

Studies on the Synthesis of Some Novel 2-[2-(4-Oxo-4-P-Tolyl-4-Thia-1,3,3a,5 Tetraaza-Cyclo-Penta [A] Naphthalen-2-Yl Sulphanyl) -2-Aryl-Ethyl]-2-Phenyl-2,3-Dihydro-6 Substituted/Unsubstituted Benzo[E] [1,3]Oxazin-4 Ones

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Abstract: Anthranilic acid **1** on treatment with *p*-toluene sulphonyl chloride in pyridine yields 4-oxo-2*p*-tolyl-2-benzo[d][1,2,3]oxathiazin-4-one (**2**) which on reaction with thiosemi-carbazide in pyridine, on refluxing for 4 hrs affords 4-oxo-4*p*-tolyl-4-thia 1,3,3a,5-tetraaza cyclopenta[a]naphthalene-3-thione (**3**). Compound **3** and an α,β -unsaturated carbonyl compound in dimethyl sulphoxide containing trimethylamine on heating gives 3-(4-Oxo-4-*p*-tolyl-4-thia-1,3,3a,5-tetra azacyclopenta[a]naphthalen-3-yl-sulphonyl)-1-phenyl-3-aryl-propan-1-ones (**4**) which on reaction with salicylamide/5-arylamido/ imidoalkyl salicylamide in glacial acetic acid gives 2-[2-(4-oxo-4*p*-tolyl-4-thia-1,3,3a,5 tetra azacyclopenta[a]-naphthalen-2-yl-sulphanyl)-2-aryl-ethyl-2-phenyl-2,3-dihydro-6-substituted/unsubstituted benzo [e] [1,3] oxazin-4-ones **5**.

Keywords: Benzoxazines, Thiosemicarbazide, Anthranilic acid

1. INTRODUCTION

Benzoxazines as biologically active compounds have been extensively studied in the past¹⁻². Among the various classes of benzene fused six-membered nitrogen containing heterocyclic compounds benzoxazines form important classes of pharmacologically active compounds³⁻⁵. Very recently, benzoxazine derivatives have been found to be associated with a wide variety of biological activities including antibacterial⁶, antifungal⁷, antitumour⁸ and anti-HIV⁹. In continuation of our ongoing research on the synthesis and designing of new bioactive molecules, it was considered of interest to synthesize substituted benzoxazines and study their antiviral activity against highly pathogenic RNA Japanese Encephalitis virus (JEV). Title compounds were synthesized by the reaction of azacyclopenta[a] naphthalene -yl-sulphonyl)-1-phenyl-3-aryl-propan-1-ones with salicylamide/ 5-arylamido/ imido alkyl salicylamide, which in turn were obtained from 4-oxo-4*p*-tolyl-4-thia1,3,3a-5-tetra-aza cyclopenta [a]naphthalene-thione (**I**) and α,β -unsaturated carbonyl compounds. Compound (**I**) was synthesized by treatment of 4-oxo-2*p*-tolyl-2benzo[d] [1, 2, 3] oxathiazin-4-one with thiosemicarbazide in pyridine. New compounds were characterized by spectral studies.

2. EXPERIMENTAL

The melting points of the compounds were determined in a Toshniwal electric melting point bath and are uncorrected. The infrared (IR) spectra of the compounds were recorded in the region of 4000-400 cm⁻¹ using KBr on a FT-IR Perkin-Elmer spectrophotometer. ¹H NMR spectra were

recorded on a DRX-300 Bruker FT-NMR spectrometer in CDCl_3 solvent. The values of the chemical shifts are expressed in δ units. The ^{13}C NMR spectra were recorded on a DRX-300 Bruker FT-NMR spectrometer. All the compounds were checked for purity by thin layer chromatography (TLC).

3. PHENYL-SUBSTITUTED STYRYL-KETONES

An aromatic aldehyde (0.1 mole) and acetophenone (0.1 mole) were dissolved in 50 ml of absolute ethanol by stirring. Subsequently, a 10% solution hydroxide (50 ml) was added to it. The resultant reaction mixture was stirred vigorously and was cooled to 0°C . A pale yellow solid separated out on cooling for an hour. It was filtered off, washed several times with cold water and air-dried. It was recrystallized from rectified spirit as yellow-crystalline solid.

Phenyl-styryl ketone (benzal aceto-phenone), m.p. 56°C [$56\text{-}57^\circ\text{C}$]¹⁰, yield, 76%.

Phenyl-2-methoxy styryl ketone (2-methoxy-benzal aceto-phenone), m.p. 50°C [$50\text{-}51^\circ\text{C}$]¹¹, yield, 70%.

