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SYNTHESIS OF SOME MANNICH BASE CYCLOHEXANONE DERIVATIVES AND THEIR PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

In the present investigation an attempt is carried out for the synthesis of Mannich base cyclohexanone and to carry out their pharmacological activity. The Micro-wave irradiation method has been employed for their synthesis and a comparative study is also carried out with conventional method. A number of Mono as well as Double Mannich base cyclohexanones have been synthesized, purified and characterized with the help of their analytical and spectral (IR, NMR & Mass) data. The required 3-aryl-2, 4-diacetyl- 5- hydroxy- 5-methylcyclohexanone has been synthesized from appropriate aldehyde and acetonyl acetone. By the use of primary and secondary amines and formaldehyde the Mono and Double Mannich base cyclohexanones were prepared by both MWI & conventional methods. The synthesized compounds were screened for their analgesic activity by standard methods. The compound shows analgesic activity in comparisation with the standard.

Key words: Mannich base, Cyclohexanone, Analgesic activity.

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INTRODUCTION

Cyclohexanone is an aliphatic cyclic Ketone. The naming starts from the carbon on which Ketonic group is attached [1,2]. The condensation of aliphatic or aromatic aldehydes with β-diketo esters or β-diketones in molar ratio of one to two and in the presence of a basic catalyst, leads to bis-compounds. Various aldehydes, β-ketones and β-diketones have been used [3-6]. A survey of literature reveals that cyclohexanone moiety constitutes an important structural feature in several anti-inflammatory, analgesic, local anesthetic and anti-histaminic activity. In this study towards the synthesis of 8-aryl-1, 7-diacetyl-6-hydroxy-6-methyl-3-(substituted) azabicycol [3.3.1] nonan-9-ones the application of Double Mannich reactions to 3-aryl-2, 4-diacetyl-5-hydroxy-5-methylcyclohexanone has been investigated. Thus, treatment of 3-aryl-2,4-diacetyl-5-hydroxy-5-methyl cyclohexanone with formaldehyde (2 mol.), potassium carbonate & primary amine in a molar ration (1:2:1) afforted 8-aryl-1,7-diacetyl-6-hydroxy-6-methyl-3-substituted-azobicyclo nonan-9-one . The treatment of 3-aryl-2,4-diacetyl-5-hydroxy-5-methylcyclohexanone with secondary amines and formaldehyde result in 3-aryl-2,4-diacetyl-2[substituted amino methyl]-5-hydroxy-5-methylcyclohexanone in the presence of potassium carbonate and reflux.

MATERIAL AND METHODS

All chemicals were obtained from Center Drug House (CDH), New Delhi. All chemicals and solvents used were of analytical grade.

EXPERIMENTAL

All the melting all the melting points were determined in open capillary and are uncorrected. The purity is checked by TLC. IR spectras were recorded in KBr on shimadzu F.T. – IR 8300spectrophotometer. Analytical data were also confirmed from its 1H–NMR Spectra.

I. Acetonyl acetone.
II. Aromatic aldehydes.
III. 3-aryl-2, 4-diacetyl-5-hydroxy-5-methyl cyclohexanone.
IV.8-aryl-1, 7-diacetyl-6-hydroxy-6-methyl-3-substituted-azobicyclo [3.3.1.] nonan-9-one.
V .3-aryl-2, 4-diacetyl-2-[substituted amino methyl]-5-hydroxy-5-methyl cyclohexanone.
X = H, Cl, OCH_3, NO_2 and CH_3

CONDENSATION REACTION OF ACETONYL ACETONE WITH DIFFERENT AROMATIC ALDYHYDES

Four different aromatic aldehydes, viz., benzaldehyde (II; X=H); 4-methoxybenzaldehyde (II; X=OCH_3), 4-chlorobenzaldehyde (II; X=-Cl) and 4-nitrobenzaldehyde (II; X=NO_2) have been condensed with acetonyl acetone (I) in 1:2 ratio by stirring in ethanol in

