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THE NUCLEOPHILIC DISPLACEMENT OF HALOGEN IN PYRIDAZINES WITH PHOSPHORUS PENTASULFIDE

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THE direct displacement of oxygen by sulfur using phosphorus pentasulfide as the thiating agent has been applied widely to heterocyclic systems where the hydroxyl group attached to the ring is tautomeric with the cyclic amide structure.[1] When 3,5-diiodo-2-pyridone or 3,5-diiodo-4-pyridone was allowed to react with phosphorus pentasulfide in refluxing pyridine solution, 3,5-diiodo-2-pyridinethiol and 3,5-diiodo-4-pyridinethiol were obtained respectively.[2]

In this laboratory when either 4,5-dichloro-3-pyridazone (I) or 4,5-dibromo-3-pyridazone (II) was allowed to react with phosphorus pentasulfide in refluxing pyridine solution, 3,4,5-pyridazinetrithiol (III), m.p. $>400^{\circ}$, (Found: C, 27.37; H, 2.05; N, 15.77. $C_4H_4N_2S_3$ requires C, 27.25; H, 2.29; N, 15.89) was obtained in 76 per cent yield from I and in 89 per cent yield from II.[3]

In order to establish the structure of III, the following reactions

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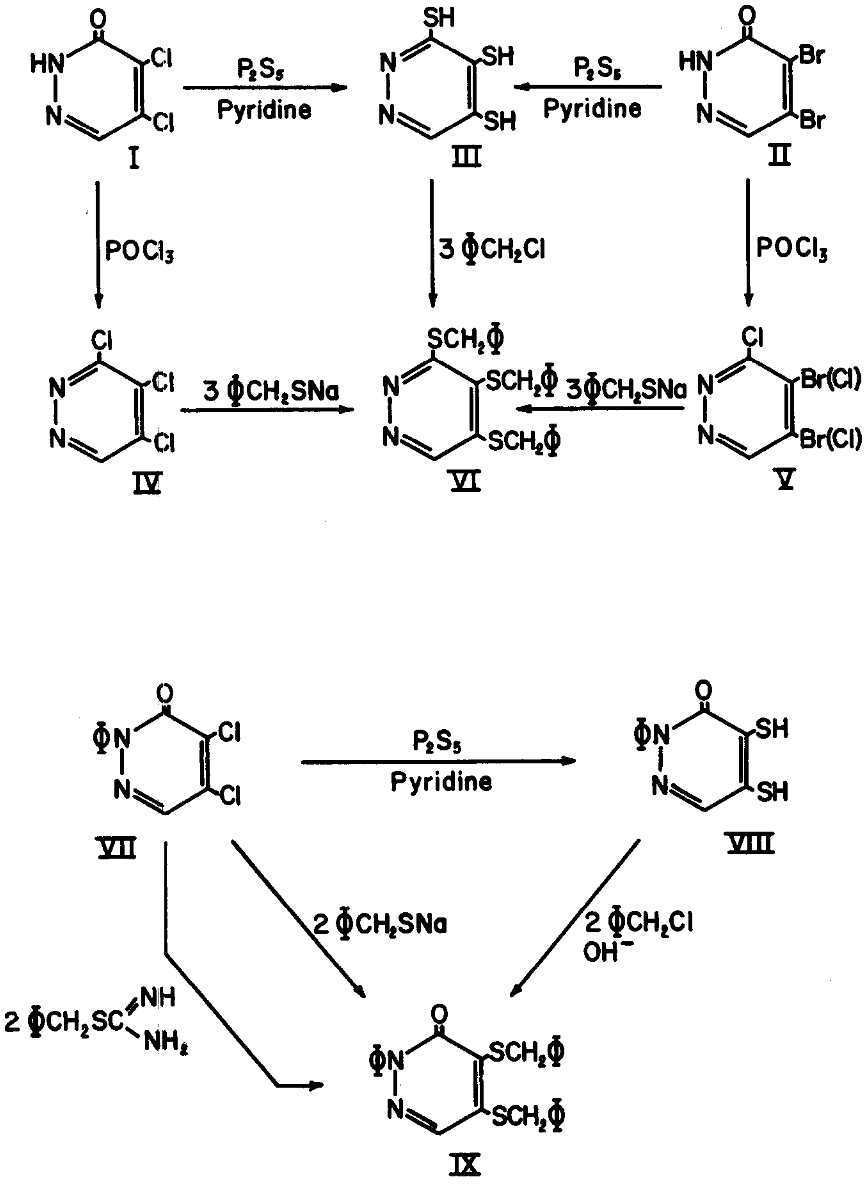
[1a] H.C. Carrington, J. Chem. Soc. 124 (1944); [b] G.B. Elion and G.H. Hitchings, J. Amer. Chem. Soc. 69, 2138 (1947); [c] R.K. Robins and H.H. Lin, Ibid. 79, 490 (1957); [d] H. Gregor, W.G. Overend and L.F. Wiggins, J. Chem. Soc. 2199 (1948); [e] R.N. Castle, H. Ward, N. White and K. Adachi, J. Org. Chem. 25, 570 (1960); [f] R.N. Castle and W.S. Seese, Ibid. 23, 1534 (1958) and many other references.

