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Aminocyclanols, I:

Synthesis and Analgetic Activities of Some Aminobenzylcyclanols Derived from Menthone

Aminocyclanole, 1. Mitt.: Synthese und analgetische Wirkung einiger vom Menthon abgeleiteter Aminobenzylcyclanole

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Several cyclohexanamines such as Tilidin[1-3)], Tramadol[4-7)], and Ciramadol[8-17)] have been used as opiate analgesic drugs[3,6,7,16,17)]. Here, we describe synthesis and analgesic activity of some aminocyclanols from (-)-menthone (1R,4S-1-methyl-4-isopropyl-cyclohexan-3-one).

Two synthetic routes are described for the preparation of amino-benzylcyclanols and related derivatives[1-3)]: One is the reaction of α-benzylidenecyclanones with various amines to obtain aminobenzylcyclanones which upon reduction yield amino-benzylcyclanols[9-15)]. In the other approach, benzisoxazols are first formed from benzylnitrones and cycloalkene, then treatment of benzisoxazoles with an allyl-halide produces the corresponding benzoxazoline halide and hydrogenolysis of these halides give the desired compounds[17)].

In this work, (-)-menthone (**1**) was reacted with benzaldehyde in the presence of base in dry ether to yield an *E/Z*-isomere mixture of 2-benzylidenecyclohexanone **2, 3**. Only the *E* isomer reacted at room temp. with some cyclic sec. amines to yield compounds **4a-d**. Compounds **4a-d** were then reduced with $LiAlH_4$ to give the corresponding amino-alcohols **5a-d** (Scheme 1).

Results and Discussion

2-Benzylidenmenthone **2, 3** could not be synthesized with the procedures in lit. reported because of low yield (Table 1). We improved the yield to 46-56% using NaH in dry diethyl ether instead of aquos NaOH, sodium ethoxide or piperidine in an organic solvent[8-15)].

The *E/Z* ratio in 1R,4S-2-benzylidene-1-methyl-4-isopropyl-cyclohexan-3-one was determined by GC analysis: *E* = 68% and *Z* = 31 %. Baltzly and other groups[8-13)] showed that trans benzylidene-cyclohexanones give Michael type addition with sec. amines. In our study only the *E* isomer **3** gave an addition product with cyclic amines. A11 attempts were unsuccessful with the *Z* isomer **2**.

The Claisen-Schmidt product of rac-camphor was also synthesized with the *E/Z* ratio 6/94 but this mixture did not undergo any addition reaction with all sec. amines considered.

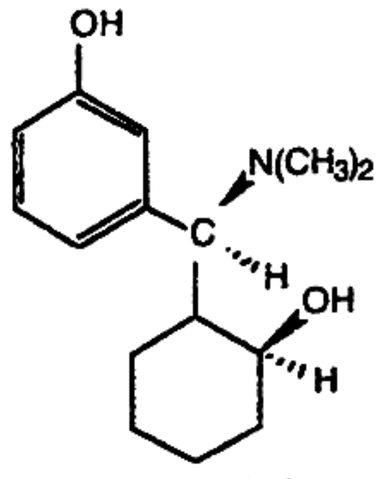
The C-2 and C-11 centers of compounds **4** may cause the formation of four isomers during the addition of sec. amines. However, we obtained only one diastereomer. This result indicates the high stereoselectivity at these two centers. The stereochemistry of these compounds will be published separately.

2-(α-Aminobenzyl)-(-)-menthones **4** were reduced with $LiAlH_4$ to obtain the corresponding aminoalcohols **5a-d**[11-16)]. These compounds show reduced analgesic activity only (Table 2) as compared with the ketones **4a-d**.

