# Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XXV (1). Synthesis of 1,6-Diazathianthrene From 3-Mercaptopyridin-2(1*H*)-thione *via* A Novel Dehydrothiolation Reaction in the Presence of Triethylamine



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The generation of the dianion of 3-mercaptopyridin-2(1*H*)-thione with triethylamine in *N,N*-dimethylformamide followed by reaction in the presence of 2-chloronitrobenzene fails to give 1-azathianthrene which is formed in good yield when sodium hydride was employed as the base. The principle product isolated from the reaction was instead 1,6-diazathianthrene. Mechanistic considerations are discussed.

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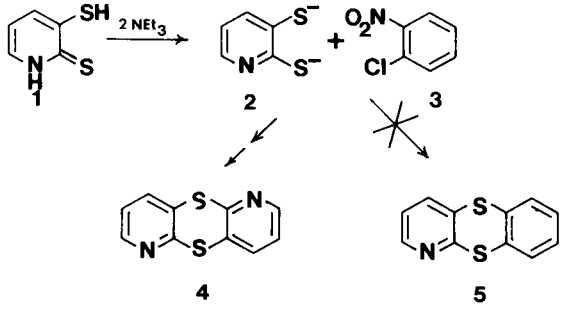
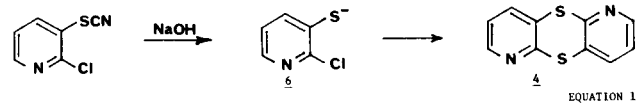
As a part of our continuing investigation of novel phenoxathiins and other potentially psychoactive compounds related to the phenothiazines, we have recently reported the first example of a monoazathianthrene, **5** (3), prepared *via* the reaction of the dianion of 3-mercaptopyridine-2(1*H*)-thione (**2**) with 2-chloronitrobenzene (**3**) (Scheme I).

SCHEME I




In our previous report (3), sodium hydride was used as the base to generate the dianion and a good yield of 1-azathianthrene (**5**) was obtained. However, during an attempt to prepare a further quantity of **5**, triethylamine was employed as the base instead of sodium hydride, according to the general procedure of Elliott and co-workers (4) which has been utilized in the preparation of 1-azaphenoxathiin analogs *via* the reaction of the dianion of 3-hydroxypyridin-2(1*H*)-thione. Interestingly, none of the anticipated 1-azathianthrene (**5**) was obtained. Instead, the major product, which formed in a nearly quantitative yield, was 1,6-diazathianthrene (**4**), a compound which had previously been prepared by the self-condensation of 2-chloropyridine-3-thiolate (**6**) as shown in Equation 1 (5).



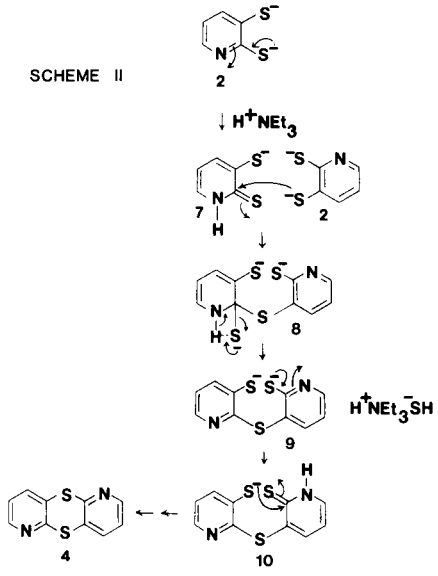

EQUATION 1

Repetition of the reaction under identical conditions except for the omission of the chloro-2-nitrobenzene (**3**) also led to the exclusive formation of **4**.

The identity of **4** was established by comparison of its mass spectrum, $^{1}H$- and $^{13}C$-nmr spectra and melting point with those of an authentic sample of **4**. When chloro-2-nitrobenzene was present in the reaction mixture, it was quantitatively reisolated from the reaction mixture by chromatography.

The change in the course of the reaction is rather interesting in view of the successful syntheses of 1-azaphenoxathiin analogs previously reported (4). This behavior can, however, be rationalized if it is assumed, reasonably, that when triethylamine is employed as the base a significant proportion of 3-mercaptopyridin-2(1*H*)-thione (**1**) exists at equilibrium in the monoionic form, as for example **7** in Scheme II. It is then feasible that the 2-position of **7** could be attacked by the powerfully nucleophilic 3-thiolate anion of a second molecule of either **2** or **7** to yield **8** in which the two pyridine rings are connected *via* a sulfide linkage. Subsequent loss of a thiolate anion would thus provide **9**. Repetition of the process, *via* **10**, would then provide the observed 1,6-diazathianthrene (**4**) with a net elimination of two molecules of hydrogen sulfide Alternatively, a concerted mechanism could also account for the formaton of **4**, this possibility supported by the observed lack of formation of 3,3'-dimercapto-2,2'-dipyridyl sulfide.

