SYNTHESIS OF SOME 6-(ALKYLAMINO) METHYL HEXAHYDRO-5-ARYL-AND ARALKYL-4, 7-METHANOINDAN-5-OLS AND CERTAIN OF THEIR PROPIONATE ESTERS AS ANALGESICS

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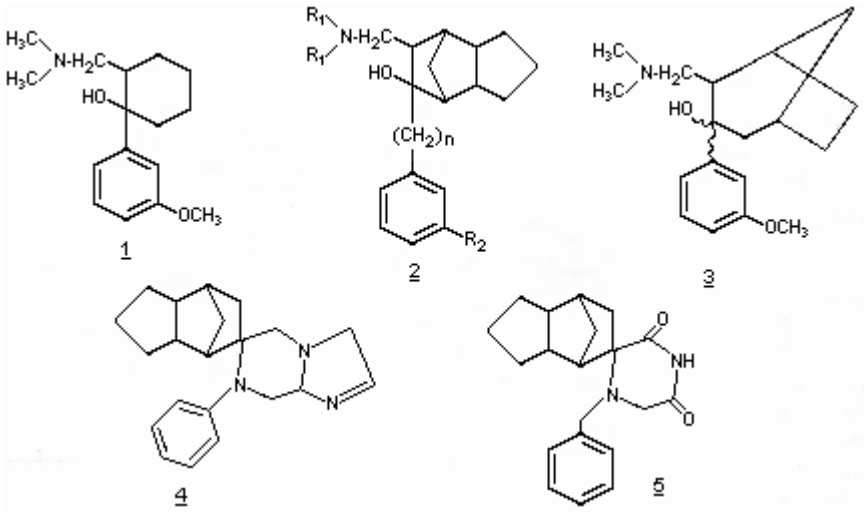
SUMMARY : The synthesis and screening of the analgesic activity of a series of 6-(alkylamino) methyl hexahydro-5-aryl-and aralkyl-4,7-methanoindan-5-ols (2 a-p) and the corresponding propionate esters 6b, c, g, k and m are described. Some of these tertiary alcohols exhibited slight analgesic potency comparable with that of Tramadol i the hot-plate test.

Key Words : 6-(Alkylamino) methyl hexahydro-5-aryl-and aralkyl-4, 7-methanoindan-5-ols, propionate esters, analgesics.

INTRODUCTION

Tramadol (1), which is the trans (+) 1-(3-methoxy-phenyl)-2-dimethylaminomethyl cyclohexanol (1), is an efficient centrally acting analgesic agent that evokes minor untoward side effects especially tolerance, euphoria and drug-dependence (2), without inducing respiratory depression and constipation (3). To study



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the structure-activity relationship of Tramadol, Beckett *et. al.* (4) synthesized and screened the bridged norbornane system 3 as a rigid frame work to which the functional groups of Tramadol are attached.

Recently, Aboul-Enein *et. al.* (5) found that compounds 4 and 5 which are derived from the tricyclic bridged system, hexahydro-4,7-methanoindane, exhibited antinociceptive potency. This activity might be attributed to the increase of the lipophilicity of the molecule, a factor that enhances its crossing of the blood-brain barrier, as well as its distribution and binding properties (6).

bases *7a-d* (Scheme 1 and Table 2) were synthesized following the general prodcedure of Mannich reaction (7). Refluxing tetrahydro-4,7-methanoindan-5'4-H)-one 8 with paraformaldehyde and the appropriate secondary amine hydrochloride in acetic acid afforded *7 a-d* in 80-89% yields.

The target tertiary alcohols 2 a-p were furnished in 34-95% yields via refluxing the appropriate Grignard reagent with the corresponding ketone Mannich bases *7 a-d*, in tetrahydrofuran as a solvent (Scheme 1 and Table 3).

The propionic acid esters 6 of the most analgetically active tertiary basic alcohols, namely 2b, c, g, k

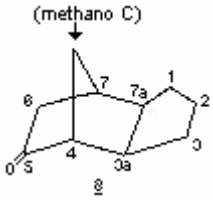

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Table 1: 13 C-Chemical shifts (in ppm, TMS=0) of calculated and measured 4,7-methanoindan -5-one (8).