4. 4-OXO-2P-TOLYL-2-BENZO[D][1,2,3] OXATHIAZIN-4-ONE (2)

Anthranilic acid 1 (0.1 mole) was dissolved in anhydrous pyridine (in minimum quantity) (25 ml) by stirring. To this solution, a solution of p-toluene sulphonylchloride (0.1 mole) in dry pyridine (25 ml) was added with constant shaking. Before Anthranilic acid 1 (0.1 mole) was dissolved in anhydrous pyridine (in minimum quantity) (25 ml) by stirring. To this solution, a solution of p-toluene sulphonylchloride (0.1 mole) in dry pyridine the addition, both the solutions were thoroughly cooled. When the addition was completed the resultant solution was stirred vigorously for one hour mechanically. A solid separated out which was filtered off and washed with a solution of sodium bicarbonate (10%). When the effervescence ceased, the residual solid was filtered off and washed repeatedly with water till there was no smell of pyridine. The crude compound thus synthesized, was air dried and purified by recrystallization from diluted ethanol as a light brown crystals, m.p. $160\text{-}161^\circ\text{C}$, yield, 85%.

5. 4-OXO-4-P-TOLYL-4-THIA-1,3,3A, 5-TETRAAZACYCLO-PENTA [A] NAPHTHALEN-3-THIONE (3)

A mixture consisting of 3-oxo-2-p-tolyl-2-benzo [d] [1,2,3] oxathiazin-4-one 2 (0.01 mole) and thiosemicarbazide (0.01 mole) in pyridine (100 ml) was heated under reflux for four hours. Subsequently, the solution after cooling to room temperature was poured into crushed ice containing diluted hydrochloric acid (100 ml) with stirring. A thick precipitate separated out which was filtered off and washed with water. The compound thus obtained, was dried with the vapours of ethanol. It was recrystallized from ethanol as brown crystals, m.p. $184\text{-}185^\circ\text{C}$, yield, 65%.

6. 3-(4-OXO-4-P-TOLYL-4--THIA-1,3,3A,5-TETRAAZACYCLO-PENTA[A] NAPHTHALEN-3-YL-SULPHANYL)-1-PHENYL-3-ARYL-PROPAN-1-ONES (4)

A mixture of 4-oxo-p-tolyl-4--thia-1,2,3a,5-tetraazacyclopenta [a] naphthalene-3-thione 3, (0.02 mole) and α,β -unsaturated carbonyl compound (0.02 mole) in dimethylsulphoxide (DMSO) (50 ml) containing triethylamine (5 ml) was heated under reflux for six hours. Subsequently, the contents were poured into crushed ice containing 10 ml diluted hydrochloric acid. On vigorous stirring solidification occurred and the separated solid was allowed to settle down. It was filtered off and was washed successively with cold water. The crude compound was dried at 100°C and was recrystallized from diluted ethanol.

3-(4-Oxo-4-p-tolyl-4-thia-1,3,3a,5-tetraazacyclo-penta [a] naphthalene-3-yl-sulphanyl)-1-phenyl-3-o-methoxyphenyl propan-1-one, m.p. 220°C , yield 62%.

3-(4-Oxo-4-p-tolyl-4-thia-1,3,3a,5-tetraazacyclo-penta [a] naphthalene-3-yl-sulphanyl)-1,3-diphenyl-propan-1-one, m.p. 212° , yield, 60%.

7. 2-[4-(4- OXO-4-P- TOLYL-4- THIA- 1,3,3A,5- TETRAAZA CYCLOPENTA [A] NAPHTHALEN-2-YL-SULPHANYL)-2-ARYLETHYL]-2-PHENYL-2,3-DIHYDRO-6- SUBSTITUTED/ UNSUBSTITUTED BENZO[E] [1,3] OXAZIN-4-ONES (5)

