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Synthetic, Structural and Antimicrobial Studies of Some Substituted 2,6-diphenyl-1-aza-7-oxa-4-spiro[2,5]octanes

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Different methyl substituted 2,6-diphenyl piperidones have been synthesized and subjected to the reaction with dimethyl sulphoxonium methyl ylide in the presence of potassium tertiary butoxide for the preparation of the corresponding spiro oxiranes. The structures of the products have been confirmed by various physical techniques.

Key Words: Synthesis, Antimicrobial studies, Spiro oxiranes, Substituted 2,6-diphenyl-1-aza-7-oxa-4-spiro[2,5]octanes.

INTRODUCTION

In the recent past we have been engaged in the preparation of the spiro oxiranes derived from the various substituted 2,6-diphenyl piperidones[1] based on the following observations reported earlier. Generally the inbuilt spiro carbocyclic or heterocyclic systems in a ring increase the biological potency, more so with the systems having smaller rings[2].

The reactivity of the carbonyl functionality of piperidin-4-ones is being extensively used for various interconversions and modifications by researchers. The carbonyl group of ketones had been converted to oxiranes in the early 60's using sulphur ylides[3].

The reaction is carried out by treating the ketone with the trimethyl sulphoxonium methyl ylide in the presence of potassium tertiary butoxide, with constant stirring for 2–4 h yielding the expected product. The reacting dimethyl sulphoxonium methyl ylide is generated *in situ* by the reacton of both trimethyl sulphoxonium methyl ylide and potassium tertiary butoxide. The structures of the products were confirmed by IR, NMR (^{1}H, ^{13}C), mass spectral studies, elemental analysis, etc.

All the 2,6-diphenyl piperidin-4-ones used in the preparation of various 2,6-diphenyl-1-aza-7-oxo-4-spiro[2,5]octanes have been shown from their ^{1}H and

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^{13}C studies to exist in their chair conformation with the phenyl and alkyl substituents occupying the least strained equatorial positions[4].

The objective of the present investigation is centred on the investigation of the reactivity of the carbonyl group of various substituted piperidin-4-ones towards the dimethylsulphoxonium methyl ylide, structural elucidation and biological potentials like antibacterial and antifungal activities of the resultant oxiranes.

EXPERIMENTAL

Melting points were determined on a Bortius micro heating table and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with tertramethylsilane as internal standard in av300 spectrometer operating at 300.13 MHz. ^{13}C NMR spectra were recorded in the same solvent in av300 spectrometer operating at 75.4 MHz using TMS as internal standard. IR spectra were recorded in Shimadzu IR spectrophotometer model IR-435 instrument using KBr pellets. Mass spectra were recorded in Qstar multiview 1.5.0 model spectrometer.

Solvents used such as alcohol, dimethyl sulphoxide, ethyl acetate and water in these experiments were purified according to literature procedure[5].

Chemicals used in the preparations of 2,6-diarylpiperidin-4-one and various 3-alkyl-2,6-diarylpiperidin-4-ones were of AnalaR grade.

Antimicrobial Activity: The in-built spiro carbocyclic or heterocyclic system in a ring increases the biological potency, more so with the systems having smaller rings. On this basis, the compounds synthesized were evaluated for the *in vitro* antibacterial and antifungal activities.

The evaluations were carried out using paper disc diffusion method for antibacterial activity and the turbidity method for antifungal activity.

Antibacterial activity: All the compounds synthesized **(2a–d)** were evaluated for their *in vitro* antibacterial activity against the pathogenic micro-organisms *Escherichia coli* (gram-positive) and *Staphylococcus aureus* (gram-negative) using paper disc diffusion method.

Sterilized 10 mm Whatmann No. 1 paper discs, impregnated with 0.1 mL of the sample solutions (200 μg in DMF), were placed in petri-dishes containing 25–30 mL of nutrient agar inoculated with 18–24 h old test culture.

Incubation was carried out at 37°C for 24 h and the zone of inhibition was measured in mm. All the experiments were done in triplicate. Phenol was taken as a standard.

Antifungal activity: Antifungal activity of the compounds was determined *in vitro* against *Aspergillus niger* adopting the turbidity method. In this method, 0.1 mL of the sample solution (200 μg in DMF) in 5 mL sterilized fungi medium was treated with 3–4 drops of 48 h old culture in a test tube. The test tube was then shaken well and incubated for 48 h at 37°C. The extent of inhibition was determined by measuring the decrease in turbidity in terms of per cent transmission at 660 μ. Salicylic acid was taken as a standard.

