STUDIES ON PHENOTHIAZINES. PART 10[1] : SYNTHESIS OF 1-ETHOXY-7-SUBSTITUTED PHENOTHIAZINES

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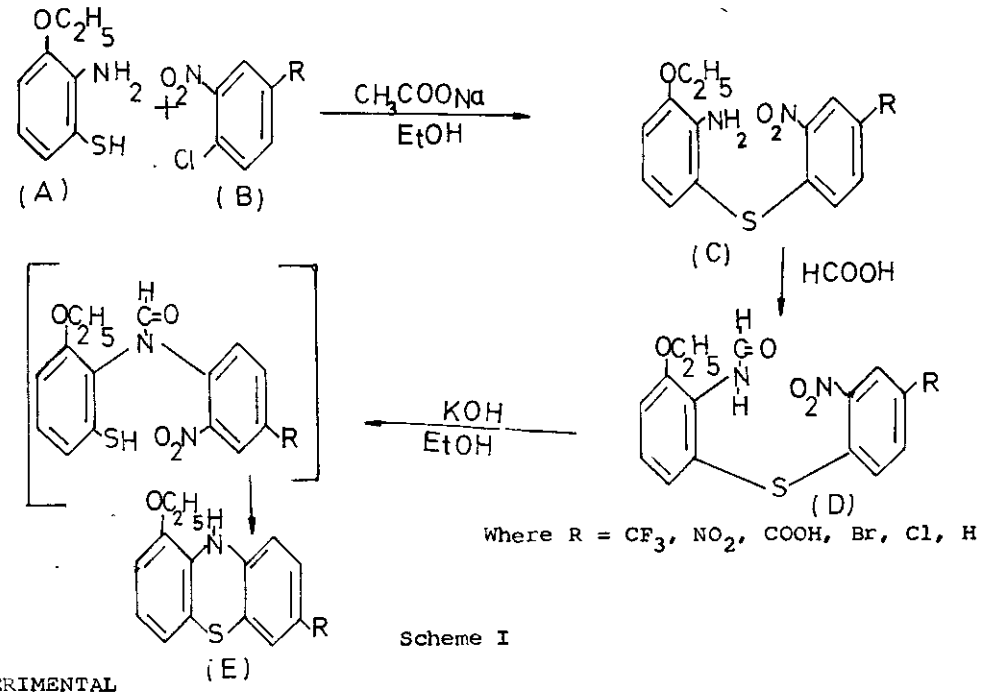
Abstract - Synthesis of 1-ethoxy-7-substituted phenothiazines via Smiles rearrangement is reported. 2-Amino-3-ethoxybenzenethiol was condensed with halonitrobenzenes and the substituted diphenylsulphides, so obtained, were converted into substituted formyl derivatives by formic acid. The latter on treatment with alcoholic KOH underwent Smiles rearrangement and yield 1-ethoxy-7-substituted phenothiazines. The structure of the synthesized compounds have been confirmed by their elemental analysis and spectral studies.

Phenothiazines find numerous applications in medicine and industry[2-5] and a number of phenothiazines have been synthesized for studying their biological activity and spectral studies. Much works[5-13] have been done on synthesis of 1-nitrophenothiazines. 1-Nitrophenothiazines can be easily prepared by Smiles rearrangement (in situ) of 2-aminobenzenethiols with reactive halonitrobenzenes in one step but 1-ethoxy-7-substituted phenothiazines cannot be prepared similarly and no reference appears to deal with synthesis of such phenothiazines. It has been considered worthwhile to extend synthetic study to 1-ethoxy-7-substituted phenothiazines in order to make them available for pharmacological screening.

In this communication we are reporting the synthesis of 1-ethoxy-7-substituted phenothiazines. These have been prepared by the Smiles rearrangement of substituted 2-formamidodiphenyl sulphides (D_{1-6}) which were obtained by the condensation of 2-amino-3-ethoxybenzenethiol (A) with halonitrobenzenes (B) and subsequent formylation with formic acid. Schematic representations of title compounds are represented in Scheme I. 2-Amino-3-ethoxybenzenethiol (A) required in the synthesis of 1-ethoxy-7-substituted phenothiazines has been prepared following the details reported elsewhere[14].



Scheme I

EXPERIMENTAL

All the mps are uncorrected. The purity of all the synthesized compounds were checked on thin-layer chromatography.

Preparation of substituted diphenylsulphides (C_{1-6}). - In a hot solution of 2-amino-3-ethoxybenzenethiol (A;0.01 mol) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mol) in ethanol (5 ml), was added to an alcoholic solution of halonitrobenzene (B; 0.01 mol) in ethanol (12 ml) and refluxed for 1 h**. The excess of the solvent was removed by evaporating solution on water bath and cooled in ice overnight. The solid separated was filtered and washed with 30% alcohol ; and recrystallised from methanol. The physical data of substituted diphenylsulphides are summarised in Table-1.