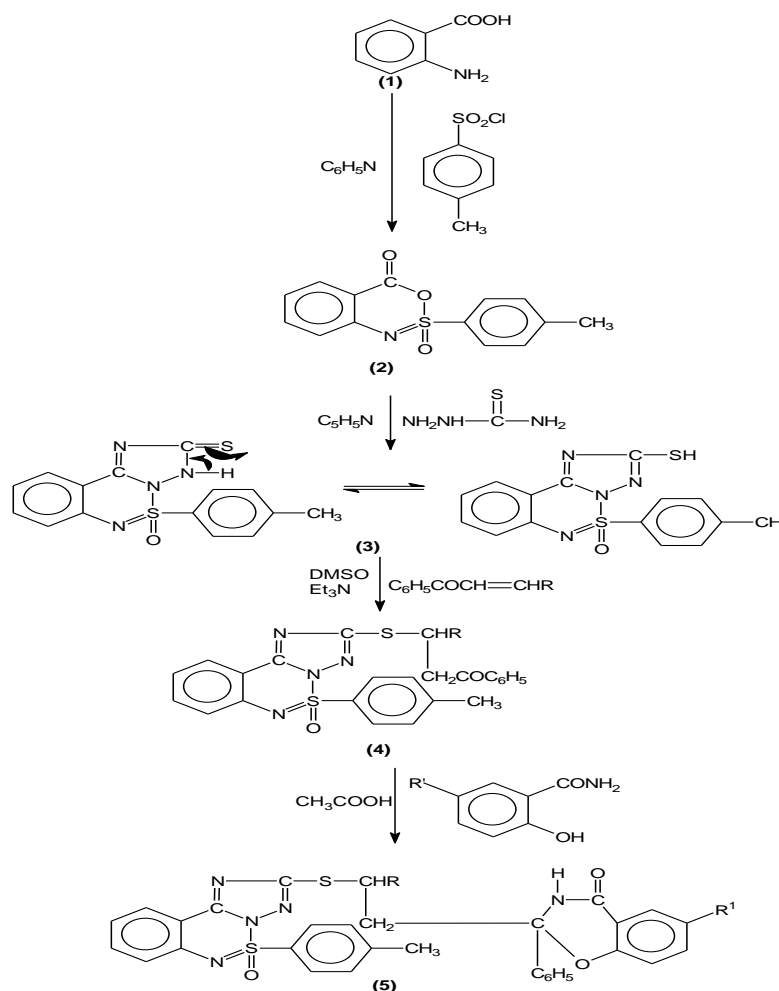
The reaction mixture consisting of 3-(4-oxo-4-p-tolyl-4-thia-1,3,3a,5-tetraazacyclopenta [a] naphthalen-3-yl-sulphanyl)-1-phenyl-3-aryl-propan-1-one (4) (0.01 mole) and salicylamide/5-arylamido/imidoalkyl salicylamide (0.01 mole) in glacial acetic acid (100 ml) was heated under reflux for five hours. The resultant solution was cooled to room temperature and poured onto the crushed ice and stirred vigorously. A solid was precipitated out which was filtered off and after washing with cold water it was dried *in vacuo* for twenty-four hours. The crude product thus obtained, was subjected to recrystallization from ethanol. The compounds thus synthesized, are presented in Table 1 along with their characterization data.

5e: IR (KBr) * ν_{\max} in cm^{-1}): 1680 (sec. amide C=O), 1660 (lactam C=O), 3450 (N-H), 1090 (C-O-C cyclic), 1630 (C=N), 1030 (s=O), 2955 (CH_3 asymmetric), 2875 (CH_3 -symmetric), 2920 (CH_2 asymmetric) 2850 (CH_2 symmetric).

^1H NMR (MeOD) (in δ ppm): 6.95-7.85 (complex m, 26H, ArH), 2.25 (s, 3H, AR- CH_3), 4.95 (t, 1H, s-CH- CH_2 , J = 5.5), 4.35 (d, 2H, s- CHCH_2 , J = 5.5), 8.85 (brs, 1H, CONH), 9.25 (brs, 1H, CONH).

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Scheme-1

Table1. Characterization data of 2-[2(4-oxo-4-p-tolyl-4-thia-1,3,3a-tetrazacyclopenta [a] naphthalen-2-yl-sulphanyl)-2-arylethyl]-2-phenyl-2,3-dihydro-6-substituted/unsubstituted benzo[e] [1,3] oxazin-4-ones (5)

Compd. no.	R	R ¹	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular weight	Analysis	
								Nitrogen, %	
								Calcd.	Found
5a.	phenyl	Hydrogen	298	45	Pink	C ₃₇ H ₂₉ N ₃ O ₃ S ₂	641	10.92	10.90
5b.	2-methoxy phenyl	Hydrogen	>300	50	Grey	C ₃₈ H ₃₁ N ₅ O ₄ S ₂	685	10.22	10.18
5c.	phenyl	Phthalimido-methyl	>300	40	Brown	C ₄₆ H ₃₄ N ₆ O ₅ S ₂	814	10.32	10.30
5d.	2-methoxy phenyl	Phthalimido-methyl	>300	42	Green	C ₄₇ H ₃₆ N ₆ O ₆ S ₂	844	9.95	9.90
5e.	phenyl	Benzamido-methyl	296	50	Brown	C ₄₅ H ₃₆ N ₆ O ₄ S ₂	712	11.79	11.75

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