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## Imidazo[4,5-d]pyridazines. V.

### The Reaction of Methylthioimidazo[4,5-d]pyridazines with Chlorine in Methanol

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The extensive report by Noell and Robins (3) on the reaction of gaseous chlorine in methanol upon variously substituted methylthiopurines prompted the application of this reaction to methylthioimidazo[4,5-d]pyridazines. These authors have reported replacement of the methylthio group with chlorine, with hydroxyl and the oxidation of the methylthio group to the methylsulfonyl group.

Attempts to replace a methylthio group with chlorine in the imidazo[4,5-d]pyridazine ring system were unsuccessful, however, several reactions did occur as shown in Flow Sheet I.

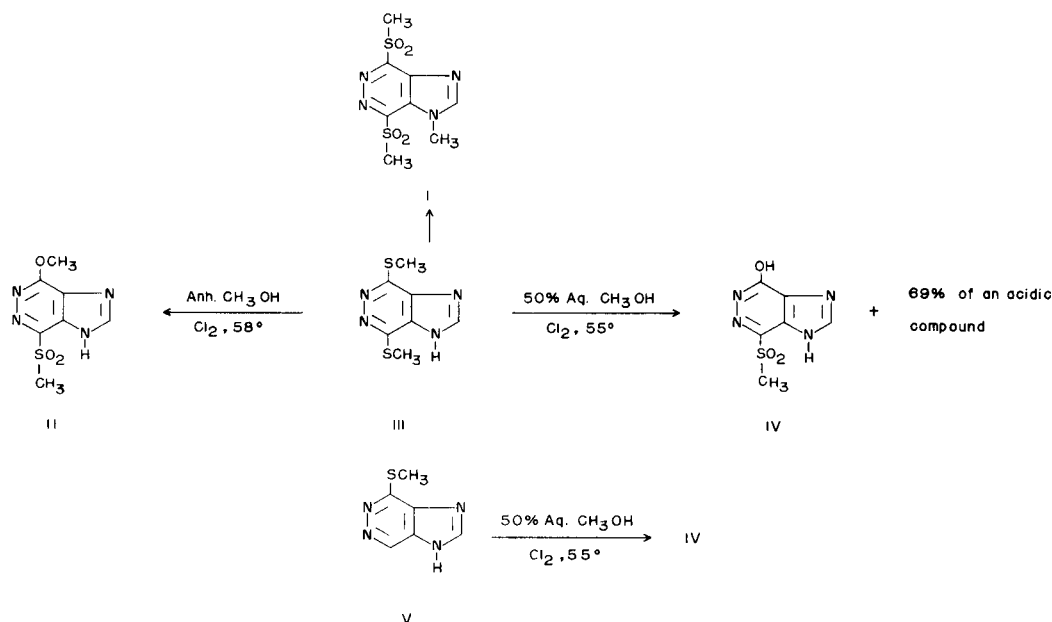
4,7-Bis(methylthio)imidazo[4,5-d]pyridazine (III), when allowed to react with chlorine gas in anhydrous methanol at 58° with previous flushing of the system and solution with dry nitrogen gave 4(7)-methoxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (II) in 54% yield. A strong absorption band at 8.1  $\mu$  in the infrared spectrum confirmed the presence of the methoxyl group. When III was allowed to react with chlorine gas in 50% aqueous methanol at 55°, 4(7)-hydroxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (IV) was obtained together with an acidic product, m.p. 211-212° of variable composition. Furthermore, when 4-methylthioimidazo[4,5-d]-

pyridazine (V) (5) was allowed to react with chlorine gas in 50% aqueous methanol at 55°, 4(7)-hydroxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (IV) was obtained. Compound IV obtained from either III or V was shown to be identical by mixed melting point and identical infrared spectra. The infrared spectrum of IV possessed bands at 3.1  $\mu$  (N-H), 5.9  $\mu$  (Amide I) and 8.75-8.85  $\mu$  and 7.57  $\mu$  (sulfone).

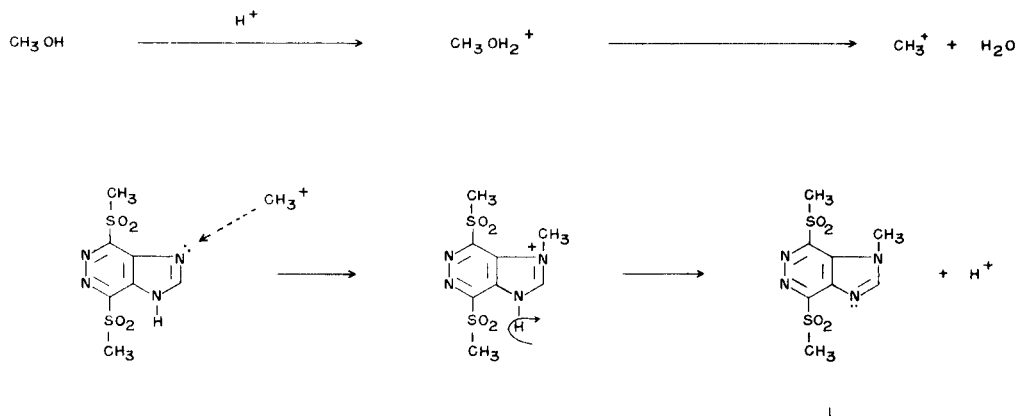
When 4,7-bis(methylthio)imidazo[4,5-d]pyridazine (III) was allowed to react with chlorine gas in 50% aqueous methanol under the same conditions wherein IV was obtained except the reaction time was increased, 1-methyl-4,7-bis(methylsulfonyl)imidazo[4,5-d]pyridazine (I) was obtained. The assignment of structure of compound I was based upon C, H, N and S analysis; the insolubility of the compound in either alkaline solution or in dilute acid solution, and the infrared absorption spectrum. The 6.52  $\mu$  band normally seen in imidazo[4,5-d]pyridazines with the hydrogen atom attached to the 1-nitrogen atom was absent in the spectrum of compound I.

