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Synthesis and Biological Evaluation of new 1-[(halo/nitro/methyl substituted phenyloxy) -acetyl/propionyl] Indoles

P. Bhatt, S. D. Srivastava, P. Mehta and S. K. Srivastava

Department of Chemistry, Dr. H. S. Gour University, Sagar, India

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Abstract : Indole and its derivatives are biologically active, similarly phenols are well known for their bioactive nature. These evidences have prompted us to undertake the synthesis of several 1-[(halo/nitro/methyl substituted phenyloxy)-acetyl/propionyl] Indoles, 3 (a - t). Elucidation of the structures of products were accomplished on the basis of elemental analysis and spectral data. The synthesised compounds were screened for their antimicrobial, anti-inflammatory and analgesic activities. Some of the compounds were displayed promising activities.

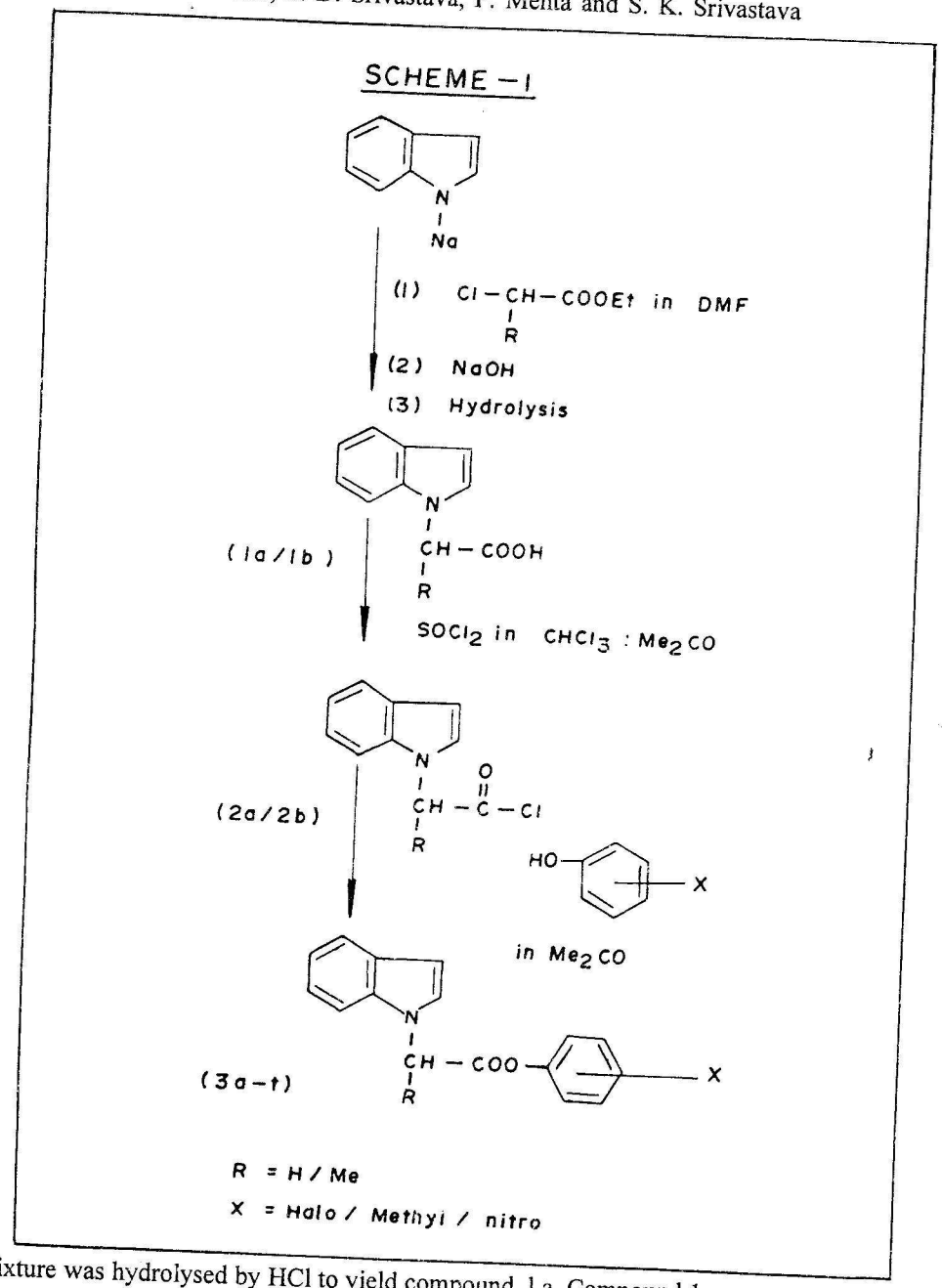
1. Introduction

As a matter of fact indole and its derivatives possess high therapeutic values.[1-3] Compounds in which a substituted phenol is linked with an indole moiety through acetic or propionic acid group, are endowed with antimicrobial, anti cancer and psychomotor slimulation activities.[4-6] We report herein the synthesis of the title compounds (3a – t). Sodium salt of indole on treatment with ethyl chloro acetate/propionate gave an ester which on saponification followed by hydrolysis yields 1-indolyl acetic/propionic acid (1a/1b). Compound 1 on reaction with thionyl chloride gave 1-indolyl-acetyl propionyl chloride (2a/2b). This acid chloride 2 on condensation with various substituted phenols in alkaline medium furnished the corresponding esters, (3a - t). The structures of 3a - t were established by their elemental analysis IR and ^{1}H NMR spectra.

