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Synthesis and Anesthetic Activity of Some Mannich Bases of *p*-Dimethylamino Benzylidene Acetanilide

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Some Mannich bases of *p*-dimethylamino benzylidine acetanilide are synthesized. The synthesized compounds have been characterized by IR and ^{1}H NMR analysis. An attempt to determine the hydrophobic parameter (partition coefficient) is also established. All the test compounds have been screened for their local anaesthetic activity by Sollmann method.

Key Words: Acetanilide, Mannich base, Anaesthetic activity.

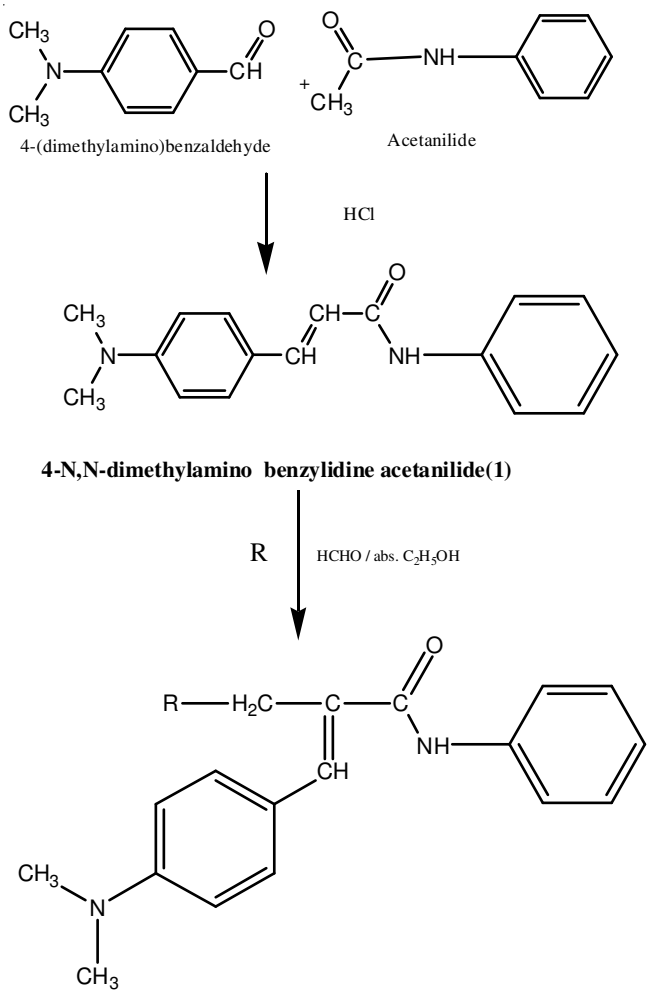
INTRODUCTION

A large number of Mannich bases were reported for various biological activities[1-5]. Among the different biological activities some Mannich bases are reported to possess potent local anaesthetic activity. For instance Mannich bases of *p*-substituted acetophenones have been reported for potent local anaesthetic action[6]. In view of above, it was worthwhile to synthesize Mannich bases from 4-N,N-dimethyl amino benzylidene acetanilide. Local anaesthetic activity and partition coefficient were also established for the synthesized compounds.

In present study, *p*-dimethyl amino benzaldehyde is treated with acetanilide in the presence of dilute hydrochloric acid to form 4-N,N-dimethyl amino benzylidene acetanilide. The above said compound is treated with various secondary amines in the presence of ethanol and formaldehyde in acid medium to convert the corresponding Mannich bases (**2a-h**, **Scheme-I**).

EXPERIMENTAL

Melting points were determined in open capillary tubes and were found uncorrected. IR spectra were recorded on FT-IR spectrometer (Perkin Elmer) using KBr disc method. ^{1}H NMR spectra were recorded on AMX-400 liquid state NMR spectrometer in $CDCl_3$ using TMS as an internal standard. The λ_{max} of the synthesized compounds for determination of log P was recorded on UV-visible spectrophotometer (Systronics model SL-150, 200-400 nm). The compounds were analyzed for elemental analysis and the values were found to be ± 0.9 % of calculated values.



Compounds - 2 a,b,c,d,e,f,g,h

Scheme-I

Synthesis of 4-N,N-dimethyl amino benzylidene acetanilide (1): 4-N,N-dimethyl amino benzaldehyde (0.1 mol) and acetanilide (0.1 mol) in 20 mL of ethyl alcohol was shaken to get a clear solution. 2 mL of dilute hydrochloric acid was added to the solution and heated for 15 min. The heating mixture was poured into the beaker containing ice water and the crystals were collected.

General method of synthesis of Mannich bases (2a-h): To the solution of compound **1** (1 mol) in 20 mL of ethanol, 0.5 mol of respective secondary amines and 0.25 mol formaldehyde were added and refluxed for 2 h. On cooling, the product formed was filtered, dried in vacuum and recrystallized. Physical data of the compounds are recorded in Table-1.

