>C=C<); 1235, 1130, 1030, (aromatic ether and pyrone ring); 1000, 825, 810, 800 (1,4-disubstituted phenyl nucleus). 80 MHz ^{1}H NMR ($CDCl_3$, δ): 2·61–2·97 (4H, m; C–7–H$_2$ and C–8–H$_2$), 3·75 (6H, s; 4 OCH$_3$ and 12–OCH$_3$); 5·37 (1H, d, J = 1·8 Hz; C–3–H); 5·66 (1H, d, J = 1·8 Hz; C–5–H); 6·78 (2H, d, J_o = 8·8 Hz; C–11–H and C–13–H); 7·05 (2H, d, J_o = 8·8 Hz; C–10–H, C–14–H). MS M$^+$ 260.

ACKNOWLEDGEMENT

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SOME NEWER PIPERAZINO SILANES AS CARDIOVASCULAR AGENTS

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ABSTRACT

Some new N^1-aryl-N^4-(Trimethylsilyl) piperazines have been prepared by the condensation of appropriate piperazines with trimethyl chlorosilane in presence of sodium methoxide and these have been evaluated for their cardiovascular activity. Some of these compounds are found to have marked cardiovascular activity. Compound N^1-(*m*-tolyl)-N^4-(trimethylsilyl) piperazine showed potent and sustained hypotensive activity of long duration.

INTRODUCTION

SILYL group incorporated compounds have got high permeability and affect the surface of biological membranes. They have also been reported to possess diverse types of biological properties[1]. It is reported that phenethylamines containing silyl groups at various positions in the aromatic nucleus have a blood pressure lowering activity, the extent of which depends on the type of substituents attached to the silicon atom[2]. Substituted piperazines have been reported to possess potent anti-hypertensive activity[3–6]. It was, therefore, thought worthwhile to synthesize some newer N^1-aryl-N^4-(trimethylsilyl) piperazines and to evaluate them for their cardiovascular activity.

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EXPERIMENTAL

The structures of all the compounds were checked by I.R. spectra recorded on Perkin Elmer 337 infracord or Perkin Elmer 337 grating spectrophotometer. NMR was recorded on Varian A–60 D instrument and chemical shifts were expressed in τ scale. Melting points were determined in a capillary tube on an electrically heated block and are uncorrected. The compounds were checked for their homogeneity by TLC on Silica gel G.

Substituted Piperazines

Various substituted piperazines were prepared by the method already reported in literature[7–8].

N^1-Aryl-N^4-(Trimethylsilyl Piperazine)

0·05 mole of phenyl piperazine, 0·05 mole sodium methoxide and 50 ml of dry benzene were taken in a

100 ml round bottom flask. The reaction mixture was cooled to 0 C and 0 05 mole of trimethyl silicon chloride was then added dropwise with continuous shaking. The reaction was conducted in an anhydrous atmosphere. After complete addition of trimethyl silicon chloride at C° C, the contents were refluxed on a water-bath for 6-8 hours. The reaction mixture was filtered hot to remove the precipitated sodium chloride. Benzene and methyl alcohol formed in the reaction were removed by distillation and the desired compound was obtained in the pure state by reduced pressure distillation.

Infrared spectrum was consistent with the structural assignment and showed bands at 8·0 μ–$Si(CH_3)_3$. NMR spectra showed following PPM, τ values—$Si(CH_3)_3$, τ 10·01, $C-CH_3$ τ 7·8, $N-CH_2-CH_2$ τ 7·1.

Boiling points, melting points, yield and elemental analysis are given in Table I.

Stability of N-Trimethylsilyl Piperazine in water and Ethanol

The hydrolysis of Si-N bonds was studied by the method of Chang and Jain[9] as it was considered important to find out whether these compounds underwent cleavage to regenerate free piperazines, which are known to possess hypotensive activity[3,5].

Samples (1 mg) were incubated with 10 ml of distilled water or ethanol at 37° C for 24 hrs. Each incubation mixture was then extracted with methylene dichloride and the extract was subjected to separation by paper chromatography. Spots containing piperazines and unchanged N-trimethyl silyl piperazines were eluted.

