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STUDIES ON AZABICYCLO SYSTEMS - SYNTHESES AND PHARMACOLOGICAL EVALUATION OF 3B-AMINO-9-METHYL-9-AZABICYCLO [3.3.1]NONANE ANALOGS

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ABSTRACT

Introduction: *The bicyclic systems, 8-methyl- 8-azabicyclo[3.2.1]octane and 9- azabicyclo[3.3.1]nonanes commonly known as tropane and N-methyl- granatane are found in number of therapeutically useful alkaloids. Their diazaanalogs have shown wide variety of pharmacological activities including antihypertensive, anti-inflammatory, antibacterial, ganglionic-blocking, antiserotonin, analgesic ; antiarrhythmic, and antihistaminic activities.*

Objective: *The synthesis of various hydroxyamines and hydroxyphenoxides from 3β-(1',2'-epoxypropylamino)-9- methyl-9- azabicyclo[3.3.1]-nonane is being reported here. The compounds so synthesized have been further evaluated for their effects on CNS as well as their effect on spasmogenic activity of acetylcholine, adrenaline, and histamine. In continuation of our studies on bicyclic systems we had reported the syntheses and pharmacological studies of 3β-amino analogs of 9-methyl- 9-azabicyclo[3.3.1] nonane . In the present communication we now report the syntheses and pharmacological activities of some newer analogs of 3β-amino-9- methyl-9-azabicyclo[3.3.1]nonane.*

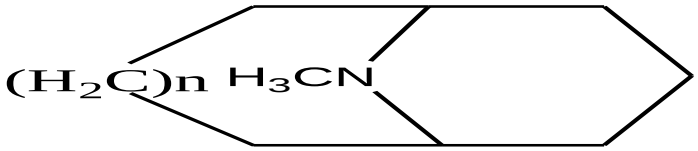
Material and methods: *Pseudopelletierine and its oxime , for this purpose were synthsized . The oxime on further reduction with metallic sodium and amyl alcohol yielded the desired amine. The amine was then , treated with epichlorhydrin to yield the epoxy analog .The epoxy analog on treatment with amines yielded the hydroxylamine.Treatment of epoxy analog with concentrated hydrochloric acid gave the hydroxychloro analog which on treatment with various phenols yielded the corresponding hydroxyphenoxide. All compounds were characterised on the basis of spectral studies.*

Results and conclusion *The results of studies showed that few of the compounds exhibit very good depressant, anticholinergic and antihistaminic activities which could be further investigated and may lead to a potent drug*

KEY WORDS :Bicyclo Compounds; Azabicyclo[3.3.1]Nonanes; 3β-Amino N-Methylgranatane; Hydroxyamines Of Azabicyclononanes; Hydroxyphenoxides Of Azabicyclo- Amines;

I. INTRODUCTION

The bicyclic systems, 8-methyl-8-azabicyclo[3.2.1]octane and 9-methyl-9-azabicyclo[3.3.1]nonanes commonly known as tropane and *N*-methyl granatane, are found in number of therapeutically useful alkaloids. Their di-aza analogs have shown wide variety of pharmacological activities including antihypertensive,[1,2] antiinflammatory & antibacterial,[1] ganglionic-blocking,[3] antiserotonin,[3-5] analgesic & antiarrhythmic,[4] and antihistaminic[5] activities. In continuation of our studies on bicyclic systems we had recently reported the syntheses and pharmacological studies of 3β-amino analogs of 9-methyl-9-azabicyclo[3.3.1] nonane (1) & (2). In the present communication we now report the syntheses and pharmacological activities of some newer analogs of 3β-amino-9-methyl-9-azabicyclo[3.3.1]nonane. Pseudopelletierine (7) and its oxime (8), for this purpose were obtained by the method of Razdan and Sharma.[7] The oxime on further reduction with metallic sodium and amyl alcohol[8] yielded the desired amine (9). The amine was then, treated with epichlorhydrin to yield the epoxy analog (10) (Scheme 1). The epoxy analog (10) on treatment with 1^0 & 2^0-amines yielded the hydroxylamine (11a-11h)(Scheme 2,Table 1). Treatment of epoxy analog (10) with concentrated hydrochloric acid gave the hydroxychloro analog (12)(Scheme 2) which on treatment with various phenols yielded the corresponding hydroxyphenoxide (Scheme 2, Table 2).



