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SYNTESIS AND ATICONVULSANT ACTIVITY OF MANNICH BASES AND UNSATURATED AMIDES : ROLE OF HYDROGEN BONDING

S. N. PANDEYA*, U. K. SINGH[a], J. P. STABLE[b] and A. PANDEY[c]

Department of Pharmacy, Saroj Institute of Technology and Management,
LUCKNOW – 226002 (U. P.) INDIA
[a]KNMIPER, Modinagar, GHAZIABAD (U. P.) INDIA
[b]NIH, BETHESDA, USA
[c]Applied Chemistry, STTM, LUCKNOW – 226002 (U. P.) INDIA

ABSTRACT

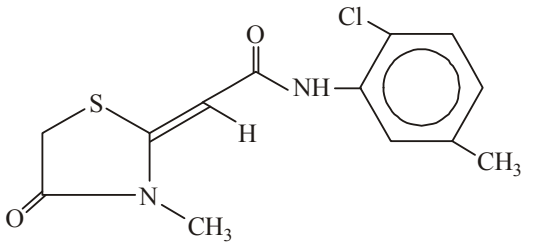
Some Mannich bases of camphor and menthone have been prepared. p-chloroacrylamide derivatives have also been synthesized. The compounds have been screened for their anticonvulsant activity in MES and ScDTZ tests. Structures possessing H-bonding sites were found to be active.

Key words : Mannich bases, Anticonvulsant activity, H-bonding

INTRODUCTION

Epilepsies are characterized by recurrent seizures, which can cause motor, sensory, cognitive, psychic or autonomic disturbances. Estimaes suggest that epilepsy affects between 0.5 and 2% of the world's population[1]. For the available anticonvulsant agents, a surprising bulk of efficacy for many seizures types and for tolerance development leads to polytherapy and / or increased dosage regimens, often with the emergence of undesirable side effects or toxicity.[2] Improved acticonvulsants are clearly required and, with poor prospects for non-pharmacologic therapeutics advances, the development of new drugs offers the most reasonable hope for patients with uncontrolled seizures.[3] Recently, Mannich bases[4] and an unsaturated amide, ralitoline (A)[3] have shown anticonvulsant activities.

* Author for correspondence



(A)

These observations prompted us to prepare a series of Mannich bases and unsaturated amides. The selection of various groups was based on the anticonvulsant action of these fragments, like isatin[5], p-chlorophenyl[6] and p-nitophenyl[7]. In this paper, we report details of synthesis and evaluation of the anticonvulsant and toxicological properties of these compounds.

EXPERIMENTAL

Melting points were determined on a Thomos Hoover apparatus and are uncorrected. IR spectra were recorded on JASCO IR Report 100 spectrometer in KBr. ^{1}H NMR spectra were recorded on a JEOL Fx 90Q Fourier Transform NMR employing TMS as the internal standard. Elemental analysis was performed on Perkin-Elmer Model 240C analyzer. The homogeneity of the compounds was monitored by thin layer chromatography (TLC) on Silicon-G (Merck) coated glass plates, visualized by iodine vapour.

Synthesis of Mannich bases (1-4) : General method

Camphor and menthone (0.25 mole) were condensed with para formaldehyde (0.33 mole) and various secondary amines (0.326 mole). The reaction mixture was refluxed in 40 mL ethanol (95%) with concentrated hydrochloric acid (0.5 mL) for 2 hrs. the contents were cooled and left overnight. The solid was separated and washed with acetone (10 mL) and dried. Physical properties of the products are described in Table 1.

Synthesis of β-(p-chlorophenyl)-α-(p-nitrophenyl) acrylamide (5-8)

Preparation of acrylic acid derivative (5-8)

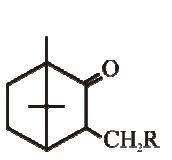
A mixture of p-nitrophenyl acetic acid (20 m mol.), p-chlorobenzaldehyde (20 m mol.) and triethylamine (5 mL) in acetic anhydride (50 mL) was refluxed at 120^{o}C for 12 hours, poured into hot saturated sodium carbonate solution (500 mL) and left

overnight. The mixture was extracted with ether (5 x 200 mL), and the ether extracts were discarded. The aqueous solution was acidified with dilute HCl, and the precipitated product was filtered and dried. Product was purified with column chromatography.

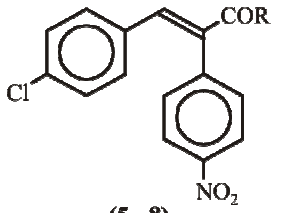
Preparation of acid chloride derivative

A mixture of carboxylic acid (5 m mol) and thionyl chloride (10mL in benzene (100 mL) was refluxed for six hrs. The excess thionyl chloride and benzene were removed at reduced pressure, and residue was kept under vaccum for 30 minutes to obtain the derived product.