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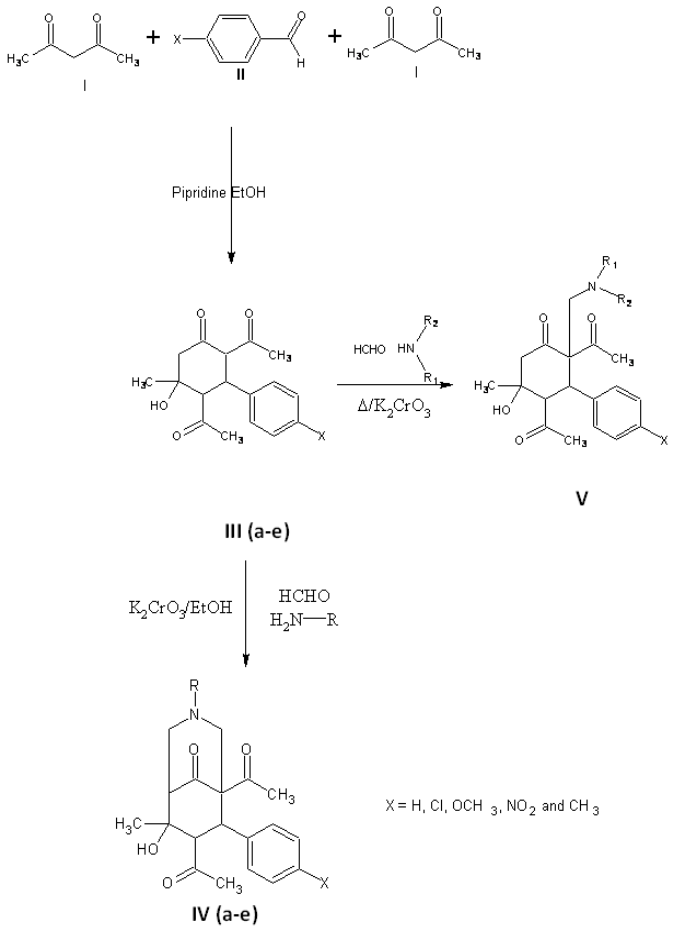
the presence of piperidine as a base catalyst, for 3 hr. The product obtained in each case has been purified by crystallization from ethanol to get a colourless, crystalline solid.

Scheme: 1



A mixture of an aldehyde (II) and acetonyl acetone (I) in ethanol and a catalytic amount of piperidine has been irradiated in a microwave oven at 160 W for 2-3 min. The product has been recrystallized from alcohol and found to be quite identical in all respects with that obtained by the conventional method. Excellent yields and reduced reaction times have been recorded in MW-irradiation method. Each of these products has been characterized as the respective 3-aryl-2, 4-diacetyl-5-hydroxy-5-methylcyclohexanones (III), on the basis of their analytical and spectral data.

For instance, 4-methoxybenzaldehyde (II; X=OCH_3) has been condensed with acetonyl acetone by conventional method and also by microwave irradiation in ethanol and in the presence of piperidine to get the same product (TLC), by both the methods. It has been purified by recrystallizaiton from ethanol to obtain a colourless crystalline solid.

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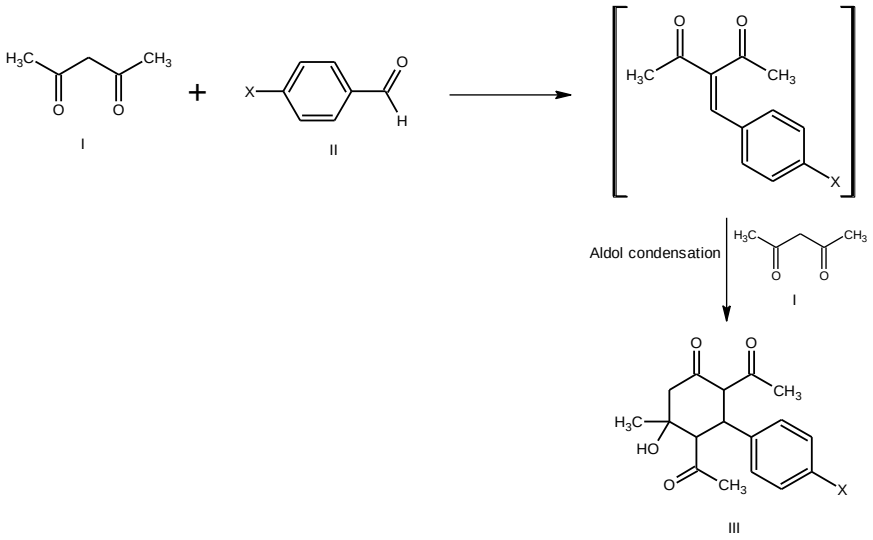

