Studies on Phenothiazines, Part 6[1]. Synthesis of 3-alkoxy-1-nitro-7-substituted phenothiazines via Smiles rearrangement

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Abstract - Synthesis of 3-alkoxy-1-nitro-7-substituted phenothiazines via Smiles rearrangement is reported. 5-Alkoxy-2-amino-3-nitro benzenethiols prepared by hydrolytic fission of 6-alkoxy-4-nitrobenzo-1,2,3-dithiazolium chloride (The Herz Compound) were condensed with substituted o-chloro-nitrobenzenes and the diaryl sulfides so obtained were converted into formyl derivatives by formic acid. The latter on treatment with alcoholic KOH underwent Smiles rearrangement yielding 3-alkoxy-1-nitro-7-substituted phenothiazines.

Phenothiazines find a number of uses in medicines such as tranquilizers[6], anticancer drugs[7], antiinflammatory[8] agents, antihistamines[9], anthelmintics[10], local anesthetics[11], antiseptic[12], growth inhibitors[13] and in treatment of neuropsychatric[14] disorders; in addition to its uses as insectisides[15] and in industry as antioxident[16], stabilizers[17].

Keeping in view a wide spectrum of uses of phenothiazines series it has been considered worthwhile to extend studies on synthesis of phenothiazines in continuation of our work[1-5] with an object to get phenothiazines with different pattern of nuclear substituents.

In the present investigation 3-alkoxy-1-nitro-7-substituted phenothiazines were prepared by Smiles rearrangement of 5-alkoxy-2-formamido-2'; 3-dinitro-4'-substituted (nitro, chloro, methyl) diphenyl sulfides with alcoholic KOH. Formyl derivatives were prepared by the formylation with formic acid of 5-alkoxy-2-amino-2',3-dinitro-4'-substituted diphenyl sulfides which are the condensation products of 5-alkoxy-2-amino-3-nitro benzenethiols and substituted o-chloronitrobenzenes. Overall reaction taking place in the synthesis of phenothiazines is shown in a Scheme I.

1 For Part 5 see reference1

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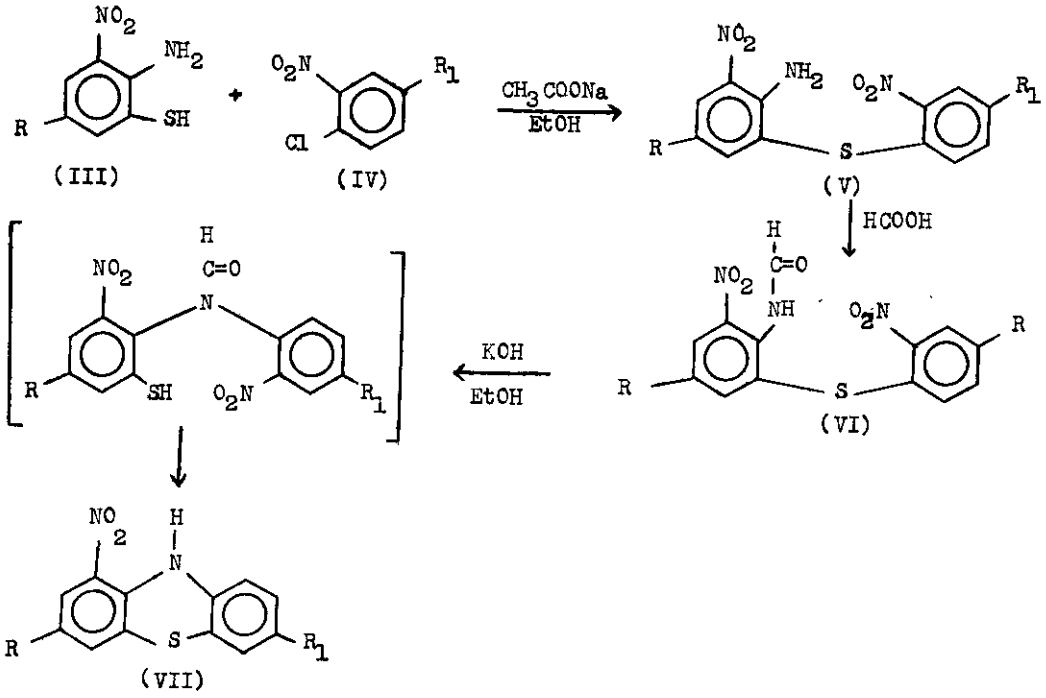
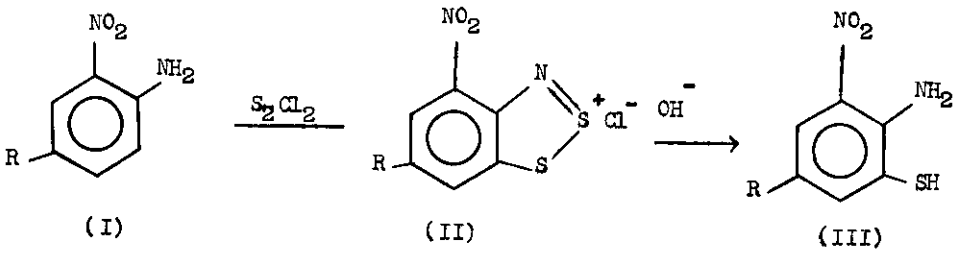


