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Synthesis of Some New Substituted Isatin Derivatives with Possible Antipyretic Activity

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Abstract:

Substituted isatin derivative have been prepared by treating substituted aromatic amines with hydroxylamine hydrochloride with chloralhydrate in presence of sodium sulphate to form 2-hydoxyimino-N-p-tolyacetamide which on reaction with conc. H2SO4 to give 5-subsituted isatin which when condensed with 2-amino-4-Aryl thiazole to yield indolin-2-one derivatives with possible anti pyretic activity.

Keywords: Synthesis, Aromatic amines, Isatin, Antipyretic activity.

Introduction

Substituted indol-n-2-one are in important class of biologically active molecule shown to possess vivid pharmacological activity have been reported in literature which includes the antipyretic1-2, anti-inflammatory3-4, analgesic3, antifungal5-6, antibacterial7-8, anticonvulsant9-10, antiviral11 activities.

Owing the versatility of indolino-2-one we have synthesized new (Z)-3-(4-substituted thiazo-2-yl-imino)-indolin-2-one from 2-hydroxy imino-N-p-tolyl acetamide which is prepared by heating paratoluidine, chloral hydrate and hydroxyl amine, hydochloride in presence of sodium sulphate which on further treatment with conc. H2SO4 give 5-substituted isatin, which on further treated with various aromatic primary amines to yield the required product.

Experimental

Preparation of 2-hydroxyimino-N-p-tolylacetamide : In a 5 litre round bottom flask 90gm (0.54 mole) of chloralhydrate and 1200 cc water are placed and stirred. To this

solution added 1300gm crystallized sodium sulphate, 53.5 gm (0.5 mole) paratoluidine in 300 cc water to which (43cc) concentrated hydrochloric acid has been added to dissolve the paratoluidine and finally a solution of 110 gm (1.58 mole) of hydroxylamine hydrochloride in 500 cc water was added. The flask is heated on a burner so that vigrous boiling begins within an hour. After one (or) two minutes of vigrous boiling reaction is complete. During the heating period, some crystals of 2-hydroxyimino-N-p-tolylacetamide separates. On cooling the solution under the tap remainedr crystallizes, filtered with suction and air-dried. The yield is 65-75 gm M.P. 1750C.

Preparation of 5-substituted isatin

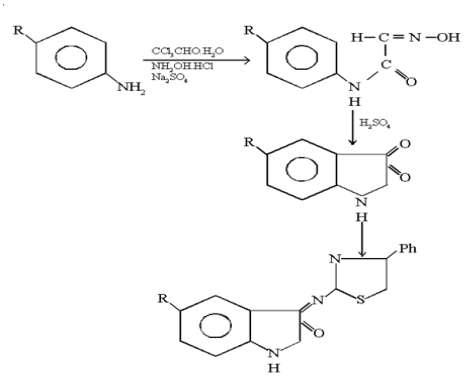
326(C.C.) concentrated sulphuric acid is warmed to 500C in a one litre round bottom flask fitted with a stirrer, to this 75(gm) dry 2-hydroxyimino-N-p-tolylacetamide is added at such a rate to maintain the temperature between 60-700C. External cooling should be applied at this stage so that the reaction can be carried out more rapidly. After the addition of 2-hydroxyimino-N-p-tolyl acetamide, the solution is heated to 800C and kept at this temperature for about ten minutes to complete the reaction. Then the reaction mixture is cooled to room temperature and poured the crushed ice. After standing about two hours; the isatin is filtered with suction, washed several time with cold water to remove the sulphuric acid and than dried in air. The yield is 70-75% M.P. 191-1930C.

Preparation of (Z)-3-(4-Phenyl thiazole-2-ylimino)indolin-2-one

Equimolecular quantity of Isatin/5-subsituted isatin and the aromatic primary amine was dissolved in warm ethanol and heated on a stream bath for 30-40 minutes. After standing 24 Hours at room temperature, the products were separated by filteration and recrystallized from warm ethanol.