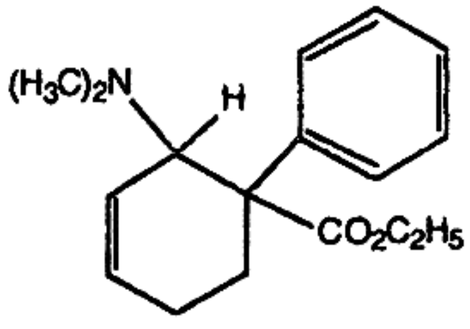
Preliminary pharmacological screening

Methods

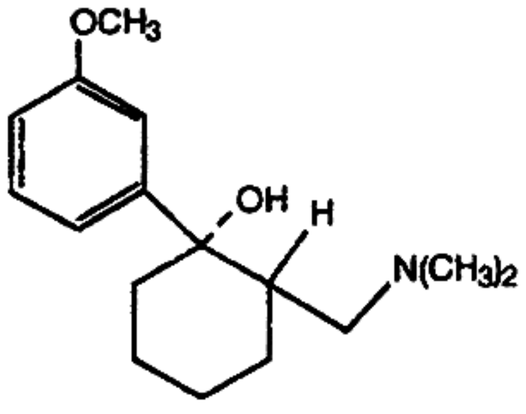
Animals: Local bred male albino mice weighing 20 ± 2 g were housed in groups of six with free access to food and water. Hot plate test:[18,19)]. Animals were placed on the hot plate and the latency to the first hind paw licking was



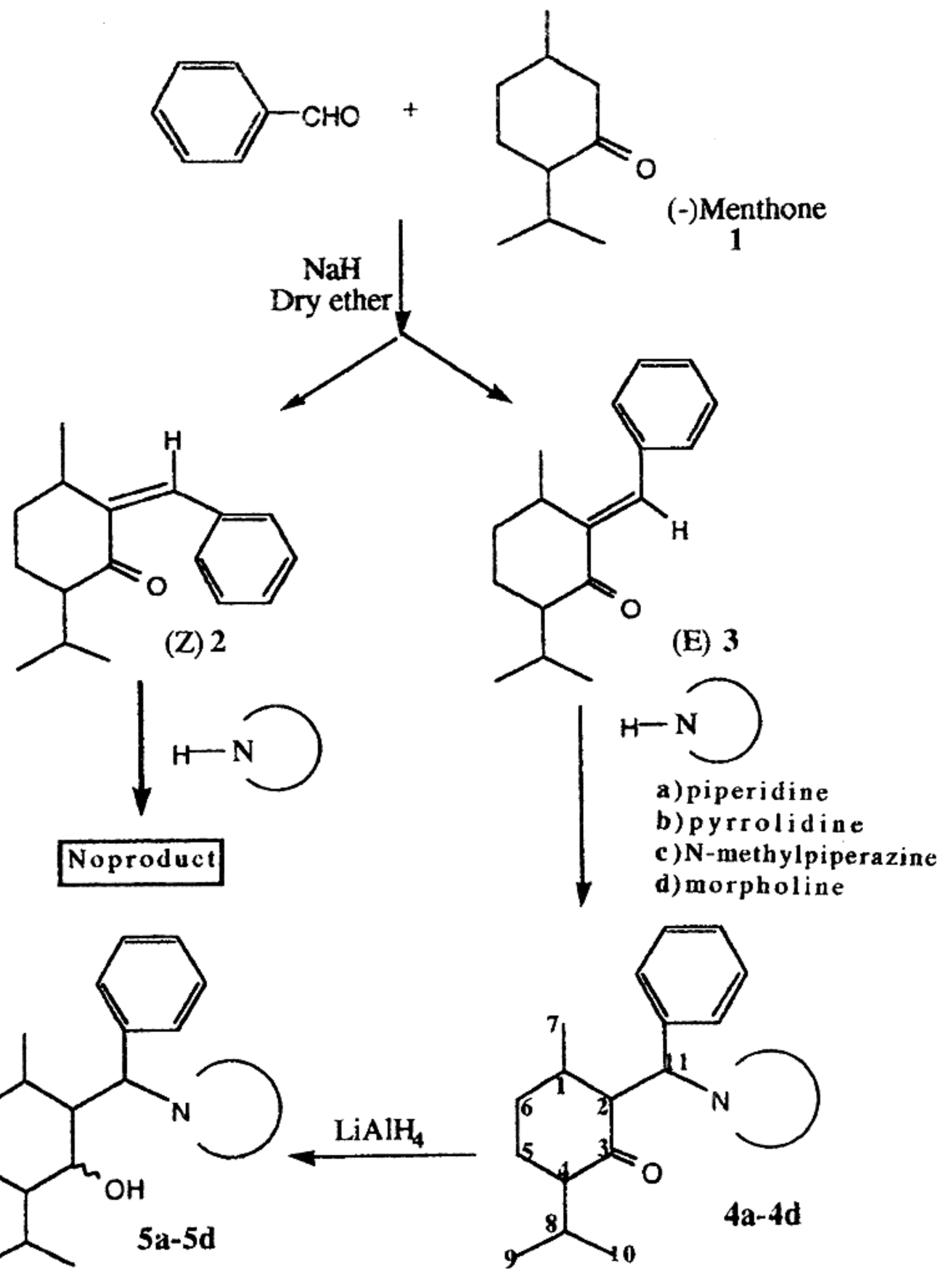
(-)Ciramadol



rac-Tilidin



rac-Tramadol



Scheme 1

Table 1:

Compound	Base	Solvent	Reac. Time	Yield %
(-)-Menthone	NaOH (10%)	Water	6 h, reflux	5
	NaOH (50%)	Water	6 h, reflux	10
	NaOH (s)	-	6 h, reflux	16
	NaOH (s)	Dry ether	6 h, reflux	12
	Na=Et (15%)	Abs. EtOH	6 h, reflux	14
	NaH	Dry ether	6 h, reflux	45
d1-Camphor	NaOH (50%)	Water	6 h, reflux	16
	NaH	Dry ether	6 h, reflux	56

recorded. The test was terminated if no hind paw lick occurred in 30 seconds (Table 2). The data were analysed by Anova.

Table 2 shows the preliminary results: **4a-d** enhanced the latency to the first hind paw licking. The values obtained were significantly higher than those of tramadol and morphine.

Compounds **4c**, **5a-d** were not as active as the other compounds, but again they enhanced morphine analgesia. Naloxone did not induce withdrawal syndromes in mice that received the compounds **4a-d**, however, with compounds **4c**, **5a-d** withdrawal symptoms were observed.

Table 2: Response to latency in the constant temp. hot plate test.

Drugs	Latency (s) to the first hind paw licking	
	Test compound alone[1]	Enhancement morphine analgesia[2]
4a	24.84* ± 1.3	21.40 ± 3.1
4b	23.15* ± 1.9	24.00 ± 2.3
4c	15.33 ± 1.5	23.20 ± 2.0
4d	21.83* ± 2.0	22.10 ± 1.9
5a	11.16 ± 1.7	19.40 ± 2.8
5b	8.33 ± 1.4	24.98 ± 1.8
5c	10.50 ± 2.0	24.80 ± 2.1
5d	9.83 ± 1.4	18.20 ± 2.9
tramadol	16.13 ± 4.2 (3)	24.10 ± 1.4
morphine	18.66 ± 2.4 (4)	------
control	8.00 ± 1.9	------

(n = 6 per group)

1) 1.5 mg/kg i.p injection

2) To 10 mg/kg morphine received mice the test compounds were administered.

*) No withdrawal syndromes after injection of naloxone following 5 days of test compound administration.

3) 25 mg/kg i.p injection of tramadol-HCl.

4) 5 mg/kg i.p injection of morphine-HCl.

Experimental Part

Melting points: Reichert hot stage melting point apparatus, uncorrected.- Elemental analyses: Hewlett Packard 185 CHN analyser.- IR-spectra: Unicam 9706 IR-spectrometer.- ^{1}H-NMR spectra: Bruker FT 80 MHz, $CDCl_3$, TMS as internal standard. Chemical shifts in δ (ppm) - EI-MS: VG TR 10-2 GC-mass spectrometer.- Merck silicagel 60 HF 254 was used for analytical and prep. tlc.- Column chromatography: kieselgel 100 (70-230 mesh), mobil phase a) diethyl ether/hexane 1:15, b) diethyl ether/hexane 1:5.

1R,4S-2-Benzylidene-1-methyl-4-isopropylcyclohexan-3-one (**2, 3**) *(mixture of diastereomers)*