4,7- Methanoindane-5-one	C-1	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	methano C
Endo-(calculated)	27.00	28.70	27.00	38.60	53.50	216.50	37.10	39.00	41.60	51.20
Exo-(calculated)	32.60	27.40	32.60	41.50	52.80	216.80	43.00	38.30	44.50	40.10
ketone 13 (measured)	32.65	27.50	32.80	41.83	52.83	216.71	43.78	38.33	45.33	40.24

Tetrahydro-4,7-methanoindan-5(4-H)-one 8 was prepared following the procedure of Blicke (7) and exists mainly in the exo-stereoform (4, 8-11). This was confirmed by application of the 13C-substituent rules and chemical shifts reported for norbornane (14), 2-norbornanone (15), as well as for both endo-and exotetrahydrodicyclo-pentadiene (14), 2-norbornanone (15), as well as for both endo-and exotetrahydrodicyclopentadiene (16), and compared with our measured results for the ketone 8; (Table 1).

The close agreement of both the measured chemical shifts for C-3 a, C-5, C-7 a and methano C, and those calculated for the exo-ketone 8, led to the conclusion that 8 exists mostly in the exo-form.

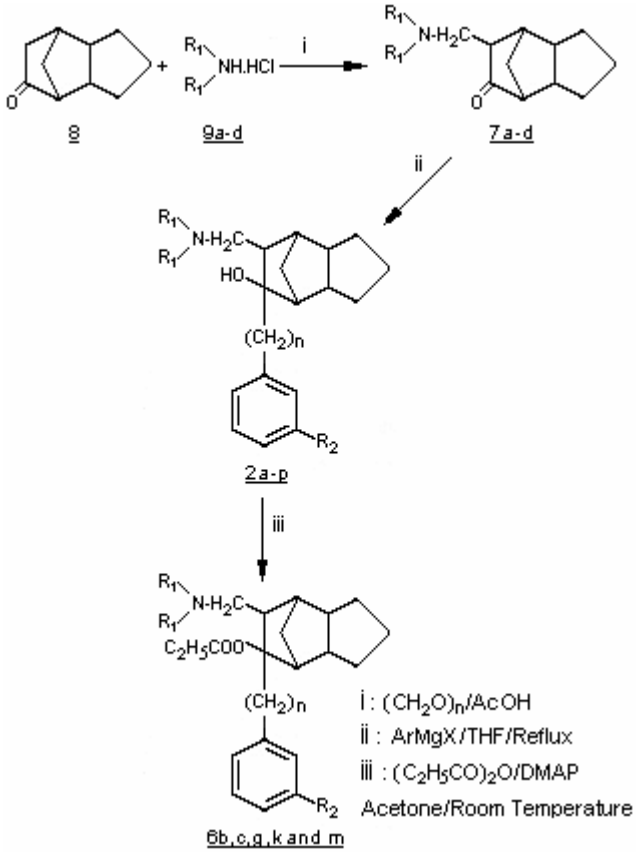
The tricyclic ketone alkylamino methyl Mannich

and m were obtained by the reaction with prop-ionic anhydride in the presence of a catalytical amount of 4-dimethylaminopyridine (DMAP) in dry acetone at 45-50° for four days (Scheme 1 and Table 4).

Surprisingly, the propionate esters 6b, c and g were found to be very labile when subjected to acids. Attempts to prepare their hydrochlorides, maleates or fumarates proved futile and they were immediately converted to the salts of their corresponding original tertiary basic alcohols 2b, c and g.

MATERIALS AND METHODS

All melting points were determined with Electrothermal capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on philips PU 9412 IR and



IRIS data station spectrophotometer. ^{1}H-NMR and ^{13}C (CDCl3 TMS) were recorded on a varian 90 MHz and Brucker WM-250 (250 MHz, 1H) spectrophotometer. The mass spectra were performed with a JEOL-DX 300 mass spectrometer, with electroenergy of 70 eV. The micro-analytical data were carried out at the National Research Center, Dokki, Cairo. The analytical results deviated maximally ± 0.4% from the theoretical values of C, H and N.

General procedure for the preparation of 6-(alkylamino) methyl-tetrahydro-4,7-methanoindan-5 (4-H)-ones (7 a-d Table 2).