Results and Discussion

Similarly different indolin-2-one derivatives were prepared by taking substituted isatin and different primary amines, by replacing te R wit H, CH3, NO2 and by replacing the R' with 2-Amino-4-phenyl thiazole, 2-Amino-4-chlorophenyl thiazole, 2-Amino-4-methoxyphenyl thiazole. The synthesized compounds have been characterized by I.R., P.M.R., spectral studies and elemental analysis, their analytical data are incorporated in table-1. The purity of the compounds have been checked by T.L.C. The m.p. were determined in open capillarie's and are uncorrected. The general reaction sequence is as follows.



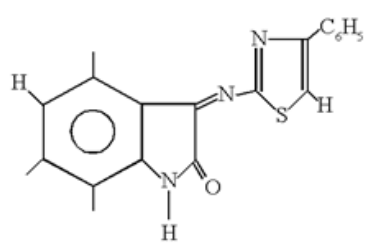
(Z)-3-(4-Phenylthiazo-2-ylimino) indolin-2-one

IR(KBr) : 1750-1740 cm-1 (>C=O); 3215-3175 cm-1 (-N-); 695 cm-1 (C-S-C)

H

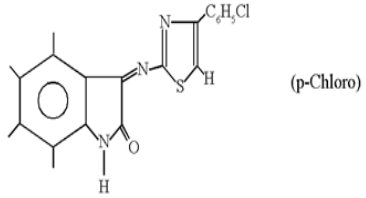
Compounds

1.



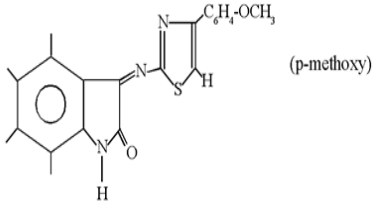
PMR- 7-7.75 (m, 6H, ArH), 8.0-8.2 (S, 1H, -NH),
7-7.75 (m, 4H, ArH), 6.7-7.1 (1H, S, -CH)

2.



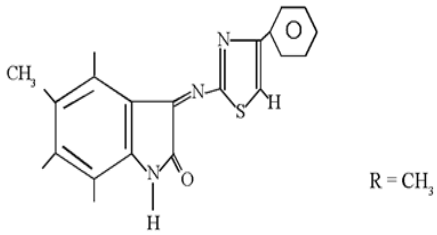
PMR- 7.0-7.8 (m, 4H, ArH), 8.0-8.2 (S, 1H, -NH),
7-7.75 (m, 4H, Ar-H), 6.7-7.1 (S, 1H, -CH)

3.



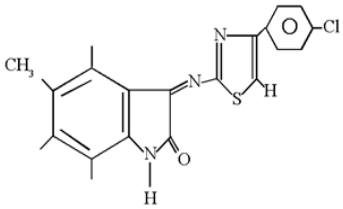
PMR- 6.89-7.6 (m, 4H, ArH), 8.0-8.2 (S, 1H, -NH),
6.9-7.1(S, 1H, -CH), 6.7-7.1 (m, 4H, ArH)
6.7-7.1(m, 4H, ArH), 3.5-3.7 (t, 3H, -OCH3)

4.



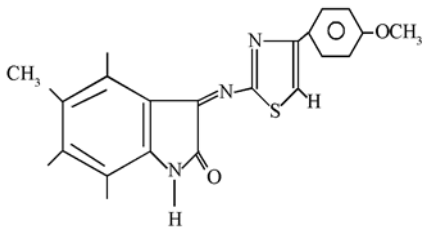
PMR- 7.0-7.5(m, 3H, ArH), 2.2-2.3 (m, 3H, -CH3), 8.0-8.2(S, 1H, NH),
7.0-7.3 (m, SH, -CH3), 6.7-7.1(S, 1H, -CH)

5.



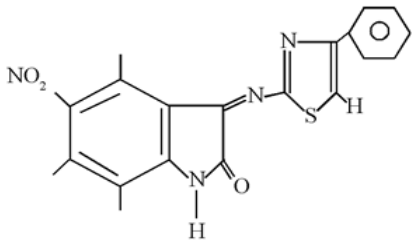
PMR- 6.8-7.4(m, 3H, ArH), 2.2-2.3 (m, 3H, -CH3),
8.0-8.2(S, 1H, -NH), 6.7-7.1 (S, 1H, -CH), 7.1-7.3(m, 4H, ArH)

6.