2. Experimental

Melting points were determined in a melting point apparatus (Toshiwal, India) and are uncorrected. The purity of the compounds was checked on TLC. IR spectra were recorded in KBr on an Acculab-10 spectrophotometer (v max in cm^{-1}), and ^{1}H NMR spectra were obtained in $CDCL_3$ on 400 MHz on Bruker WM 400 instrument with TMS as an internal standard (chemical shift in δ, ppm).

1-Indolyl acetic acid (1a) : Equimolar solution of ethyl-chloroacetate (0.34 mole) and sodium salt of indole (0.34 mole was refluxed in DMF for about 6 hr. The resultant ester was saponified using 2M sodium hydroxide at 45° for 12 hr. After saponification the



mixture was hydrolysed by HCl to yield compound, 1 a. Compound 1 a was recrystallized by ether-hexane; m.p. 175-176°, yield 63% (Found; C, 68.53; H, 5.11; N, 7.97; $C_{10}H_9O_2N$ requires; C, 68.57; H, 5.14; N, 8.0%).

1-indolyl propionic acid, (1b) was synthesised similarly and crystallised form ether, yield 57% (Found; C, 69.79; H, 5.78; N, 7.36; $C_{11}H_{11}O_2N$ requires C, 69.84; H, 5.82; N, 7.40%).

1-indolyl acetyl chloride (2a) : To a solution of 1a (0.198 mole in $CHCl_3$: Me_2CO), thionyl chloride (0.2 mol) was added and the mixture was refluxed for 8 hrs. on boiling water bath. Excess of thionyl chloride was distilled off under reduced pressure, the residue cooled and the acid chloride, 2a, thus separated, was crystallized from chloroform, yield 81%.

Table 1. Physical data of the Compounds 3a – t

Compd* Code	R	X	Yield (%)	m.p. (°C)	Molecular Formula
3a	H	2,4,6-tribromo	61	112-14	$C_{16}H_{10}NO_2Br_3$
3b	H	2,4-dibromo	67	103-05	$C_{16}H_{11}NO_2Br_2$
3c	H	2,4,6-trichloro	83	128-30	$C_{16}H_{10}NO_2Cl_3$
3d	Me	2,4,6-trichloro	80	82-84	$C_{17}H_{12}NO_2Cl_3$
3e	H	2,4-dichloro	65	91-93	$C_{16}H_{11}NO_2Cl_2$
3f	Me	2,4-dichloro	78	110-112	$C_{17}H_{13}NO_2Cl_2$
3g	H	2-chloro	75	67-69	$C_{16}H_{12}NO_2Cl$
3h	Me	2-chloro	72	86-88	$C_{17}H_{14}NO_2Cl$
3i	H	4-chloro	81	150-52	$C_{16}H_{12}NO_2Cl$
3j	Me	4-chloro	60	121-23	$C_{17}H_{14}NO_2Cl$
3k	H	2-CH_3	73	107-09	$C_{17}H_{15}NO_2$
3l	Me	2-CH_3	70	117-19	$C_{18}H_{17}NO_2$
3m	H	3-CH_3	76	112-14	$C_{17}H_{15}NO_2$
3n	Me	3-CH_3	81	98-00	$C_{18}H_{17}NO_2$
3o	H	4-CH_3	66	133-35	$C_{17}H_{15}NO_2$
3p	Me	4-CH_3	81	124-25	$C_{18}H_{15}NO_2$
3q	H	2, 4, 6-trinitro	80	155-57	$C_{16}H_{10}N_4O_8$
3r	H	2-nitro	78	87-89	$C_{16}H_{12}N_2O_4$
3s	H	3-nitro	77	107-09	$C_{16}H_{12}N_2O_4$
3t	H	4-nitro	72	99-01	$C_{16}H_{12}N_2O_4$

*All the compounds gave satisfactory C, H & N analysis.

1-Indolyl propionly chloride (2-b) was similarly prepared and crystallized from ethyl acetate, yield 71%.

1-[(2, 4, 6-Tribromo phenyloxy) acetyl] indole (3a) : To an equimolar solution of **2a** (0.01 mol) in acetone an ice- cooled alkaline (5 ml, 4N, NaOH) solution of 2, 4, 6-tribromophenol (0.01 mol) was added and the mixture was stirred at room temperature for about 4 hr. The solid thus obtained was crystallized from ether to give 3a yield 61%, (Found; C, 39.29; H, 2.01; N, 2.82; $C_{16}H_{10}O_2NBr_3$ requires; C, 39.34; H, 2.04; N, 2.86%); IR : 1725 and 1180 (ester carbonyl), 1565 and 700 (substituted phenyl ring),

1460 (-CH_2-) 1430 (aromatic C = C), 740, 720, 640 (heteronucleus); ^{1}H NMR : 8.20-8.10 (8 H, m, Ar-H) and 4.40 (2H, s, CH_2).

Compounds, 3b-t were synthesized similarly from acetyl/propionyl chloride and different substituted phenols (Table 1).

3. Results and Discussion

Antimicrobial Activity : The compounds, 3a-t were screened for their antibacterial activity against three bacteria *S dysenteriae, S aureus* and *S flexnai* by single disc method[7] and antifungal activity against *C pannical, A niger* and *R Oryzae* by filter paper disc tachnique[8] at two different concentrations (25 and 50 μg/ml). Standard drugs streptomycin and mycostatin were also screened under similar conditions for comparison. The activity of compounds 3a, 3c, 3d and 3q were quite comparable with standard drug.

Anti-inflammatory Activity : Carrageenan induced rat paw odema method was used for evaluating the anti-inflammatory activity of the compounds, 3 (a-t) at a dose of 100 mg/kg body weight in albino rats (weighing 100-120 gm). The rate paw odema was produced by the method of Winter et al.[9] The percentage inhibition of the inflammation was calculated by applying Newbould formula.[10] The compounds 3a, 3c, 3d and 3q were found effective.

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