30 g of (-)-methone (**1**) and 5 g (excess) NaH were stirred for 30 min at 25°C in dry ether. 20 g (0.19 moles, 20 ml) of redistilled benzaldehyde were introduced dropwise during 2 h. A solid mass was decomposed with 50 ml N HCl. The supernatant layer was extracted with ether and washed with satd. $NaHCO_3$. Ether was evaporated at 15 torr, the crude material was purified by cc (column chromatography) with mobile phase (a): 14.4 g, 32%. M.p. **3** (*E*) = 48-51°C, **2** (*Z*) = 46-49°C, Rf: *E* = 0.77, *Z* = 0.70 (mobil phase a).- $C_{17}H_{22}O$ (242.3) Calcd. C 84.3 H 9.0 Found C 84.2 H 9.16.- IR ($CHCl_3$): 1675 cm^{-1} (C=O of E), 1695 cm^{-1} (C=O of Z), 1590 cm^{-1} (C=C of E), 1600 cm^{-1} (C=C of Z).- ^{1}H-NMR ($CDCl_3$): 0.96 (6H; m; $(CH_3)_2$), 1.2 (3H; d; J = 7.1 Hz, 1-CH_3), 1.8 (4H; m; 5,6-CH_2), 2.16 (2H; m; 1-H, 8-H), 3.44 (1H; m; 4-H), 7.02 (1H; s; 11-H (*Z*)), 7.13 (1H; s; 11-H (*E*)), 7.3 (5H; m, C_6H_5).- ^{13}C-NMR ($CDCl_3$): 205 (C=O) (*E*), 203 (C=O) (*Z*), 143 and 140.9 (C-11's of (*E*) and (*Z*)), 126.2-129.2 (arom. C), 60 and 59.1 (C-2's of (*E*) and (*Z*)), 57.8 and 55.6 (C-1's of (E) and (*Z*)), 53.5 (C-4), 31.7 (C-5, C-6), 27.6 (C-10), 19.5 (C-8, C-9).- MS (70 eV): m/z (rel.intens.%) = 242 ($M^{+\bullet}$; 60), 200 (50), 171 (80), 129 (100), 91 (75), 77 (15). Same for both isomers.

1R,4S-2-(α-Aminobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-ones (**4**)

2 g (8.2 mmoles) of **3** or mixture of **2** and **3** were dissolved in an excess of amine and allowed to stand at room temp. for one or two days. After the reaction mixture had solidified, the solid material was suspended by cold dry ether and filtered to give white crystals. The filtrate was extracted three times with N HCl. The acid phases were combined and basified with NaOH. The oily precipitate was extracted with diethyl ether and dried over $MgSO_4$. Removal of ether gave a white crystalline product which was combined with the previously recovered crystals. Recrystallisation from ether:hexane (1:2).

1R,4S-2-(α-N-Piperidinobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-one (**4a**)

1.6 g, 95% related to **3**. M.p. 141-143°C.- Rf: aminobenzyl-menthones are rather unstable on silica and alumina based tlc.- $C_{22}H_{33}NO$ (327.5) Calcd. C 80.7 H 10.15 N 4.3 Found C 80.4 H 9.88 N 4.0.- IR ($CHCl_3$): 1680 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): 0.8 (9H; m; $(CH_3)_2$) and 1-CH_3), 1.47 (6H, m; pip. $(CH_2)_3$), 1.9 (4H, m; menthone $(CH_2)_2$), 2.24 (4H; m; pip. $(CH_2)_2$), 2.7 (1H; m; 4-H), 3.4 (1H; dd; 2-H, $J_{2\text{-}11}$ = 11.74 Hz, $J_{2\text{-}1}$ = 4.8 Hz), 3.8 (1H; d; 11-H, $J_{11\text{-}2}$ = 11.74 Hz), 7.2 (5H; m; arom. H).- ^{13}C-NMR ($CDCl_3$): 211 (C=O), 137 (C-2), 127-128.3 (arom. C), 64.7 (C-11), 58.7 (C-4), 55.5 (C-1), 50.7 (C-7), 35 (pip. C-2, C-5), 32.7 (C-5 and C-6), 26 (pip. C-3, C-5, C-4).- MS (70 eV): m/z (rel.intens.%) = 327 ($M^{+\bullet}$; 0.65), 242 (60), 200 (40), 174 (90), 171 (60), 129 (100), 91 (75).

1R,4S-2-(α-N-Pyrrolidinobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-one (**4b**)

1.5 g, 92% related to **3**. M.p. 144-147°C.- $C_{21}H_{31}NO$ (313.5) Calcd. C 80.5 H 9.96 N 4.5 Found C 80.4 H 10.11 N 4.9.- IR ($CHCl_3$): 1685 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): 0.75 (9H; m; $(CH_3)_2$ and 1-CH_3), 1.54 (4H; m; pyrr.$(CH_2)_2$), 1.96 (4H; m; $(CH_2)_2$), 2.33 (4H; m; pyrr.$(CH_2)_2$), 2.76 (1H; m; 4-H), 3.4 (1H; dd; 2-H, $J_{2\text{-}11}$ = 11.74 Hz, $J_{2\text{-}1}$ = 4.8 Hz), 4.1 (1H; d; 11-H, $J_{11\text{-}2}$ = 11.74 Hz), 7.2 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 313 ($M^{+\bullet}$; 0.50). 242 (25), 200 (13), 171 (15), 160 (100), 129 (30), 91 (400), 70 (18).