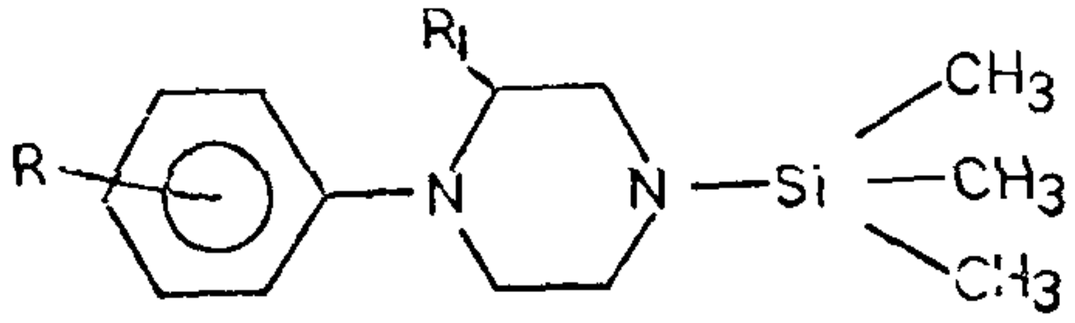
These compounds did not undergo alcoholysis and were only partially hydrolysed (5–10%).

Biological Studies

Dogs were anaesthetized with pentobarbitone sodium (30 mg/kg I.V.) and maintained on positive pressure

TABLE I

N^1–aryl–N^4–(trimethylsilyl) piperazines



Sl. No.	R	R_1	B.P. or M.P. °C (*a*)	Yield %	Recryst. solvent	Density	Molecular formula	Nitrogen %	
								Calcd.	Found
1	H	H	250–55/10 mm	55	..	1·217	$C_{23}H_{22}N_2Si$	11·96	11·92
2	3-Cl	H	260-65/10 mm	50	..	1·5014	$C_{13}H_{21}N_2SICl$	10·42	10·38
3	3-CH_3	H	240–45/10 mm	55	..	0·9030	$C_{16}H_{24}N_2Si$	11·29	11·25
4	2-OCH_3	H	240–50/10 mm	45	..	0·910	$C_{16}H_{24}N_2OSi$	10·60	10·69
5	3-OCH_3	H	230–40/10 mm	50	..	0·970	$C_{16}H_{24}N_2OSi$	10·60	10·54
6	4-Cl	2-CH_3	162-65/10 mm	55	..	0·9542	$C_{14}H_{23}N_2SiCl$	9·91	9·98
7	3-Cl	2-CH_3	164-66/10 mm	50	..	0·930	$C_{14}H_{23}N_2SiCl$	9·91	9·75
8	3,4-$(CH_3)_2$	H	135–38/10 mm	60	..	0·9046	$C_{14}H_{26}N_2Si$	11·29	11·24
9	2-CH_3	H	112	40	Ether	..	$C_{15}H_{26}N_2Si$	10·68	10·76
10	4-Cl	H	200	55	Methanol	..	$C_{14}H_{24}N_2Si$	11·29	11·34
11	4-CH_3	H	250	65	Ether	..	$C_{15}H_{21}N_2SiCl$	10·42	10·36
12	$C_6H_5\cdot CH_2-N$ CH_2CH_2 CH_2CH_2 N–110			55	Methanol	..	$C_{14}H_{24}N_2Si$	11·29	11·21

(*a*) Melting points were taken in an open capillary and are uncorrected.

artificial respiration. The blood pressure (B.P.) was recorded from the carotid artery through a mercury manometer on kymograph paper. Electrocardiogram (Lead II) was recorded on one channel of Encardiorite Polygraph (India) in some of the experiment, drugs were administered through the cannulated right femoral vein. The effect of newly synthesized compounds was studied on resting blood pressure (B.P.), heart rate (H.R.) and on pressor responses evoked either by carotid occlusion (CO) for a period of 10–30 secs or by 1–2 μg/kg of noradrenaline given intravenously.

