SYNTHESIS OF PYRITHIAMINE

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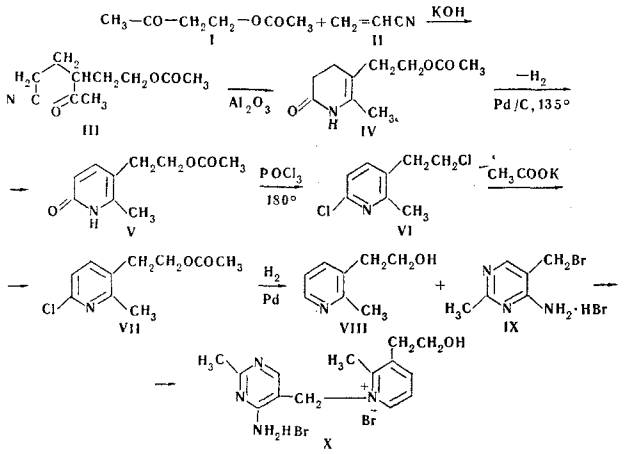
A new seven-stage method for the synthesis of pyrithiamine has been elaborated.

A study was made of a method which is simpler than the one already reported [1], for synthesizing pyrithiamine:



To synthesize 2-methyl-3-(β-hydroxyethyl)pyridine (VIII), the pyridine component of pyrithiamine, a condensation was conducted between acrylonitrile and 3-butanonyl acetate (I) with subsequent ring formation of 3-aceto-5-cyano-pentyl acetate (III) into 2-methyl-3-(β-acetoxyethyl)-4, 5-dihydropyrid-6-one (IV) according to a previously described method [2].

It has recently been shown [3] that dehydrogenation of 2, 3-dialkyl-4, 5-dihydropyrid-6-ones is usually conducted either with sulfuryl chloride or with sulfur trioxide according to a method described in the literature [4]. The use of sulfuryl chloride for dehydrogenation of compound IV was not successful because there was great resinification, possibly on account of polymerization of the corresponding vinyl pyridine. It was possible to dehydrogenate compound IV into 2-methyl-3-(β-acetoxyethyl)pyrid-6-one (V) with a quantitative yield by using palladium on carbon at 140° in a solution of xylene. It was not possible to dehydrogenate compound IV using Raney nickel.

The subsequent conversion of compound V into compound VIII was conducted by a method described in the literature [5]. By treating the hydrochloride of compound V with phosphorous oxychloride in a sealed tube at 180°, it was possible to obtain 2-methyl-3-(β-chlorethyl)-6-chloropyridine. In addition, the chlorine atom of the side chain was substituted by the acetoxy group and the product of the reaction was hydrogenated on freshly reduced palladium.

The 2-methyl-3-(β-hydroxyethyl)pyridine (VIII) obtained was condensed with the pyrimidine component of thiamine, forming pyrithiamine. An aqueous solution of pyrithiamine at a concentration of $1 \cdot 10^{-7}$ % inhibited the growth of plant seedings.

EXPERIMENTAL

2-Methyl-3-(β-acetoxyethyl)pyrid-6-one (V). A suspension of 1 g of 5% palladium on carbon and 5 g (0.026 mole) of 2-methyl-3-(β-acetoxyethyl)-4, 5-dihydropyrid-6-one [2] (IV) in 50 ml m-xylene was heated for 24 hr until colorless crystals were deposited on the walls of the flask. The xylene solution was decanted, and the product of the reaction was dissolved in methanol and removed from the catalyst. After the xylene had been removed by distillation the residue was combined with the methanolic extracts. Most of the methanol was removed and the residue crystallized on standing, mp 170–171° C (from methyl alcohol). Found, %: C 60.80; H 6.61; N 7.20. Calculated for $C_{10}H_{13}NO_3$, %: C 60.95; H 6.66; N 7.18. Infrared spectrum: 1735, 1685, 1622, 1565, 1275, 1038 cm^{-1}.

2-Methyl-3-(β-chlorethyl)-6-chloropyridine (VI). An alcoholic solution of HCl was added to a solution of 2.6 g (0.013 mole) of compound **V** in 10 ml of alcohol until the reaction of the solution was acid in relation to Congo indicator. The alcohol was removed by distillation under vacuum. The residue was heated with 10 ml of phosphorous oxychloride in a sealed tube at 180°–190° C for 6 hr. The chilled reaction mixture was poured onto ice. The solution was made alkaline with excess of sodium carbonate and the oily substance which separated out was extracted with ether. The ethereal solution was dried with potash. The ether was removed by distillation and the residue was sublimed under vacuum. A 2.6 g quantity (77%) of compound VI was obtained in the form of a colorless oily substance with bp 113–114° (4 mm), n_D^{20} 1.5530; hydrochloride mp 107–109° C.

2-Methyl-3-(β-acetoxyethyl)-6-chloropyridine (VII). A 1 g quantity (0.053 mole) of compound VI and 1 g (0.01 mole) of anhydrous potassium acetate in 5 ml glacial acetic acid were heated with mixing at 140° for 6 hr. A 50% solution of potash was added to the cooled mass until there was an alkaline reaction with phenolphthalein, and the separated oily substance was extracted with benzene. The benzene solution was dried with potash. The solvent was removed by distillation under vacuum. A 20 ml volume of ether was added to the residue. A 0.1 g quantity of compound V was removed by filtration, mp 169° (from acetone). Mixture with a known sample caused no melting-point depression.

The ethereal solution was evaporated and the residue was distilled under vacuum, bp 145°–146° C (5 mm). Found, %: C 56.62; H 5.78; Cl 16.59; N 6.55. Calculated, %: C 56.21; H 5.62; Cl 16.63; N 6.56.

2-Methyl-3-(β-hydroxyethyl)pyridine. A solution of 0.1 g palladium chloride in 1 ml of 17% hydrochloric acid heated to boiling was added to a solution of 0.5 g (2.3 mM) of compound VII in 10 ml of alcohol. The reaction mixture was hydrogenated at room temperature. Reduction was complete within two hr. The catalyst was removed by filtration and the filtrate was evaporated under vacuum.

A 5 ml volume of a 25% solution of potassium hydroxide was added to the hydrochloride of 2-methyl-3-(β-hydroxyethyl)-pyridine and the separated base VIII was extracted with chloroform. The chloroform solution was dried with potash. The chloroform was removed by distillation and 0.3 g (95%) of colorless crystals

was obtained, mp 62–63° (from a mixture of chloroform and petroleum ether). The displacement test did not produce a depression of the melting point with 2-methyl-3-(β-hydroxyethyl)-pyridine, obtained by a method described in the literature [1]. Infared spectrum of VIII: 3280, 1580, 1050, 785, 739 cm^{-1}.

Pyrithiamine (X). A 120 mg quantity of the hydrobromide of 2-methyl-5-bromoethyl-6-aminopyrimidine (IX) was added to a solution of 300 mg of compound VIII in isopropyl alcohol, and the mixture was stirred until the contents had completely dissolved. The solution was filtered and left overnight at 25–30°. On the following day the separated compound was centrifuged, washed with isopropyl alcohol and petroleum ether, and then dried. The yield of the hydrobromide of pyrithiamine was 100 mg, 73% calculated from compound IX. Mp 207–210°. From data in the literature, mp 205–210°.

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