A mixture of 30 (0.2 mol) tetrahydro-4,7-methanoindan-5(4-H)-one 8, 0.2 mol of the appropriate amine 9 *a-d*. HCl and 6 g (0.2 mol) of para-formaldehyde in 60 ml of glacial acetic acid, was stirred and heated at 100-5°C for 24 h. The excess acetic acid was evaporated under reduced pressure. The residual brown viscous oil was acidified under cooling with 5 N hydrochloric acid (50 ml) then washed with diethyl ether (2x50 ml). The aqueous acidic layer was basified under cooling, with 40% sodium hydroxide solution (30 ml) and extracted with methylene chloride (4x50 ml). The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford the Mannich bases 7 *a-d* as dark brown viscous oils, which were purified by column chromatography using alumina neutral I as an adsorbent and and n-pentane as an eluent to give 7 *a-d* as yellowish viscous oils. IR (films) of 7 *a-d* showed carbonyl band at 1745 cm^{-1}.

The bases were converted to either their hydrochloride or maleate salts for characterization (Table 1).

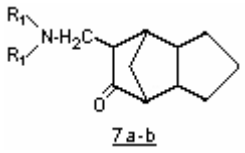
7 a. base[8] : ^{1}H-NMR : δ (ppm) = 0.66-2.70 [br. m, 13H, methanoindane protons and 8H, CH_2-N $(CH_3)_2$ of which at 2.10, s, 6H, of N (CH_3)2].

7 d. base : 1H-NMR : δ (ppm) = 0.79-2.87 [br. m, 13H, methanoindane protons and 6H, CH_2, -N $(CH_2$-$)_2$], 3.45-3.84 [t, 4H, 0 $(CH_2$-$)$].

MS (m/z) : 7 a. base : 207 (M+, C13H21NO), base peak, 91; 7d. base : 249 (M+, C15H23NO_2), base peak, 100 (M+ - 149; $C_{10}H_{13}O$+, loss of O ⟨⟩ N-CH_2+).

General procedure for the preparation of 6-[(alkylamino) methyl] hexahydro-5aryl-(aralkyl)-4,7-methanoindan-5-ols (2 a-p) Table 3.

Table 2: (Alkylamino) methyl tetrahydro-4,7-methanoindan-5-(4-H) one (7a-d).



7a-b

No. of Comp.	$R_1.R_1$	mp.C°	Yield[a]	Formula (Mol.wt.)		Analysis % C	H	N
7a	$-(CH_2)_3-$	200 - 3[b,c]	81	$C_{13}H_{21}NO.HCl$ (243.779)	Calc.	64.05	9.09	5.74
					Found	64.28	8.96	5.52
7b	$-(C_2H_2)_2-$	78 - 80[d,e]	80	$C_{15}H_{25}NO.C_4H_4O_4$ (315.448)	Calc.	64.93	8.31	3.98
					Found	64.78	8.19	3.72
7c		171 - 2[d,e]	89	$C_{16}H_{25}NO.C_4H_4O_4$ (363.459)	Calc.	66.09	8.04	3.85
					Found	65.98	8.09	3.79
7d		22°[b,c]	86	$C_{15}H_{23}NO_2.HCl$ (285.817)	Calc.	63.03	8.46	4.90
					Found	62.95	8.51	4.77

(a) Yields of chromatographer ketone Mannich bases using alumina neutral I as adsorbent and n-pentane as eluent,

(b) Hydrochloride salt,

(c) Crystallization solvent: methanol: acetone,

(d) Maleate salt,

(e) Crystallization solvent: isopropanol.

To an activated mixture of 3.5 g (0.145 gram-atom) of magnesium with, 0.82 ml of ethylene bromide in 24 ml of dry tetrahydrofuran, was added in drops, a solution of 0.1 mol of the requisite aryl of aralkyl halide in 30 ml of dry tetrahydrofuran at such a rate that the tetrahydrofuran refluxed without external heating. The mixture was gently refluxed for 30 min., where nearly all the magnesium had been dissolved. The reaction mixture was cooled to 20-25°C, and a solution of 0.02 mol of the desired ketone Mannich base 7 *a-d* in 30 ml of dry tetrahydrofuran was added drop wisely under stirring to the previously formed Grignard reagent. The reaction mixture was stirred under reflux for further 9 h, then cooled and decomposed with 30 ml of saturated solution of ammonium chloride. Thereafter, the decomposed reaction mixture was filtered if necessary, to give a clear filtrate which was evaporated under reduced pressure to remove tetrahydrofuran. The remaining mixture was acidified under cooling with 5 N hydrochloric acid (10 ml) and washed with diethyl ether (3x30 ml) to remove any un-reacted materials. The aqueous acidic layer was basified under cooling with 40% sodium hydroxide solution (6 ml) and extracted with methylene chloride (4x50 ml). the organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to afford a dark brown thick oil, which was purified by column chromatography using alumina neutral I as an adsorbed and n-pentane : methylene chloride (4:1) as an eluent to give a transparent yellowish thick oil of the Grignard product 2 a-p. (Table 2). IR (film) of 2 a-p showed -OH band at 3500-3200 cm^{-1}, aromatic C=C band at 1600 cm^{-1} and disappearance of carbonyl band.