1R,4S-2-(α-N,N'-Methylpiperazinobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-one (**4c**)

1.6 g, 87%, related to **3**. M.p. 144-147°C.- $C_{22}H_{34}N_2O$ (342.5) Calcd. C 77.1 H 10.0 N 8.2 Found Ç 77.1 H 10.0 N 8.1.- IR ($CHCl_3$): 1670 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): 0.8 (9H; m; $(CH_3)_2$ and 1-CH_3), 1.96 (4H; m; $(CH_2)_2$), 2.18 (3H; s; N-CH_3), 2.36 (8H; m; piperaz.$(CH_2)_4$), 2.8 (1H; m; 4-H), 3.36 (1H; dd; 2-H, $J_{2\text{-}11}$ = 11.74 Hz, $J_{2\text{-}1}$ = 4.8 Hz), 2.89 (1H; d; 11-H, $J_{11\text{-}2}$ = 11.74 Hz), 7.2 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 342 ($M^{+\bullet}$; 12), 242 (50), 200 (25), 189 (100), 171 (50), 129 (60), 91 (75), 70 (52).

1R,4S-2-(α-N-Morpholinobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-one (**4d**)

1.6 g, 90%, related to **3**. M.p. 148-150°C.- $C_{21}H_{31}NO_2$ (329.5) Calcd. C 76.55 H 9.48 N 4.3 Found C 76.5 H 9.66 N 4.8.- IR ($CHCl_3$): 1680 cm^{-1} (C=O).- ^{1}H-NMR ($CDCl_3$): 0.48 (9H; m; $(CH_3)_2$ and 1-CH_3), 1.94 (4H; m; $(CH_2)_2$), 2.29 (4H; t; morph. N-$(CH_2)_2$), 2.79 (1H; m; 4-H), 3.39 (1H; dd; 2-H; $J_{2\text{-}11}$ = 11.74 Hz, $J_{2\text{-}1}$ = 4.8 Hz), 3.6 (4H; t; morph. O-$(CH_2)_2$), 3.87 (1H; d; 11-H, $J_{11\text{-}2}$ = 11.74 Hz), 7.24 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 342 ($M^{+\bullet}$; 12), 242 (50), 200 (25), 189 (100), 171 (50), 129 (60), 91 (75), 70 (52).

1R,4S-2-(α-N-Aminobenzyl)-1-methyl-4-isopropyl-cyclohexan-3-oles (**5**)

2 g (5 mmole) $LiAlH_4$ were refluxed for 30 min in dry ether and 1 g of the corresponding aminobenzyl ketone **4a-d** in dry diethyl ether was added during 15 min. The mixture was refluxed for 3 h. After cooling, excess reagent was decomposed by 5 ml 5% NaOH. It was extracted with diethyl ether and dried over $MgSO_4$. Removal of the solvent gave a light yellow oil. The oily material solidified in the cold. Tlc was applied for purification (mobile phase: diethyl ether:n-hexane 1:5), and recrystallisation from ether:n-hexane 1:5.

1R,4S-1-Methyl-2-(α-N-piperidino-benzyl)-4-isopropyl-cyclohexan-3-ol (**5a**)

