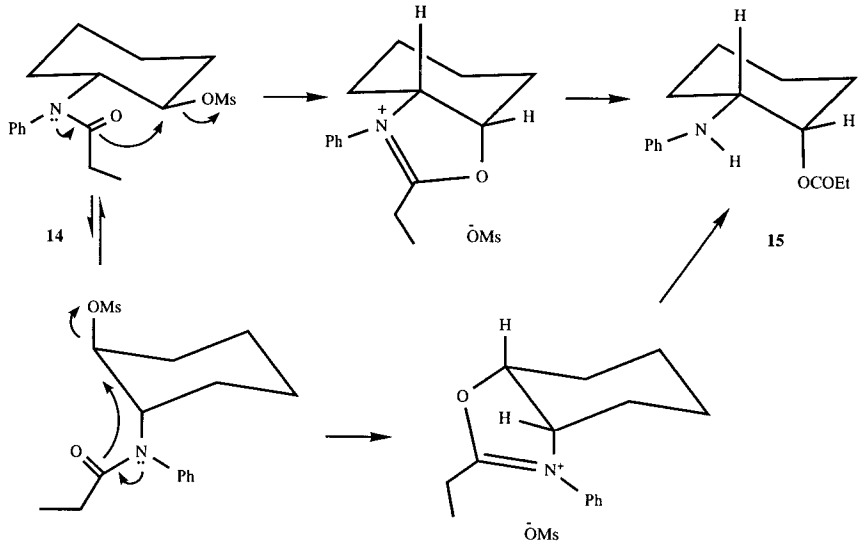


Table: Analgesic response to *N*-substituted propanamides in the mouse hot-plate test

Compd.	Dose[b] (mg/kg)	% Change in HPL[a]				
		Time (min)				
		15	30	60	90	120
5 · HCl	40	14 ± 7	3 ± 16	−18 ± 4	–	–
6 · HCl	30	25 ± 7*	44 ± 11*	35 ± 7*	49 ± 14	–
	60	124 ± 21*	61 ± 13*	42 ± 9*	35 ± 12	–
7 · HCl	20	18 ± 11	35 ± 9*	35 ± 9*	60 ± 14*	45 ± 22
	40	50 ± 16*	56 ± 21	65 ± 15*	65 ± 16*	52 ± 15*
	60	109 ± 32*	51 ± 42	18 ± 7	10 ± 6	–
Fentanyl[c]	0.5	136 ± 25*	127 ± 27*	61 ± 17*	39 ± 13*	25 ± 16
Morphine[d]	20	123 ± 27*	150 ± 25*	108 ± 12*	72 ± 11*	52 ± 11*

[a] Calculated as T-To/To X 100, where T and To are the drug and control hot-plate latency (HPL), respectively; a cut off latency time of 30 s was used; Values are the mean ± SE of the mean; 6–8 animals were used for each dose; asterisks (*) signify values statistically different from control (student t, $P < 0.05$). [b] Doses were calculated in mg (base)/kg; Solutions of compounds were prepared in H_2O and administered by the i.p. route in a volume equivalent to 10 ml/kg. [c] Fentanyl citrate (Janssen Pharmaceutical). [d] Morphine sulfate (El-kahira Co).

vulsions, and 25% lethality was observed from apparent respiratory depression. A dose of 60 mg/kg of **5** resulted in 100% lethality. Weak analgesic activity was shown by 20–40 mg/kg of compounds **6** and **7**, and animals appeared sedated and cofined to one location. Higher doses of **6** or **7** (60 mg/kg) resulted in considerable analgesic activity, which was accompanied by apparent fast respiration, and locomotor disfunction (and tremors in case of **6**). A dose of 80 mg/kg of compounds **6** or **7** resulted in 40–60% lethality from respiratory depression. Also, a cataleptic immobility particularly in the case of **7** was observed at this dose.