Synthesis of 2, 4-diacetyl-5-hydroxy-5methyl-3-phenyl cyclohexanone:

For instance, 4-benzylaldehyde (II; X=H) has been condensed with acetonyl acetone by conventional method and also by microwave irradiation in ethanol and in the presence of piperidine to get the same product (TLC), by both the methods. It has been purified by recrystallizaiton from ethanol to obtain a colourless crystalline solid.

Synthesis of 2,4-diacetyl-3-(4-chloro phenyl)-5-hydroxy-5-methylcyclohexanone

For instance, 4-chloro benzyl aldehyde (II; X=Cl) has been condensed with acetonyl acetone by conventional method and also by microwave irradiation in ethanol and in the presence of piperidine to get the same product (TLC), by both the methods. It has been purified by recrystallizaiton from ethanol to obtain a colourless crystalline solid.

Similarly 4-nitro benzyaldehyde has been condensed with acetonyl acetone by conventional method and also by microwave irradiation in ethanol and in the presence of piperidine to get the same product (TLC), by both the methods. It has been purified by recrystallizaiton from ethanol to obtain a colourless crystalline solid.

Synthesis of 2,4-diacetyl-3-(4-methyl phenyl)-5-hydroxy-5-methylcyclohexanone.

4-methyl benzaldhyde has been condensed with acetonyl acetone by conventional method and also by microwave irradiation in ethanol and in the presence of piperidine to get the same product (TLC), by both methods. It has been purified by recrystallization from ethanol to obtain a colourless crystalline sold.

Synthesis of 8-aryl-1,7-diactyl-6-hydroxy-6-methyl-3-substituted azobicyclo[3.3.1]nonan-9-one (V; X=H, Cl, OCH_3, NO_2; R_1= H, R_2 = primary amine)

Conventional method-general procedure

An equimolar mixture of 3-Aryl-2, 4-diacetyl-5-hydroxy-5-methyl cyclohexanones. (III; 0.01 mole) appropriate primary amine (IV; 0.01 mole) formaldehyde (0.01 mole) and potassium carbonate (1 g) was taken in to a round bottom flask dissolved in ethanol (20 ml) and the mixture was heated under reflux for 3 hr on water-bath. The resultant reaction mixture was cooled and poured on to the crushed ice with stirring. It was allowed to settle and the product was filtered, washed with small portions of cold water and dried. The crude product was purified by column chromatography using neutral alumina as an adsorbent and a suitable solvent system for elution

Micro-wave method-general procedure:

An equimolar (III; 0.03 moles) mixture of 3-Aryl-2, 4-diacetyl-5-hydroxy-5-methylcyclohexanones and an appropriate primary amine (IV), was taken into a beaker dissolved in dimethylformamide (20ml). Formaldehyde (0.03 mole) solution was added while shaking and potassium carbonate (1.0g) was placed to the reaction mixture. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the micro-wave irradiation at 40% power level (320 W) 2-4 min in the domestic LG little chef micro-wave oven at a pulse rate of 1 min, each. It was cooled and triturated with ice-cold water to get a product. It was filtered, washed with portions of cold water and dried. The crude product was purified by column chromatography using alumina (neutral) as an adsorbent and a suitable solvent system for elution.