(1), n = 2
(2), n = 3

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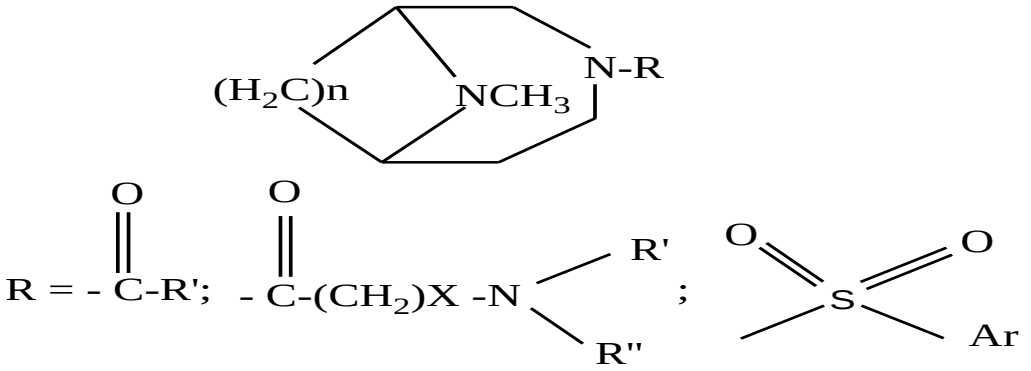
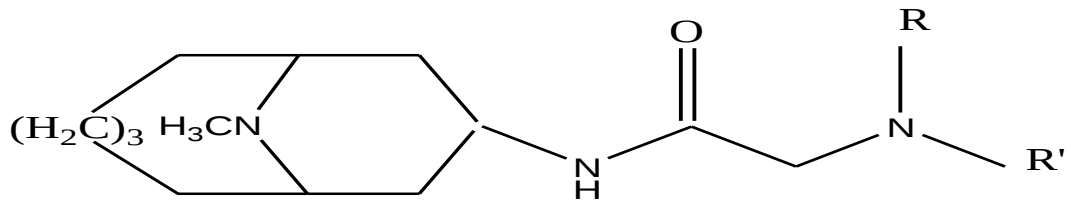


(3), n = 2
(4), n = 3



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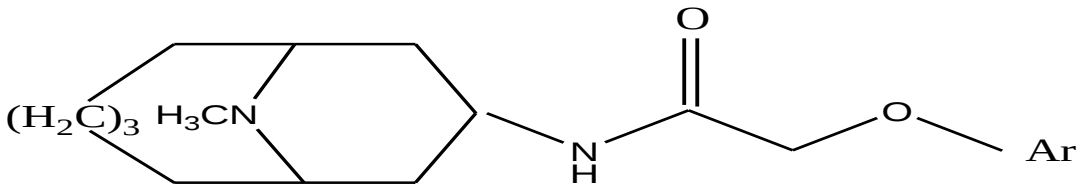

(6)

II. MATERIAL AND METHODS

Melting points were taken in open capillary and are uncorrected. IR spectra was recorded on Thermo Nicolet 200IR Spectrometer. The ^{1}HNMR spectra was recorded on Brucker AC 300 FNMR Spectrometer 300 MHz. Mass spectra (m/z) of the synthesized compounds was taken on Brucker Daltonics Mass Spectrometer. The reactions were monitored by tlc on silica gel G using the solvent system chloroform: methanol (70:30).

