Synthesis and Pharmacological Activities of 2-(3′-substituted-2′-hydroxypropylamino)pyridines

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In the present study, a series of 2-(3′-substituted-2′-hydroxypropylamino)pyridines were synthesized and characterized by IR, ^{1}H-NMR and elemental analysis. The compounds were investigated for anticonvulsant (150, 300 mg/kg) and cardiac activity. 2-(3′-Diethylamino-2′-hydroxypropylamino)pyridine 3 was found to exhibit the highest anticonvulsant activity. 2-(3′-Dimethylamino-2′-hydroxypropylamino)pyridine 2 and 2-[3′-(4″-nitrophenylamino)-2′-hydroxypropylamino]pyridine 6 were found to exhibit negative ionotropic activity. 2-(3′-Dimethylamino-2′-hydroxypropylamino)pyridine 2, 2-[3′-(4″-nitrophenylamino)-2′-hydroxypropylamino]pyridine 6 and 2-(3′-piperidino-2′-hydroxypropylamino)pyridine 8 were found to antagonize exhibit β-adrenergic activity.

Key words pyridine; arylaminopropane; anticonvulsant; ionotropic; β-adrenergic

Pyridine derivatives were reported to be associated with anticonvulsant,[1,2] cardiotonic,[3] antihypertensive[4] and β-adrenergic blocking activity.[5] Aminopropanes were reported to possess CNS depressant,[6] neuroleptic,[7] antiarrhythmic,[8] hypotensive[9] and β-adrenergic blocking activity.[10,11] Therefore, it was envisaged that chemical entities with both pyridine and aminopropane moieties would result in compounds of interesting biological activities. In the present study, a series of 2-(3′-substituted-2′-hydroxypropylamino)-pyridines were synthesized. The compounds were characterized by IR, ^{1}H-NMR spectral and elemental analysis. The compounds were evaluated for anticonvulsant activity at the dose level of 150 and 300 mg/kg by Maximal electroshock method and cardiac activity on isolated frog heart.

CHEMISTRY

Melting points were determined in open capillary tubes and are uncorrected. IR spectra was recorded (in KBr) on Perkin-Elmer IR spectrophotometer 298. ^{1}H-NMR Spectra was recorded on 300 MHz Bruker DPX 200 using tetramethylsilane as internal standard. Elemental analysis was performed on Heraeus CHN rapid analyzer. Analysis indicated by the symbols of the elements are within ±0.4% of the theoretical values.

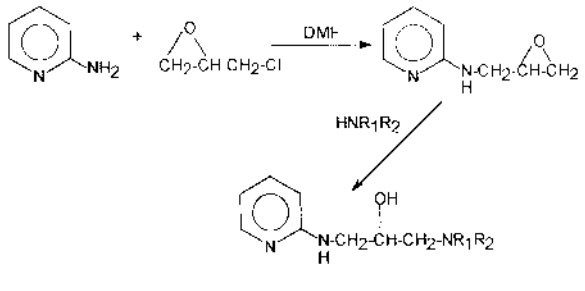
Synthesis of 2-(2′,3′-Epoxypropylamino)pyridine A solution a sodium methoxide (0.113 mol of sodium and 75 ml of methanol) was added to 0.113 mol of 2-aminopyridine and refluxed for 1 h. Then methanol was completely removed from the medium and 10 ml of anhydrous dimethyl formamide (DMF) was added to the dry residue. A solution of epichlorohydrine (0.113 mol) in 10 ml anhydrous DMF was then added dropwise to the reaction mixture with stirring. The mixture was stirred for 1 h at room temperature. The product was filtered, dried in vacuum and recrystallized using 1 : 1 acetone–ether. Yield=34%, mp 140—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.7642—7.9740 (m, 4H; 3, 4, 5, 6H), 7.4319—7.5468 (s, 1H; NH), 3.4178—3.5692 (d, J=5.2 Hz, 2H; 3′-CH_2), 3.2561—3.4178 (d, J=6.4 Hz, 2H; 1′-CH_2), 2.1201—2.2431 (m, 1H; 2′-CH). IR (KBr) cm^{-1}: 1420 (C–H), 1321 (N–H), 1110 (C–O), 890, 854 (Ar-H). *Anal.* Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.18; H, 6.60; N, 18.90.