0.9 g, 90%. M.p. 117-120°C.- $C_{22}H_{35}NO$ (329.5) Calcd. C 80.2 H 10.7 N 4.25 Found C 80.5 H 10.30 N 4.2.- IR ($CHCl_3$): 3400 cm^{-1} (OH).- ^{1}H-NMR ($CDCl_3$): 0.69 (3H; d; J = 5.2 Hz, i.propyl-CH_3), 0.95 (3H; d; J = 5.2 Hz,. i.propyl-CH_3), 1.35 (3H; d; J = 5.5 Hz, 1-CH_3), 1.50 (6H; m; pip.$(CH_2)_3$), 1.60 (4H; m; $(CH_2)_2$), 2.1 (3H; m; 1-H, 2-H, 4-H), 2.3 (4H; m; pip.$(CH_2)_2$), 3.5 (1H; 3-H), 3.8 (1H; d; J = 11.7 Hz, 11-H), 4.6 (1H; s; OH), 7.3 (5H; m; arom. H).- ^{13}C-NMR: 122-132 (arom. C), 64.6 (benzylic C), 64.0 (C-3), 46.2-44.8 (C-1, C-4, C-7), 29.6 (pip. C-2, C-6), 24-18.5 (C-5, C-6 and pip. C-3, C-5, C-4), 14.9 (C-7), 11.6-11.0 (C-9, C-10).- MS (70 eV): m/z (rel.intens.%) = 329 ($M^{+\bullet}$; 4), 252 (5), 174 (100), 131 (10), 91 (70).

1R,4S-1-Methyl-2-(α-N-pyrrolidino-benzyl)-4-isopropyl-cyclohexan-3-ol (**5b**)

0.88 g, 88%. M.p. 122-124°C.- $C_{21}H_{33}NO$ (315.5) Calcd. C 79.9 H 10.54 N 4.4 Found C 78.9 H 10.17 N 5.0.- IR ($CHCl_3$): 3400 cm^{-1} (OH).- ^{1}H-NMR ($CDCl_3$): 0.87 (3H; d; J = 5.1 Hz, i.propyl. CH_3), 0.9 (3H; d; J = 5.2 Hz, i.propyl. CH_3), 1.2 (3H; d; J = 5.6 Hz; 1-CH_3), 1.55 (4H; m; pyrro.

($CH_2)_2$), 1.6 (4H; m; 5,6-CH_2), 2.1 (3H; m; 1-H, 2-H, 4-H), 2.3 (4H; m: pyrro. ($CH_2)_2$), 3.5 (1H; s; 3-H), 4.0 (1H; d; J = 11.7 Hz, 11-H), 7.3 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 315 ($M^{+\cdot}$; 6), 161 (100), 131 (23), 91 (75), 70 (50).

1R,4S,1-Methyl-4-isopropyl-2-(α-N,N'-methylpiperazino)benzyl-cyclohexan-3-ol (**5c**)

0.86 g, 86%. M.p. 137-140°C.- $C_{22}H_{36}N_2O$ (344.5) Calcd. C 76.7 H 10.53 N 8.1 Found C 76.4 H 10.15 N 8.4.- IR: 3400 cm^{-1} (OH).- ^{1}H-NMR ($CDCl_3$): 0.7 (3H; d; J = 5.3 Hz; i.propyl. CH_3), 0.96 (3H; d; J = 5.3 Hz, i.propyl. CH_3), 1.24 (3H; J = 5.6, 1-CH_3), 1.6 (4H; m; ($CH_2)_2$), 1.97 (3H; m; 1-H, 2-H, 4-H), 2.25 (3H; s; pip. CH_3), 3.6 (1H; s; 3-H), 3.9 (1H; d; J = 11.7 Hz, 11-H), 7.3 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 344 ($M^{+\cdot}$; 5), 190 (100), 146 (20), 91 (75), 70 (55).

1R,4S,1-Methyl-2-(α-N-morpholino-benzyl)-4-isopropyl-cyclohexan-3-ol (**5d**)

0.85 g, 85%. M.p. 110-113°C.- $C_{21}H_{33}NO_2$ (331.5) Calcd. C 76.0 H 10.00 N 4.2 Found C 76.4 H 9.93 N 4.5.- IR: 3400 cm^{-1} (OH).- ^{1}H-NMR ($CDCl_3$): 0.65 (3H; d; J = 5.3 Hz, i.propyl CH_3), 0.89 (3H; d; J = 5.3 Hz; i.propyl CH_3), 1.18 (3H; d; J = 5.7 Hz, 1-CH_3), 1.55 (4H; m; ($CH_2)_2$), 2.1 (3H; m; 1-H, 2-H, 4-H), 2.3 (4H; m; ($CH_2)_2$), 3.5 (1H; s; 3-H), 3.65 (4H; m; ($CH_2)_2$), 3.9 (1H; d; J = 11.7 Hz, 11-H), 7.3 (5H; m; arom. H).- MS (70 eV): m/z (rel.intens.%) = 331 ($M^{+\cdot}$; 5), 226 (5), 177 (100), 131 (50), 91 (75).

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