[2] E. Klingsberg and D. Papa, J. Amer. Chem. Soc. 73, 4989 (1951).

[3] S. Linholter, Private communication. Dr. Linholter has observed the conversion of 6-chloro-5-methyl-3-pyridazone into 4-methyl-3,6-pyridazinedithiol with phosphorus pentasulfide in carbon disulfide solution.

Flow Sheet


I
II
III
IV
V
VI
VII
VIII
IX
P_2S_5 Pyridine
$POCl_3$
3 ΦCH₂Cl
3 ΦCH₂SNa
2 ΦCH₂SNa
2 ΦCH₂Cl OH⁻
2 ΦCH₂SC(=NH)NH₂

were carried out. Compound III obtained either from I or II when allowed to react with benzyl chloride in alkaline solution gave the same compound, namely, 3,4,5-tribenzylthiopyridazine (VI), m.p. 157°, (Found: C, 66.89; H, 4.62; N, 6.38. $C_{25}H_{22}N_2S_3$ requires C, 67.22; H, 4.97; N, 6.27). When I was allowed to react with phosphorus oxychloride, 3,4,5-trichloropyridazine[4] (IV) was obtained. The reaction of 3 moles of sodium benzyl mercaptide prepared from benzyl mercaptan and sodium amide in anhydrous benzene solution with IV gave VI identical in all respects with that prepared from III.

When II was allowed to react with phosphorus oxychloride a mixture of chlorination and exchange products was obtained as indicated by the elementary analyses. These are represented by structure V. None of the pure, non-exchanged 3-chloro-4,5-dibromopyridazine was obtained. The mixture when allowed to react with 3 moles of sodium benzyl mercaptide prepared from benzyl mercaptan and sodium amide in anhydrous benzene solution also produced VI identical in all respects to that prepared by the two other methods. Thus the constitution of III is established.

4,5-Dichloro-2-phenyl-3-pyridazone[5] (VII) when allowed to react with phosphorus pentasulfide in refluxing pyridine solution gave 4,5-dimercapto-2-phenyl-3-pyridazone (VIII) in 78 per cent yield, m.p. 110°, (Found: C, 50.33; H, 3.15; N, 11.47. $C_{10}H_{18}N_2OS_2$ requires C, 50.82; H, 3.41; N, 11.86). In order to establish the structure of VIII, it was allowed to react with 2 moles of sodium benzyl mercaptide prepared from benzyl mercaptan and sodium amide in anhydrous benzene solution to give 4,5-dibenzylthio-2-phenyl-3-pyridazone (IX) in 71 per cent yield, m.p. 163°, (Found: C, 69.40;

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[4] T. Kuraishi, Pharm. Bull. 4, 497 (1956). We have observed that 3,4,5-trichloropyridazine produces severe blisters when solutions are allowed to come in contact with the skin.

[5] D.T. Mowry, J. Amer. Chem. Soc. 75, 1909 (1953).

H, 4.42; N, 7.22. $C_{24}H_{20}N_2OS_2$ requires C, 69.19; H, 4.48; N, 6.72). In order to show with certainty that IX has the structure proposed, VII was converted into IX by two methods: (a) VII was allowed to react with 2 moles of sodium benzyl mercaptide prepared from benzyl mercaptan and sodium amide in absolute benzene solution and (b) VII was allowed to react with 2 moles of benzylisothiouronium hydrochloride in alkaline solution. The 4,5-dibenzylmercapto-2-phenyl-3-pyridazone (IX) prepared by the three different methods were identical in all respects, therefore the constitution of VIII is demonstrated with certainty.

This novel nucleophilic displacement of halogen in pyridazines by phosphorus pentasulfide is being studied further in this laboratory. This reaction is also being studied using other heterocyclic ring systems.

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