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Synthesis and Analgesic Activity of Some New Benzoyl Derivatives

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(±) Menthol (**1**) was oxidized to menthone (**2**) which was reacted with hydroxylamine hydrochloride to yield menthone oxime (**3**). The menthone oxime (**3**) was converted to (2s, 5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one (**4**) *via* Schmidt reaction, which was reacted with various substituted aromatic benzoyl chlorides in alkaline medium to yield various phenyl substituted 1-benzoyl-7-isopropyl-4-methylazepan-2-one derivatives (**5a-g**). The structure of newly synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for analgesic activity.

Key Words: Synthesis, Benzoyl derivatives, Analgesic activity.

INTRODUCTION

Benzoyl derivatives possess varying degree of antibacterial and antifungal activity. Recently benzoyl pyrrolopyrole carboxylic acids had demonstrated that the analgesic potencies of benzoyl compounds are satisfactorily correlated with the steric and hydrogen bonding properties of benzoyl substituents[1]. Further a series of substituted derivatives of 2-amino-3-benzoyl phenyl acetic acid had been synthesized and evaluated for anti-inflammatory, analgesic and COX inhibiting activity[2]. Further, lactam derivatives constitute an important class of compounds possessing diverse biological activities such as antibacterial, antifungal and analgesic activities.

Therefore, it was thought of interest to combine above mentioned rings together in a molecular framework to see additive effect of these rings towards biological activities. In addition the investigation was found to be of further interest because compactness and planarity of such ring systems

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may be an additional factor for enhancing biological activities. Thus, synthesis of series of systems containing benzoyl and lactam moiety was attempted and the synthesized compounds were screened for analgesic activity.

EXPERIMENTAL

All the melting point were taken in open capillaries and are uncorrected. IR spectra (KBr, cm^{-1}) were recorded on Shimadzu 8400-S FTIR spectrphotometer. ^1H NMR spectra were recorded on Brucker 300 MHz NMR spectrometer using $CDCl_3$ as solvent and TMS as internal standard (Chemical shift in δ ppm). The course of all reactions and purities of products were checked by means of TLC, carried out on silica gel G. Chromatograms were developed with mixtures of carbon tetrachloride and chloroform. Crystalline samples of benzoyl derivatives were grown from ethanol.

Synthesis of menthone (2): Chromic acid solution was made using potassium permanganate (60 g), water (300 mL) and sulphuric acid (27 mL). Menthol (100 g) was dissolved in chromic acid solution by continuous stirring till fumes subsided. This reaction mixture was extracted with ether 2-3 times and ethereal layer was separated. The separated ethereal layer was shaken with 5 % NaOH and then NaOH layer was discarded and same procedure was repeated until green colour in NaOH layer disappeared. Now ethereal layers were taken in beaker and evaporated to yield menthone[3].

Synthesis of (1E)-2-isopropyl-5-methylcyclohexanone oxime (menthone oxime) (3): A mixture of menthone (7 mL, 0.05 mol), sodium hydrogen carbonate (6.00 g, 0.07 mol) and hydroxylamine hydrochloride (4.48 g, 0.07 mol) in 40 mL methanol and 5 mL distilled water was heated to 65ºC for 3 h. After completion of the reaction the mixture was diluted with 50 mL distilled water and then extracted three times with hexane. The extract was washed successively with 5 % $NaHCO_3$ and saturated NaCl solution. After evaporation of solvent the crude product was distilled under reduced pressure. Distillation *in vacuo* gave 0.04 mol (76 %) of *ca.* oxime[4]; m.p. 54-56.5°C; IR (KBr, cm^{-1}): 3205 ν(O-H), 2995 ν(C-H), 1610 ν(C=N), 1180-820 ν(C-C); ^1H NMR ($CDCl_3$) δ: 0.93 (2d, 6H at C-8 and C-9), 1.03 (d, 3H at C-10), 1.16-1.47 (m, 2H at C-5 and C-7), 1.23 (S, 1H, OH), 1.67-2.01 (m, 4H at C-3 and C-4), 2.22-2.50 (d, 2H at C-6), 3.12-3.22 (m, 1H at C-2).

