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NOVEL STRUCTURAL HYBRIDS OF MESCALINE WITH PCP-ANALOGS: POTENTIAL ANTAGONISTS FOR CENTRAL PCP-RECEPTORS

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بالإشارة إلى العلاقة الفراغية بين أحد الأشكال المحتملة لعقار ميسكالين (وهو بالتحديد كونفورمار "سينكلاينال") وعقار فينسايكليدين والمعروف بإسم "بى.سى.بى." ، وذلك بالنسبة إلى البعد الفراغي بين مجموعة الفينيل وذرة النيتروجين ، فإنه يمكن إستنباط أن يرتبط عقار ميسكالين تنشيطيا بالمستقبلات البيولوجية الخاصة بعقار بى.سى.بى. حيث قد يتسبب هذا فى أعراض الهلوسة المصاحبة لتعاطى عقار ميسكالين.

ونظرا لذلك فقد أقترح فى هذا البحث تصميم بعض من مشتقات هذين العقارين على هيئة مهجنات من جزيئاتها الشكلية ، على أمل أن ترتبط هذه المهجنات تنشيطا بمستقبلات بى.سى.بى. ، وقد يؤدى ذلك إلى علاج أو إلى تخفيض القابلية الملحة لتعاطى عقار ميسكالين. ولإثبات ذلك فقد تم تشييد بعض من هذه المهجنات المنشودة ، وكذلك تم تحميل بعض منها بمجموعة "ن-(٢-كلورو-ايثيل)" المعروفة بقدرتها البيوكيميائية على ألكلة المستقبلات بحيث قد يزيد ذلك من قدرة الإرتباط التنشيطى لهذه المهجنات.

The possible involvement of the synclinal conformation of mescaline with phencyclidine (PCP)-receptors has promoted the synthesis of certain novel structural hybrids of mescaline with PCP-analogs.

The effect of mescaline and the potential antagonistic activity of the newly proposed derivatives at central PCP-receptors of albino rat brains will await investigation.

The suggested compounds were chemically 1-aryl-1-(3,4,5-trimethoxy; or trihydroxy) phenethylamino; or N-substituted-phenethylamino cycloalkanes. An N-(2-chloroethyl) moiety was also incorporated into some of the designed analogs for exploration of the possible participation of such alkylating arm to the elicited activity.

INTRODUCTION

Mescaline (I) and phencyclidine (PCP) have been well documented to act as potent hallucinogens that promote a variety of symptoms[1] which might include psychosis, agitation, catatonic rigidity, disorientation, incoordination and nystagmus. It was also reported that PCP in the form of powder has been abusely marketed as a street drug in place of mescaline as well as other hallucinogens[2]. The presence of PCP-receptor sites, in the central nervous systems of both vertebrates and invertebrates, was recognized promptly by different workers[3,4,5]. The similarity between the psychtomimetic output of PCP and that produced by certain other hallucinogens, such as sigma opiates[6], have initiated the investigation of the potential involvement of PCP-receptors with such abused agents. The possibility that mescaline (I) might as well be cross-linked with central PCP-receptors has not yet been assumed. As in case of dopamine[7]; the most probable conformations of mescaline molecule would be the antiperiplanar (I) and the synclinal (Ia) dispositions. The nonbonded distance between the aromatic function and the nitrogen head of Ia could be shown to resemble that of PCP-molecule. Therefore, it might be apprehended that Ia would interact with PCP-receptors

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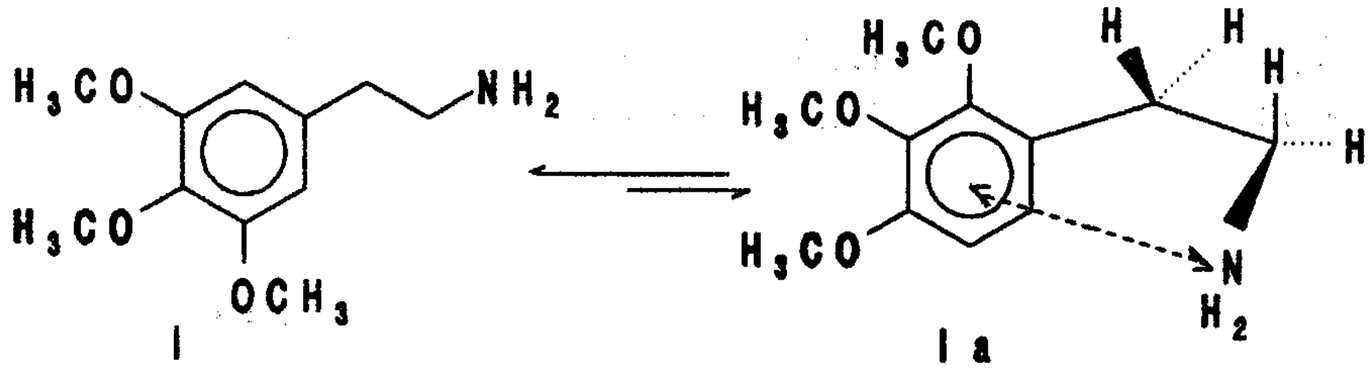