3. Discussion

U50488 (**1**) is reported to possess potent antinociceptive activity against pressure and thermal stimuli in mice [7]. Its ED_{50} in the mouse hot-place test was estimated as 12 mg/kg [7]. The above initial results showed that structural modification of **1** as in **5**–**7** has a detrimental effect on analgesic activity *in vivo*. If this effect is not due to dispositional or pharmacokinetic factors (which is not unlikely), it may be ascribed to a loss of receptor affinity. Structure-activity relationship and conformational studies of U50488 and other κ-selective ligands identified the structure moiety $N^+-C-C-N(CO)$ as a common pharmacophore with a torsional angle of 60° and in which the carbonyl oxygen is oriented toward the basic *N*-substituent [11, 12]. These, however, are or can be stable conformations of **5**–**7**. Perhaps more significant in this case is the relative orientation of the phenyl group to the amidic function [13]. In a *gauche* conformer of U50488-arylacetamido chain (conformer **a**, Fig.), the corresponding phenyl binding site at the receptor would be in the trajectory of, per se, an *N*-aryl substituent of **5** (conformer **b**). On the other hand, a pharmacophoric *anti* conformation of the phenyl ring (with respect to the amidic nitrogen) would explain why **5** is such an inactive compound. Although molecular mechanics and NMR studies of **1** indicated a preferred *gauche* phenyl conformer(s) stabilized by attractive van der Waals interactions, crystal structures of the active enantiomer of **1** showed an *anti* conformation with *trans* dihedral angles [14].

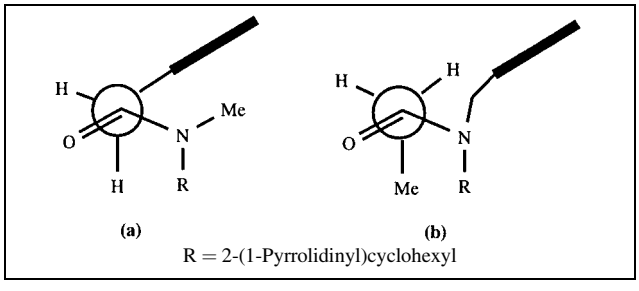


Fig.: A *gauche* conformer of arylacetamido group of U50488. (b) A possible conformation of *N*-benzylproponamido group of **5**

The results of this study emphasize the very particulate disposition of the arylacetamido group in **1**. However, the effect of replacing this group by the propananilide structure of fentanyl (**3**) (as proposed in compound **4**) remains to be investigated. It may be possible that the coplanarity of this anilide structure [15] represents a "μ-conformation" to which the benzamide moiety of the μ-like U50488 derivative **2** is related. It is also conceivable that the spacing and orientation of these amidic structures in relation to the basic *N*-substituent as disposed by the cyclohexane or piperidine ring is contributing significantly to opioid selectivity of U50488 and fentanyl, respectively. This view is supported by the fact that the *cis*-isomer of **1** is a selective ligand for σ binding sites [16]. Further studies of compounds described in this report may shed more light on the steric requirements of κ agonists; recently sought as safer and of less abuse-potential than morphine, and as possible neuroprotective agents [17].

4. Experimental

Melting points (uncorrected) were determined in open capillary tubes with a Griffin apparatus. IR spectra were recorded on a Shimadzu-IR 435 spectrometer. ^1H NMR spectra were measured on a Jeol FX 90, Bruker 200 MHz or a Jeol EX-270 MHz spectrometer. ^{13}C NMR were measured at 67.5 MHz on a Jeol EX-270 MHz. Chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane. Mass spectra were obtained with Finingan SSQ 7000. Elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt, and gave satisfactory values. TLC was performed on Merck silica gel F254 aluminium or polyester-backed sheets, using the eluent EtOAC/methylcyclohexane/TEA (5:3:0.2). THF was distilled from $LiAlH_4$. *trans*-(±)-2-(1-Pyrrolidinyl)cyclohexan-1-ol (**8**) was prepared as reported [8] (b.p. 125–126 °C/15 mmHg) [IR (Neat) 3450 cm^{-1}, HCl salt: m.p. 148–152 °C; ^1H NMR ($CDCl_3$) δ 11.02 (brs, N^+H), 4.68–2.74 (m, 7 H including one D_2O-exchangeable proton), 2.74–1.42 (m, 12 H)]. Cyclohexene oxide and MsCl were obtained from Merck; all other fine chemicals from Aldrich.