TABLE-1
RESULT OF THE ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES

Compound	Antibacterial activity		Antifungal activity
	Escherichia coli	Staphylococcus aureus	*Aspergillus niger*
2a	–	–	+
2b	++	+	++
2c	+	+	++
2d	+	+	++
Phenol	+++	++	
Salicylic acid			+++

Antibacterial activity: Zone of inhibition in mm 14–16 = '–' (no activity); 17–19 = '+' (positive); 20–22 = '++' (positive); 23–25 = '+++' (positive).

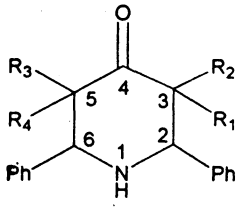
Antifungal activity: Per cent transmission 1–25 = '–' (no activity); 26–50 = '+' (positive); 51–75 = '++' (positive); 76–100 = '+++' (positive).

Solvent control: DMF.

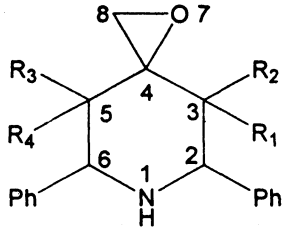
From the result it was observed that the compounds with methyl group as a substituent **(2b, 2c** and **2d)** exhibit moderate activity when compared to the compound that does not contain methyl group as a substituent **(2a).**

RESULTS AND DISCUSSION

The prepared 2,6-diphenyl piperidin-4-ones **(1a–d)** and the various synthesized oxiranes **(2a–d)** are given as follows:



(1)

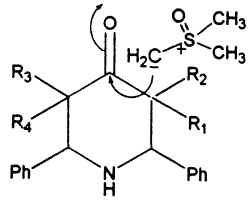


(2)

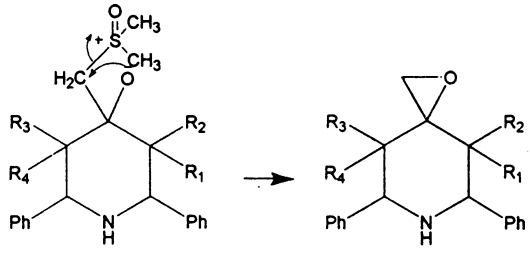
Compd.	R_1	R_2	R_3	R_4	Compd.	R_1	R_2	R_3	R_4
(1a)	H	H	H	H	**(2a)**	H	H	H	H
(1b)	CH_3	H	H	H	**(2b)**	CH_3	H	H	H
(1c)	CH_3	CH_3	H	H	**(2c)**	CH_3	CH_3	H	H
(1d)	CH_3	H	CH_3	H	**(2d)**	CH_3	H	CH_3	H

The synthesis of the various 2,6-diphenyl-1-aza-7-oxo-4-spiro[2,5]octanes **(2a–d)** is believed to have the following mechanism[6]:

The dimethylsulphoxonium methyl ylide generated *in situ* by the reaction of potassium tertiary butoxide with trimethylsulphoxonium iodide (TMSOI) undergoes nucleophilic substitutions (S_{N^2}) to give a sulphur containing adduct.



The next step involves the intramolecular nudeophilic substitution to give the expected oxiranes.



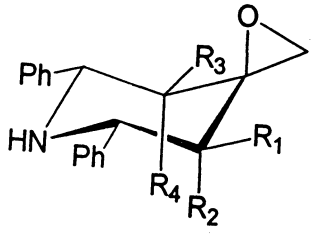


TABLE-2
PHYSICAL PARAMETERS OF VARIOUS SUBSTITUTED 2,6-DIPHENYL-1-AZA-7-OXA-4-SPIRO[2,5]OCTANES (**2a–d**)

Compound	m.f.	m.w.	m.p. (°C)	Yield (%)	Solvent for crystallization
2a	$C_{18}H_{19}NO$	265	68–70	50	Ethanol
2b	$C_{19}H_{21}NO$	279	96–97	76	Ethanol
2c	$C_{20}H_{23}NO$	293	—	74	EtOH/EtOAc
2d	$C_{20}H_{23}NO$	293	125–127	78	Ethanol