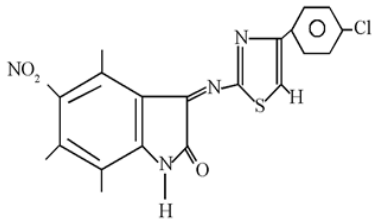
PMR- 6.8-7.4(m, 3H, ArH), 2.2-2.3 (m, 3H, -CH3), 8.0-8.2(S, 1H, -NH), 6.7-7.1 (S, 1H, -CH), 6.7-7.0(m, 4H, ArH)

7.



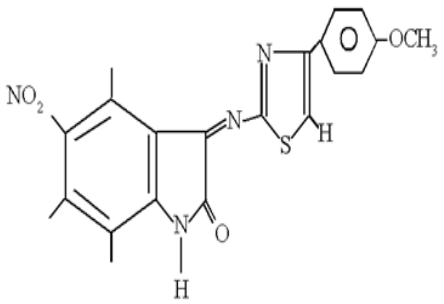
PMR- 7.7-7.9(m, 3H, ArH), 8.0-8.2 (S, 1H, -NH), 6.9-7.1(S, 1H, -CH), 7.0-7.2 (m, SH, ArH)

8.



PMR- 7.7-7.4(m, 3H, ArH), 8.0-8.2 (S, 1H, -NH), 6.9-7.0(S, 1H, -CH), 7.1-7.3 (m, 4H, ArH)

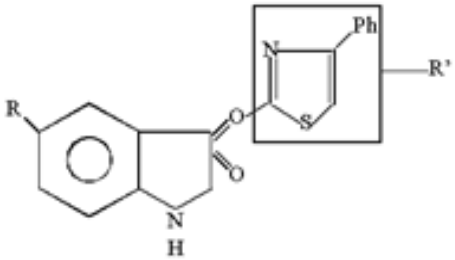
9.



PMR- 7.7-7.9(m, 3H, ArH), 8.0-8.2 (S, 1H, -NH), 6.9-7.0(S, 1H, -CH), 6.8-7.1 (m, 4H, ArH), 3.5-3.7 (t, 3H, -OCH3)

Table-1

Analytical data of (Z)-3-(4-substituted-thiazo-2-ylimino)-inodolin-2-one



Sl. No.	Nature of R	Nature of R'	Molecular Formula	Mol. Wt.	M.P.	Elemental Analysis			
						% of Nitrogen		% of Sulphur	
						Calculated	found	Calculated	found
1.	H	2-Amino-4-Phenyl thiazole	$C_{17}H_{11}N_3OS$	305	219	13.77	13.58	10.49	10.36
2.	H	2-Amino-4-Chloro Phenylthiazole	$C_{17}H_{10}ClN_3OS$	339.5	225	12.37	12.17	9.42	9.25
3	H	2-Amino-4-Methoxy Phenylthiazole	$C_{18}H_{13}N_3O_2S$	335	224	12.53	12.41	9.55	9.36
4.	CH_3	2-Amino-4-Phenylthiazole	$C_{18}H_{13}N_3OS$	319	223	13.16	13.02	10.03	9.80
5.	CH_3	2-Amino-4-Chloro Phenylthiazole	$C_{18}H_{12}ClN_3OS$	353.5	228	11.88	11.79	9.05	8.74
6.	CH3	2-Amino-4-methoxy Phenylthiazole	$C_{19}G_{15}N_3O_2S$	349	226	12.03	11.95	9.17	8.86
7.	NO_2	2-Amino-4-Phenylthiazole	$C_{17}H_{10}N_4O_3S$	350	227	16.00	15.82	9.14	8.92
8.	NO_2	2-Amino-4-Chloro Phenylthiazole	$C_{17}H_9ClN_4O_3S$	384.5	231	14.56	14.34	8.32	8.22
9.	NO_2	2-Amino-4-Methoxy Penylthiazole	$C_{18}H_{12}N_4O_4S$	380	230	14.73	14.58	8.42	8.27

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