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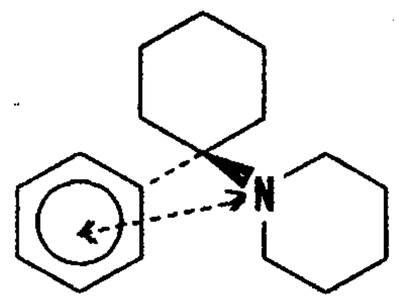
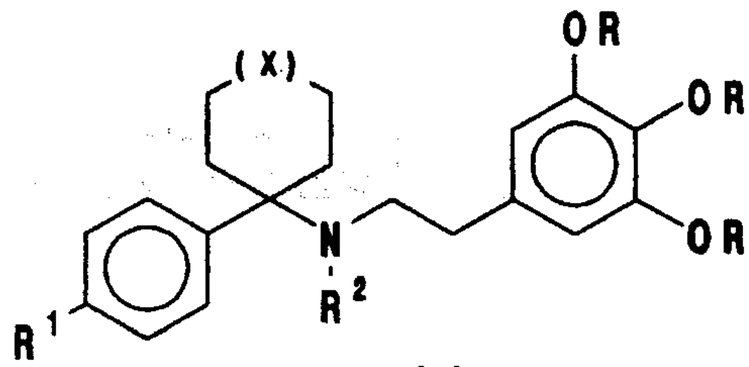


PCP



I I

through such a conformation.

The incentive of the present work was thus directed, primarily, to investigate such an assumption. The synthesis of certain structural hybrids of mescaline (I) with PCP-analogs was manipulated in an effort to explore their potential antagonistic potency to wntral PCP-receptors and hence might be used for prevention or treatment of such drug hazards. The proposed compounds would be chemically classified as 1-aryl-1-(3,4,5-trimethoxy; or trihydroxy) phenethylamino; or N-substituted phenethylamino cycloalkanes (II). Some derivatives of (II) were also designed to incorporate a chloroethyl grouping on the N-atom. Such compounds might possess potential alkylating capacity upon interaction with the PCP-receptors.