Acute Toxicity Study

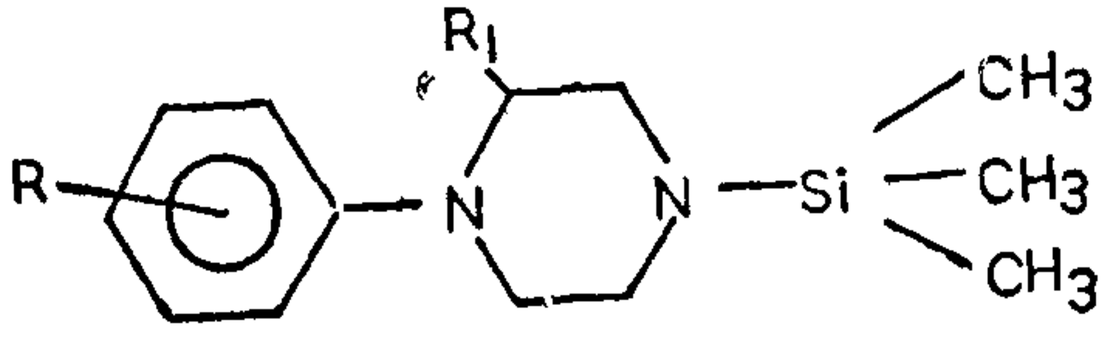
Approximate 50% lethal dose (ALD_{50}) of the compounds was determined in albino mice of either sex weighing 18–25 gms according to the reported method[10].

The cardiovascular effects of this group of compounds are summarized in Table II. Out of the 12 compounds of the present series, only compound (3) exhibited promising hypotensive activity. When administered intravenously in 5, 10 and 15 mg/kg doses, it induced dose dependent fall in blood pressure and heart rate. In addition, it completely blocked the carotid occlusion response (COR) but only slightly inhibited the noradrenaline response (NAR). The hypotensive and bradycardiac effects of this compound appeared within 2 minutes of its administration, reached its peak in 10 minutes and lasted for approximately 200 minutes depending upon the dose (Table III).

Intravenous administration of other compounds elicited hypotensive activity of varying magnitude and duration. At 5 mg/kg I.V. dose two compounds (10 and 12) exhibited potent hypotensive activity (25%

TABLE II

Cardiovascular activity of N^1-aryl-N^4-(trimethylsilyl) piperazines



Compd. No.	R	R_1	Dose mg/kg I.V.I.	No. of expts.	*% change in B.P. 10 min.	*% change in B.P. 20 min	Effect on CO response	Effect on NA response	ALD_{50} mg/kg
1	H	H	8·0	3	−16·6	..	Inhibited	Inhibited	150
			12·0	3	−27·2	..			
			16·0	3	−23·2	..			
2	3-Cl	H	16·0	2	− 7·7	..	No effect	No effect	150
3	3-CH_3	H	5·0	3	−41·7	−41·7	Blocked	Sightly	
			10·0	3	−57·1	−57·1		inhibited	150
			15·0	5	−69·2	−69·2			
4	2-OCH_3	H	10·0	2	16·6	..	No effect	No effect	125
5	3-OCH_3	H	10·0	2	20·0	..	,,	,,	150
6	4-Cl	2-CH_3	2·5	3	− 7·1	..	,,	,,	150
7	3-Cl	2-CH_3	2·5	3	− 7·4	..	,,	,,	125
8	3,4-$(CH_3)_2$	H	2·5	3	−42·8	−17·1	,,	,,	150
9	2-CH_3	H	2·5	3	−35·7	−14·2	,,	,,	100
10	4-Cl	H	5·0	3	−25·0	−16·6	Inhibited	Inhibited	150
11	4-CH_3	H	5·0	3	−45·4	− 9·0	Inhibited	No effect	125
12	$C_6H_5.CH_2$–N(CH$_2$CH$_2$)$_2$N–		5·0	3	−66·6	−23·3	Inhibited	Inhibited	125

* % change as compared to control in blood pressure; (−) indicates decrease in blood pressure.