General Method for the Synthesis of 1 to 9 A solution of 2-(2′,3′-epoxypropylamino)pyridine (0.013 mol) and the appropriate amine (0.013 mol) in 40 ml of methanol was refluxed for 24 h. The product obtained was filtered, vacuum dried and recrystallized using 1 : 1 chloroform–ether (Fig. 1).

2-(3′-Methylamino-2′-hydroxypropylamino)pyridine **1**: Yield=40%, mp 210—211 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.15—7.62 (m, 4H; 3, 4, 5, 6H), 6.95—7.15 (s, 1H; Ar-NH), 6.80—6.93 (s, 1H; NH), 3.39—3.54 (m, 4H; 1′, 3′-CH_2), 3.15—3.35 (s, 1H; OH), 1.35—1.41 (m, 1H, 2′-CH), 0.97—1.34 (s, 3H; CH_3). IR (KBr) cm^{-1}: 3440 (O–H), 1491 (C–H), 1395 (C–N), 1321 (N–H), 880, 868 (Ar-H). *Anal.* Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.18. Found: C, 59.36; H, 8.18; N, 22.96.

2-(3′-Dimethylamino-2′-hydroxypropylamino)pyridine **2**: Yield=30%, mp 170—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.19—8.20 (m, 4H; 3, 4, 5, 6H), 7.25—7.31 (s, 1H; NH), 3.68—3.99 (m, 6H; 1′, 3′-CH_2); 3.27—3.34 (s, 1H; 2′-OH); 2.15—2.23 (m, 1H; 2′-CH), 1.16—1.29 (s, 6H; $(CH_3)_2$). IR (KBr) cm^{-1}: 3406 (O–H), 1484 (C–H), 1360 (C–N), 1333 (N–H), 756, 722 (Ar-H). *Anal.* Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.32; H, 8.99; N, 21.78.

2-(3′-Diethylamino-2′-hydroxypropylamino)pyridine **3**:



–NR_1R_2 : **1**, methylamino; **2**, dimethylamino; **3**, diethylamino; **4**, bis(2-hydroxyethyl)amino; **5**, phenylamino; **6**, 4-nitrophenylamino; **7**, diphenylamino, **8**, piperidino; **9**, morpholino

Fig. 1. Synthetic Scheme

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Yield=45%, mp 240—241 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.95—7.62 (m, 4H; 3, 4, 5, 6H), 6.41—6.55 (s, 1H; NH), 3.57—3.97 (m, 4H; 1′, 3′-CH_2), 3.08—3.51 (s, 1H, 2′-OH), 1.63—1.86 (m, 1H; 2′-CH), 0.94—1.63 (s, 10H; $(C_2H_5)_2$). IR (KBr) cm^{-1}: 3024 (O–H), 1459 (C–H), 1334 (C–N), 1296 (N–H), 778, 738 (Ar-H). *Anal.* Calcd for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.68; H, 9.66; N, 19.04.

2-(3′-Diethanolamino-2′-hydroxypropylamino)pyridine **4**: Yield=42%, mp 187—188 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.95—7.62 (m, 4H; 3, 4, 5, 6H), 6.53—6.89 (s, 1H; NH), 3.39—3.55 (m, 4H; 1′, 3′-CH_2) 2.94—3.16 (s, 1H; 2′-OH), 2.65—2.89 (m, 8H; 1″, 2″-CH_2), 2.47—2.62 (s, 2H; 2″-$(OH)_2$), 1.34—1.47 (m, 1H; 2′-CH). IR (KBr) cm^{-1}: 3186 (O–H), 1408 (C–H), 1368 (C–N), 1321 (N–H), 778, 721 (Ar-H). *Anal.* Calcd for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.21; H, 8.36; N, 16.31.

2-(3′-Phenylamino-2′-hydroxypropylamino)pyridine **5**: Yield=65%, mp 85—86 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.78—7.99 (m, 4H; 3, 4, 5, 6H), 7.23—7.46 (s, 2H; $(NH)_2$), 6.45—6.67 (m, 5H; 2″, 3″, 4″, 5″, 6″H), 3.38—3.67 (m, 4H; 1′, 3′-CH_2), 3.12—3.38 (s, 1H; 2′-OH), 1.48—1.72 (m, 1H; 21-CH). IR (KBr) cm^{-1}: 3424 (O–H), 1408 (C–H), 1392 (C–H), 1321 (N–H), 810, 792 (Ar-H). *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.12; H, 7.05; N, 17.27. Found: C, 68.92; H, 6.80; N, 17.36.