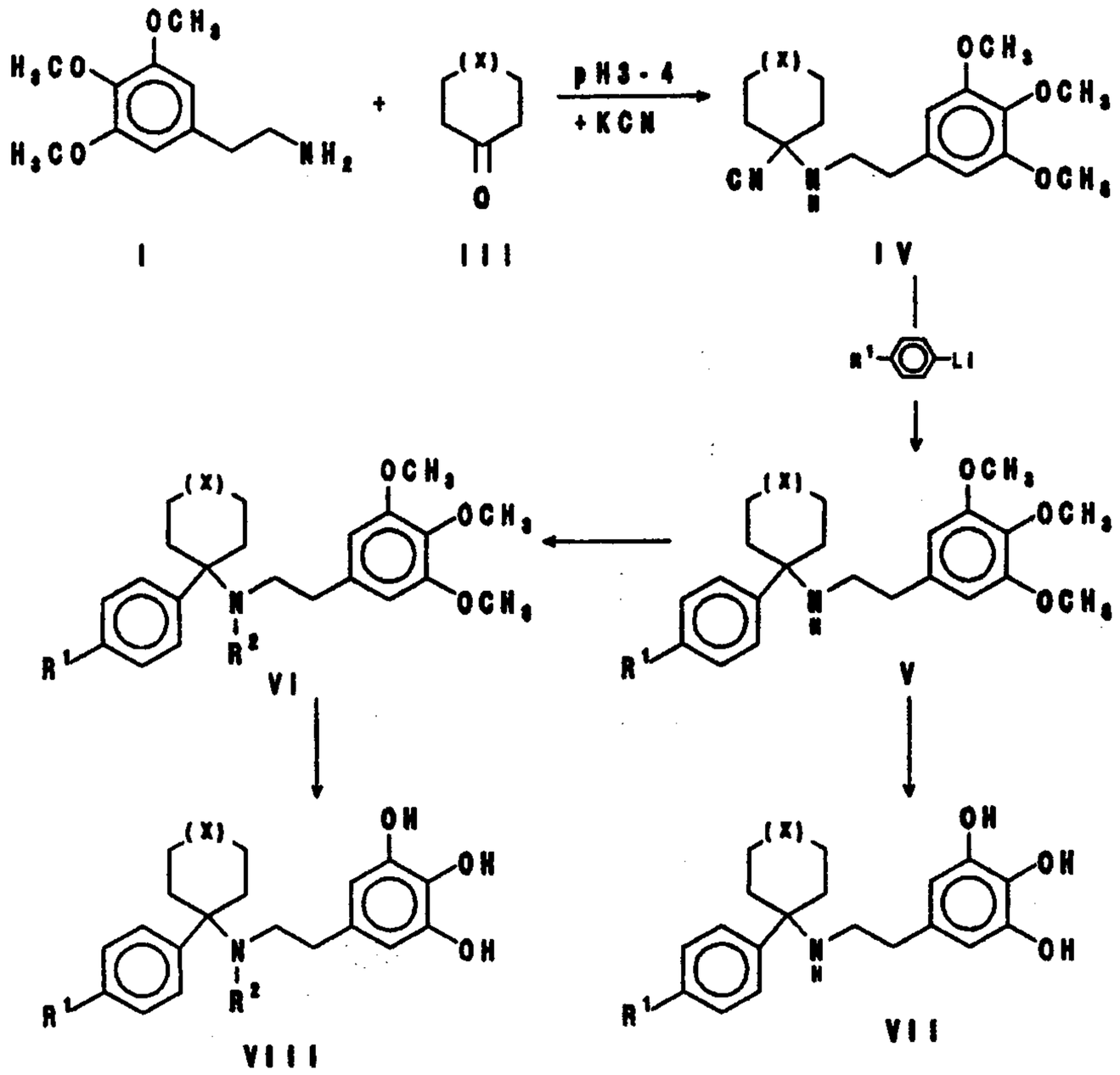
Synthesis

The synthetic approaches utilized are illustrated in Schemes 1 and 2. In Scheme 1; mescaline (I) was primarily prepared[8] by $LiAlH_4$-reduction of 3,4,5-trimethoxynitro-styrene; obtained from the reaction between 3,4,5-trimethoxybenzaldehyde and nitromethane. It was then reacted with the proper cycloalkanone (III) and KCN at pH 3-4 to obtain the corresponding 1-carbonitrilo-1-(3,4,5-trimethoxy) phenethylaminocycloalkanes (IV)[9]. The arylation of the latter was achieved using phenyl lithium or p-tolyl lithium to produce the target 1-aryl derivatives (V)[10]. The N-alkyl analogs (VI) were produced from the appropriate (V) through an N-alkylation process utilizing a proper alkyl iodide in presence of anhydrous K_2CO_3[11]. The demethylation step was performed using boron tribromide to afford the corresponding 3,4,5-trihydroxyderivatives (VII, VIII)[12,13].

