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A NOVEL SYNTHESIS OF 4-HYDROXYMETHYL-2-PHENYLTHIAZOLE INVOLVING AN EPOXY-2-THIAZOLINE INTERMEDIATE

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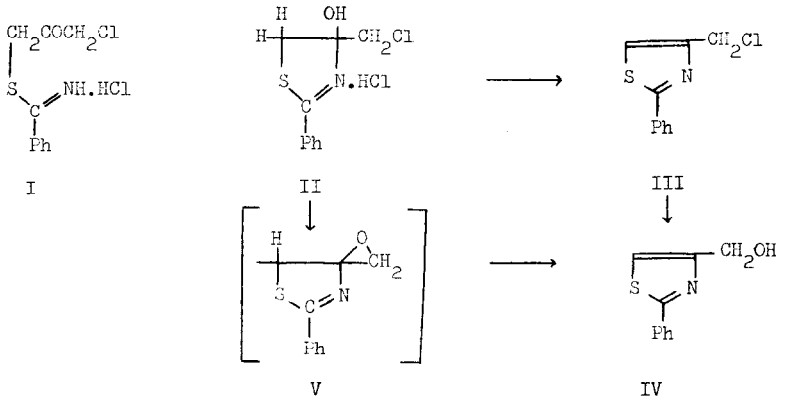
When sym-dichloracetone is treated with thiobenzamide in acetone at room temperature an insoluble hydrochloride salt is formed. This salt, which was previously reported to be thioimidic ester (I),[1-4] is the 2-thiazoline (II).[5] Heating (II) in refluxing methanol for about 30 min. gives the thiazole (III) in almost quantitative yield. Other workers carried out this conversion in either a refluxing mixture of concentrated hydrochloric acid and acetone[1,2] or cold concentrated sulphuric acid.[3] The treatment of (III) with refluxing 0.1N sodium hydroxide for 2.5 hr. is reported to give the hydroxymethylthiazole (IV) in 75% yield.[2]



Here we report that treatment of a suspension of (II) in methanol with three mole equivalents of sodium hydroxide (1ON aqueous solution) at 40-45° for 30 min. (reaction

followed by UV) gave the thiazoles (III) and (IV) in a ratio of about 1:9 (glc) respectively. Two mechanisms were considered for the reaction, (a) that dehydration to the thiazole (III) was followed by elimination of chloride ion by hydroxyl ion (III→IV), and (b) that the most acidic proton in (II), the hydroxyl proton, was removed with formation of the epoxide (V) which then rearranged to (IV). The latter mechanism was indicated when we found that treatment of the chloromethylthiazole (III) with sodium hydroxide under the conditions of the above reaction did not give any detectable amount (glc) of the hydroxymethyl derivative (IV). Repeating the reaction of (II) in dry methanol using sodium methoxide as the base we were able to isolate, after only 15 min. at room temperature, a 92% yield of (IV), m.p. 66-68° (lit.[2] m.p. 67.4-68.4°), thus establishing that the reaction proceeds via the epoxide intermediate (V).

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