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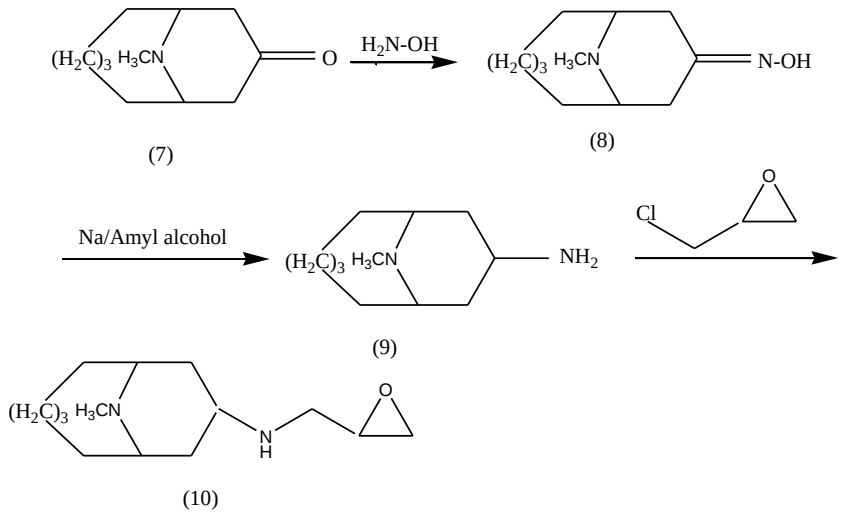
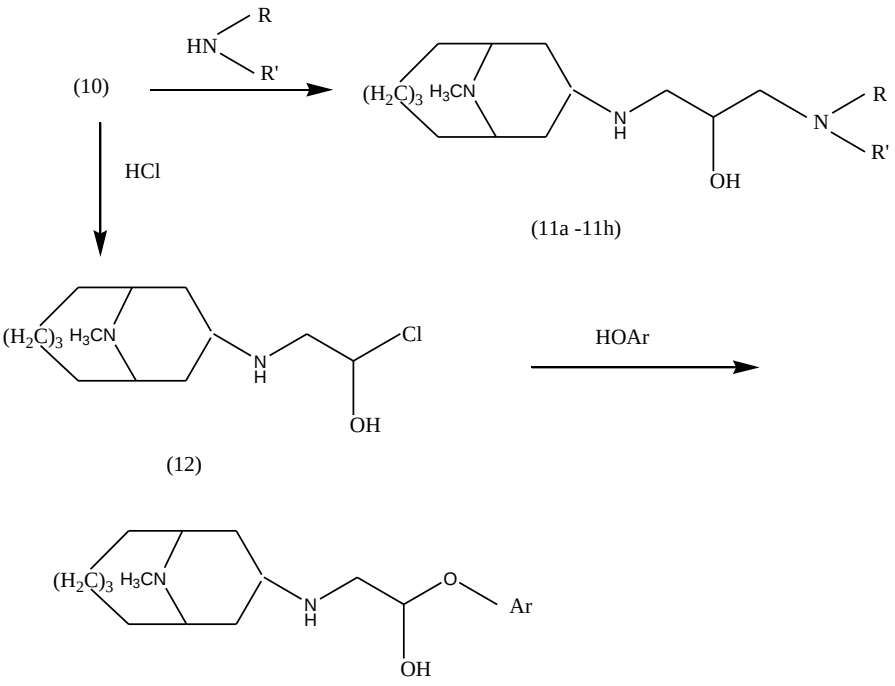
2.1 **Synthesis**

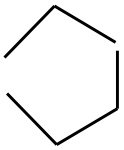
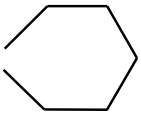
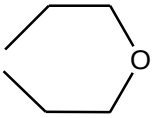
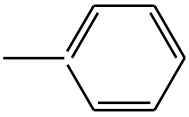
General scheme of synthesis of various compounds are represented in scheme 1 and scheme 2

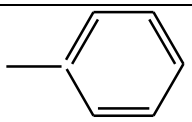
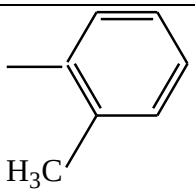
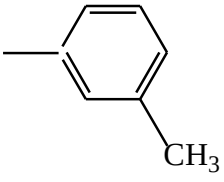


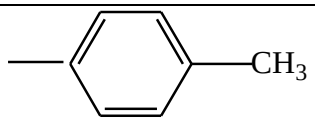
Scheme 1



Scheme 2

Compound	R	R'(Ar)
11a	-H	$-CH(CH_3)_2$
11b	$-CH_2CH_3$	$-CH_2CH_3$
11c	$-CH_2CH_2CH_3$	$-CH_2CH_2CH_3$
11d	$-CH(CH_3)_2$	$-CH(CH_3)_2$
11e		
11f		
11g		
11h	H	

13a	
13b	
13c	

13d	

2.3 synthesis and analytical profile of the compounds

2.3.1 β-(1',2'-Epoxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (10) hydro-chloride

A solution of 10 mMol of 3β-amino-9-methyl-9-azabicyclo[3.3.1]nonane (9)[8] in

10 ml of ethanol was treated with 1.06 ml of epichlorhydrin and refluxed for 6 hr. Next, the solvent was removed and the residue dissolved in water (20 ml), basified with potassium carbonate and extracted with chloroform (4x 20 ml). The chloroform extract after processing yielded a pale yellow sticky mass, which was converted to its hydrochloride, yield 1.73 g (70.18%), mp 232^0C.

Anal: IR(KBr)cm^{-1}: 3490(N-H), 3292(N-H), 2925(C-H), 1260(C-N), 945(C-O-C, cyclic).

Mass(base) m/z (rel. int.): 210 $[M+1]^+$ (100), 138 $[M-72]^+$ (40).

^{1}HNMR$CDCl_3$ δ ppm: 3.68 (m,- C<u>H</u> – CH_2), 2.79 (s, 3H,N-C<u>H</u>$_3$), 2.92 (br s, 4H, \O/N-C<u>H</u>), 2.49 (m, 4H, N-CH_2), 1.95 (m, 2H, N-CH-<u>CH_2</u>), 1.93 (m, 2H, N-CH-<u>CH_2</u>), & (m, 2H, N-CH-CH2-<u>CH_2</u>).