2-[3′-(4″-Nitrophenylamino)-2′-hydroxypropylamino]pyridine **6**: Yield=42%, mp 140—141 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.14 (m, 4H; 3, 4, 5, 6H), 6.47—6.64 (s, 2H; $(NH)_2$), 6.32—6.45 (m, 4H; 2″, 3″, 5″, 6″H), 3.65—3.83 (m, 4H; 1′, 3′-CH_2), 3.14—3.58 (s, 1H; 2′-OH), 1.07—1.26 (m, 1H; 21-CH). IR (KBr) cm^{-1}: 3342 (O–H), 1600 (N–O), 1474 (C–H), 1340 (C–N), 1318 (N–H), 850, 825 (Ar-H). *Anal.* Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.34. Found: C, 58.07; H, 5.68; N, 19.61.

2-(3′-Diphenylamino-2′-hydroxypropylamino)pyridine **7**: Yield=25%, mp 75—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.92—7.65 (m, 4H; 3, 4, 5, 6H). 6.65—6.85 (s, 1H; NH), 6.19—6.46 (m, 10H; $N(C_6H_5)_2$), 3.29—3.59 (m, 4H; 1′, 3′-CH_2), 3.07—3.18 (s, 1H; 2′-OH), 1.07—1.35 (m, 1H; 2′-CH). IR (KBr) cm^{-1}: 3340 (O–H), 1486 (C–H), 1391 (C–N), 1304 (N–H), 846, 812 (Ar-H). *Anal.* Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.04; H, 6.79; N, 13.32.

2-(3′-Piperidino-2′-hydroxypropylamino)pyridine **8**: Yield=29%, mp 165—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.95—7.62 (m, 4H; 3, 4, 5, 6H), 3.65—3.83 (m, 4H; 1′, 3′-CH_2), 3.27—3.60 (s, 1H; 2′-OH), 2.65—2.89 (m, 10H; 2″, 3″, 4″, 5″, 6″-CH_2), 1.08—1.51 (m, 1H; 2′-CH). IR (KBr) cm^{-1}: 3371 (O–H), 1471 (C–H), 1350 (C–N), 1338 (N–H), 760, 746 (Ar-H). *Anal.* Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.08; H, 8.69; N, 17.52.

2-(3′-Morpholino-2′-hydroxypropylamino)pyridine **9**: Yield=36%, mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—715 (m, 4H; 3, 4, 5, 6H), 6.39—6.55 (s, 1H; NH), 3.34—3.62 (m, 4H; 1′, 3′-CH_2), 3.18—3.48 (s, 1H; 2′-OH), 2.82—3.01 (m, 8H; 2″, 3″, 5″, 6″-CH_2), 1.03—1.25 (m, 1H; 2′-CH). IR (KBr) cm^{-1}: 3248 (O–H), 1426 (C–H), 1378 (C–N), 1314 (N–H), 1118 (C–O), 871, 842 (Ar-H). *Anal.* Calcd for $C_{12}H_{19}N_3O_3$: C, 60.74; H, 8.07; N, 17.71. Found: C, 60.29; H, 8.41; N, 18.08.

PHARMACOLOGY

All the synthesized compounds were screened for anticonvulsant activity at the dose of 150 and 300 mg/kg. The anticonvulsant dose was selected between the minimal effective dose and maximal non-lethal dose. All the compounds were soluble in water and administered to the animals as a solution in triple glass distilled water. The compounds were also screened for cardiac activity on isolated frog heart. Wistar albino rats (150—200 g) of either sex were procured from King Institute, Guindy, Chennai. They were kept in colony cages at 25±2 °C, relative humidity 45—55% under 12 h light and dark cycle. All the animals were acclimatized for a week before use. Small frogs (Rana tigrina, 80—120 g) were procured locally and used on the same day. Unpaired Student-*t*-test[12] was performed to ascertain the significance of the exhibited anticonvulsant activity of the compounds.

Anticonvulsant Activity The anticonvulsant activity[13] of the synthesized compounds were tested against maximal electroshock induced convulsions in rats. Wistar albino rats (n=6) of either sex were selected by random sampling technique. The compounds were administered at the dose level of 150 and 300 mg/kg orally by intragastric tube 30 min prior to an electric shock of 150 mA current for 0.2 s. Phenytoin sodium (25 mg/kg, oral) was used as the standard drug. The percentage reduction of tonic extensor phase by the compounds is presented in Table 1.