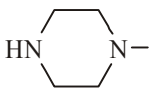
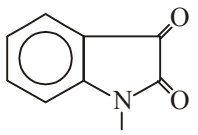
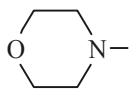
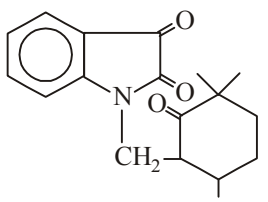
Table 1 : Physical properties of Mannich bases and unsaturated amides



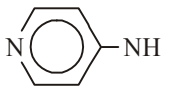
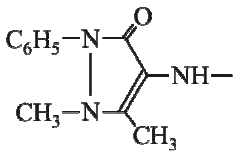
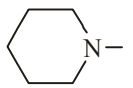
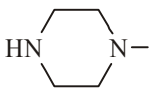
(1 - 3)



(5 - 8)

Compd.	R	Yield (%)	m.p. (°C)	R_{f*}	Mol. formula
1.		65	134	0.60	$C_{15}H_{26}N_2O$
2.		60	80	0.56	$C_{19}H_{21}NO_3$
3.		65	138	0.26	$C_{15}H_{25}NO_2$
4.		55	72	0.78	$C_{18}H_{21}NO_3$

Cont…

Compd.	R	Yield (%)	m.p. (°C)	R_{f*}	Mol. formula
5.		52	155	0.53	$C_{20}H_{14}ClN_3O_3$
6.		56	115	0.435	$C_{26}H_{21}ClN_4O_4$
7.		55	132	0.407	$C_{20}H_{19}ClN_2O_3$
8.		58	162	0.585	$C_{19}H_{18}ClN_3O_3$

*Solvent system $CHCl_3$: CH_3OH (9 : 1)

**Elemental analyses (CHN) were undertaken for all compounds and were within ± 0.4% of calculated values.

Preparation of compound (5)

A solution of p-amino pyridine (95 m mol.) in THF (50 mL) was added to a solution of the acid chlorides (5 m mol.) in THF (100 mL). The mixture was stirred for 3 hours. Solvents were removed at reduced pressure and the residure was poured onto ice (200 mg). The product was extracted with ether (4 x 100 mL, washed with water and dried. Evaporation of ether gave crude product. Product was purified by recrystallization from EtOAc-hexane. Physical properties of the compounds are described in Table 1.

Spectra data

Compound 1

FTIR (KBr) cm^{-1} : 3440 (-NH), 2965 (>CH_2), 2873 (-CH_3), 1710 (C = O), 1372 and 1390 (>C-NH_2)

^{1}H NMR ($CDCl_3$)δ : δ 0.93 (3H, s), 0.88 (3H, s), 0.83 (3H, S), 1.43 (CH, bt), 1.5 (CH, m), 2.5 (CH_2, m), 2.07 (CH_2, m) 3.0 (CH_2-N, s), 3.45 (8 H, (4 x CH_2), m) and 4.5 (NH, D_2O exchangeable).

Compound 2

FTIR (KBr) cm^{-1} : 2965 (>CH_2), 2873 (-CH_3), 1714 (>C = O), 1710 (>C=O), 1700 (-N-C=O, 1610 (aryl) 1374 and 1391 (>C-(CH_3)$_2$)

^{1}H NMR ($CDCl_3$) δ : δ 0.93 (3H, s), 0.88 (3H, s), 0.83 (3H, S), 1.43 (CH, bt), 1.5 (CH, m), 2.5 (CH_2, m), 2.07 (CH_2, m) 3.01 (CH_2-N, s) and 7.45 (4 H, m).

Compound 3

FTIR (KBr) cm^{-1} : 2960 (>CH_2), 2872 (-CH_3), 1716 (>C = O), 1374 and 1390 (>C-(CH_3)$_2$)

^{1}H NMR ($CDCl_3$) δ : δ 0.93 (3H, s), 0.88 (3H, s), 0.83 (3H, S), 1.42 (CH, bt), 1.50 (CH, m), 2.5 (CH_2, m), 2.06 (CH_2, m) 2.8 (4H, 2 x CH_2, m), 2.95 (4 H, (2 x CH_2), m), 3.02 (>NCH_2, s).

Compound 4

FTIR (KBr) cm^{-1} : 2964 (>CH_2), 2870 (-CH_3), 1714 (>C = O), 1710 (>C=O) 1705 (>C=O), (aryl), 1370 and 1385 (>C-(CH_3)$_2$).

^{1}H NMR ($CDCl_3$) δ : δ 0.96 (3H, -CH_3 s), 1.01 (6H, 2 x CH_3, s), 1.68 (4H, 2 x CH_2 m), 1.7 (CH, bt), 3.00 (>NCH_2, s) and 7.5-7.8 (4H, m).