2.3.2 Synthesis of Amino Analogs of (11a – 11h) of 3β-(1',2'-Epoxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (10)

A solution of 3β-(1',2'-epoxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-

nonane (10) hydrochloride (10.6 mMol) and amine (15.5 mMol) in 25 ml of

n-propanol was refluxed for 10 hr. After removal of the solvent, the residue was taken in chloroform, basified and extracted with chloroform (4 x 20 ml). The chloroform extract after processing yielded a residue which was converted to dipicrate.

2.3.3β-(1'-Isopropylamino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]- nonane (11a) dipicrat*e*

Yield, 1.67 g(58.18%); mp(dipicrate), 218^0-20^0C(dec)(ethanol).

Anal:IR (Base) (Nujol) cm^{-1}: 3365 (O- H), 2929 (C-H), 1250 (C-N).Mass (Dipicrate) m/z (rel. int.): 727 $[M]^+$ (0.1), 211 $[M-458-58]^+$ (5), 138 $[M-458-73-58]^+$ (100).^{1}HNMR(dipicrate) $CDCl_3$ δ ppm: 8.85 (d, J=1.2Hz, Ar

H-NO_2, 7.51 (br band NH), 4.90 (br band NH), 3.65 (s, 3H, N-CH_3), 3.36 (s, 1 H, -(HO)CH-CH_2),2.90 (s, 1H, N-CH), 2.58 (m, 1H,CH$(CH_3)_2$), 2.53 (m, 2H, CH_2), 1.35 (d, J= 1.2 Hz,6H, -CH(C$H_3)_2$).

2.3.4 3β-(1'-Diethylamino-2'hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-

Nonane (11b) dipicrate

Yield, 1.2g (4o%); mp (dipicrate), 236-7^{0}C(dec)(ethanol)

Anal:

IR (base) (Nujol) cm^{-1}: 3351 (O-H), 2901 (C-H), 1260(C-N).

Mass (Dipicrate) m/z (rel. int.): 7 41 $[M]^+$ ().1), 284 $[M+1-458]^+$ (5), 186 $[M+2-458-27-72]^+$ (50), 138[M-458-145]+ (100).

^{1}HNMR(Dipicrate) $CDCl_3$ δppm: 8.8 (d, J=1.2Hz, $ArNO_2$), 3.74 (m,1H, -(HO)CH-CH_2), 3.22 (s, 3H, N-CH_3), 3.03 (s, 1H,N-CH), 2.95 (t, J= 3Hz, 2H, -(HO)CH-CH_2), 2.59 (br s, 1H, N-CH), 2.39(d, J= 1.2Hz,CH_2-CH-(OH)-), 2.25 (m, 4H, N-CH_2), & 1.67 (t, J= 2.8Hz, 6H, CH_2CH_3).

2.3.5 3β-(1'-Dipropylamino-2'hydroxypropylamino)-9-methyl-9azabicyclo[3.3.1]-

Nonane (11c) dipicrate

Yield, 1.66g (50%); mp (dipicrate), 228^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3388 (O-H), 2922 (C-H), 1265 (C-N).

Mass (Dipicrate) m/z (rel. int.): 769 $[M]^+$ ().1), 186 $[M+2-458-27-100]^+$(100),

138 $[M-458-173]^+$(15).

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 8.73 (d, J=1.2Hz,ArH-NO2), 3.72 (m, 1H, -(HO)CH-CH2), 3.33 (s, 3H, N-CH_3), 3.16 (s, 1H, N-CH),2.93(t, J=3Hz, 2H, -(HO)-CH-CH_2), 2.58 (br s, 1H, N-CH), 2.31 (d, J=1.2Hz, 2H,

CH_2-CH(OH)-), 2.14 (m, 4H, N-CH_2), 1.71 (m, 4H, -CH_2CH_3), & 0.95 (t, J=2.8Hz,

6H, -CH_2CH_3).

2.3.6 3β-(1'-Diisopropylamino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-nonane (11d) dipicrate

Yield, 1.33g (40%), mp (dipicrate), 192-4^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3362 (O-H), 2944(C-H), 1243 (C-N).

Mass (Dipicrate) m/z (rel. int.): 769 $[M]^+$ ().1), 186$[M+2-458-27-100]^+$ (80),

138$[M-458-173]^+$ (15).

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 8.91 (d, J=1.2 Hz, ArH-NO2), 3.67 (m, 1H,

(-(HO)C<u>H</u>-CH_2), 3.09 (s, 1H, N-C<u>H</u>), 2.93 (t, J=3Hz, 2H, -(HO)CH-C<u>H_2</u>),

2.59(br s, 1H, N-C<u>H</u>), 2.58 (d, J=1.2Hz, 2H, C<u>H_2</u>-CH(OH)-), 2.17(m, 4H, N-C<u>H_2</u>), 1.98 (m, 2H, C<u>H</u>$(CH_3)_2$, & 1.25 (m, 12H, CH(C<u>H_3</u>$)_2$).