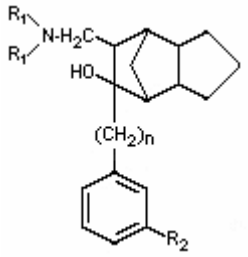
2 a. base ^{1}H-NMR : δ (ppm) = 0.76-2.91 [br. m, 21H, dimethyl-amino methyl methanoindane protons, of which 2.02-2.11 (s, 6H, -N $(CH_3)_2$], 6.06-6.81 (br. s, 1H, OH exchangeable with D_2O), 7.08-7.43 (m, 3H, aromatic), 7.43-7.77 (m, 2H, aromatic).

2 e. base : ^{1}H-NMR : δ (ppm) = 0.73-2b62 [br. m, 13H, methanoindane protons and 8H, CH_2-N $(CH_3)_2$ of which 1.93, OH, methanoindane protons and 8H, OCH_3), [.93 (s, 1H, OH), 6.6-7.33 (m, 4H, aromatic protons).

2 f. base : ^{1}H-NMR : δ (ppm) = 0.53-0.70 [t, 6H, $(CH_3-CH_2)_2$ N-CH_2], 0.83-2b70 [br. m, 13H of methanoindane protons and 6H, $(CH_3CH_2)_2$ N-CH_2-], 3.61 (s, 3H, OCH_3, 6.15 (s, 1H, OH exchangeable with D_2O), 6.6-7.17 (m, 4H, aromatic).

2 g. base : ^{1}H-NMR : δ (ppm) = 0.81-2.81 [br. m, 13H

Table 3: 6-(Alkylamino) methyl hexahydro-5-aryl (aralkyl)-4, 7-methanoindan 5-ols (2a-p).



No. of Comp.	R_1R_1	R_2	n	mp.C°	Yield[a] %	Formula (Mol.wt.)	Analysis %			
								C	H	N
2a	$-(CH_3)_2$	H	0	127[b] 225[c,d]	72.7	$C_{19}H_{27}NO$ (285.43)	Calc. Found	79.95 79.73	9.53 9.69	4.90 4.78
2b	$-(CH_3)_2$	H	0	174-8[e,b]	95.0	$C_{21}H_{31}NO.C_4H_4O_4$ (429.561)	Calc.	69.90 69.70	8.21 8.35	3.28 3.10
2c	-	H	0	258-9[c,d]	84.0	$C_{22}H_{31}NO.HCl$ (361.95)	Calc. Found	73.00 72.91	8.91 8.75	3.86 3.75
2d		H	0	237[c,d]	75.0	$C_{21}H_{29}NO_2.HCl$ (363.93)	Calc. Found	69.30 69.02	8.30 8.52	3.84 3.68
2e	$-(CH_3)_2$	OCH_3	0	205-9 [g,b]	85.4	$C_{20}H_{29}N_2C_4H_4O_4$ (431.53)	Calc. Found	66.79 66.58	7.70 7.82	3.24 3.09
2f	$-(C_2H_5)_2$	OCH_3	0	oil[f]	74.0	$C_{22}H_{23}NO_2$ (333.0)	Calc. Found	76.92 77.13	9.68 9.45	4.07 3.90
2g		OCH_3	0	203-5 [g,b]	56.0	$C_{23}H_{33}NO_2.C_4H_4O_4$ (471.6)	Calc. Found	68.76 69.11	7.90 8.21	2.97 2.83
2h		OCH_3	0	187-8[c,d]	92.0	$C_{22}H_{31}NO_3.HCl$ (393.95)	Calc. Found	67.07 66.96	8.18 8.32	3.55 3.38
2i	$-(CH_3)_2$	H	1	293-4[c,d]	78.2	$C_{20}H_{29}NO.HCl$ (335.92)	Calc. Found	71.51 71.48	9.00 8.89	4.14 4.29
2j	$-(C_2H_5)_2$	H	1	247-8[c,d]	89.6	$C_{22}H_{33}NO.HCl$ (363.97)	Calc. Found	72.59 72.72	9.41 9.47	3.84 3.59
2k		H	1	322-5[c,d]	89.0	$C_{23}H_{33}NO.HCl$ (375.98)	Calc. Found	73.47 73.39	9.11 9.00	3.72 3.58
2l		H	1	299-300[c,d]	78.0	$C_{22}H_{31}NO_2.HCl$ (377.95)	Calc. Found	69.91 70.03	8.53 8.34	3.70 3.58
2m	$-(CH_3)_2$	H	2	221-4[c,d]	73.0	$C_{21}H_{31}NO.HCl$ (349.94)	Calc. Found	72.07 72.30	9.21 8.99	4.00 3.95
2n	$-(C_2H_5)_2$	H	2	173-6[c,d]	34.0	$C_{21}H_{25}NO.HCl$ (378.00)	Calc. Found	73.08 73.13	9.59 9.38	3.70 3.84
2o		H	2	208-210[c,d]	53.4	$C_{24}H_{25}NO.HCl$ (390.01)	Calc. Found	73.91 73.77	7.3 9.37	3.59 3.62
2p		H	2	233-5[c,d]	71.0	$C_{24}H_{33}NO.HCl$ (391.98)	Calc. Found	70.47 70.87	8.74 8.43	3.57 3.88