TABLE III

Effect of intravenous (I.V.) administration of N^1-(m-toylyl)-(N^4-)trimethylsilyl) piperazine (3) on blood pressure and heart rate in pentobarbitone anaesthetized dogs

Dose mg/kg	No. of expts	** Decrease in blood pressure and heart rate									
		10 minutes		20 minutes		50 minutes		100 minutes		200 minutes	
		*% Change in B.P.	*% Change in H.R.	*% Change in B.P.	*% Change in H.R.	*% Change in B.P.	*% Change in H.R.	*% Change in B.P.	*% Change in H.R.	*% Change in B.P.	*% Change in H.R.
5	3	−41·7	−12·6	−41·7	−10·2	−33·3	− 7·3	−25·0	− 4·8	..	..
10	3	−57·1	−17·6	−57·1	−12·4	−45·7	−8·6	−39·6	− 5·9	..	..
15	5	−69·2	−22·2	−69·2	−18·6	−53·4	−10·4	−42·3	− 6·8	..	..

* % Change as compared to control in blood pressure and heart rate.
− indicates % decrease in blood pressure and heart rate.
** Mean values.

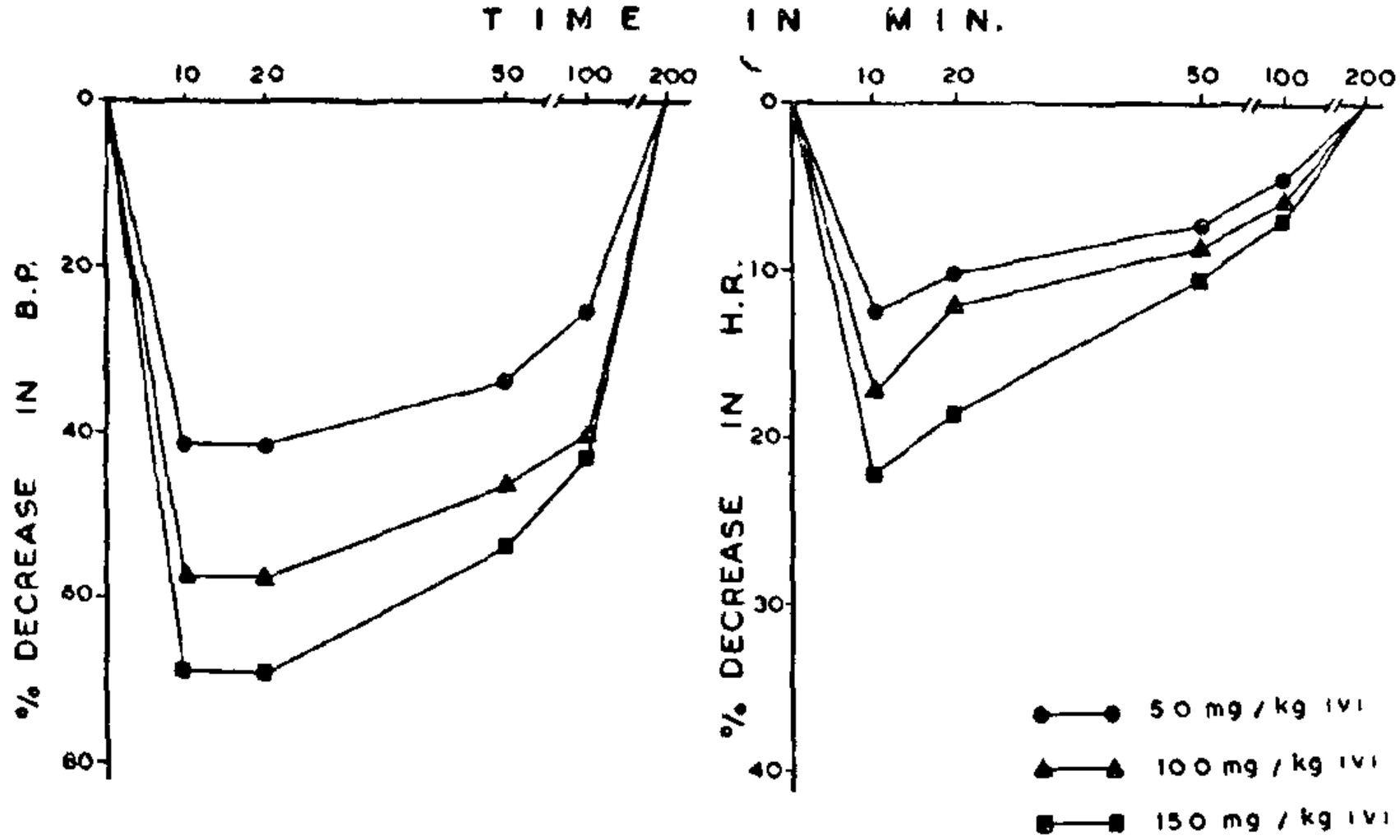


FIG. 1. Shows the time course of the effect of three graded doses (5, 10 and 15 mg/kg I.V.I.) of compound 3 on resting blood pressure (mean % decrease in B.P.) and heart rate (Mean % decrease in H.R.) in anaesthetized dogs.

and 66·6% decrease in B.P. as compared to the control). The hypotensive effect of both compounds lasted for about 60 minutes. These compounds inhibited both CO and NA responses. Two compounds (8 and 9) also showed marked hypotensive activity which lasted for 50 minutes. However, they did not affect the CO and NA responses.

Compound 11 induced a decrease in blood pressure (45·4% decrease) for about 30 minutes when injected intravenously in a dose of 5 mg/kg. COR was inhibited and NAR remained unaffected. Compound 1 induced hypotension of only 10 minutes duration and inhibited both COR and NAR suggesting a weak hypotensive effect of short duration arising from peri-