2.3.7 **3β-(1'-Pyrrolidino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-nonane (11e) dipicrate**

Yield, 1.13g (43%), mp (dipicrate), 196-8^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3393 (O-H), 2925(C-H), 1050 (O-H).

Mass (Dipicrate) m/z (rel. int.): 739$[M]^+$(5), 282$[M-458+1]^+$ (80),

186$[M+2-458-27-70]^+$ (40), 138$[M-458-143]^+$ (100).

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 8.70 (d, J=1.2Hz, Ar H-NO_2),3.70 (m, 1H, -(HO)C<u>H</u>-CH_2), 3.59 (s, 3H, N-C<u>H_3</u>), 2.93 (s, 1H, N-C<u>H</u>), 2.75(t, J= 3Hz, 2H, -(HO)CHC<u>H_2</u>),2.58 (br s, 1H, N-C<u>H</u>), 2.51 (d, J=1.2Hz, C<u>H_2</u>-CH(OH)-), 2.29 (m, 4H, N-CH2), & 1.77 (m, 2H, N-CH2-CH2).

2.3.7 3β-(1'-Piperidino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-nonane (11f) dipicrate

Yield, 1.27g (40%), mp (dipicrate), 146-8^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3392 (O-H), 2931(C-H), 1110 (O-H).

Mass (Dipicrate) m/z (rel. int.): 755 $[M+2]^+$ (5), 296 $[M+1-458]^+$ (85),

186 $[M+2-458-27-84]^+$ (87), 138 $[M-458-157]^+$.

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 8.6 (d, J=1.2Hz, Ar-H-NO_2), 3.71 (m,1H,-(HO)-C<u>H</u>-CH_2), 3.61 (s, 3H, N-C<u>H</u>$_3$), 3.02 (s, 1H, N-C<u>H</u>), 2.94 (t,J=3Hz, 2H, -(HO)CH-C<u>H</u>$_2$), 2.58 (br s, 1H, N-C<u>H</u>), 2.54 (d, J=1.2Hz,C<u>H</u>$_2$-CH(OH)-, 2.31 (m, 4H, N-C<u>H</u>$_2$), 1.87 (m, 4H, N-CH_2-C<u>H</u>$_2$), & 1.50,(m, 2H, N-CH_2-C<u>H</u>$_2$).

2.3.8 3β-(1'-Morpholino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]-nonane (11g) dipicrate

Yield, 1.3g (40%), mp (dipicrate), 198-200^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3392 (O-H), 2925(C-H), 1296 (C-N), 1116 (C-O-C).

Mass (Dipicrate) m/z (rel. int.): 755$[M]^+$ (0.1), 186 $[M-458-27+2]^+$ (100),

138 $[M-458-159]^+$(25).^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 7.26(d, J=1.2Hz, Ar- H-NO_2), 4.72 (m, 1H,C<u>H</u>(OH)-CH_2), 3.68 (t, J=1.7Hz, 4H, OC<u>H</u>$_2$), 2.97 (s, 3H, N-C<u>H</u>$_3$), 2.92 (br s, 4H,

N-C<u>H</u>), 2.51 (m, 2H, NH-C<u>H</u>$_2$-CH(OH)-), 2.49 (m, 4H, N-C<u>H</u>$_2$), 1.95 (m, 2H, N-CH-C<u>H</u>$_2$), 1.93 (m, 2H, N-CH-C<u>H</u>$_2$), & 1.53 (m, 2H, N-CH-CH_2-C<u>H</u>$_2$).

2.3.9 3β-(1'-Anilino-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (11h) dipicrate

Yield, 1.32 g (40%), mp (dipicrate), 109-10^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3342 (O-H), 2936(C-H), 1265 (C-N).

Mass (Dipicrate) m/z (rel. int.): 304 $[M+1-458]^+$ (65), 211 $[M-458-92]^+$ (50),

138 $[M-458-92-73]^+$ (100).

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 8.73 (d, J=1.2Hz, Ar-H-NO2), 8.3 (m, 5H, Ar-H),3.69 (m, 1H, -(HO)C<u>H</u>-CH_2), 3.36 (s, 3H, N-C<u>H</u>$_3$), 3.22 (s, 1H, N-C<u>H</u>), 2.94 (t, J=3Hz, 2H, -(HO)CH-C<u>H</u>$_2$), 2.58 (br s, 1H, N-C<u>H</u>), 2.27 (d, J=1.2Hz, C<u>H</u>$_2$-CH-(OH)-), & 2.15 (m, 4H, N-C<u>H</u>$_2$).

2.4 3β-(1'-Chloro-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (12).