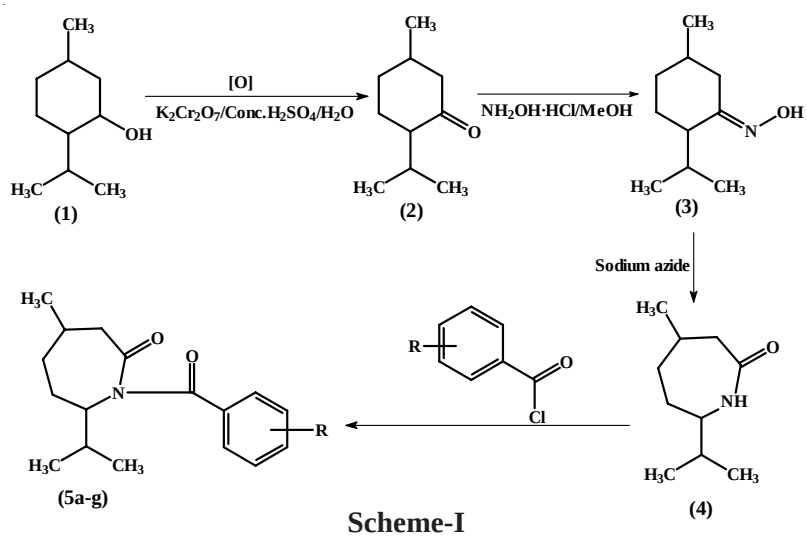
Synthesis of (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one (4): To a solution of oxime (0.08 mol) in 100 mL chloroform (100 mL) maintained at -5ºC, was added dropwise with stirring conc. H_2SO_4 (25 mL). The addition was carried out at such a rate, so that temperature did not rise above 15ºC. After the addition was over, the temperature was

brought down to 5ºC and sodium azide (10.4 g) was added in portions keeping the temperature below 35ºC. The addition required *ca.* 2 h, next the reaction mixture was stirred at 50ºC for 2 h. it was then poured in to crushed ice and stirred till clear solution resulted. The mixture was next made alkaline with 60% aqueous KOH. The precipitated inorganic salt was filtered and filtrate extracted with chloroform. The chloroform extract was then evaporated to yield (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one[4]; m.p. 121-122°C; IR (KBr, cm^{-1}) : 3271 ν(-NH), 2993 ν(C-H), 1661 ν(C=O), 1180-820 ν(C-C); ^{1}H NMR ($CDCl_3$) δ : 0.91 (6H at C-9 and C-10), 1.01 (3H at C-11), 1.17-1.45 (2H at C-5 and C-8), 1.68-2.03 (4H at C-3 and C-4), 2.23-2.51 (2H at C-6), 3.10-3.20 (1H at C-2), 5.95 (1 H from -NH) D_2O exchangeable.

Synthesis of various phenyl substituted 1-benzoyl-7-isopropyl-4-methylazepan-2-one derivatives (5a-g): In a dilute substituted aromatic acid chloride solution containing 5 mL of pure ether, a solution of lactam in 15-20 mL of same solvent was added until odour of acid chloride had disappeared. Shake with excess of dil. HCl to remove amide and it's salts, wash the ethereal layer with 3-5 mL of water and evaporate the solvent. Recrystallized from dil. ethanol; (**5a**) IR (KBr, cm^{-1}): 2980 ν(C-H), 1678 ν(C=O), 1321 ν(C=C, aromatic), 820 ν(C-H, aromatic), 572 ν(C-Br); ^{1}H NMR ($CDCl_3$) δ : 0.95 (6H at C-9 and C-10), 1.07 (3H at C-11), 1.10-1.50 (2H at C-5 and C-8), 1.62-2.05 (4H at C-3 and C-4), 2.20-2.55 (2H at C-6), 3.10-3.21 (1H at C-2), 7.30-7.79 (d, 4H, Ar-H); (**5e**) IR (KBr, cm^{-1}): 2977 ν(C-H), 1675 ν(C=O), 1324 ν(C=C, aromatic), 820 ν(C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ : 0.91 (6H at C-9 and C-10), 1.02 (3H at C-11), 1.11-1.45 (2H at C-5 and C-8), 1.60-2.03 (4H at C-3 and C-4), 2.29-2.31 (2H at C-6), 3.15-3.35 (1H at C-2), 7.25-8.14 (m,4H, Ar-H).

RESULTS AND DISCUSSION

(±)Menthol (**1**) was reacted with chromic acid solution to give menthone (**2**). The menthone (**2**) was reacted with hydroxylamine hydrochloride in presence of sodium bicarbonate using methanol as solvent to give menthone oxime (**3**). The menthone oxime was converted to (2s,5r)-(±)-2-isopropyl-5-methyl-1-azacycloheptane-7-one (**4**), a seven membered lactam *via* Schmidt reaction. The compound (**4**) was reacted with various substituted aromatic benzoyl chloride in alkaline media to give various phenyl substituted 1-benzoyl-7-isopropyl-4-methylazepan-2-one derivative (**5a-g**) (**Scheme-I**). The characterstic properties of compound (**5a-g**) are presented in Table-1.