TABLE-3
ELEMENTAL ANALYSES DATA OF COMPOUNDS **2b** AND **2d**

Compound	% of carbon		% of hydrogen		% of nitrogen	
	Analytical	Calculated	Analytical	Calculated	Analytical	Calculated
2b	81.85	81.72	7.54	7.52	5.03	5.01
2d	82.01	81.91	7.86	7.84	4.80	4.77

TABLE-4
^{1}H NMR CHEMICAL SHIFT VALUES (δ, PPM) OF THE VARIOUS 3-ALKYL-3,5-DIALKYL-2,6-DIPHENYLPIPERIDIN-4-ONES (**1a–d**)

Compd.	H-2	H-3	H-5	H-6	NH	Others
1a	4.0 (dd)	2.5 (m)	2.5 (m)	4.0 (dd)	2.1 (s)	7.24–7.52 (m, 10H, Ar—H)
1b	3.61 (dd)	2.5 (m)	2.7 (m)	4.0 (dd)	2.09 (s)	7.22–7.46 (m, 10H, Ar—H) 0.71–0.9 (3H, C_3—CH_3)
1c	3.8 (s)	—	2.8 (m)	4.0 (dd)	1.94 (s)	7.1–7.5 (m, 10H, Ar—H) 0.8–1.2 (6H, C_3–CH_3)
1d	3.5 (dd)	2.7 (m)	2.7 (m)	3.5 (dd)	2.0 (s)	7.2–7.5 (m, 10H, Ar–H) 0.7–1.0 (6H, C_3, C_5—CH_3)

TABLE-5
^{1}H NMR CHEMICAL SHIFT VALUES (δ, ppm) OF THE VARIOUS 2,6-DIPHENYL-1-AZA-7-OXA-4-SPIRO[2,5]OCTANES (**2a–d**)

Compd.	H-2	H-3	H-5	H-6	NH	H-8	Others
2a	4.16 (dd)	2.13 (m)	2.13 (m)	4.16 (dd)	1.5 (s)	2.72 (s)	7.0–7.4 (m, 10H, Ar—H)
2b	3.7 (dd)	2.49 (m)	2.2 (m)	4.17 (dd)	1.8 (s)	2.89 (s)	7.18–7.44 (m, 10H, Ar—H) 0.47–0.567 (3H, C_3—CH_3)
2c	3.97 (s)	—	2.44 (m)	4.16 (dd)	1.69 (s)	2.89 (s)	7.2–7.5 (m, 10H, Ar—H) 0.8–1.2 (6H, C_3—CH_3)
2d	3.74 (dd)	2.2 (m)	2.2 (m)	3.74 (dd)	1.77 (s)	2.80 (s)	7.2–7.4 (m, 10H, Ar—H) 0.44–0.60 (6H, C_3, C_5—CH_3)

A comparison of the ^{1}H NMR chemical shift data of the oxiranes (Tables 4 and 5) with those of the corresponding piperidin-4-ones shows four different trends:

- Exactly as in the piperidin-4-one precursors, the six-member ring in the corresponding oxiranes also adopts the chair conformation with all the substituents occupying more stable equatorial positions (except in the

oxirane (**2c**) where one of the C_3 methyl groups must necessarily be axially oriented).

- The signals due to H-3 and H-5 protons are shifted upfield.
- The signals due to H-2 and H-6 are shifted downfield.
- The proton of N—H group also experiences a slight upfield shift.

Jayaraman and coworkers[5] and Ramarajan and coworkers[7] reported the same trend of the chemical shift variations when they attempted the conversion of 2,4-diphenylpiperidin-4-ones into the corresponding lactones and thioketals respectively.

The downfield shift of the protons at C-2 and C-6 of the oxiranes, compared to the benzylic protons in the corresponding piperidin-4-ones could be traced to the proximity interaction between the axial oxygen at C-4 and the axial hydrogens H-2 and H-6. This is an evidence for the presence of the axial oxygen at C-4.

Moreover, the specific formation of one of the possible isomers, namely, the oxirane with C—O axial to the piperidine ring, is a clear case of pi-facial selectivity at the carbonyl carbon. Since the ylide usually attacks from the most hindered side of the ring, the resulted oxirane naturally has the C—O bond axial to the piperidine ring[4].