3β-(1',2'-Epoxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (10) (1g,

4.1 mMol) was treated with 5 ml of concentrated hydrochloric acid and refluxed for 4 hr. After removal of hydrochloric acid under vacuum, the residue was taken up in water (10 ml), basified with sodium carbonate, and

extracted with chloroform (4 x 20 ml). The chloroform extract after processing yielded a residue (1.35 g, 50 %), mp 111-2^{0}C, which was used further as such.

Anal:

IR (base) (Nujol) cm^{-1}: 3490(N-H), 3300(O-H), 3287 (N-H), 2918 (C-H), 1260

(C-N).

Mass (Base) m/z (rel. int.): 247 $[M+1]^+$ (80), 196 $[M-49]^+$ (20),

138 $[M-108]^+$ (40).

^{1}HNMR (Dipicrate) $CDCl_3$ δppm: 2.92 (s, 2H, -(HO)-CH-C$\underline{H}_2$-Cl), 1.95(m, 2H, N-CH-C$\underline{H}_2$), 1.93 (m, 2H, N-CH-C$\underline{H}_2$), & !.53 (m, 2H, N-CH-CH$_2$-C$\underline{H}_2$).

2.4.1 Synthesis of Phenoxy Analogs (13a-13d) 3β-(1'-Chloro-2'-hydroxypropyl-amino)-9-methyl-9-azabicyclo[3.3.1]nonane (12).

To a solution of 3β-(1'-chloro-2'-hydroxypropylamino)-9-methyl-9-azabicyclo-[3.3.1] nonane (12) (1 g, 4.3 mmol) in ethanol (10 ml) was added a phenol (5 mMol) and anhydrous potassium carbonate (0.75 g) and the reaction mixture refluxed for 12 hr. Next, the solvent was removed and the residue taken up in water (15 ml) and extracted with chloroform (4 x 20 ml). The chloroform layer was next washed with 10 % sodium hydroxide solution (2 x 10 ml) and with water (2 x 10 ml). The chloroform layer after processing yielded a residue which was crystallized as picrate.

2.4.2 3β-(1'-Phenoxy-2'-hydroxypropylamino)-9-methyl-9-azabicyclo[3.3.1]nonane (13a) picrate

Yield, 0.74 g (60%), mp (dipicrate), 214-6^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3335(O-H), 2933(C-H), 1245 (C-N), 1044(C-O-C).

Mass (Picrate) m/z (rel. int.): 533 $[M]^+$ (0.1), 211 $[M-229-93]^+$ (20),

138 $[M-229-93-73]^+$ (80).

^{1}HNMR (Picrate) $CDCl_3$ δppm: 8.70 (d, J=1.2 Hz, Ar-H-NO$_2$), 7.8(m, 2H, ArH), 7.62 (br band N$\underline{H}$), 7.46 (m, 3H, ArH), 4.71 (m, 1H, -(HO)C$\underline{H}$-CH$_2$), 4.45 (br band N$\underline{H}$), 3.71 (s, 2H, -OC$\underline{H}_2$), 3.59 (s, 3H, N-C$\underline{H}_3$), 2.94 (s, 1H, N-C$\underline{H}$), 2.58 (br s, 1H, N-C$\underline{H}$), & 2.35 (m, 2H, C$\underline{H}_2$-CH(OH).

2.4.3 3β-{1'-(o-Methylphenoxy)-2'-hydroxypropylamino}-9-methyl-9-azabicyclo[3.3.1]nonane (13b) picrate

Yield, 0.8 g (62 %), mp (dipicrate), 202^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3347(O-H), 2923(C-H), 1248 (C-N), 1044(C-O-C).

Mass (Picrate) m/z (rel. int.): 547 $[M]^+$ (0.2), 211 $[M-229-107]^+$ (65),

138 $[M-229-73-107]^+$ (100).

^{1}HNMR (Picrate) $CDCl_3$ δppm: 8.77 (d, J=1.2Hz, ArH-NO_2), 7.0-7.26 (m, 4H, ArH), 3.69(s, 2H,O-C$\underline{H}_2$), 3.65(m, 1H,-(HOC$\underline{H}$-CH_2), 3.13(S,1H, N-C$\underline{H}$), 2.93 (t,J=3HZ, 2H, -(HO)CH-C$\underline{H}_2$), 2.59(br s, 1H, N-C$\underline{H}$), 2.21(d, J=1.2Hz, C$\underline{H}_2$-CH(OH)-), & 1.84 (s, 3H, $ArCH_3$).

2.4.4 3β-{1'-(m-Methylphenoxy)-2'-hydroxypropylamino}-9-methyl-9-azabicyclo[3.3.1]nonane (13c) picrate

Yield, 0.6 g (42 %), mp (dipicrate), 210-2^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3363(O-H), 2943(C-H), 1260 (C-N), 1030(C-O-C).