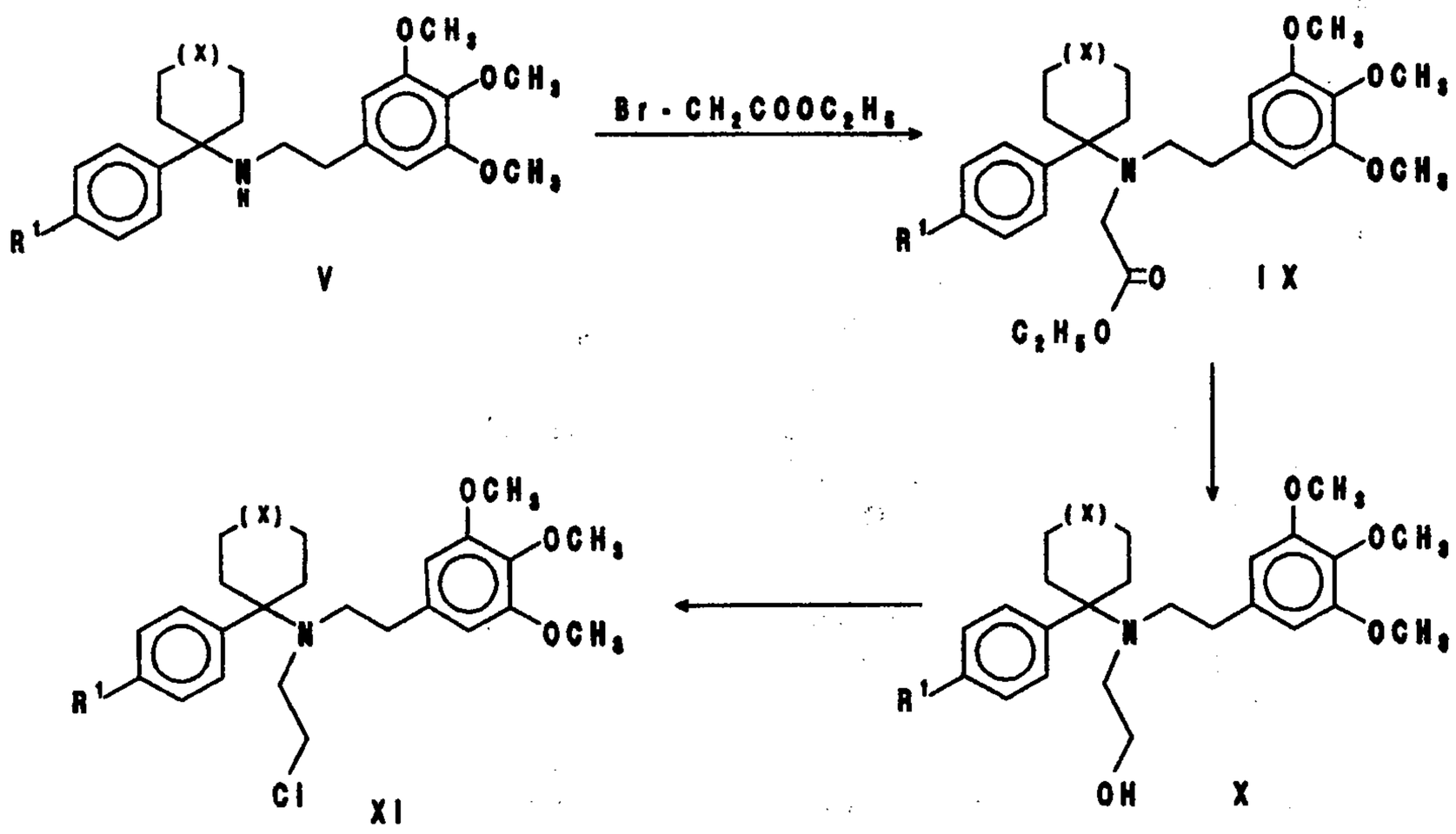
In Scheme 2; the N-(2-chloroethyl) analogs (XI) were prepared from the selected V by reacting with ethyl bromoacetate to obtain the N-(ethylcarboxymethyl) analogs (IX)[11] followed by reduction with $LiAlH_4$/anhydrous $AlCl_3$ to the corresponding N-(2-hydroxyethyl) derivatives (X)[14] and then treated with thionyl chloride[15] to obtain the chloroethyl analog (XI).

Experiments

Melting points, determined in open glass-capillaries, with a Giriffin and George apparatus, are uncorrected. Infrared-spectra were recorded on a Perkin Elmer 781 spectro-photometer using KBr discs. Proton magnetic resonance were scanned on a Varian EM-390 spectrometer. Elemental analysis was performed on Perkin-Elmer 2400 series II CHNS/O



Scheme 1



Scheme 2

analyzer at the Central Laboratory, Faculty of Science, University of Alexandria.

1-Carbonitrilo-1-(3,4,5-triemthoxy)phenethyl-aminocycloalkanes (IVa,b; Table 1)

The proper cycloalkanone (III) (0.1 mol) was added to a solution of mescaline (I) (21.1 g, 0.1 mol) dissolved in a mixture of 10 ml conc. HCl and 20 g of ice (adjusted to pH 3-4). The resulting mixture was then treated, while magnetically stirred, with a solution of KCN (6.8 g, 0.11 mol) in 15 ml of water. Stirring was maintained for 4 h. and left aside at room temperature for 15 h. The reaction mixture was extracted with $CHCl_3$, washed with water, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue was recrystallized from methanol.

The yield for IVa (X= CH_2) was 80%; m.p. 83-85°C.