. Compound 5

FTIR (KBr) cm^{-1} : 3446 (N-H), 3057 and 856 (C-H), 1688 (C = O), 1643 (C=N-C), 1600 (C = C of Ar), 1519 and 1342 (C-NO_2), 748 (Ar-H) and 698 (C-Cl).

^{1}H NMR ($CDCl_3$) δ : 8.47 (2H, d). 8.26 (2H, d), 7.70 (1H, d), 7.50-7.25 (6H, s, 6.91 (2H, d) and 5.78 (1H, 6s).

Compound 6

FTIR (KBr) cm^{-1} : 3421 (N-H), 3029 and 856 (C-H), 2915 and 1473 (CH_3), 1760, 1713 and 1675 (C=O), 1601 (C = C of Ar), 1519 and 1342 (C-NO_2), 750 and 704 (Ar-H), 681 (C-Cl).

^{1}H NMR ($CDCl_3$) δ : 8.27 (2H, d). 7.78 (1H, s),7.61 (2H, d), 7.50-7.25 (8H, m,

7.15 (1H, t), 5.65 (1H, s), 2.5 (3H, s) and 1.76 (3H, s).

Compound 7

FTIR (KBr) cm^{-1} : 3008 and 857 (C-H), 2950 and 1455 (CH_2), 1675 (C=O), 1632 (C=C), 1599 (C = C of Ar), 1518 and 1342 (C-NO_2), 7501 (Ar-H) and 691 (C-Cl).

^{1}H NMR ($CDCl_3$) δ : 8.27 (2H, d). 7.82 (1H, s), 7.50-7.25 (6H, m), 2.91 (4H, t) and 1.55 (6H, m).

Compound 8

FTIR (KBr) cm^{-1} : 3441 (N-H), 3041 and 857 (C-H), 2951 and 1454 (CH_2), 1666 (C=O), 1598 (C = C of Ar), 1520 and 1341 (C-NO_2), 748 (Ar-H) and 691 (C-Cl).

^{1}H NMR ($CDCl_3$) δ : 8.26 (2H, d). 7.72 (1H, s), 7.50-7.25 (5H, m), 3.03 (4H, m), 2.81 (4H, t), 1.84 (1H, s) and 2.3 (1H, -NH, D_2O exchangeable).

Pharmacological screening

The data in Table 2 were generated by the National Institute of Neurological Disorder and Stroke, NIH, Bethesda, Md., USA. Electroshock method, subcutaneous pentylenetetrazole (Sc PTZ) seizure pattern test and rotorod test were performed according to literature method[6].

Table 2 : Anticonvulsant profile of Mannich bases and unsaturated amide

Compound	Intraperitoneal injection in mice					
	MES (time in hours)		PTZ (time in hours)		Toxicity	
	0.5	4.0	0.5	4.0	0.5	4.0
1	-	-	-	300	300	
2	300	-	-	-	300	
3	-	-	-	-	300	
4	300	-	-	-	-	

Cont…

Compound	Intraperitoneal injection in mice				
	MES (time in hours)		PTZ (time in hours)		Toxicity
5	-	-	-	-	-
6	-	-	-	-	-
7	-	-	-	-	-
8	-	-	-	-	-
Phenytoin	30	30	-	-	100
Carbamazepine	30	100	100	300	100
Sod. valproate	300		300	-	

*Doses of 30, 100 and 300 mg/kg were administered. The figures in the table are the minimum dose whereby bioactivity was demonstrated. The dash (-) indicates an absence of activity at maximum dose administered (300 mg/kg).

Compounds **4,**5** and **6** were screened at 6Hz dose 100 mg/kg with current (mA) : 32 upto 4 hrs. Compound **5** was active after 0.25 hr.

RESULTS AND DISCUSSION

The compounds were screened at 30, 100 and 300 mg/kg in the MES, ScPTZ and NT screens after intraperitioneal injection into mice. Compounds **4**, **5** and **6** were also screened at 6Hz at a dose of 100 mg/kg with constant (mA) : 32 upto 4 hrs. These data are presented in Table 2. The table reveals that only compounds with isatin fragment were active in the MES tests at 300 mg/kg, while rest of the compounds were not active. Compound **1** showed activity in the ScPTZ at 300 mg/kg. Surprisingly compound **6** exhibited activity in 6Hz test. The results are in accordance with the proposed pharmacophase hypothesis by us for anticonvulsant activity. The active compounds should posses : (i) Hydrophobic sites (ii) H-bonding site (iii) Two electrodonor group and (iv) Distal aryl bonding site. In the present case, the inactive compounds lack H-bonding moiety in their structure.

CONCLUSION

The present study has confirm the importance of H-bonding in the pharmacophore

model for anticonvulsant activity.

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