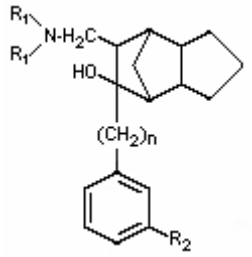
methanoindane protons and 12H ($C_5H_{10}N$-CH-), 2H ($CH_2C_6H_5$) and 1H, OH exchangeable with D_2O), 7.11-7.24 (m, 5H, aromatic and OH exchangeable with D_2O).

2 k. base : ^{1}H-NMR : δ (ppm) = 0.85-3.3.26 [br. m, 13H methanoindane protons and 12H ($C_5H_{10}N$-CH_2-), 2H ($CH_2C_6H_5$) and 1H, OH exchangeable with D_2O), 7.11-7.24 (m, 5H, aromatic).

2 m. base : ^{1}H-NMR : δ (ppm) = 0.71-2.96 (br. m, 13H, methanoindane protons, 8H (-CH_2 -N (CH_3)$_2$), 4H (CH_2-CH_2-C_6H_5) and 1H, OH exchangeable with D_2O), 7.09-7.39 (m, 5H, aromatic.)

MS (m/z) : 2 a. base : 285 (M+, $C_{19}H_{27}NO$), base peak, 77 (M+ -208); $C_{13}H_{22}NO$+, loss of C_6H_5-); 2 c. base : 325 (M+, $C_{22}H_{31}NO$), base peak, 98 (M+ -227; $C_{16}H_{19}O$+, loss of $C_5H_{10}N$-CH_2+); 2 d. base : 327 (M+, $C_{21}H_{29}NO_2$), base peak 100 (M+ -227; $C_{16}H_{19}O$+, loss of C_4H_8NO-CH_2+); 2 h. base : 357 (M+, $C_{22}H_{31}NO_3$), base peak, 100 (M+ -257; C_{17}H21O2+, loss of C4H8NO-CH2+) 2 i. base : 229 (M+, C20H29NO), base peak, 91 (M+ -208; C13H22NO+, loss of C6H5CH2+ rearranged to tropylium ion); 2 j. base : 327 (M+, C22H33NO), base peak, 86 M+, C23H33NO) base peak, 98 (M+ -241; C17H31NO2), base peak, 100 (M+ -241; C17H21O+, loss of C4H8NO-CH2+); 21 base : 341 (M+, C22H31NO2), base peak, 100 (M+ -241; C17H21O+, loss of C4H8NO-CH+); 2 m. base : 313 (M+, C23H35NO), base peak, 86 M+ -255; C18H23O+, loss of (C2H5)2 NCH2+; 2 o. base :

Table 4: 6-(Alkylamino) methyl hexahydro-5-aryl (aralkyl)-4, 7-methanoindan -5-ols propionate (esters) (6b, c, g, k and m).