Cardiac Activity[14] Isolated frog heart was mounted using frog ringer locke solution. The effect of the compounds on the rate and force of contraction was observed from 1 to 100 μg. The effect of the compounds at 20 μg concentration when administrated simultaneously with adrenaline (100, 200, 400, 800 μg) was also studied (Table 2).

RESULTS AND DISCUSSION

All the synthesized compounds exhibited significant anticonvulsant activity except **4**, **7** and **9**. 2-(3′-Diethylamino-2′-hydroxy-propylamino)pyridine **3** was found to exhibit the highest anticonvulsant activity. None of the synthesized compounds influenced the cardiac rate but 2-(3′-dimethylamino-2′-hydroxypropylamino)pyridine **2**, 2-[3′-(4″-nitro-phenylamino)-2′-hydroxypropylamino]pyridine **6** and 2-(3′-piperi-

Table 1. Anticonvulsant Activity of the Compounds

Compound	Dose (mg/kg)	% Reduction of tonic extensor phase
1	150	42.65**
	300	70.58**
2	150	9.72*
	300	22.62**
3	150	61.29**
	300	92.17**
5	150	32.51**
	300	72.35**
6	150	36.59**
	300	72.61**
8	150	41.25**
	300	69.17**
Phenytoin	25	93.15**

Significance levels: * $p<0.01$, ** $p<0.001$ compared to control.

Table 2. Cardiac activity of the Compounds

Compound	Concentration	Effect on Systole
2	1 μg to 100 μg of **2**	Negative ionotropic
	20 μg of **2**+100 μg of adrenaline	Normal
	20 μg of **2**+200 μg of adrenaline	Normal
	20 μg of **2**+400 μg of adrenaline	Normal
	20 μg of **2**+800 μg of adrenaline	Normal
6	1 μg to 100 μg of **6**	Negative ionotropic
	20 μg of **6**+100 μg of adrenaline	Normal
	20 μg of **6**+200 μg of adrenaline	Normal
	20 μg of **6**+400 μg of adrenaline	Normal
	20 μg of **6**+800 μg of adrenaline	Normal
8	1 μg to 100 μg of **8**	Normal
	20 μg of **8**+100 μg of adrenaline	Normal
	20 μg of **8**+200 μg of adrenaline	Normal
	20 μg of **8**+400 μg of adrenaline	Normal
	20 μg of **8**+800 μg of adrenaline	Normal

dino-2′-hydroxypropylamino)pyridine **8** were found to exhibit β-adrenergic blocking activity. 2-(3′-Dimethylamino-2′-hydroxypropylamino)pyridine **2**, 2-[3′-(4″-nitro-phenylamino)-2′-hydroxypropylamino]pyridine **6** exhibited negative ionotropic activity when administered alone whereas 2-(3′-piperidino-2′-hydroxypropylamino)pyridine **8** was only found to antagonize the positive ionotropic effect of adrenaline. The cardiac activity exhibited by these compounds may be correlated to the presence of the pharmacophore similar to the chemical functionality present in β-adrenergic blocking agents (Fig. 2).

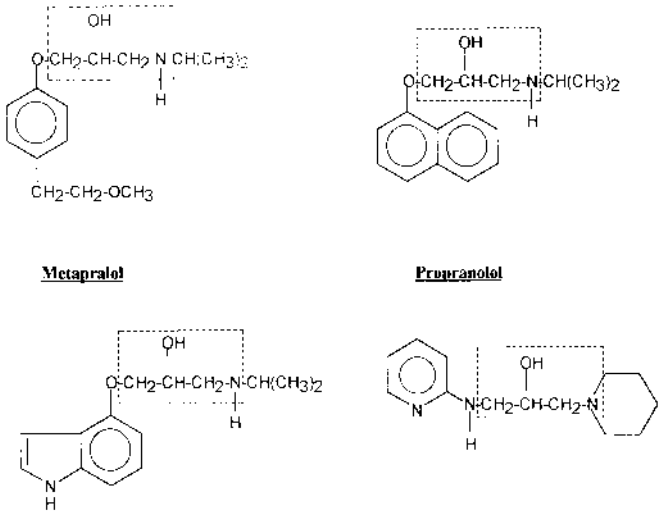

Fig. 2. Depiction of Presence of Pharmacophore in **8** Similar to Sympatholytic Drugs

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