In the compound (**2a**), the singlet appearing at δ 2.72 is assigned to OCH_2 protons. But in the compounds (**2b–d**), the values for the same protons increase due to the introduction of the alkyl group at C-3 and C-3 & C-5 in the case of compound **1d.**

TABLE-6
^{13}C-NMR CHEMICAL SHIFT VALUES (δ, ppm) OF THE VARIOUS 3-ALKYL-3,5-DIALKYL-2,6-DIPHENYLPIPERIDIN-4-ONES (**1a–d**)

Compd.	C-2	C-3	C-4	C-5	C-6	Others
1a	61.5	50.8	208.60	50.8	61.5	143.11 (ipso-C)
1b	68.9	52.1	210.13	51.3	62.0	142.34–143.22 (ipso-C) 10.6 (C_3—CH_3)
1c	69.9	50.3	213.30	47.7	62.0	139.677–143.56 (ipso-C) 20.4, 20.8 (C_3—CH_3)
1d	69.2	52.4	211.60	52.4	69.2	142.420 (ipso-C) 10.6, 10.9 (C_3 & C_5—CH_3)

TABLE-7
^{13}C-NMR CHEMICAL SHIFT VALUES (δ, PPM) OF THE VARIOUS 2,6-DIPHENYL-1-AZA-7-OXA-4-SPIRO [2,5] OCTANES (**2a–d**)

Compound	C-2	C-3	C-4	C-5	C-6	C-8	Others
2a	57.4	46.4	59.9	46.4	57.4	42.0	144.667 (ipso-C) 143.825
2b	60.2	44.2	66.8	50.7	59.8	40.0	144.776 (ipso-C) 10.037 (C_3—CH_3)
2c	63.6	40.7	68.6	50.1	60.4	38.0	141.518 145.091 (ipso-C) 19.439 20.250 (C_3—CH_3)
2d	62.2	46.8	66.5	46.8	62.2	41.6	144.050 (ipso-C) 10.635 (C_3 & C_5CH_3)

The comparison of the ^{13}C data of the piperidin-4-ones and their corresponding oxiranes resulting from the replacement of the carbonyl by the spiro oxirane show two trends: (a) Signals for all the ring carbons are shifted upfield. (b) Ipso carbons of the phenyl groups are shifted downfield.

Similar downfield shifts for the ipso carbons when 2,6-diphenyl piperidin-4-ones were reduced to the corresponding piperidines were noted[5]. As rationalized by them, the partial positive charge on the C-4 carbons in piperidin-4-ones withdrew electron density along both C_3—C_4 and C_4—C_5 bonds, inducing a similar flow of electron density along the antiperiplanar C_2-phenyl and C_6-phenyl bonds. Due to this π-polarization, the electron density around the ipso carbons was enhanced and this caused the upfield shift for these carbons in the piperidin-4-ones compared to the situation in the corresponding oxiranes.

Although the upfield shift experienced by carbons C_3 and C_5 may be due to the loss of electron withdrawing carbonyl group, the same may not be true for the upfield shift of C_2 and C_6 carbons. The van der Waals repulsive interaction between the two lone electron pairs on O(7) and the electron clouds around H-2 and H-6 is expected to repel the electron density away from these hydrogens and accumulate them around C_2 and C_6 carbons is probably the cause for the observed upfield shift.

Another explanation regarding the upfield shift of the C-2 and C-6 carbons of compounds (**2a–d**) by about 3–5 ppm from those of the corresponding piperidones has been ascribed to the gamma-gauche effect, which because of steric interaction polarizes the C—H bonds of C-2 and C-6 carbons in such a way that the carbon nucleus is shielded while the attached protons are deshielded[5].

This upfield shift of the C-2 and C-6 carbons also indicates the presence of C-4 oxygen, axial to the piperidine ring.

The absence of the carbonyl stretching frequency 1702 cm^{-1} in the compound **(2b)** shows the involvement of the carbonyl group in the conversion. The frequency 1270 cm^{-1} which is the characteristic absorption for the symmetrical stretching or the ring breathing frequency of an epoxy ring, of all the ring bonds stretching and contracting in phase, coincides with the compound **(2b)** indicating the presence of the epoxide unit. Another band observed at 796.55 cm^{-1} is attributed to the asymmetrical ring stretching in which the C—C bond is stretching during contraction of the C—O bond, which also proves the presence of the epoxide unit.

The mass spectra of the compounds **2b** and **2d** reveal the molecular ion (M^+) peaks at the m/z, amu values 278.53 and 292.62 respectively. These values are in accordance with the theoretical values 278 and 293 of the compounds **2b** and **2d** respectively.

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