No. of Comp.	R_1R_1	R_2	n	mp.C°	Yield[a] %	Formula (Mol.wt.)	Analysis %			
								C	H	N
6b	-(C_2H_5)$_2$	H	0	Oil	26	$C_{24}H_{35}NO_2$ (369.551)	Calc. Found	78.00 78.21	9.54 9.38	3.79 3.90
6c		H	0	Oil	30	$C_{25}H_{35}NO_2$ (381.562)	Calc. Found	78.60 78.47	9.24 9.31	3.67 3.72
6g		OCH_3	0	Oil	22	$C_{26}H_{37}NO_3$ (411.589)	Calc. Found	75.87 75.68	9.06 9.14	3.40 3.26
6k		H	1	135-7	27	$C_{26}H_{37}NO_2$.HCl (432.048)	Calc. Found	72.28 72.09	8.86 8.99	3.24 3.18
6m	-(CH_3)$_3$	H	2	92-3 125-8	82	$C_{24}H_{35}NO_2$ (369.551)	Calc. Found	78.00 78.21	9.54 9.38	3.79 3.82

(a) Yields of chromatographer bases, except 6m,

(b) Compound purified by gravity column chromatography using alumina neutral I as adsorbent and petroleum ether (60:80) as eluent,

(c) Hydrochloride salt,

(d) Solvent of crystallization : methanol : acetone,

(e) Solvent of crystallization : n-pentane : diethyl ether.

353 (M+, C24H35NO), base peak, 98 (M+ -255;C18H23O+, loss of C5H10R ,c N2+); 2 p. base : 355 (M+, C23H33NO2), base peak, 100 (M+ -255; C18H23O+, loss of C4H8NO-CH2+).

General procedure for the preparation of 6-[(alkylamino) methyl)] hexahydro-5-aryl (aralkyl)- 4,7-methanoindan-5-ol pro-pionic acid esters (Table 4)

A solution of 0.005 mol of the tertiary basic alcohol 2, 13 g (0.1 mol) of pro-pionic anhydride and 0.2 g (0.0016 mol) of 4-dimethylaminopyridine in 60 ml of dry acetone, was stirred at 50°C for 4 days. Excess acetone was evaporated under reduced pressure. The residual oily substance was dissolved in 60 ml of diethyl ether and shaken with 10% sodium bicarbonate solution (5x30 ml) then with water (3x30 ml). The ethereal layer was dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give the desired esters 6 b, c, g, k and m as dark viscous oils which were purified by column chromatography using alumina neutral I as an adsorbent and petroleum-ether (60:80) as an eluent to give 6 b, c, g, k and m as yellowish viscous oils as well as 6 m as crystalline solid (Table 3). The esters of 2b, c and g were very sensitive to acids, so that it was unsuccessful to prepare their hydrochlorides, maleates or fumarates. They were cleaved to the salts of their corresponding original tertiary basic alcohols 2b, c and g. Accordingly, these esters were purified twice by column chromatography using the above mentioned condition then identified. IR (film) of 6 k and m, (KBr disc) of 6 b, c and g showed ester carbonyl band at 1738-1745 cm^{-1} and aromatic C=C band at 1600^{-1} with the disappearance of OH absorption band.

MS (m/z) : 6 k. base : 395 (M+, $C_{26}H_{37}NO_2$), base peak, 98 (M+ -297;$C_5H_{10}N$-CH_2+, loss of $C_{20}H_{25}O_2$); 6 m. base : 369 (M+, $C_{24}H_{35}NO_2$), base peak, 91 (M+ -278; C_6H_5-CH_2+ rearranged to tropylium ion, loss of (C_5 H_{10} N O_2).

Pharmacology

Analgesic activity

The mouse hot-plate technique was performed (17) for the determination of the analgesic potency. Male albino mice (17-20 g) were used. The test compounds *2a-p* and *6b, c, g, k* and *m* were administered intraperitoneally in 0.1 ml/10 g body eight as their hydrochloride, maleate or fumarate salts, or as the base suspended in 5% gum acacia solution. Using groups of six mice the reaction time was measured 10 and 15 minutes before and 15, 30, 45, 60, 75, 90, 120 and 180 minutes after administration of the test compounds. If the control value exceeded 15 seconds, or the difference between the two control measurements was greater than 4 seconds, the animal was rejected. The mice were considered positive for analgesia if the reaction time was increased by at least 2.5 times of the corresponding control value. Each group was observed for at least five different doses starting from the sub-analgesic dose to 250 mg/kg. The analgesic activity of the screened compounds peaked about 30 minutes after interaperitoneal treatment. The data obtained at the peak time were used for statistical evaluation (18).