Synthesis of 3-aryl-2,4-diacetyl-2-[substituted amino methyl]-5-hydroxy-5-methyl cyclohexanone (V X=H, Cl, OCH_3, NO_2; R_1= H, R_2 = primary amine) [7,8]

Conventional method-general procedure

An equimolar mixture of 3-Aryl-2, 4-diacetyl-5-hydroxy-5-methylcyclohexanones (III; 0.01 mole) appropriate secondary amine (IV; 0.01 mole) formaldehyde (0.01 mole) and potassium carbonate (1 g) was taken in to a round bottom flask dissolved in ethanol (20 ml) and the mixture was heated under reflux for 3 hr on water-bath. The resultant reaction mixture was cooled and poured on to the crushed ice with stirring. It was allowed to settle and the product was filtered, washed with small portions of cold water and dried. The crude product was purified by column chromatography using neutral alumina as an adsorbent and suitable solvent system for elution.

Micro-wave method-general procedure

An equimolar (0.03 mole) mixture of 3-aryl-2,4-diacetyl-5-hydroxy-5-methyl cyclohexanone and an appropriate secondary amine (IV), was taken into a beaker dissolved in dimethylformamide (20ml) formaldehyde (0.03 mole) solution was added while shaking and potassium carbonate (1.0g) was placed to the reaction mixture. A funnel was hanged in the beaker and covered with a watch glass. The reaction mixture was subjected to the micro-wave

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irradiation at 40% power level (320 W) 2-4 min in the domestic LG little chef micro-wave oven at a pulse rate of 1 min, each. It was cooled and triturated with ice-cold water to get a product. It was filtered, washed with portions of cold water and dried. The crude product was purified by column chromatography using alumina (neutral) as an adsorbent and a suitable solvent system for elution.

REACTIONS OF 3-ARYL-2,4-DIACETYL-5-HYDROXY-5-METHYL CYCLOHEXANONES WITH FARMALDEHYDE AND SECONDARY AMINES. THE MANNICH CONDENSATION OF 3-ARYL-2,4-DIACETYL-5-HYDROXY-5-METHYLCYCLOHEXANONES [9-11].

By conventional and microwave irradiation methods

In view of the presence of an active methine (C-H) group at C_2 and an active methylene ($-CH_2$) group at C_6 position either sides of the carbonyl carbon in each of the 2,3,4,5 substituted cyclohexanones, and attempt has been made to conduct the Mannich reaction and characterize the products. This approach is also prompted by the significant biological a pharmacological applications of various Mannich bases. In mono Mannich condensation, it can be presumed that the C-H at 2-position will be preferably involved in the condensation as it is flanked by two acetyl groups, thereby its more labile nature.

For this purpose, each of the four different 2, 4-diacetylcyclohexanones (III) has been subjected to a reaction with formaldehyde and an appropriate primary or secondary amine (IV) in an equimolar ratio. As many as seven primary amines, viz., n-propylamine n-butyl amine, aniline, benzyl amine, 4-methoxyaniline, 4-methylaniline and 3-nitroaniline and an equal number of secondary amines, viz, dimethyalmine, morpholine, piperidine, piperazine, 4-ethylpiperazine, N-methyl aniline and diphenylamine have been employed in the condensation.

In the conventional method an alcoholic solution of equimolar mixture of cyclohexanone (III) formaldehyde and primary/secondary amine (IV) has been stirred in the presence of potassium carbonate and heated for 3 hr on a water-bath. Alternatively, the reaction has been also carried out by the micro-wave irradiation method using dimethylformamide as the solvent in place of alcohol since the former happens to be a better solvent for microwave reactions. The reaction mixture has been subjected to irradiation at 320 W for 3-5 min while monitoring by TLC.

The product obtained from each of such a condensation reactions by either method has been purified by column chromatography with appropriate solvent systems and has been characterized as the respective Mannich base on the basis of its analytical and spectral data.

For instance, 3,4-diacetyl-5-hydroxy-5-methyl-3-(4-methoxy-phenyl) cyclohexanone ($X=OCH_3$) has been condensed with formaldehyde and aniline (IV;R_1=H; $R_2=C_6H_5$) by heating an alcoholic solution in potassium carbonate, on a water both for 3 hr in conventional method or by irradiating in a microwave oven at 320 W for 4 min in 4 pulses with an interval of 30 sec. in

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dimethylformamide. The product obtained has been purified by recrystallization from alcohol to yield a colourless crystalline solid. Based on its analytical spectral characteristics, the compound obtained has been characterized as the 3-methoxyphenyl-2,4-diacetyl-2-(substituted amino methyl)-5-hydroxy-5-methyl cyclohexanone .