4.1. trans-(±)-N-Arylalkyl-N-[2-(1-pyrrolidinyl)cyclohexyl]propanamide hydrochlorides (5 · HCl, 6 · HCl and 7 · HCl)

To a stirred solution of **8** (4.0 g, 23.6 mmol) in CH_2Cl_2 (30 ml) at −5 °C TEA (3.9 ml, 28,4 mmol) was added followed by a dropwise addition of MsCl (2.0 ml, 26.0 mmol). Stirring was continued for 2 h at −5 °C. The mixture was diluted with cold CH_2Cl_2 (25 ml), washed will ice-H_2O (2 × 50 ml), cold brine (30 ml), dried (Na_2SO_4) and the solvent was evaporated at ambient temperature. The oily sulfonate ester residue (3.1 g, 12.5 mmol) was dissolved in dry THF (10 ml), cooled and treated with a

solution of the appropriate arylalkylamine (25 mmol) in THF (5 ml). The mixture was heated at reflux for 14 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (50 ml), washed with H_2O (3 × 50 ml), brine (50 ml), dried (Na_2SO_4) and evaporated. This crude material (containing the diamine product and excess of the used arylalkylamine) (4 g) was dissolved in CH_2Cl_2 (25 ml), cooled, treated with TEA (30 mmol) then with propionyl chloride (25 mmol) and the mixture was stirred for 4 h at ambient temperature. The mixture was evaporated and the residue was treated with ice-H_2O (70 ml), acidified to litmus by HCl, and extracted with CH_2Cl_2 (2 × 50 ml). The aqueous layer was cooled, basified (K_2CO_3) and extracted with CH_2Cl_2 (2 × 50 ml). The extract was dried (Na_2SO_4), cooled and treated dropwise with $(Et)_2O$/HCl. The precipitated salts were washed with cold $(Et)_2O$, dried i.vac. and recrystallized from CH_2Cl_2/$(Et)_2O$ to give 60% yield (based on **8**) of **5**–**7** as hydrochloride salts (hygroscopic needles). Compound **7** could also be crystallized from $(Et)_2O$.

4.1.1. Compound **5** · *HCl*

M.p. 204–205 °C; R_f 0.64; IR (KBr) 1630 cm^{-1}, ^1H NMR ($CDCl_3$) δ 11.8 (brs, N^+H), 7.34 (m, 5 H, ArH), 5.39 (d, J = 17.67 Hz, 1 H, CHPh), 4.86 (t, J = 11.31 Hz, 1 H, H-1), 4.43 (d, J = 17.67 Hz, 1 H, CHPh), 4.07 (m, W_H = 23.4 Hz, 1 H, H-2), 3.87–1.1 (m, 21 H); EIMS m/z 314 $(M)^+$ (6.1%), 189 $[PhCH_2N(COEt)CH{=}CH_2]^+$ (5%), 151 $(M\text{-}PhCH_2NHCOEt)^+$ (96.8%), 148 (100%), 91 (43.6%).
$C_{20}H_{30}N_2O$ · HCl (350.9)