Scheme I

5-Alkoxy-2-amino-3-nitro benzenethiols used in these syntheses have been prepared by the hydrolytic cleavage of 6-alkoxy-4-nitrobenzo-1,2,3-dithiazolium chloride (The Herz Compound) which were prepared by the Herz reaction[18] of 4-alkoxy-2-nitroaniline with sulphur monochloride following the details reported by us elsewhere[1]. The Herz reaction is shown in Scheme II.



R= OCH_3 , OC_2H_5

Scheme II

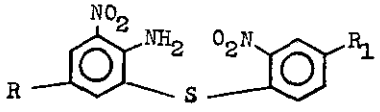
Experimental

Preparation of Diaryl Sulphides (V a-f)

To a refluxing solution of the substituted 2-amino-benzenethiol (III, 0.012 mol) in ethanol (20 ml), a solution of anhydrous sodium acetate (0.01 mol) in ethanol (5 ml) was added. An alcoholic solution of halogenonitrobenzene (IV, 0.01 mol) was then slowly added with stirring. After refluxing for 4 hours, the solution was concentrated and cooled in ice overnight. The solid which separated was collected and washed with water until the filtrate was colourless. Recrystallization from methanol afforded the desired product. Their physical data are recorded in Table I.

Table I

The physical data of substituted diaryl sulphides (V a-f)



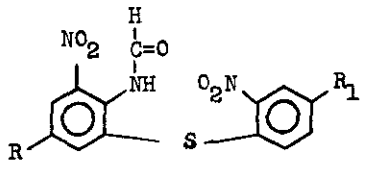
	Compound V	Yield %	Molecular formula	M.P. °C	N (%) Found	N (%) Calcd
a	R=OCH_3 ; R_1=NO_2	59	$C_{13}H_{10}N_4O_7S$	145	15.25	15.30
b	R=OCH_3 ; R_1=Cl	62	$C_{13}H_{10}ClN_3O_5S$	124	11.76	11.81
c	R=OCH_3 ; R_1=CH_3	60	$C_{14}H_{13}N_3O_5S$	160	12.60	12.53
d	R=OC_2H_5 ; R_1=NO_2	59	$C_{14}H_{12}N_4O_7S$	157	14.70	14.74
e	R=OC_2H_5 ; R_1=Cl	65	$C_{14}H_{12}ClN_3O_5S$	137	11.35	11.36
f	R=OC_2H_5 ; R_1=CH_3	60	$C_{15}H_{15}N_3O_5S$	140	12.00	12.03

Preparation of the 2-Formamidodiaryl Sulphides (VI a-f)