A possible mechanism for the formation of I is outlined in Flow Sheet II which postulates an intermediate methyl carbonium ion generated from the methanol in the acid solution.

FLOW SHEET I



## FLOW SHEET II



## EXPERIMENTAL (4)

## 4(7)-Methoxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (II).

4,7-Bis(methylthio)imidazo[4,5-d]pyridazine (5) (1.0 g., 0.0047 mole) was nearly dissolved in 260 ml. of absolute methanol. Dry nitrogen was bubbled through the mixture for 10 minutes, then dry chlorine was bubbled through the mixture for 30 minutes. The mixture immediately became a clear pale yellow solution and during the course of the addition of the chlorine the temperature rose to 58°. The solvent was removed under reduced pressure leaving a white solid. This was recrystallized twice from absolute ethanol to yield a white solid, m.p. 312-313°.

*Anal.* Calcd. for  $\text{C}_7\text{H}_8\text{N}_4\text{O}_3\text{S}$ : C, 36.84; H, 3.54; N, 24.55; S, 14.05. Found: C, 37.18; H, 3.79; N, 24.36; S, 13.99.

## 4(7)-Hydroxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (IV).

## (a) Preparation from 4-Methylthioimidazo[4,5-d]pyridazine.

In 150 ml. of 50% aqueous methanol was suspended 1 g. of 4-methylthioimidazo[4,5-d]pyridazine. Chlorine gas was passed through the mixture for 15 minutes during which time the starting material dissolved, whereupon the reaction mixture became cloudy. The solvent was partially removed under reduced pressure and a light grey solid was removed by filtration. The nature of this substance is unknown. The filtrate deposited fine yellow crystals after standing ten days at room temperature. These were further purified by recrystallization from water, m.p. 342-343°. This compound had the following infrared absorption bands: 3.1  $\mu$  (NH), 5.9  $\mu$  (Amide I band), 7.75  $\mu$  and 8.75-8.85  $\mu$  (sulfone) (6).

*Anal.* Calcd. for  $\text{C}_8\text{H}_8\text{N}_4\text{O}_3\text{S}$ : C, 33.64; H, 2.82; N, 26.16. Found: C, 33.63; H, 3.11; N, 26.10.

## (b) Preparation from 4,7-Bis(methylthio)imidazo[4,5-d]pyridazine.

4,7-Bis(methylthio)imidazo[4,5-d]pyridazine (3 g.) was suspended in 450 ml. of 50% aqueous methanol and chlorine gas passed into the suspension for 25 minutes. During this period the temperature rose to 55° and all of the solid went into solution. Slowly a flocculent white precipitate began to separate. This was removed by filtration and amounted to 2.7 g. This product was recrystallized from 95%

ethanol, m.p. 210-211°. This compound has given variable analytical results, e.g., C, 28.29 to 33.83; H, 3.09 to 4.22; N, 18.40 to 19.63; and S, 14.63 to 22.63; it is halogen-free and acidic.

The filtrate upon evaporation to dryness and recrystallization of the residue (IV) twice from hot water (Norite) gave a pale yellow solid, m.p. 342-343°, identical with the compound, 4(7)-hydroxy-7(4)-methylsulfonylimidazo[4,5-d]pyridazine (IV), obtained as described under part (a) above.

## 4,7-Bis(methylsulfonyl)-1-methylimidazo[4,5-d]pyridazine (I).

One gram (0.0047 mole) of 4,7-bis(methylthio)imidazo[4,5-d]pyridazine was suspended in 150 ml. of 50% aqueous methanol. Chlorine gas was bubbled through the mixture for 20 minutes. It appeared that the starting material went into solution while at the same time a grey-white solid began to precipitate from the reaction mixture. The solid was filtered and washed with aqueous methanol, m.p. 233-234°. A portion was recrystallized from 95% ethanol yielding a white fluffy solid decomposing at 236°. A sulfur test was positive and the halogen test was negative.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_4\text{S}_2\text{O}_4$ : C, 33.11; H, 3.47; N, 19.31; S, 22.10. Found: C, 33.07; H, 3.32; N, 19.29; S, 21.82.

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## REFERENCES

- (1) Present address, E. I. du Pont de Nemours and Company, Kingston, S. C.
- (2) To whom inquiries concerning this paper should be directed.
- (3) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).
- (4) The melting points were taken in a stirred bath or a copper block and are uncorrected. The infrared spectra were determined on a Perkin-Elmer Infracord Model 137 in Nujol mulls.
- (5) R. N. Castle and W. S. Seese, *J. Org. Chem.*, **23**, 1534 (1948).
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