4.1.2. Compound **6** · *HCl*

M.p. 162–165 °C (dec.); R_f 0.66; IR (KBr) 1635 cm^{-1}, ^1H NMR ($CDCl_3$) δ 11.84 (brs, N^+H), 7.35 (s, 5 H, ArH), 4.23 (td, J = 12.85 and 4.11 Hz, 1 H, H-1), 3.9–1.1 (m, 26 H); ^{13}C NMR (67.5 MHz) ($CDCl_3$) δ 176.55, 138.32, 129.10, 127.12, 127.0, 63.35, 52.76, 50.37, 50.32, 50.23, 37.27, 37.20, 31.54, 28.06, 25.29, 24.92, 24.70, 24.41, 9.61; EIMS m/z 328 $(M)^+$ (3.5%), 151 $(M\text{-}PhCH_2CH_2NHCOEt)^+$ (100%), 258 $[M\text{-}(CH_2)_4N]^+$ (3.7%), 237 $(M\text{-}CH_2Ph)^+$ (0.7%).
$C_{21}H_{32}N_2O$ · HCl (364.9)

4.1.3. Compound **7** · *HCl*

M.p. 92–95 °C; R_f 0.71; IR (KBr) 1625 cm^{-1}, ^1H NMR ($CDCl_3$) δ 11.6 (brs, N^+H), 7.53 (s, 5 H, ArH), 4.68–0.74 (m, 29 H); EIMS m/z 342 $(M)^+$ (1.2%), 151 $[M\text{-}Ph(CH_2)_3NHCOEt]^+$ (100%), 272 $[M\text{-}(CH_2)_4N]^+$ (1.9%), 251 $(M\text{-}CH_2Ph)^+$ (4.6%).
$C_{22}H_{34}N_2O$ · HCl (378.9)

4.2. trans-(±)-2-(N-Phenylamino)cyclohexan-1-ol (12)

Cyclohexene oxide (5 ml, 49.6 mmol) and freshly distilled aniline (4.5 g, 48.3 mmol) were dissolved in propan-2-ol (15 ml) and heated at reflux for 24 h. The solvent was evaporated and the residue was dried i.vac., washed with cold $(Et)_2O$ (25 ml) and crystallized from $(Et)_2O$ to give 7.2 g of **12**: m.p. 56–58 °C (HCl salt: m.p. 172–176 °C); IR (KBr) 3400, 1600, 1500, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71–6.79 (m, 5 H, ArH), 3.68–2.45 (m, 4 H, H-1 and H-2 + 2 D_2O-exchangeable protons), 2.42–0.71 (m, 8 H); EIMS m/z 191 $(M)^+$ (76%), 133 $[PhNHC(Me){=}CH_2]^+$ (10.7%), 132 (100%).
$C_{12}H_{17}NO$ (191.2)

4.3. trans-(±)-1-(Ethylcarbonyloxy)-2-(N-phenylpropanamido)cyclohexane (13)

To stirred solution of **12** (4 g, 20.9 mmol) in dry benzene (35 ml) at 0 to 5 °C TEA (7.8 ml, 55.9 mmol) was added portionwise followed by a dropwise addition of propionyl chloride (4.8 ml, 55.2 mmol). The mixture was stirred for 1 h at 0–5 °C, and for another hour at ambient temperature. Then it was heated in an oil bath (95–100 °C) at reflux for further 4 h. The mixture was evaporated, the residue was treated with ice-H_2O (100 ml) and extracted with CH_2Cl_2 (2 × 50 ml). The extract was dried (Na_2SO_4) and evaporated to give 5.4 g (85%) of **13** as an oil which solidified upon standing: m.p. 50–52 °C; IR (Neat) 1730, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9–7.1 (m, 5 H, ArH), 5.05 (td, J = 10.28 and 4.11 Hz, 1 H, H-1), 4.71 (td, J = 10.28 and 4.11 Hz, 1 H, H-2), 2.79–0.77 (m, 18 H).
$C_{18}H_{25}NO_3$ (303.3)

4.4. trans-(±)-2-(N-Phenylpropanamido)cyclohexan-1-ol (14)