Anal. Calcd for $C_{18}H_{26}N_2O_3$: C, 67.89; H, 8.23; N, 8.79.

Found: C, 68.12; H, 8.60; N, 8.55.

The yield for IVb (X= zero) was 91%; m.p. 69-71°C.

Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.21.

Found: C, 67.35; H, 7.88; N, 9.21.

The characteristic bands for IR; (cm^{-1}) are at 2210-2212 (CN), 3300-3310 (NH).

^{1}H-NMR ($CDCl_3$) for IVa; δ: 1.2-1.9 (m, 6H, CH_2 at C-3, CH_2 at C-4, and CH_2 at C-5, in cyclohexyl); 2.32 (t, 2H, CH_2-Ar); 2.86 (m, 4H, CH_2 at C-2 and CH_2 at C-6 in cyclohexyl); 3.19 (m, 2H, -CH_2-NH); 3.5 (s, 3H, CH_3O); 3.65 (s, 3H, CH_3O); 3.8 (s, 3H, CH_3O); 6.5-6.7 (double singlet, 2H, Ar); 7.9 (s, 1H, NH); D_2O exchangeable).

The MS for IVa; m/z (relative abundance, %): 319 (15, M+1), 274 (21), 256 (18), 138 (100), 126 (5), 58 (7), 55 (12).

1-Aryl-1-(3,4,5-trimethoxy) phenethylamino-cyclohexanes (Va-d; Table 1)

Phenyl lithium or p-tolyl lithium (0.15 mol); prepared from Li metal (2.1 g; 0.3 atom) and bromobenzene (23.6 g, 0.15 mol) or bromotoluene (25.6 g, 0.15 mol), was treated dropwise with a solution of the appropriate carbonitrile derivative (IVa, b) (0.1 mol) in dry ether (100 ml). The rate of addition was adjusted so that only gentle reflux was obtained. The resulting reaction mixture was further refluxed for 4 h, cooled and poured onto a mixture of crushed ice and NH_4Cl. The etherial layer was separated, washed with water and the amine was extracted with dilute HCl (4x100 ml). The combined acidic solution was extracted several times with ether and then basified with 10% $NaHCO_3$ solution. The liberated amine was extracted with $CHCl_3$, dried over anhydrous Na_2SO_4 and filtered. The volatiles were removed under reduced pressure and the residue was recrystallized from the appropriate solvent (Table 1).

The characteristic bands for IR; (cm^{-1}) are at 2600-2655 (-$^+$NH).

^{1}H-NMR ($CDCl_3$) for Va; δ; 1.2-1.6 (m, 6H, CH_2 at C-3, CH_2 at C-4 and CH_2 at C-5, in cyclohexyl); 2.42 (t, 2H, CH_2-Ar); 2.85 (m, 4H, CH_2 at C-2 and CH_2 at C-6, in cyclohexyl); 3.15 (m, 2H, CH_2-NH); 3.5 (s, 3H, CH_3O); 3.85 (s, 6H, 2x CH_3O); 6.5-6.8 (double singlet, 2H, Ar); 7.4-7.8 (m, 5H, Ar); 9.5 (s, 2H, NH_2).

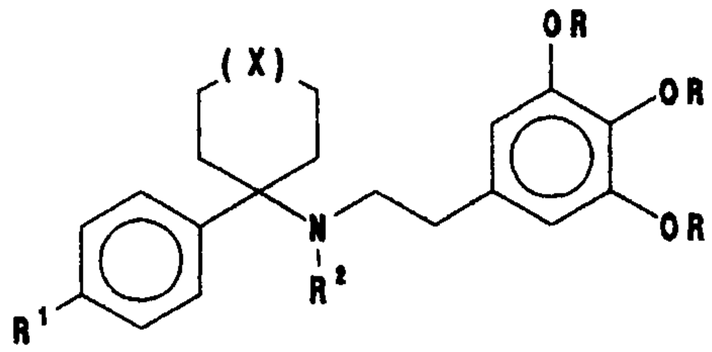
The MS for Va; m/z (relative abundance, %) 368 (23, M+1); 367 (100, $M^{+\cdot}$), 252 (18), 187 (20), 179 (10), 159 (5), 56 (29).

