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Synthesis and CNS Depressant Activity of Some New Mannich Bases of 1-(4-Dimethylamino)phenyl-4-methyl-pent-1-en-3-one

A. RAJASEKARAN* AND S. MURUGESAN
Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, Krishnankoil-626 190, India

4-Dimethylaminobenzaldehyde was condensed with 2-butanone in presence of 10% sodium hydroxide to yield 1-(4-dimethylamino)phenyl-4-methyl-pent-1-en-3-one (**1**). Six new mannich bases have been synthesized by the interaction of **1** with six different secondary amines in the presence of paraformaldehyde. All the synthesized compounds were characterized by IR and ^{1}H-NMR spectra and evaluated for CNS depressant activity.

Key Words: Synthesis, CNS-Depressant, Mannich Base, 1-(4-Dimethylamino)phenyl-4-methyl-pent-1-en-3-one.

INTRODUCTION

Mannich bases were reported to possess diverse pharmacological actions[1–9]. Among the different pharmacological activities some mannich bases are reported to possess significant CNS depressant activity. Based on these observations, it was felt worthwhile to synthesize some mannich bases of 1-(4-dimethylamino)phenyl-4-methyl-pent-1-en-3-one and to evaluate CNS depressant activity.

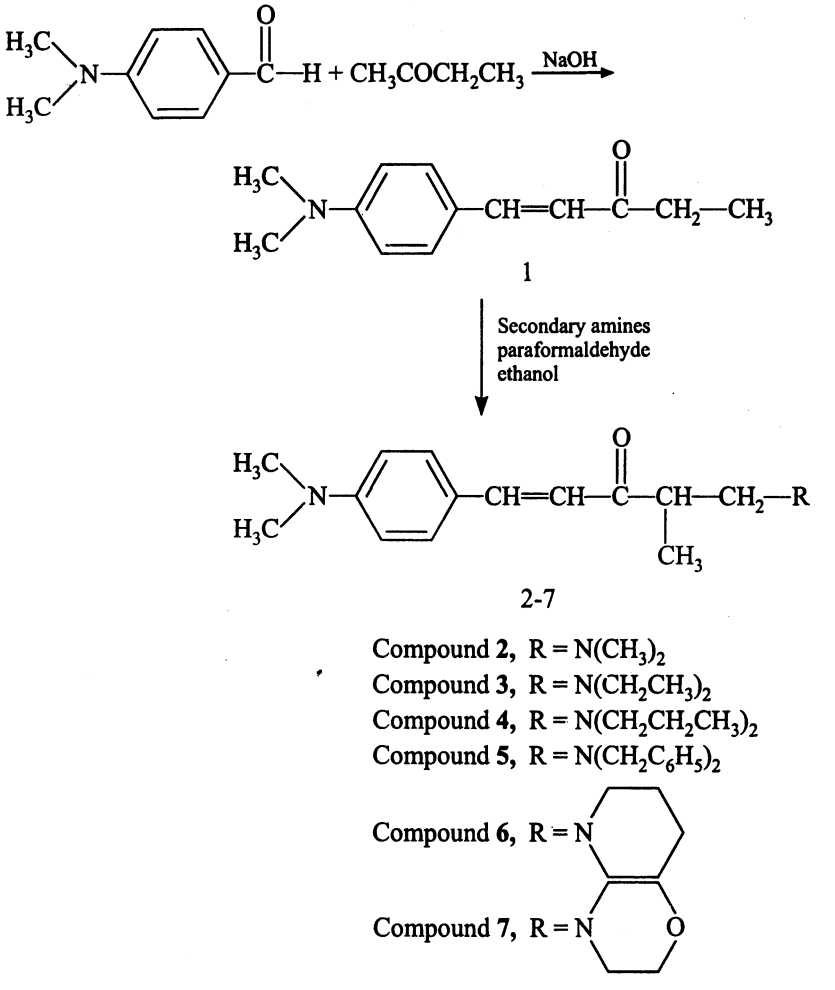
EXPERIMENTAL

Melting points were determined in open capillaries using Toshniwal melting point apparatus and are not corrected. The IR spectra were recorded on Perkin-Elmer 6000 FTIR spectrophotometer using KBr discs. ^{1}H-NMR spectra were recorded on EM-390 90 MHz NMR spectrophotometer using TMS as internal standard.