Preparation of substituted 2-formamidodiphenylsulphides (D_{1-6}). - A solution of substituted diphenylsulphides (C; 0.01 mol) in 90% formic acid (20 ml) was refluxed for 3 h. The contents of the flask were then poured into beaker containing crushed ice, filtered, washed with water until the filtrate was neutral. The

** It has been observed in the case of 1-ethoxy derivatives that over heating or a long time heating of the reaction mixture of 2-amino-3-ethoxybenzenethiol and halonitrobenzenes during the formation of diphenylsulphides resulted in the only liquids which were difficult to crystallise.

crude product was recrystallised from benzene. Physical data of substituted 2-formamidodiphenylsulphides are given in Table-2.

Preparation of 1-ethoxy-7-substituted phenothiazines(E_{1-6}). - To a refluxing solution of the substituted formyl derivatives (D; 0.01 mol) in acetone (15 ml) was added an alcoholic solution of potassium hydroxide (0.2 g in 5 ml ethanol). The colour of the reaction mixture darkned immediately on addition of an alcoholic potassium hydroxide solution. The contents were heated for 30 min. To this solution, a second lot of potassium hydroxide [0.2 g in ethanol (5 ml)] was added and refluxed for 2 h. The contents were poured into a beaker containing crushed ice and filtered. The residue was washed with cold water and finally with 30% ethanol and crystallised from methanol-benzene to give pure compounds. Physical data of 1-ethoxy-7-substituted phenothiazines are given in Table-3.

Infrared spectra .- Infrared spectra of 1-ethoxy-7-substituted phenothiazines exhibited a single peak at 3200-3350 cm^{-1} which is assigned to NH group. Bands between 1050-1120 cm^{-1} are probably associated with the C-O-C stretching mode.

Nmr spectra .- In the nmr spectra of 1-ethoxy-7-substituted phenothiazines, a singlet at δ 8.5-8.4 is observed for NH proton. The triplets in the region δ1.25-1.05 and quarters in the region δ3.6-4.0 are observed due to CH_3 and CH_2 groups of ethoxy linkage at 1-position respectively.

Mass spectra .- The molecular ion is the base peak and suggests the high stability of the phenothiazine nucleus due to a high degree of conjugation.

Table 1. Physical data of substituted Diphenylsulphides(C_{1-6})

Compd. No.	Compound R	Yield (%)	Mp (^oC)	Molecular Formula	% N Calcd.	% N Found
1.	CF_3	40	127	$C_{15}H_{13}N_2SO_3F_3$	7.82	7.78
2.	H	48	95	$C_{14}H_{14}N_2SO_3$	9.65	9.61
3.	NO_2	60	139	$C_{14}H_{13}N_3SO_5$	12.53	12.58
4.	COOH	55	134	$C_{15}H_{14}N_2SO_5$	8.38	8.41
5.	Br	58	149	$C_{14}H_{13}N_2SO_3Br$	7.58	7.53
6.	Cl	52	115	$C_{14}H_{13}N_2SO_3Cl$	8.64	8.59

Table 2. Physical data of Substituted 2-Formamidodiphenylsulphides(D_{1-6})

Compd. No.	Compound R	Yield (%)	Mp (^{o}C)	Molecular Formula	% N	
					Calcd.	Found
1.	CF_3	43	141	$C_{16}H_{13}N_2SO_4F_3$	7.25	7.28
2.	H	45	103	$C_{15}H_{14}N_2SO_4$	8.80	8.84
3.	NO_2	58	151	$C_{15}H_{13}N_3SO_6$	11.57	11.53
4.	COOH	52	146	$C_{16}H_{14}N_2SO_6$	7.73	7.69
5.	Br	54	163	$C_{15}H_{13}N_2SO_4Br$	7.05	7.10
6.	Cl	48	132	$C_{15}H_{13}N_2SO_4Cl$	7.95	8.02

Table 3. Physical data of 1-Ethoxy-7-substituted phenothiazines(E_{1-6})

Compd. No.	Compound	Yield (%)	Mp (^{o}C)	Molecular formula	Calcd. (%)			Found(%)		
					C	H	N	C	H	N
1.	CF_3	58	166	$C_{15}H_{12}NSOF_3$	57.87	3.85	4.50	57.90	3.90	4.53
2.	H	48	120	$C_{14}H_{13}NSO$	69.13	5.34	5.76	69.18	5.39	5.78
3.	NO_2	60	178	$C_{14}H_{12}N_2SO_3$	58.33	4.16	9.72	58.30	4.21	9.76
4.	COOH	50	169	$C_{15}H_{13}NSO_3$	62.71	4.52	4.87	62.68	4.54	4.90
5.	Br	55	190	$C_{14}H_{12}NSOBr$	52.71	3.72	4.34	52.20	3.77	4.36
6.	Cl	50	159	$C_{14}H_{12}NSOCl$	60.64	4.33	5.65	60.68	4.37	5.63

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