1-Aryl-1-(3,4,5-trimethoxy)-N-alkyl-N-phenethylaminocyclohexanes (VIa-c, Table 1)

A solution of CH_3I (2.8 g; 0.02 mol) in dry $(CH_3)_2CO$ (10 ml) was added, dropwise, during 30 min to a magnetically stirred suspension of the proper V (0.01 mol) and anhydrous K_2CO_3 (2.6 g) in a mixture of dry $(CH_3)_2CO$ (40 ml) and absolute C_2H_5OH (10 ml). The reaction mixture was refluxed for 24 h, allowed to cool and filtered. The volatiles were removed under reduced pressure and the residue was recrystallized from the appropriate solvents (Table 1).

^{1}H-NMR ($CDCl_3$) for VIa; δ: 1.7-1.9 (m, 10H, in cyclohexyl); 2.5 (s, 3H, N-CH_3); 2.6-3.5 (m, 4H, N-CH_2-CH_2-Ar); 3.7 (s, 9H, 3 xCH_3O); 6.9 (s, 2H, Ar); 7.9 (m, 5H, Ar).

Table 1: 1-Arayl-1-(3,4,5-trisubstituted) phenethylaminocycloalkanes.



Comp. No.	R	R^1	R^2	(X)	% Yield	MP°C (Cryst. Solv.)[a]	Molecular Formula	Anal. %		
									Calcd	Found
Va	CH_3	H	H	CH_2	65	173-174 (EE)	$C_{23}H_{32}ClNO_3$[b]	C H N Cl	68.04 7.94 3.45 8.73	68.15 7.90 3.55 8.62
Vb	CH_3	CH_3	H	CH_2	66	210-212 (EE)	$C_{24}H_{34}ClNO_3$[b]	C H N Cl	68.63 8.16 3.33 8.44	68.80 7.90 3.55 8.65
Vc	CH_3	H	H	-	58	161-163 (IE)	$C_{22}H_{30}ClNO_3$[b]	C H N Cl	67.41 7.71 3.57 9.04	67.63 7.90 3.66 8.92
Vd	CH_3	CH_3	H	-	79	195-197 (EE)	$C_{23}H_{32}ClNO_3$[b]	C H N Cl	68.04 7.94 3.45 8.73	68.30 8.10 3.35 8.95
VIa	CH_3	H	CH_3	CH_2	60	203-205 (IE)	$C_{24}H_{34}ClNO_3$[b]	C H N Cl	68.63 8.16 3.33 8.44	68.77 8.23 3.35 8.85
VIb	CH_3	CH_3	CH_3	CH_2	68	220-222 (EE)	$C_{25}H_{36}ClNO_3$[b]	C H N Cl	69.18 8.36 3.22 8.16	69.30 8.45 3.33 8.32
VIc	CH_3	H	CH_3	-	72	198-199 (IE)	$C_{23}H_{32}ClNO_3$[b]	C H N Cl	68.04 7.95 3.45 8.73	68.25 8.15 3.45 8.65
VId	CH_3	H	C_2H_5	-	69	165-167 (EE)	$C_{24}H_{34}ClNO_3$[b]	C H N Cl	68.63 8.16 3.33 8.44	68.85 8.25 3.62 8.45
VIIa	H	H	H	CH_2	45	230-232 (EE)	$C_{20}H_{26}BrNO_3$[c]	C H N Br	58.82 6.41 3.43 19.57	59.10 6.62 3.45 19.80