To a stirred ice-cold solution of **13** (5.4 g, 17.8 mmol) in 80% aqueous MeOH (75 ml) K_2CO_3 (6.2 g, 44.8 mmol) was added portionwise. The mixture was stirred for 24 h at ambient temperature, filtered and the filtrate was evaporated. The residue was treated with ice-H_2O (50 ml), extracted with CH_2Cl_2 (3 × 50 ml), dried ($CaCl_2$) and evaporated to give 3.7 g (84%) of **14**: m.p. 83–85 °C (CH_2Cl_2); IR (KBr) 3400, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.82–7.14 (m, 5 H, ArH), 4.74 (td, J = 11.57 and 4.49 Hz, 1 H, H-2), 3.36 (td, J = 11.57 and 4.49, 1 H, H-1), 2.79 (br, 1 H, D_2O-exchangeable, OH), 2.62–0.62 (m, 13 H).
$C_{15}H_{21}NO_2$ (247.3)

*4.5. cis-(±)-1-(Ethylcarbonyloxy)-2-(N-phenylamino)cyclohexane hydrochlorides (***15** · *HCl)*

To a stirred solution of **14** (0.7 g, 2.8 mmol) in CH_2Cl_2 (15 ml) at −5 °C TEA (0.5 ml, 3.5 mmol) was added followed by a dropwise addition of MsCl (0.24 ml, 3.1 mmol). Stirring was continued for 2 h at −5 °C. The mixture was diluted with cold CH_2Cl_2 (20 ml), washed with ice-H_2O (50 ml), brine (30 ml), dried (Na_2SO_4) and evaporated. The residue was dissolved in $(Et)_2O$ (30 ml), cooled and ethereal-HCl was added dropwise. The precipitated solid was washed with $(Et)_2O$ and recrystallized from CH_2Cl_2/$(Et)_2O$ to give 0.31 g (39%) of **15** · HCl: m.p. 157–160 °C (dec.); IR (KBr) 3000–2300, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.76 (brs, 1 H, N^+H), 7.93–7.22 (m, 5 H, ArH), 4.85 (m, W_H = 10.28 Hz, 1 H, H-1), 3.36 (dd, J = 11.66 and 3.33 Hz, 1 H, H-2), 3.14–0.85 (m, 13 H); EIMS m/z 248 $(MH)^+$ (10.6%), 247 $(M)^+$ (40.8%), 174 $(M\text{-}OCOEt)^+$ (14.7%), 173 $(M\text{-}EtCOOH)^+$ (45.4%), 132 (100%).
$C_{15}H_{21}NO_2$ · HCl (283.7)

*4.6. cis-(±)-2-(N-Phenylamino)cyclohexan-1-ol hydrochloride (***16** · *HCl)*

A concentrated solution of $(Et_2)O$/HCl (3 ml) was added to a solution of **15** · HCl (0.1 g, 0.35 mmol) in MeOH (10 ml) and the mixture was stirred for 2 h at ambient temperature. The mixture was cooled, CCl_4 was added portionwise, the precipitated solid was washed with $(Et)_2O$ and recrystallized from MeOH/CCl_4 to give 60 mg (75%) of **16** · HCl: m.p. 198 to 200 °C; IR (KBr) 3300–3000, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.3 (br, N^+H_2), 8.19–7.25 (m, 5 H, ArH), 4.68 (m, W_H = 12.1 Hz, 1 H, H-1), 3.39 (dd, J = 10.28 and 3.85 Hz, 1 H, H-2), 2.62–0.4 (m, 8 H); EIMS m/z 191 $(M)^+$ (74.9%), 148 (62.3%), 147 $(M\text{-}CH_2{=}CHOH)^+$ (2.3%), 119 $(PhNHCH{=}CH_2)^+$ (79.3%), 132 (100%).
$C_{12}H_{17}NO$ · HCl (227.7)

[1] A preliminary account of this work has been presented at the XXV Conference of Pharmaceutical Sciences; The Pharmaceutical Society of Egypt, Cairo, Egypt, 24–26 Dec 1996; Abstracts pp 66

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