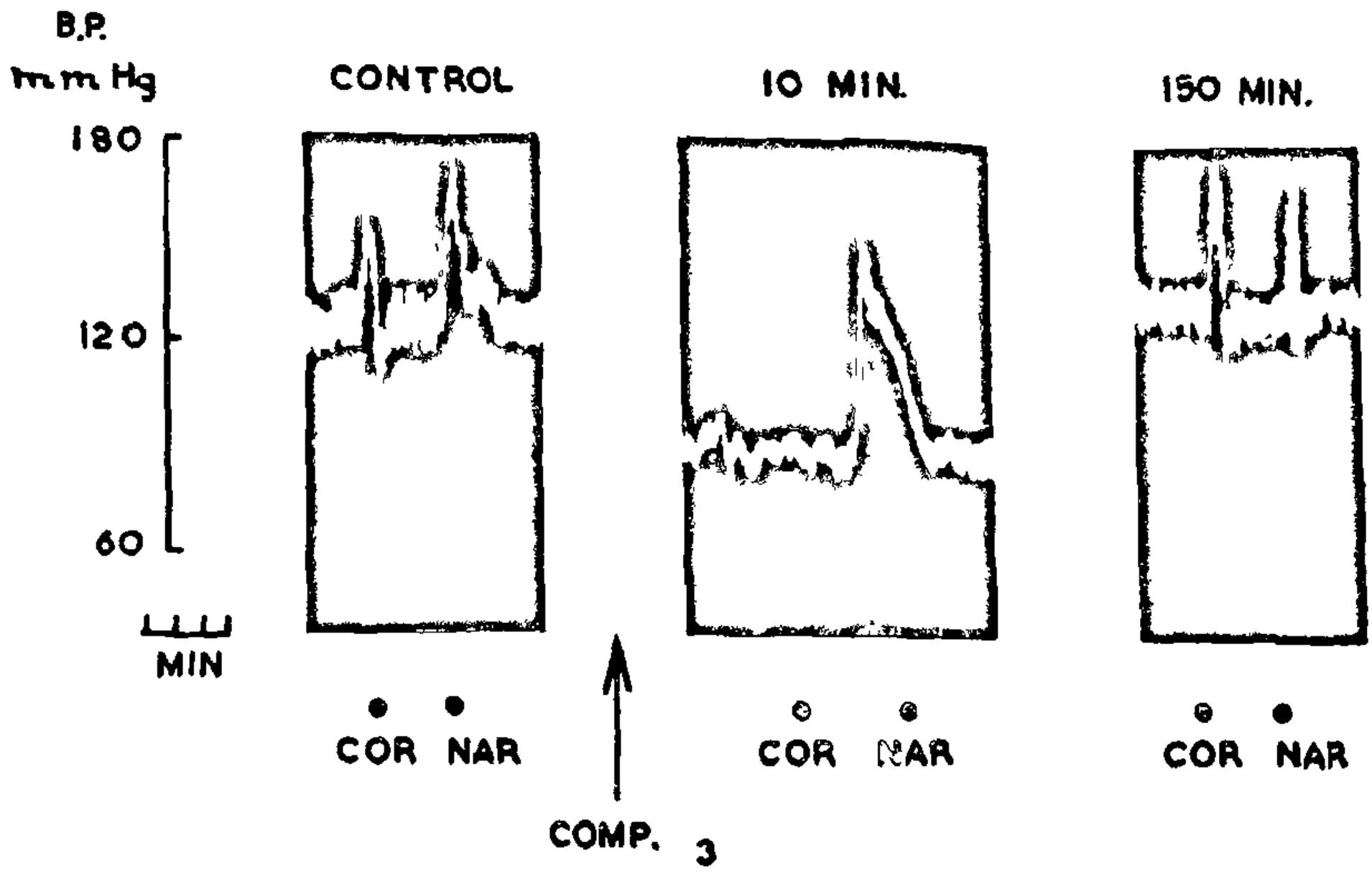


FIG. 2. Shows the records of one typical experiment with compound 3 (5 mg/kg I.V.I.) on resting blood pressure (B.P.) and the pressor responses induced by bilateral carotid occlusion (COR) and by intravenous injection of noradrenaline (NAR) in pentobarbitone anaesthetized dog. It can be seen that compound 3 induced fall in blood pressure and inhibited COR without significantly affecting NAR (10 min). Almost complete recovery could be observed after 200 minutes in this experiment.

pheral adrenolytic activity. Two compounds (4 and 5) also exhibited a weak hypotensive effect of very short duration (<10 min). The remaining three compounds (2, 6 and 7), however, showed insignificant fall in blood pressure without affecting the CO and NA responses.

In the present study, only N^1-(*m*-tolyl)-N^4-(trimethyl silyl) piperazine, compound 3 showed potent hypotensive activity of sufficiently long duration. The persistent and prolonged hypotensive effect of this compound which was associated with complete blockade of carotid occlusion response and slight inhibition of noradrenaline response is indicative of a pharmacological profile suggesting the involvement of both central and peripheral mechanisms.

Substitution with a *m*-tolyl group at position N^1- of the piperazine nucleus in piperazino silane yielded the most active compound (3). Substitution with benzyl (12), *p*-chlorophenyl (10), *o*-tolyl (9), *p*-tolyl (11) or 3,4-dimethyl-1-phenyl (8) at N^1-position of the piperazine moiety also exhibited marked hypotensive activity.

Substitution with phenyl (1) *o*-methoxyphenyl (4) or *m*-methoxy phenyl (5) in the piperazine nucleus showed hypotensive effect of varying duration.

Replacement of phenyl group attached to piperazine by 1-(*p*-chlorophenyl)-2-methyl or (1-*m*-chlorophenyl)-2-methyl (6, 7) or *m*-chlorophenyl (2) at N^1-position of the piperazine nucleus exhibited a weak hypotensive effect.

In conclusion it can be stated that N^1-(*m*-tolyl)-N^4-(trimethyl silyl) piperazine (3) possesses potent and sustained hypotensive activity. Furthermore, several compounds (8, 9, 10, 11 and 12) of the present series also exhibited marked hypotensive activity.

Moreover, the acute toxicity studies of the present series revealed that ALD_{50} doses are at least ten times more than those of the effective hypotensive doses of the compounds, studied in this investigation.