Preparation of 1-(4-dimethylamino)phenyl-4-methyl-pent-1-en-3-one

4-Dimethylaminobenzaldehyde (0.2 mole) was mixed with 2-butanone (1 mole); 10% w/v sodium hydroxide solution was added dropwise to this reaction mixture at a temperature of 30°C (**Scheme-1**). A yellow coloured product obtained was recrystallized using petroleum ether (60–80°C). Yield 68%. Pure compound **1** melted at 68–69°C. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 3 (6H, s), 6.2 (1H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz, 7.7 (4H, m). IR (KBr) cm^{-1}: 2897 ν(C—H), 1670 ν(C=O), 1605 ν(C=C), 1230 ν(C—N), 813 (*p*-dis-

ubstitutedbenzene). Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.78; H, 8.43; N, 6.91. Found: C, 76.91; H, 8.37; N, 6.87.



1

2-7

Compound **2**, R = $N(CH_3)_2$
Compound **3**, R = $N(CH_2CH_3)_2$
Compound **4**, R = $N(CH_2CH_2CH_3)_2$
Compound **5**, R = $N(CH_2C_6H_5)_2$

Compound **6**, R = N

Compound **7**, R = N O

Scheme-1

Preparation of Mannich bases (2–7)

Compound **1** in ethanol (25 mL) was refluxed with an equimolar proportion of six different secondary amines, *viz.*, dimethylamine, diethylamine, dipropylamine, dibenzylamine, piperidine and morpholine in the presence of paraformaldehyde for 2 h **(Scheme-1).** The contents were cooled and filtered. The crude compound was recrystallised from petroleum ether (60–80°C). Yield 74%. Pure compound 2 melted at 69–70°C. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 3 (12H, s), 5.8 (1H, d, J = 2 Hz), 6.2 (1H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.7 (4H, m). IR (KBr) cm^{-1}: 2901 ν(C—H), 1661 ν(C=O), 1593 ν(C=C), 1165 ν(C—N), Anal: Calcd. for $C_{16}H_{24}N_2O$: C, 73.77; H, 9.30; N, 10.80. Found: C, 73.72; H, 8.98; N, 10.84.

Compound **3** melted at 59–60°C. Yield 35%. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 3 (12H, s), 3.6 (4H, m), 5.8 (1H, d, J = 2 Hz), 6.2 (1 H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.7 (4H, m). IR (KBr) cm^{-1}: 2904 ν(C–H), 1661 ν(C=O), 1590 ν(C=C), 1236 and 1165 ν(C—N). Anal.: Calcd. for $C_{18}H_{28}N_2O$: C, 74.92; H, 9.73; N, 9.80. Found: C, 74.86; H, 9.12; N, 9.84.

Compound **4** melted at 64–65°C. Yield 96%; ^{1}H-NMR($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J= 2 Hz), 3 (12H, s), 3.6 (8H, m), 5.8 (1H, d, J = 2 Hz), 6.2 (1H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.7 (4H, m). IR (KBr) cm^{-1}: 1673 ν(C=O), 1614 ν(C=C), 1233 and 1167 ν(C—N). Anal.: Calcd for $C_{20}H_{32}N_2O$: C, 75.87; H, 10.19; N, 8.80. Found: C, 75.82; H, 9.98; N, 8.64.

