GLC: Column, 5% SE 30 on Chromosorb G (80 to 100 mesh) (0.3 cm inner diameter × 2 m long stainless steel); programmed column temperature, increase in 5° per min from 60° to 260°; carrier gas, N_2 (30 ml per min).

On the other hand, thin-layer chromatography of the hydrolysate using Avicel SF cellulose was carried out. Two solvent systems were used; C, AcOEt: pyridine: H_2O (10: 4: 3, by vol.); D, AcOEt: AcOH: HCOOH: H_2O (18: 3: 1: 4, by vol.). The products were detected with periodate–permanganate–benzidine reagent.[15] Table II shows retention times of trimethylsilyl derivatives in GLC and *Rf* values in TLC.

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An Unequivocal Synthesis of 1-Methylthio-7-chlorophenazine[1]

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Recent article[1] from our laboratory has described that while irradiation of N-acetyl-4-chloro-2-nitro-2′-methylthiodiphenylamine (I) gives 1-methylthio-7-chlorophenazine-5-oxide (IV) which is readily reduced to 1-methylthio-7-chlorophenazine (V), reduction of I with triethyl phosphite followed by autooxidation leads to the formation of isomeric 1-methylthio-8-chlorophenazine (III). This interesting observation makes it possible to predict that the cyclization of I to dihydrophenazine (II) by triethyl phosphite could involve a novel molecular rearrangement as shown in Chart 1. The structure of V has been assigned on the basis of physicochemical data and mechanistic consideration[3] of the photocyclization of I leading to IV.

In this paper, we now describe an unequivocal synthesis of V, which also confirms the structure of III.

Phenazines have frequently been prepared[4] by the condensation of *o*-benzoquinones with *o*-phenylenediamines, the thermal condensation of catechols with *o*-phenylenediamines, or the Wohl-Aue condensation of nitrobenzenes and anilines. These procedures, however, are not adequate for the synthesis of V because of unaccessible starting materials and low yields with several side products. Reaction conditions for cyclizations of 2-nitrodiphenylamines to phenazines have been investigated by several groups of workers,[5] but their results are not satisfactory for synthetic purposes. More recently, Cross and co-workers[6] have reported that novel cyclization of 2-nitrodiphenylamines to phenazines and their N-oxides in both acidic

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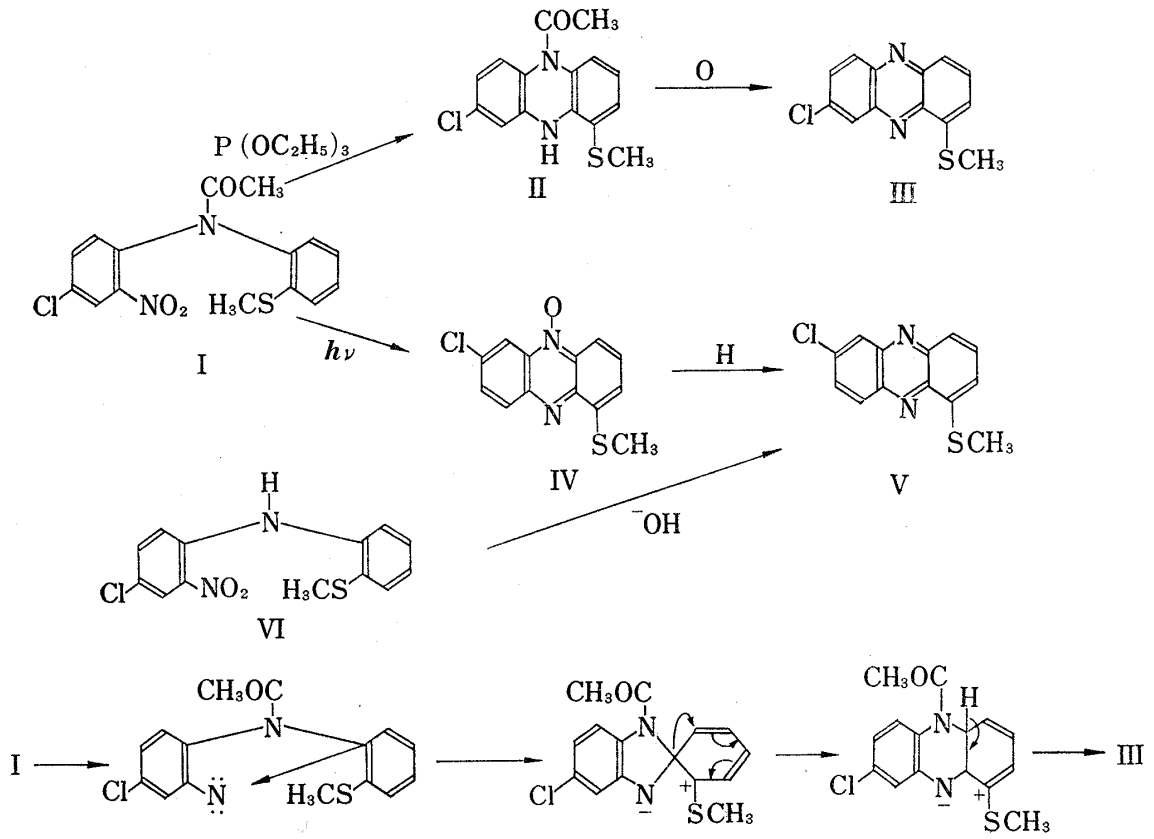

Chart 1

and alkaline media: The procedure involves heating of 2-nitrodiphenylamines in nonpolar solvents in the presence of excess potassium hydroxide or in conc. sulfuric acid. The reaction was applied to chloro or methyl substituted 2-nitrodiphenylamines and resulted in the formation of substituted phenazines and phenazine N-oxides in moderate yields.