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V(III), Cr(III), Mn(III) AND Fe(III) COMPLEXES OF DISALICYLALDIMINE OXAMIDE, -MALONAMINE AND -SUCCINAMIDE

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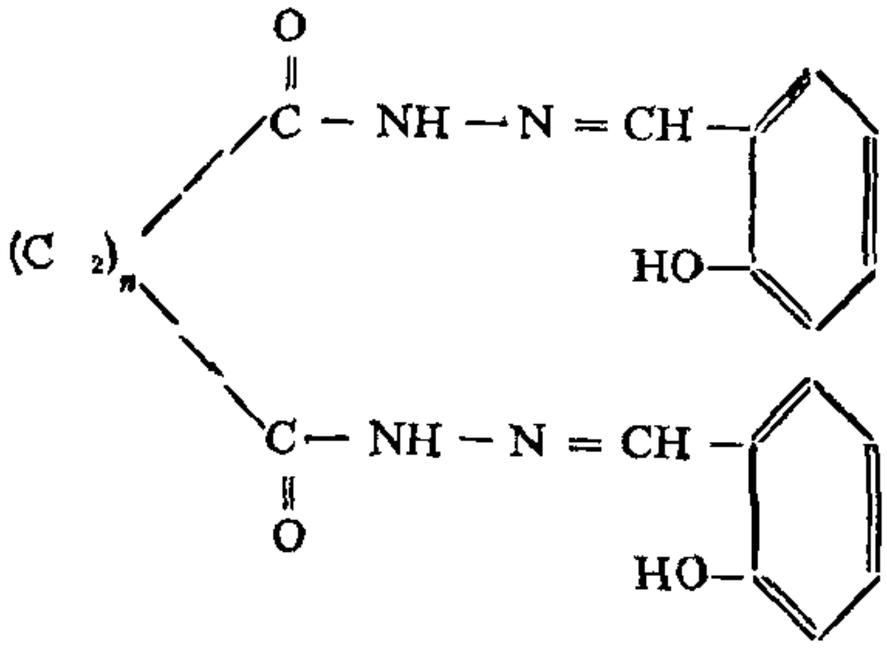
ABSTRACT

The solid complexes of type M(L-2H)X where M = Cr(III), Mn(III) and Fe(III), X = Cl or CH_3COO and V(L-H)SO_4 with some flexidentate dihydrazide Schiff bases (L) have been prepared and characterized by elemental analyses, U.V., visible, i.r. and magnetic susceptibility data. The complexes are coloured, insoluble in common organic solvents and melt or decompose above 250°C. All the complexes have octahedral stereochemistry around the metal ion. The ν M–X bands are consistent with bonded X in hexacoordinate stereochemistry. The ligands coordinate through enolized carbonyl and azomethine groups.

INTRODUCTION

BONDING potentialities of acylhydrazones especially those derived from hydroxy aldehydes and ketones provide a reasonable model for the mechanism of mono amine oxidase (MAO) enzyme inhibition by hydrazine derivatives[1]. The coordination behaviour of acylhydrazones, exhibiting keto-enol tautomerism, depends on the nature of ligand, metal ion, reaction medium and the temperature[2–4]. Recently, we have reported preparation and characterization of aluminium (III) complexes[5] with the title ligands. As a part of a systematic study, we report, hereunder, the behaviour of these ligands (Fig. 1) towards some trivalent transition metal ions.



where $n = 0, 1$, or 2.

FIG. 1

EXPERIMENTAL

The ligands were prepared as described earlier[5]. Vanadium(III) sulphate prepared by literature method[6] was dissolved in dry ethanol and reacted with solid ligands for 6–8 hours. Chromium(III) complexes were prepared by refluxing aqueous solution of metal acetate (metal excess) with solid ligands for 7–8 hours. For manganese(III) complexes, ethanolic solution of freshly prepared manganese(III) acetate[7] was refluxed with solid ligands for 5–6 hours. Iron(III) complexes were obtained by mixing aqueous solution of iron(III) chloride with alkaline solution of ligands (made neutral with acetic acid) and the mixture was warmed gently. Resulting products in all the above cases were filtered, washed with ethanol or mixture of acetic acid and ethanol and dried at ~110°C. Metal contents, chloride and sulphate were estimated by following the standard literature procedures[8]. Instruments used for physico-chemical studies were same as reported earlier[5]. The data are summarized in Table I.

RESULTS AND DISCUSSIONS

From the analytical data it is evident that V(III), Cr(III), Mn(III) and Fe(III) form 1 : 1 (M : L) complexes. All the complexes contain one anion of the original metal salt. In the complexes of Cr(III), Mn(III) and Fe(III) deprotonation of the ligands