Mass (Picrate) m/z (rel. int.): 547 $[M]^+$ (0.5), 211 $[M-229-107]^+$ (30),

138 $[M-229-73-107]^+$ (100).

^{1}HNMR (Picrate) $CDCl_3$ δppm: 8.77 (d, j=1,2 Hz, ArH-NO_2), 7.24 (br s,

1H, ArH), 7.20 (t, J=4Hz, 1H, ArH), 6.8 (m, 2H, ArH), 3.69 (s, 2H, O-C$\underline{H}_2$),

3.65 (m, 1H, -(HOC$\underline{H}$-CH_2), 3.13(s,1H, N-C$\underline{H}$), 2.93 (t, J=3 Hz, 2H, HO-CH-C$\underline{H}_2$),

2.59 (br s, 1 H, NC$\underline{H}$), 2.21 (d, J=1.2 Hz, C$\underline{H}_2$-CH-OH), & 1.89 (s, 3H, $ArCH_3$).

2.4.5 3β-{1'-(p-Methylphenoxy)-2'-hydroxypropylamino}-9-methyl-9-azabicyclo[3.3.1]nonane (13d) picrate

Yield, 0.6 g (42 %), mp (dipicrate), 210-2^{0}C (dec) (ethanol).

Anal:

IR (base) (Nujol) cm^{-1}: 3365(O-H), 2922(C-H), 1245 (C-N), 1046(C-O-C).

Mass (Picrate) m/z (rel. int.): 547 $[M]^+$ (0.2), 211 $[M-229-107]^+$ (25),

138 $[M-229-73-107]^+$ (100).

^{1}HNMR (Picrate) $CDCl_3$ δppm: 8.76 (d, J=1.2 Hz, ArH-NO_2), 7.27 (br s, 1H, ArH),7.10 (t, J=4 Hz, 1H, ArH), 6.98 (m, 2H, ArH), 3.69 (s, 2H, -OCH_2), 3.41 (m, 1H,(HO-C<u>H</u>-CH_2), 3.12 (s, 1H, N-C<u>H</u>), 2.89 (t, J=3 Hz, 2H, HO-CH-C<u>H</u>$_2$), 2.59 (br s, 1H, N-C<u>H</u>), 2.23 (d, J=1.2 Hz C<u>H</u>$_2$-CH-OH), & 1.85 (br, s, 3H, $ArCH_3$).

III. PHARMACOLOGICAL STUDIES

The pharmacological studies involved the study of effects of synthesized compounds (10-13) (henceforth designated as Test compounds), on CNS-depressant activity, sleeping time, and the effect on spasmogenic activity of acetylcholine, adrenaline, and histamine.

3.1 Effect of test compounds on cns- depressant activity[9]

The effect of CNS-depressant activity was determined on mice using locomotion as the parameter on actophotometer.[9] Normal saline was used as control and phenobarbitone as the standard. All the Test compounds and phenobarbitone were used at a dose level of 10mg/kg. The locomotion activity was measured by noting the count before and after the injection of control, standard, and the Test compounds for 10 min.

3.2 Sleeping Time[10]

The sleeping time[10] of Test compounds which showed depressant activity more than phenobarbitone was determined on mice. Both standard and Test compounds were given intraperitonially at a dose level of 45 mg/kg in a concentration of 4.5 mg/ml. The sleeping time was noted by noting the time when they went to sleep and when they were awake.

3.3 Effect of compounds on the spasmogenic activity of acetylcholine,[11] adrenaline,[12] and histamine,[13]

The effect of Test compounds on the spasmogenic activity of acetylcholine[11] (100 µg/ml), adrenaline[12] (10µg/ml), and histamine[13] (100µg/ ml), was studied on rat ileum, rabbit ileum, and guinea pig ileum, respectively. The effect of Test compounds was determined by adding 0.1 ml, 0.2 ml, 0.4 ml and a maximum of 2ml of 1 mg/ml solution.

IV. RESULTS AND DISCUSSION

4.1 Pharmacological studies

4,1.1 locomotor activity and sleeping time (table 3 & 4) The results of studies of locomotor activity are given in Table 3.Test compounds 11f, 11g, 13c, 13d, when injected in animals resulted in death of animals. All other Test compounds showed depressant activity. Test compounds 11c, 11d, 11h, and 12 showed CNS-depressant activity less than phenobarbitone. The depressant activity of other Test compounds, namely, Test compound 10, 11a, 11b, 11e, and 13a was more than phenobarbitone. They were further investigated for sleeping time (Table 4). While Test compounds 11a, 11b, 11e, and 13a were lethal at the dose level of 45mg/kg. (Table 4). Test compound 10 showed sleeping time of 30 min, which was less than the standard phenobarbitone.