SCHEME II



In general, dianions of 3-hydroxypyridin-2(1*H*)-thione have been generated using such bases as sodium hydride or sodium ethoxide (6-10). However, in that system, triethylamine may be successfully employed as the base without a change in the course of the reaction to give 1,6-diazadioxin, the product which would result from a condensation analogous to that observed in the case at hand. The difference may presumably be ascribed to the lower relative nucleophilicity of the 3-phenolate anion as compared with that of the 3-thiolate. Thus, in the case of the former, initial nucleophilic attack occurs preferentially through the 2-thiolate anion precluding the formation of 1,6-diazadioxin by self-condensation.

In conclusion, it is clear that the generation of thiolate-thione species such as **7** using bases which allow protons to remain in the reaction medium may provide access to systems different from those observed when other bases are employed. We hope to utilize this possibility in the synthetic elaboration of other ring systems. Results of these investigations will be forthcoming.

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. All nmr spectra were taken on a Varian XL-100-15 spectrometer operating at frequencies of 100.060 and 25.158 MHz for $^1$H and $^{13}$C respectively. Low resolution mass spectra were taken on a Hewlett-Packard Model 5930 GC/MS system equipped with a Model 5933 data system. Spectra were taken by direct probe insertion at an ionizing energy of 70 eV and a source temperature of 250°.

Synthesis of 1,6-Diazathianthrene (**4**) from the Reaction of 3-Mercaptopyridine-2(1*H*)-thione in the Presence of Triethylamine.

To a solution of 0.10 g (0.7 mmole) of 3-mercaptopyridine-2(1*H*)-thione (**1**) (11) in 15 ml of dry, distilled *N,N*-dimethylformamide (DMF) was added 0.4 ml of triethylamine. The solution was maintained under a dry argon atmosphere and chilled in an ethanol-dry ice bath, after which 0.11 g (0.7 mmole) of 2-chloronitrobenzene (**3**) in 20 ml of DMF was added. The solution was stirred throughout the addition, a period which lasted for 10 minutes. The resultant solution was maintained at ethanol-dry ice temperature for 2 hours after which it was allowed to come to room temperature before being brought to reflux for 10 hours. After completion of the reflux period, the solution was again allowed to return to room temperature after which it was poured into 100 ml of distilled water and extracted with 3 × 100 ml of ethyl acetate. The combined ethyl acetate extracts were then washed with 2 × 50 ml portions of 10% aqueous sodium carbonate followed by 2 × 50 ml portions of distilled water. After drying over anhydrous sodium sulfate, the ethyl acetate solution was reduced to a thick brownish oil which partially solidified.

The brownish semi-solid which was obtained from the ethyl acetate extracts was redissolved in acetone and absorbed onto silica, after which the acetone was removed *in vacuo*. The silica containing the isolated reaction mixture was then loaded onto a 15 g silica gel column which was eluted with a linear solvent gradient which was varied from pure cyclohexane to a mixture of cyclohexane:ethyl acetate (3:7) (total elution solvent volume was 500 ml). The product eluted as the second band from the column; the first band comprised of the unreacted 2-chloronitrobenzene which was quantitatively re-isolated. The 1,6-diazathianthrene (**4**) was recrystallized from methanol to give 4 (0.076 g, 97% yield) as fine needles, mp 183-184° [lit mp 183-185° (12), 186-188° (5)]. The $^1$H- and $^{13}$C-nmr chemical shifts and coupling constants were in complete agreement with those previously reported (5), which in conjunction with the mass spectrum, which gave a molecular ion at 218 as the base peak in the spectrum and a fragmentation pattern consistent with the proposed structure, provided an unequivocal confirmation of the identity of the product.

Repetition of the reaction of 3-mercaptopyridin-2(1*H*)-thione (**1**) with triethylamine in DMF without 2-chloronitrobenzene (**3**) also led to the essentially quantitative formation of 1,6-diazathianthrene (**4**) as the exclusive product of the reaction.

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## REFERENCES AND NOTES

(1) For the previous paper in this series, see: "Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XXIV. Synthesis and Characterization by $^{13}$C-NMR Spectroscopy of Isomeric Benzoxathiinopyridazinones: 1-oxo-1,2-dihydro-2,3-diazaphenoxathiin and 4-oxo-3,4 3,4-dihydro-2,3-diazaphenoxathiin. The First Observation of a Smiles Rearrangement involving Divalent Sulfur during the Synthesis of an Azaphenoxathiin", C. H. Womack, L. M. Martin, G. E. Martin and K. Smith, *J. Heterocyclic Chem.*, **19**, 1447 (1982). The present work also represents Part 13 in the series Novel Heterocyclic systems.

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