Compound **5** melted at 52–53°C. Yield 97%. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 3 (12H, s), 3.6 (4H, s), 5.8 (1H, d, J = 2 Hz), 6.2 (1H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.3–7.7 (9H, m). IR (KBr) cm^{-1}: 2908 ν(C—H), 1661 ν(C=O), 1586 ν(C=C), 1233 ν(C—N). Anal.: Calcd. for $C_{28}H_{32}N_2O$: C, 81.49; H, 7.82; N, 6.82. Found: C, 81.92; H, 7.68; N, 6.68.

Compound **6** melted at 69–70°C. Yield 86%. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 2.8 (10H, s), 3 (6H, s), 5.8 (1H, d, J = 2 Hz), 6.2 (1H, d, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.7 (4H, m). IR (KBr) cm^{-1}: 2900 ν(C—H), 1662 ν(C=O), 1590 ν(C=C), 1230 ν(C—N). Anal.: Calcd for $C_{19}H_{28}N_2O$: C, 75.92; H, 9.40; N, 9.30. Found: C, 75.79; H, 8.68; N, 8.98.

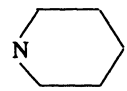
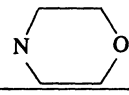
Compound **7** melted at 54–55°C. Yield 77%. ^{1}H-NMR ($CDCl_3$) δ: 1.6 (3H, t, J = 2 Hz), 1.9 (2H, q, J = 2 Hz), 3.2 (4H, q, J = 4 Hz), 3 (6H, s), 3.8 (4H, J = 4 Hz), 4.9 (8H, m), 5.8 (1H, d, J = 2 Hz), 6.2 (1H, J = 2 Hz), 6.6 (1H, d, J = 2 Hz), 7.3–7.7 (9H, m). IR (KBr) cm^{-1}: 2906 ν(C—H), 1661 ν(C=O), 1600 ν(C=C), 1231 ν(C—N). Anal.: Calcd. for $C_{18}H_{26}N_2O_2$: C, 71.46; H, 8.60; N, 8.80. Found: C, 74.12; H; 9.98; N, 8.64.

CNS Depressant Activity

The effect of synthesized mannich bases on spontaneous locomotor activity was evaluated by using actophotometer[10]. Albino rats of wistar strain weighing 120–150 g of either sex were divided into 9 groups each of six animals. The spontaneous locomotor activity of the animals were recorded by placing it individually in actophotometer for 10 min. 10% v/v Tween 80 suspension of the test compounds were administered intraperitoneally in a dose of 25 mg/kg (b.w.). The control group was given only 10% v/v Tween 80 (0.5 mL) suspension. One group was administered with phenobarbitone as standard, intraperitoneally in a dose of 45 mg/kg. After 30 min. of administration of newly synthesized compounds the spontaneous locomotor activity was recorded. Percentage change in spontaneous locomotor activity before and after administration of the compounds were calculated and recorded in Table-1.

All the synthesized mannich bases showed reduction in spontaneous locomotor activity except compounds **1, 3** and **6**. Mannich bases having the substitution of dimethylamine, dipropylamine, dibenzylamine and morpholine showed more significant reduction in spontaneous motor activity than the standard drug phenobarbitone. The neurotransmitter GABA is known to have depression action in brain[11, 12].

TABLE 1
CNS DEPRESSANT ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound	R	Locomotor activity in 10 minutes (scores)		Percentage change in activity
		Before treatment	After treatment	
Saline	–	120	120	0.00
Phenobarbitone	–	105	45	57.14
1	CH_3	120	80	33.30
2	$N(CH_3)_2$	122	49	59.83
3	$N(CH_2CH_3)_2$	381	235	38.30
4	$N(CH_2CH_2CH_3)_2$	145	52	64.13
5	$N(CH_2C_6H_5)_2$	130	50	60.00
6		105	64	39.21
7		127	45	69.56

The significant reduction in spontaneous motor activity of the synthesized mannich bases in mice may be due to the binding of the lipophilic part (4-dimethylamino benzenoid group) of the synthesized compounds with GABA receptor in brain.

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