Scheme-I

TABLE-1
PHYSICAL DATA OF COMPOUNDS (**5a-g**)

Comp.	-R	m.f. (m.w.)	m.p. (ºC)	Solubility	R_f	Yield (%)
5a	-Br	$C_{17}H_{22}NO_2Br$ (352.26)	125	DMSO/ethanol/ benzene/$CDCl_3$	0.6600	77
5b	-Cl	$C_{17}H_{22}NO_2Cl$ (307.81)	110	DMSO/ethanol/ benzene/$CDCl_3$	0.8140	82
5c	4-NO_2	$C_{17}H_{22}N_2O_4$ (318.36)	97	DMSO/ethanol/ benzene/$CDCl_3$	0.6071	92
5d	3,5-Di-nitro	$C_{17}H_{21}N_3O_6$ (363.36)	30	DMSO/ethanol/ benzene/$CDCl_3$	0.7100	66
5e	-H	$C_{17}H_{23}NO_2$ (273.37)	104	DMSO/ethanol/ benzene/$CDCl_3$	0.4770	86
5f	2,4-Di-chloro	$C_{17}H_{21}NO_2Cl_2$ (342.26)	60	DMSO/ethanol/ benzene/$CDCl_3$	0.6220	88
5g	3-NO_2	$C_{17}H_{22}N_2O_4$ (318.36)	42	DMSO/ethanol/ benzene/$CDCl_3$	0.5190	84

Screening for analgesic activity

The analgesic activity of newly formed compounds were determined by hot plate method[5] using wister mice (25-30 g) of either sex. The animals were selected by random sampling technique and were divided into group of three animals each. The time taken by each animal to show paw licking response was recorded by placing animal on a hot plate maintained at a temperature of 55 ± 0.5ºC before administration of compounds. This data was used as control reading. The test compounds at three dose levels of 2.5, 5.0 and 10.0 mg/kg were administered intraperitonially by solubilizing compounds in DMSO, while one group received piroxicam as a standard dose of 4 mg/kg body weight.

After 1 h interval, the time taken for paw licking responses was recorded for all animals and percent analgesic activity was determined. The results of analgesic activity are summarized in Table-2.

TABLE-2
ANALGESIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS (**5a-g**) USING HOT PLATE METHOD[5]

Comp.	Mean increase in latency period			% Analgesic activity$^{\chi}$			ED_{50}
	2.5 mg	5.0 mg	10.0 mg	2.5 mg	5.0 mg	10.0 mg	
5a	2.4 ± 0.20	9.3 ± 0.23	10.1 ± 0.56	20.86	80.86	87.82	4.15
5b	2.1 ± 0.19	5.8 ± 0.40	9.4 ± 0.73	18.26	50.43	81.73	5.81
5c	3.1 ± 0.21	4.7 ± 0.75	14.1 ± 0.65	26.95	84.34	122.6	3.50
5d	1.9 ± 0.20	2.8 ± 0.40	6.1 ± 0.38	16.50	24.24	53.04	9.57
5e	2.3 ± 0.09	3.2 ± 0.40	6.1 ± 0.56	20.00	29.56	53.00	9.39
5f	3.4 ± 0.34	9.9 ± 0.50	13.4 ± 0.60	29.56	86.00	116.5	3.30
5g	1.8 ± 0.30	4.2 ± 0.23	9.0 ± 0.50	15.65	36.52	78.26	6.92

$^{\chi}$ Standard used is piroxicam at a dose of 4mg/Kg 11.50 ± 0.9 s

The method of Collier *et al.*[6] was based on acetic acid induced writhing in mice. Group of three mice were administered with test compounds, control and standard. The test compound and standard compound (piroxicam) were used at dose of 2.5 and 4 mg/kg body weight intraperitonially, respectively. The results of analgesic activity are summarized in Table-3.

TABLE-3
ANALGESIC ACTIVITY DATA OF SYNTHESIZED COMPOUNDS (**5a-g**) USING WRITHING METHOD[6]

Group	Compound	Number of writhings in 15 min	Writhing inhibition (%)
1	**5a**	42	41.66
2	**5b**	39	45.83
3	**5c**	34	52.77
4	**5d**	61	15.27
5	**5e**	62	13.88
6	**5f**	35	51.38
7	**5g**	43	40.27
8	Control	72	–
9	Piroxicam (standard)	31	56.94

REFERENCES

1. J.M. Muchowski and S. Hunger, *J. Med. Chem.*, **28**, 1037 (1985).
2. D.A. Walsh and H.W. Moran, *J. Med. Chem.*, **27**, 1827 (1984).
3. S.N. Pandeya, V. Mishra, C. Pannecouque and M. Witvrouw, *Arch. Pharm. Med. Chem.*, **5**, 183 (2002).
4. S. Lochynski, J. Kuldo, B. Frackowiak, J. Holband and G. Wojcik, *Tetrahedron Asymm.*, **11**, 1300 (2000).
5. M.N. Ghosh, Fundamental of Experimental Pharmacology, Scientific Book Agency, Calcutta, edn. 2, p.153 (1984).
6. H.O.J. Collier, L.C. Dinnen and C.A. Johnson, *Br. J. Pharmacol. Chemother.*, **32**, 269 (1968).

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