TABLE-1
PHYSICAL PARAMETERS OF SYNTHESIZED COMPOUNDS

Compd.	R	m.f.	m.w. (g/m)	m.p. (ºC)	Yield (%)	log P
2a	Diethanolamine	$C_{22}H_{29}N_3O_3$	383.84	59	62	2.12
2b	Dimethylamine	$C_{20}H_{25}N_3O$	323.43	56	65	3.27
2c	Diethylamine	$C_{22}H_{29}N_3O$	351.49	65	67	3.95
2d	Dipropylamine	$C_{24}H_{33}N_3O$	379.54	71	63	4.92
2e	Diisopropylamine	$C_{24}H_{33}N_3O$	379.54	68	61	4.58
2f	Diphenylamine	$C_{30}H_{29}N_3O$	447.54	82	64	6.76
2g	Piperidine	$C_{23}H_{29}N_3O$	363.50	63	58	4.40
2h	Piperazine	$C_{22}H_{28}N_4O$	364.48	75	59	2.65

Local anaesthetic activity: The synthesized compounds were evaluated for local anaesthetics by following the method of Sollmann[7]. Frog (*Rana temporia*) of either sex was used. 0.1 N HCl is used as stimuli into which the feet of the frog were immersed every minute and the response at the intervals of 1 min was noted. The procedure is also carried out in another frog by using xylocaine 2 % (w/v) as standard drug.

Partition coefficient: Hydrophilicity is generally parameterized by partition coefficient. It was determined by using the classical shake method[8] using chloroform and phosphate buffer (pH 7.4).

Partition coefficient is determined as the ratio of the amount of the drug present in the organic phase to that present in the aqueous phase. It provides an empirical handle in screening of some biological properties and contributing factors for the rate and extent of drug absorption.

$$\text{Partition coefficient (P)} = C_{org}/C_{aqu} = B_E/B_E - A_E$$

where, B_E = absorbance before extraction, A_E = absorbance after extraction.

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by ^{1}H NMR, IR and elemental analysis (Table-2). Analysis indicated by the symbols of the elements are within ± 0.9 of the theoretical values. The compounds were evaluated for their local anaesthetic activity. All the compounds show comparable activity with that of standard (xylocaine 2 %). Among them one compound **2f** carrying phenyl group showed maximum log P value. High partition coefficient of synthesized compounds in the present study as compared to the parent compound indicates an increase in lipophilicity of synthesized compounds.

TABLE-2
SPECTRAL AND ELEMENTAL ANALYSIS OF
SYNTHESIZED COMPOUNDS

Compd.	IR (KBr, ν_{max}, cm^{-1})	^1H NMR ($CDCl_3$) δ: ppm	Calcd. (Found) (%)	
			C	N
2a	729 (Ar-H), 1450 (C-N), 1350 (N-H)	6.54-7.64 (m, Ar H), 8.2 (s, NH), 3.68 (t, CH_2), 2.3 (s, OH)	68.90 (68.72)	10.96 (10.26)
2b	1465 (C-N), 1339 (N-H), 873 (Ar-H)	6.54-7.64 (m, Ar H), 8.0 (s, NH), 3.03 (t, CH_2), 2.27 (s, CH_3)	74.27 (73.37)	12.99 (13.29)
2c	1483 (C-N), 1392 (N-H), 749 (Ar-H)	6.54-7.64 (m, Ar H), 8.5 (s, NH), 3.15 (t, CH_2), 2.40, 1.02 (m, m, ethyl)	75.18 (76.28)	11.96 (12.16)
2d	1481C-N), 1360 (N-H), 857 (Ar-H)	6.54-7.64 (m, Ar H), 8.3 (s, NH), 3.68 (t, CH_2), 2.3 (s, OH)	75.95 (75.72)	11.07 (10.85)
2e	1472 (C-N), 13702 (N-H), 758 (Ar-H)	6.54-7.64 (m, Ar H), 8.2 (s, NH), 2.36, 1.43, 0.96 (m, propyl).	75.95 (75.65)	11.07 (11.57)
2f	1478 (C-N), 1371 (N-H), 759 (Ar-H)	6.54-7.64 (m, Ar H), 8.2 (s, NH), 2.97 (m, CH_3), 1.03 (d, CH)	80.30 (81.36)	9.39 (10.09)
2g	1436 (C-N), 1322 (N-H), 833 (Ar-H)	6.54-7.64 (m, ArH), 8.0 (s, NH), 1.68 (t, CH_2, piperidine)	76.10 (75.18)	11.56 (10.86)
2h	1446 (C-N), 1369 (N-H), 739 (Ar-H)	6.54-7.64 (m, Ar H), 8.4 (s, NH), 2.68, 2.47 (t, CH_2)	72.5 (71.42)	15.37 (14.82)

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