Table 1: Continued

Comp. No.	R	R^1	R^2	(X)	% Yield	MP°C (Cryst. Solv.)[a]	Molecular Formula	Anal. %		
									Calcd	Found
VIIb	H	CH_3	H	CH_2	65	215-217 (IE)	$C_{21}H_{28}BrNO_3$[c]	C H N Br	59.71 6.68 3.31 18.92	59.88 6.75 3.40 18.83
VIIc	H	H	H	-	52	263-265 (EE)	$C_{19}H_{24}BrNO_3$[c]	C H N Br	57.87 6.13 3.35 20.26	57.66 6.32 3.43 20.45
VIId	H	CH_3	H	-	69	226-228 (IE)	$C_{20}H_{26}BrNO_3$[c]	C H N Br	58.82 6.47 3.43 19.57	58.80 6.70 3.51 19.23
VIIIa	H	H	CH_3	CH_2	55	189-191 (EE)	$C_{21}H_{28}BrNO_3$[c]	C H N Br	59.71 6.68 3.31 18.92	59.65 6.35 3.60 18.73
VIIIb	H	CH_3	CH_3	CH_2	62	149-151 (EE)	$C_{22}H_{30}BrNO_3$[c]	C H N Br	60.54 6.90 3.21 18.31	60.32 7.70 3.25 18.55
VIIId	H	H	C_2H_5	-	59	128-130 (EE)	$C_{21}H_{28}BrNO_3$[c]	C H N Br	59.71 6.68 3.31 18.92	59.40 6.83 3.62 19.72
IXa	CH_3	H	$C_4H_7O_2$[d]	CH_2	53	65-67 (B)	$C_{27}H_{37}NO_5$	C H N	71.18 8.18 3.07	71.35 8.45 3.30
IXb	CH_3	H	$C_4H_7O_2$[d]	-	59	83-85 (B)	$C_{26}H_{35}NO_5$	C H N	70.72 7.99 3.17	70.95 8.15 3.55
IXc	CH_3	CH_3	$C_4H_7O_2$[d]	CH_2	66	79-81 (B)	$C_{28}H_{39}NO_5$	C H N	71.61 8.37 2.98	71.90 8.65 3.10
Xa	CH_3	H	$(CH_2)_2OH$	CH_2	78	Oil[e,f]	$C_{25}H_{35}NO_4$	C H N	72.60 8.53 3.38	72.69 8.24 3.65
Xb	CH_3	H	$(CH_2)_2OH$	-	69	Oil[e,g]	$C_{24}H_{33}NO_4$	C H N	72.15 8.32 3.50	72.42 8.61 3.72

Table 1: Continued

Comp. No.	R	R^1	R^2	(X)	% Yield	MP°C (Cryst. Solv.)[a]	Molecular Formula	Anal. %		
									Calcd	Found
Xc	CH_3	CH_3	$(CH_2)_2OH$	CH_2	81	Oil[e,h]	$C_{26}H_{37}NO_4$	C H N	73.03 8.72 3.27	73.25 8.91 3.52
XIa	CH_3	H	$(CH_2)_2Cl$	CH_2	65	232-234 (EE)	$C_{25}H_{35}Cl_2NO_3$[b]	C H N Cl	64.09 7.53 2.99 15.13	64.25 7.83 3.21 15.35
XIb	CH_3	H	$(CH_2)_2Cl$	-	59	250-252 (EE)	$C_{24}H_{33}Cl_2NO_3$[b]	C H N Cl	63.43 7.32 3.08 15.60	63.71 7.62 3.20 15.82
XIc	CH_3	CH_3	$(CH_2)_2Cl$	CH_2	77	218-220 (EE)	$C_{26}H_{37}Cl_2NO_3$[b]	C H N Cl	64.72 7.73 2.90 14.69	64.55 7.91 2.77 14.25

a Crystallization solvents: EE= Ethanol-Ether; IE= Isopropanol-Ether; B= Benzene.
b Hydrochloride salt. c Hydrobromide salt. d $C_4H_7O_2 = CH_2COOC_2H_5$.
e purified by preparative tlc (silica gel; benzene : ethyl acetate 2:1).
f_{Rf}= 0.73, g_{Rf}= 0.69, h_{Rf}= 0.78

1-Aryl-1-(3,4,5-trihydroxyphenethylamino; or 3,4,5-trihydroxy-phenethylalkylamino)-cycloalkanes (VIIa-d; VIIIa-d, Table 1)

A solution of BBr_3 (20 g; 0.08 mol) in CH_2Cl_2 (50 ml) was added dropwise into a stirred solution of the selected trimethoxy analogs (Va-d, VIa-d) (0.02 mol) in 250 ml CH_2Cl_2 at 10°C. Cooling was discontinued, and the mixture was then stirred at 25°C for 2h. An excess of cooled CH_3OH (0°C) was added, cautiously and the solvents were then removed under reduced pressure. The residual liquid was refluxed with 200 ml CH_3OH for 15 min and the solvent was again removed under reduced pressure. This procedure was repeated twice, and the residual solids were recrystallized from the proper solvent (Table 1).

The characteristic bands for IR; (cm^{-1}) were: 3340-3350 (OH); 2640-2650 (-$^+$NH).

^{1}H-NMR (DMSO-d_6) for VIIa; δ 1.1-2.1 (m, 1OH, in cyclohexyl); 2.2-3 (m, 4H, N-CH_2-CH_2-Ar); 6.5 (s, 2H, Ar); 7.5 (m, 5H, Ar); 8.8 (s, 3H, 3 x OH).