The diaryl sulphides (V, a-f, 0.01 mol) were dissolved in 90% formic acid (20-25 ml) and heated under reflux for 4-6 hours. The contents of the flask were then poured into a beaker containing crushed ice. The solid so obtained was collected, washed with cold water until the filterate was neutral. The crude product was recrystallized from benzene (Table 2)

Table 2

The physical data of 2-formamidodiaryl sulphides (VI a-f)



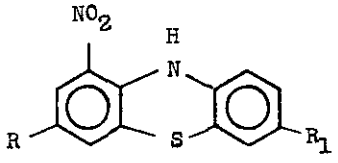
	Compound VI	Yield (%)	Molecular formula	M.P. °C	N (%) Found	Calcd
a	R=OCH_3 ; R_1=NO_2	70	$C_{14}H_{10}N_4O_8S$	182	14.26	14.21
b	R=OCH_3 ; R_1=Cl	73	$C_{14}H_{10}ClN_3O_6S$	157	10.90	10.95
c	R=OCH_3 ; R_1=CH_3	70	$C_{15}H_{13}N_3O_6S$	175	11.50	11.58
d	R=OC_2H_5 ; R_1=NO_2	70	$C_{15}H_{12}N_4O_8S$	143	13.66	13.72
e	R=OC_2H_5 ; R_1=Cl	60	$C_{15}H_{12}ClN_3O_6S$	169	10.48	10.56
f	R=OC_2H_5 ; R_1=CH_3	62	$C_{16}H_{15}N_3O_6S$	180	11.10	11.14

Preparation of the phenothiazines (VII a-f)

To the refluxing solution of the formyl derivatives (VI, a-f, 0.01 mol) in acetone (15 ml) was added and alcoholic solution of potassium hydroxide (0.2 gm in 5 ml ethanol). The colour of the reaction mixture darkened immediately on the addition of alkaline alcoholic solution. The contents were heated under reflux for 30 minutes. To this solution a second lot of alcoholic solution of potassium hydroxide (0.2 gm in 5 ml ethanol) was added and refluxing was continued for 2 hours. 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 benzene/methanol to get pure compound (Table 3).

Table 3

The physical data of phenothiazines (VII a-f)



	Compound VII	Yield (%)	Molecular formula	M.P. °C	N (%) Found	Calcd
a	R=OCH$_3$; R$_1$=NO$_2$	52	$C_{13}H_9N_3O_5S$	190	13.10	13.16
b	R=OCH$_3$; R$_1$=Cl	60	$C_{13}H_9ClN_2O_3S$	215	9.05	9.07
c	R=OCH$_3$; R$_1$=CH$_3$	65	$C_{14}H_{12}N_2O_3S$	152	9.66	9.72
d	R=OC$_2$H$_5$; R$_1$=NO$_2$	52	$C_{14}H_{11}N_3O_5S$	187	12.56	12.61
e	R=OC$_2$H$_5$; R$_1$=Cl	50	$C_{14}H_{11}ClN_2O_3S$	140	8.62	8.68
f	R=OC$_2$H$_5$; R$_1$=CH$_3$	60	$C_{15}H_{14}N_2O_3S$	172	9.20	9.27

Purity of all the compounds was checked by TLC on silica gel plates in various nonaqueous solvent systems.

Infrared Spectra

Infrared spectra of all these compounds included in this paper have been studied extensively. Spectra have been scanned in KBr on Perkin-Elmer 577 spectrophotometer. Each of the 2-amino-3-nitro-5-alkoxydiphenyl sulfide exhibits two peaks in the region 3360-3380 cm^{-1} and 3450-3480 cm^{-1} which can be assigned to symmetric and asymmetric NH streyching vibrations of primary amino group. A single sharp peak is observed in the region 3300-3380 cm^{-1} in all the phenothiazines which is due to secondary amino group. In all the compounds (V a-f, VI a-f, VII a-f) two peaks are observed in the region 1575-1565 cm^{-1} and 1350-1330 cm^{-1} corresponding to the asymmetric and symmetric valance vibration of the nitro group.

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