RESULTS AND DISCUSSION

Analgesic activity

The test compounds *2 a-p* were evaluated for their analgesic activity (Table 5). The most active compound in the present series is the tertiary alcohol 2 m, which possesses analgesic potential about 0.35 that of Tramadol.

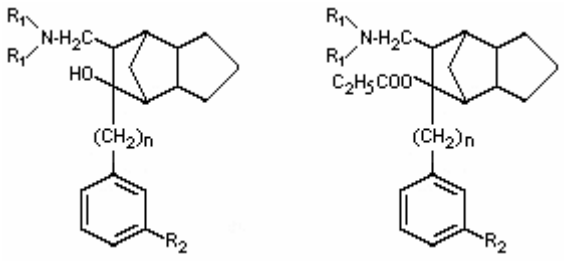
Compounds *2 a-p* were classified into 4 groups depending on the number of methylene linkages (n) between the aromatic moiety and the alkylaminomethyl-4,7-methanoindanol structure.

In group I, where n=0 and the aromatic part is unsubstituted, the presence of the diethyl-amino and the piperidine residues in the amino-methyl portion of compounds *2 b* and *2 c,* respectively, enhanced the analgesic activity. Both compounds showed nearly equipotent effect about 0.3 that of Tramadol. On the other hand, the dimethyl-amino and the morpholino groups abolished such activity in *2 a* and *2 d,* respectively.

In group II, where n=0, the 3-methoxy substituent in the aromatic ring of compound *2 g* augments the analgesic effect of the respective analogue *2 c.* Such activity is abolished in the diethyl-amino congener *2 f.* On the contrary, the 3-methoxy group enhanced the activity of both the morpholino and the dimethyl-amino analogues *2 h* and *2 e* compared with their respective analogues *2 d* and *2 a.*

In group III, where one methylene group exists between the aromatic ring and the tricyclic structure (n=1), no analgesia is observed in both the dimethyl-amino and the diethyl-amino derivatives *2 i* and *2 j,* respectively, while the piperidine moiety in *2 k* maintains such activity compared with the corresponding compounds *2 c* and *2 g* in groups I and II, respectively.

Table 5



Group	No.	R_1R_1	R_2	n	Analgesic activity ED_{50} mg/kg. (95% confidence limit)
I	2a	$(CH_3)_2$	H	O	Inactive
	2b	$(C_2H_5)_2$	H	O	56.1 (43.89-71.69)
	2c		H	O	57.5 (35.61-92.8)
	2d		H	O	Inactive
II	2e	$(CH_3)_2$	OCH_3	O	94.0 (82.45-107.16)
	2f	$(C_2H_5)_2$	OCH_3	O	Inactive
	2g		OCH_3	O	58.2 (47.45-79.79)
	2h		OCH_3	O	75.1 (62.13-90.52)
III	2i	$(CH_3)_2$	H	1	Inactive
	2j	$(C_2H_5)_2$	H	1	Inactive
	2k		H	1	58.2 (47.45-79.79)
	2l		H	1	75.2 (64.21-87.6)
IV	2m	$(CH_3)_2$	H	2	51.2 (38.75-67.11)
	2n	$(C_2H_5)_2$	H	2	79.1 (64.3-97.29)
	2o		H	2	79.2 (59.04-105.7)
	2p		H	2	82.7 (64.7 (64.4-106.18)
	6b	$(C_2H_5)_2$	H	0	Inactive
	6c		H	0	Inactive
	6g		OCH_3	1	Inactive
	6m	$(CH_3)_2$	H	2	Inactive
Tramadol					18.0 (16.21 - 19.98)

The morpholino substituent in *2 l* exhibited similar analgesic effect to *2 h,* about 0.24 that of Tramadol.

In group IV, where n=2, the dimethyl-amino moiety in *2 m* enhanced the analgesia to about 0.35 that of Tramadol, whereas the diethyl-amino, piperidine and morpholino moieties reduced such an effect in compounds *2 n,* o and p, respectively.

Conclusively, the introduction of the tricyclic structure in place of the cyclohexane in the prototype Tramadol, connected either directly with the aromatic moiety or through one and/or two methylene groups, reduced the analgesic effect.

Furthermore, evaluation of the analgesic effect of the propionate esters (*6 b, c, g, k* and *m*) of the most active compounds in groups I, II, III and IV namely (*2 b, c, g, k* and *m*) displayed no antinociceptive potency.

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