4.1.2 Effect of test compounds on the spasmogenic action of acetylcholine, adrenaline, and histamine (table 5)

None of the Test compounds showed any effect of their own on ileum of rat, rabbit, and guinea pig ileum.

The effect on spasmogenic action of acetylcholine, adrenaline, and histamine was studied on rat ileum, rabbit ileum, and guinea pig ileum, respectively (Table 5).

None of the Test compounds excepting 13c showed 100 % blockade of acetylcholine induced spasm (Table 5).

Test compounds 11b, 11h, and 12 did not show any blockade of adrenaline induced spasm of rabbit ileum. The blockade by other Test compounds varied from 11 % to 74 %.

Test compounds 11e and 11h showed a blockade of 68.42 % and 100 % , respectively, of histamine induced spasm of guinea pig ileum (Table 5). None of the other Test compounds showed any effect on the histamine induced spasm.

Preliminary pharmacological studies show that some of the compounds possess anticholinergic and antihistaminic activities which could be further investigated.

V. CONCLUSION

From the studies it can be concluded that most of the derivatives showed CNS-depressant activity more than phenobarbitone (standard drug). Preliminary pharmacological studies showed that some of the compounds possess anticholinergic and antihistaminic activities which could be further investigated. So further attempts could be made to extend the series and to achieve hopeful goal.

VI.CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest..

VII. ACKNOWLEDGEMENTS

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TABLE 3: EFFECT OF PHENOBARBITONE (STANDARD) AND TEST COMPOUNDS ON LOCOMOTOR ACTIVITY* OF MICE AT A DOSE LEVEL OF 10MG/KG

S.No	Normal saline/Standard/Test Compound	Change in Locomotor Activity
1.	Normal Saline (Control)	11 % ↓
2.	Phenobarbitone (Standard)	22 % ↓
3.	Test Compound 10	25 % ↓
4.	Test Compound 11a	64.26 % ↓
5.	Test Compound 11b	57.01 % ↓
6.	Test Compoind 11c	5.17 % ↓
7.	Test Compound 11d	9.1 % ↓
8.	Test Compound 11e	71.14 % ↓

9.	Test Compound 11f	Lethal
10.	Test Compound 11g	Lethal
11.	Test Compound 11h	13.78 % ↓
12.	Test Compound 12	16.19 % ↓
13.	Test Compound 13a	25.57 % ↓
14.	Test Compound 13b	Lethal
15.	Test Compound 13c	Lethal
16.	Test Compound 13d	Lethal

*Mean of 5 mice

↓ Indicates depression Lethal : Indicates death of animals

TABLE 4 : SLEEPING TIME* OF PHENOBARBITONE AND TEST COMPOUNDS AT A DOSE LEVEL OF 45MG/KG

S.No	Standard/Test Compound	Duration in Minutes
1.	Phenobarbitone (standard)	200 min
2.	Test Compound 10	30 min
3.	Test Compound 11a	Lethal
4.	Test Compound 11b	Lethal
5.	Test Compound 11e	Lethal
6.	Test Compound 13a	Lethal

*Mean of 5 mice Lethal: Indicates death of animal

TABLE 5 : EFFECT OF TEST COMPOUNDS ON ACETYLCHOLINE (ACH), ADRENALINE (ADR), AND HISTAMINE (HIS) INDUCED SPASM OF ISOLATED RAT ILEUM, RABBIT ILEUM, AND GUINEA PIG ILEUM, RESPECTIVELY

S.No	Test Compound	Effect on Ach induced spasm of isolated rat ileum	Effect on Adr induced spasm of isolated rabbit ileum	Effect on His induced spasm of isolated guinea pig ileum
1.	Test Compound	No effect	56.53 %↓	No effect

	10			
2.	Test Compound 11a	No effect	74 %↓	No effect
3.	Test Compound 11b	No effect	No effect	No effect
4.	Test Compound 11c	No Effect	11.78 %↓	No effect
5.	Test Compound 11d	No effect	33.34 %↓	No effect
6.	Test Compound 11e	No effect	No effect	68.42 %↓
7.	Test Compound 11f	No effect	37.50 %↓	100 %↓
8.	Test Compound 11g	No effect	56.53 %↓	No effect
9.	Test Compound 11h	No effect	No effect	No effect
10.	Test Compound 12	No effect	No effect	No effect
11.	Test Compound 13a	No effect	56.53 %↓	No effect
12.	Test Compound 13b	No effect	60.88 %↓	No effect
13.	Test Compound 13c	100 %↓	25.0 %↓	No effect
14.	Test Compound 13d	No effect	No effect	No effect

↓ indicates blockade