Table No 1: Elemental analysis of Mannich base Cyclohexanone derivatives.

Sl. No.	Compound	X	m.p.	Yield in %		Mol. Formula	Elemental analysis			Log p
				A	B		C	H	O	
1.	III (a)	OCH_3	188°C	80	95	$C_{18}H_{22}O_5$	67.91	6.97	25.13	1.97+/-0.58
2.	III (b)	H	170°C	70	90	$C_{17}H_{20}O_4$	70.81	6.99	22.20	2.06+/-0.57
3.	III (c)	Cl	168°C	85	90	$C_{17}H_{19}O_4Cl$	63.26	5.93	19.83	2.65+/-0.58
4.	III (d)	NO_2	160°C	65	70	$C_{17}H_{19}O_6N$	25.35	2.38	7.95	1.79+/-0.58
5.	III (e)	CH_3	174°C	72	83	$C_{18}H_{22}O_4$	71.50	7.33	21.17	2.52+/-0.57

A = Conventional

B = Micro wave method.

Table: 2.Physical Data of Double Mannich cyclohexanone

Sl. No.	Compound	X	R	m.p.	Yield in %		Mol. Formula	Elemental analysis				
					A	B		C	H	O	N	Cl
1.	IV (a)	OCH_3	C_3H_7	98°C	75	85	$C_{23}H_{32}O_5N$	68.83	8.01	19.87	3.48	---
2.	IV (a-1)	OCH_3	C_6H_7	120°C	70	80	$C_{26}H_{32}O_5N_2$	69.01	7.13	17.68	6.19	---
3.	IV (b)	H	C_3H_7	110°C	85	90	$C_{22}H_{31}O_4N$	74.08	7.41	15.18	3.32	----
4.	IV (b-1)	H	C_6H_7	132°C	65	70	$C_{25}H_{30}O_4N_2$	73.68	7.17	15.70	3.44	
5.	IV (c)	Cl	C_3H_7	108°C	82	88	$C_{22}H_{29}O_4NCl$	64.93	7.18	15.33	3.44	
6.	IV (c-1)	Cl	C_6H_7	125°C	60	65	$C_{25}H_{29}O_4N_2Cl$	65.71	6.40	14.61	6.13	
7.	IV (d)	NO_2	C_3H_7	122°C	75	90	$C_{22}H_{29}O_8N_3$	57.01	6.31	27.62	9.07	
8.	IV (d-1)	NO_2	C_6H_7	141°C	65	75	$C_{25}H_{29}O_8N_4$	58.47	5.69	24.93	10.91	
9.	IV (e)	CH_3	C_3H_7	112°C	80	90	$C_{23}H_{32}O_4N$	71.47	8.35	16.56	3.62	
10.	IV (e-1)	CH_3	C_6H_7	120°C	65	70	$C_{26}H_{32}O_4N_2$	71.53	7.39	14.66	6.42	

ANALGESIC ACTIVITY

The analgesic activity was assayed by the 'Eddy's hot-plate method'. In this method, groups of 10 mice of either sex with an initial weight of 18 to 22 g were used for each dose. The hot-plate consists of a electrically heated surface. The temperature was controlled at 55 ± 1^{0}C. The animals were placed on the hot plate and the time at which either licking or jumping occurs was recorded. The latency was recorded before and after 30, 60 and 90 min following intraperitoneal administration of the standard compound Pethidinehydrochloride 30mg/kg body weight.

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Table No. 3: Spectral data of Mannich base Cyclohexanone derivatives.