^{1}H-NMR (DMSO-d_6) for VIIIb; δ: 1.1-2.1 (m, 10H, in cyclohexyl); 2.1-2.4 (m, 4H, N-CH_2-CH_2-Ar); 2.5 (s, 3H, N-CH_3); 2.6 (s, 3H, CH_3-Ar); 6.6 (s, 2H, Ar); 7.4 (m, 4H, Ar); 8.9 (m, 3H, 3 x OH).

1-Aryl-1-(3,4,5-trimethoxy)-N-ethylcarboxy-methyl-N-phenethylaminocycloalkanes (IXa-c, Table 1)

A solution of ethyl bromoacetate (2.24 g; 0.0134 mol) in 10 ml dry acetone was added dropwise, during 30 min, into a well-stirred suspension of 1-aryl-1-(3,4,5-trimethoxy) phenethylaminocyclohexanes in 40 ml dry $(CH_3)_2CO$ and 10 ml absolute C_2H_5OH. The mixture was heated under reflux while stirring for 15 hr, allowed to cool and filtered. The filtrate was evaporated, the oily residue was dissolved in 50 ml benzene, washed successively with dilute HCl, aqueous Na_2CO_3, and water. The benzene extract was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residual solids were recrystallized from benzene.

The characteristic bands for IR; (cm^{-1})

were: bands at 1720-1725 (C=O).

^{1}H-NMR ($CDCl_3$) for IXb; δ: 1.0-1.95 (m, 8H, in cyclopentyl); 2.0-3.2 (m, 7H, N-CH_2-CH_2-Ar and $COOCH_2\underline{CH_3}$); 3.7 (s, 9H, 3 x CH_3O); 4.0 (s, N-$\underline{CH_2}$-COO); 4.3 (q, 2H, $COO\underline{CH_2}$); 6.7 (s, 2H, Ar); 7.4 (m, 5H, Ar).

1-Aryl-1-(3,4,5-trimethoxy)-N-(2-hydroxy-ethyl)-N-phenethylaminocycloalkanes (Xa-c, Table 1)

Under strictly anhydrous conditions, the appropriate N-(2-chloroethyl) derivative (IXa-c) (0.05 mol) was charged into a soxhlet extractor, fitted with a flask containing a mixture of $LiAlH_4$ (0.025 mol); anhyd. $AlCl_3$ (0.025 mol) and absolute $(C_2H_5)_2O$ (0.5 L). Reflux was maintained for 30 h through which the N-(2-chloroethyl) derivative (IXa-c) was solubilized slowly by the refluxing ether into the extraction flask. It was then chilled in ice-salt bath and the excess $LiAlH_4$ was cautiously decomposed using portions of crushed ice and drops of 20% NaOH, respectively. The etherial layer was separated and the granular residue was extracted with $(C_2H_5)_2O$. The combined etherial solution was extracted with 10% HCl (4 x 100 ml), rendered alkaline with conc. NH_4OH and the liberated base was extracted with $(C_2H_5)_2O$, washed several times with water, dried over anhydrous Na_2SO_4 and filtered. Rotary evaporation of the ether afforded oily residues.

The characteristic bands for IR; (cm^{-1}) were: bands at 3340-3350 (-OH).

1-Aryl-1-(3,4,5-trimethoxy)-N-(2-chloroethyl)-N-phenethylaminocycloalkanes(XIa-c,Table1)

To a well stirred solution of the proper X (0.01 mol) in 75 ml of dry benzene, a solution of $SOCl_2$ (2.4 g, 0.02 mol) in 10 ml of dry benzene was added dropwise, through a dropping funnel. The reaction mixture was then refluxed for 3 hr, the solvent was removed under reduced pressure, and the residue was crystallized from ethanol-ether.

The IR (nujol); (cm^{-1}) the absorption bands at 3350 (OH) of Xa-c disappeared.

^{1}H-NMR ($CDCl_3$) for XIc; δ: 1.1-2 (m, 10H, in cyclohexyl); 2.2-3.1 (m, 4H, N-CH_2-CH_2-Ar); 3.2 (s, 3H, CH_3-Ar); 3.7 (s, 9H, 3 x CH_3O); 3.8 (t, J= 3Hz, 2H, CH_2-N); 4.2 (t, J= 3Hz, 2H, CH_2-Cl); 6.7 (s, 2H, Ar); 7.5 (m, 4H, Ar).

The MS for XIc; m/z (relative abundance, %): 448 (10, M+1), 447 (20, M^+), 333 (25), 273 (100), 183 (50), 120 (30), 58 (12).

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