We attempted cyclization of 4-chloro-2-nitro-2′-methylthiodiphenylamine (VI), which is obtained by the Smiles rearrangement of 4-chloro-2-nitro-2′-acetamidodiphenylsulfide[7] followed by methylation and hydrolysis, under various reaction conditions. Among many trials, when VI was heated under reflux in xylene in the presence of excess potassium hydroxide (modified Cross procedure) and the reaction product was submitted to chromatography, V, mp 189°, could be isolated in 20% yield. Thus, one of the Cross' procedures can be extended successfully to synthesis of alkylthio substituted phenazine. The structure of V is unambiguous because of no possibility of a molecular rearrangement in accord with Cross' results. V was identical in every respect with a sample obtained by photocyclization of I followed by deoxygenation. Accordingly, the present unequivocal synthesis of V also leaves no doubt on the structure of III.

Experimental[8]

4-Chloro-2-nitro-2′-methylthiodiphenylamine (VI)——4-Chloro-2-nitro-2′-acetylaminodiphenylsulfide[7] (1 g) and NaOH (0.25 g) in EtOH–acetone (1: 1) was heated at reflux for 15 min. After cooling, to the reaction mixture was added excess MeI (3.5 g) and the solvent was evaporated under reduced presure. The oily residue was extracted with $CHCl_3$ and the chloroform extract was washed with H_2O, dried and concentrated. The resulting residue was crystallized by addition of ether and recrystallized from EtOH to give I, mp 139° (lit.[7] mp 142°) as yellow crystals (0.8 g). IR ν_{max}^{KBr} cm^{-1}: 1670 ($NCOCH_3$). I (1 g) was heated

7) W.J. Evans and S. Smiles, *J. Chem. Soc.*, **1935**, 181.
8) All melting points are uncorrected.

in ethanolic NaOH under reflux for 30 min. After cooling, the reaction mixture was neutralized with dil. HCl to deposit a crystalline solid. The solid was washed with H_2O, dried and recrystallized from EtOH to give VI, mp 124°, as red needles (0.7 g). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2S$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.60; H, 4.50; N, 10.68. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH).

1-Methylthio-7-chlorophenazine (V)——VI (1.7 g, 0.005 mole), powdered potassium hydroxide (1.4 g, 0.025 mole), and xylene (100 ml) was stirred and heated under reflux for 7 hr. The reaction mixture was filtered whilst hot and the residue was washed with hot xylene. The combined filtrates were evaporated to dryness and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O and dried over anhydrous Na_2SO_4. The $CHCl_3$ solution was chromatographed on silica gel to isolate yellow crystals. Recrystallization of the crystals gave V, mp 189°, as yellow needles (0.13 g). *Anal.* Calcd. for $C_{13}H_9N_2SCl$: C, 59.88; H, 3.48; N, 10.74. Found: C, 59.59; H, 3.77; N, 10.50. NMR ($CDCl_3$) δ: 8.39—7.30 (6H, multiplet, aromatic protons), 2.65 (3H, singlet, SCH_3). V thus prepared was identical in infrared, nuclear magnetic resonance and Mass spectra with a sample obtained by irradiation of I followed by deoxygenation.

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A Convenient Synthesis of 1-(2-Halogenoethyl)-3-nitro-1-nitrosoguanidines

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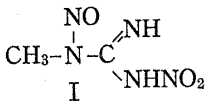
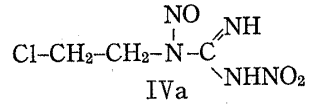
1-Methyl-3-nitro-1-nitrosoguanidine (I) has recently received much attention from the fact that, when continuously administered by dissolving in drinking water, it induces adenocarcinoma in the glandular stomach of rats with high frequency.[2] While, Skinner, *et al.*[3] reported that 1-(2-chloroethyl)-3-nitro-1-nitrosoguanidine (IVa) showed carcinostatic action against intraperitoneal L 1210.



I



IVa

In the preceding paper,[4] the present author reported that, among 1-alkyl(R=C_{1-9})-3-nitro-1-nitrosoguanidines, the chloroethyl compound IVa showed the most potent mutagenicity for bacteria, though the mutagenicity of I was remarkably high in comparison with those of other 1-alkyl derivatives.

This paper describes a convenient synthesis of 1-(2-halogenoethyl)-3-nitro-1-nitrosoguanidines (IVa, b, c). Since introduction of an N-(2-chloroethyl)-N-nitroso group [Cl-CH_2-CH_2-N(NO)-] into a molecule is sometimes difficult because of easy cyclization, this synthetic method involving an ethylenimine derivative as an intermediate will be useful for the synthesis of this type of compounds.

As shown in Chart 1, treatment of I with ethylenimine gave 1,1-dimethylene-3-nitroguanidine (II) in 82% yield, of which nuclear magnetic resonance (NMR) spectrum in hexa-

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