Compound	IR Bands (cm-1)	Types of Vibrations	d ppm	Proton nature
III-a	3409, 2985, 2815, 1694 & 1680, 1360, 1175	O-H ,, C-H, aromatic , C-H Aliphatic , C-O methyl & Cyclic ketone , O-H (bending), Ter. C-O Str.		
III-b	3446, 2983, 2936, 1715, 1601, 1377, 1176.	O-H (Str.), C-H Str. Aromatic, C-H Str. Aliphatic, C=O, C=C aromatic, O-H bending, C-O ter. Alcohol.		
III-c	3515.7, 2980.3, 2364.6, 17366 & 1717.5, 1495, 1378.4.	O-H str, C-H str. Aromatic, C-H Str. Aliphatic, C=O, C=C aromatic, O-H bending.		
IV	3433, 3029, 2917, 1723, 1723, 1597, 1376, 1167.	O-H, C-H Aromatic, C-H Aliphatic, C=O ketone, C=O Cyclic ketone, C=C Aromatic, Ter O-H bending, C-O Str.	1.21, 1.38, 2.12, 2.28, 4.24, 4.56, 4.62, 3.68, 3.74, 7.06 – 7.48.	(t, 3H, C_7-CO-CH_3), (t, 3H, C_1-CO-CH_3), (s, 3H, C_6-CH_3), (s, 1H,OH), (=N-CH_2-Ph),, (d, 2H, at-C_2), (d, 2H, at C_4), (s, 2H, C_7, CO-CH_3), (s, 2H, C_1-CO-CH_3), (m, 10H, Ar-H).
V	3447, 3367, 3035, 2939, 1725 & 1654, 1610, 1365, 1180.	-OH Str, -NH Str, C-H arom. Str, C-H alip. Str, C=O ketone & cyclic ketone, C=C arom, Ta-O-H-bend, C-O, str.	0.72 – 1.012.08, 3.32, 3.52 – 4.01, 3.46, 4.38, 6.62 to 7.48.	(2t, 6H, C_4 & C_2-CO-CH_3), (s, 3H, C_5 – CH_3), (s, 2H, CH_2 at 6-position), (m, 6H, C_4 CO-CH_3, C_2 – CO-CH_3, C_4H & C_3H), (s, 3H Ar – O-CH_3), (s, HN – CH_2), (m, 9H, Ar-H).

Table –4 Analgesic Activity of 8-(4-substituted phenyl) -1, 7 – diacetyl-6-hydroxy-6-methyl-3-(n-propyl) aza bicyclo (3.3.1) nonane-9-one.

Sl. No.	Substituent X	Effect at different intervals				P Value			
		0 min	30 min	60min	90 min	0 min	30 min	60min	90 min
1	Control	3.66±0.57	4.00±0.00	3.65±0.56	4.00±0.00	--	--	--	--
2	Standard pethidine HCl	3.65±0.10	8.09±0.24	11.99±0.09	3.96±0.90	>0.05	<0.01	<0.01	>0.05
3	H	3.66±0.19	4.18±0.22	4.67±0.16	3.82±0.08	>0.05	>0.05	<0.01	<0.05
4	OCH_3	3.46±0.08	4.06±0.05	4.16±0.08	4.20±0.04	>0.05	>0.05	>0.05	>0.05
5	NO_2	3.45±0.30	4.08±0.04	4.00±0.00	3.98±0.08	>0.05	>0.05	>0.05	>0.05
6	Cl	3.60±0.16	4.10±0.00	3.98±0.04	3.92±0.10	>0.05	>0.05	>0.05	>0.05

RESULTS AND DISCUSSION

A series of mannich base cyclohexanone derivatives IIIa-e, IV, and V were synthesized and their structure was elucidated by elemental analysis, IR and 1H-NMR data, yields and melting points, calculated in table-1, 2 and 3.In the tail flick method, data from Table – 4

indicates an analgesic potency of the derivatives of poly-substituted cyclohexanones.It is interesting that the nitro-substituted cyclohexanones are the most potent analgesic in comparison to other types tested. The compound with 4-methoxy phenyl group has been found to be the next in order of analgesic potency. An aza bicyclononane with 4-chloro-phenyl group has been observed to the 3rd in order of analgesic potency [12-15].

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