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Synthetic Studies of 2,2'-(Ethylenediimino) and 2,2'-(Thioureido)-di-1-carboxylic acids as the Antitubercular and the other Bacteriostatic Agents*

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趙允成 : 2,2'-(Ethylenediimino) and (Thioureido)-di-1-carboxylic acids 의 抗結核性및 抗菌性化合物로서의 合成研究

抗人結核菌性 및 streptomycin, isoniazid 및 para-aminosalicylic acid 에 對한 耐性人結核菌株에 현저한 抗菌作用 있는 dextro-2,2'-(ethylenediimino)-di-1-butanol(Ethambutol) 系列 및 thioureido(-NHCSNH-) 含有化合物 系列인 2,2'-(ethylenediimino)-di-1-butyric acid 및 2,2'-(thioureido)-di-1-butyric acid 를 合成했으며 또한 이들 藥物의 構造와 作用間의 相互關係를 究明코저 이들 化合物과 類似한 構造인 2,2'-(thioureido)-diacetic acid 를 合成했기에 報告함.

The strong antitubercular activity of dextro-2,2'-(ethylenediimino)-di-l-butanol (Ethambutol) against human *Mycobacterium tuberculosis* and streptomycin-resistant and isoniazid-resistant strains was reported by Wilkinson and Shepherd[1,2] and numberous investigators has reported upon the synthesis and antitubercular and the other bacteriostatic activities of various compounds containing thioureido skeleton -NH-CS-NH- such as phenylthiourea derivatives,[3] thiocarbanilides (N,N'-diarylthioureas)[4], halogenated thiocarbanilides,[5] 3-substituted 2-thiohydrouracils and substituted heterocyclic thioureas,[6] thiosemicarbazones[7] etc..

These studies prompted us to synthesize the structurally similar compounds with dextro-2,2-'(ethyenediimino)-di-1-butanol and also some of the thioureido containing compounds structurally similar with dextro-2,2'-(ethylenediimino)-di-1-butanol.

The chemical structures of derivatives containing ethylenediimino and thioureido groups of this study and dextro-2,2'-(ethylenediimino)-di-l-butanol have such a common point as structurally being able to have chelating properties which is considered as the prospective biological mechanism of the last compound's antitubercular activity.

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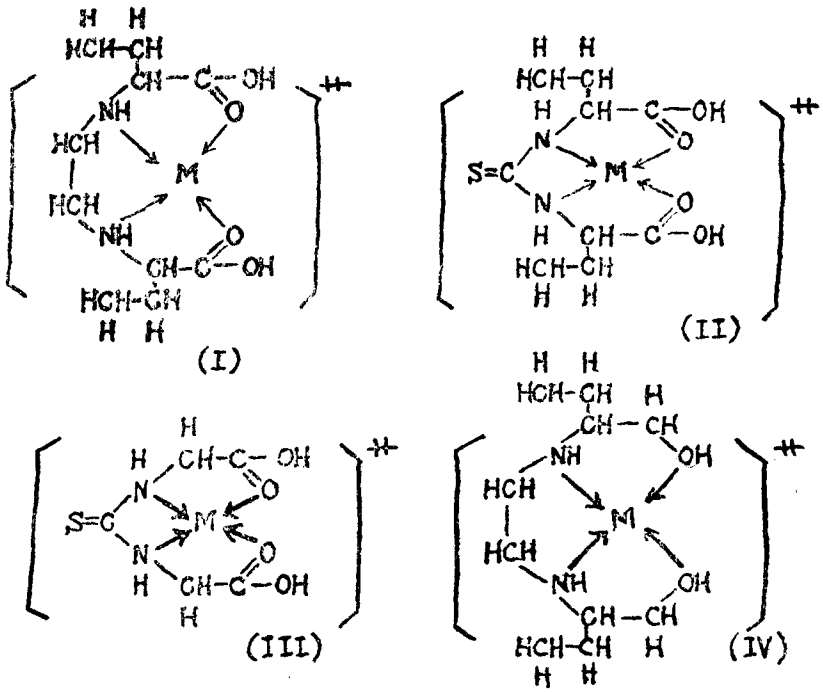
The proposed chelate forms of these compounds are as follows (Ⅰ, Ⅱ, Ⅲ and Ⅳ).



This study is concerned with studying any antitubercular and the other bacteriostatic activities of the compounds of 2,2′-(ethylenediimino)-di-1-butyric acid, 2,2′-(thioureido)-di-1-butyric acid and 2,2′-(thioureido)-diacetic acid and also any relationships among the biological activities, partition coefficients and chelating properties of these compounds.

The 2,2′-(ethylenediimino)-di-1-butyric acid is prepared by the reaction of 2-bromobutyric acid with ethylenediamine in ether at low temperature. The 2,2′-(thioureido)-di-1-butyric acid is prepared by refluxing the mixture of 2-bromobutyric acid and thiourea in methanol. The 2,2′-(thioureido)-diacetic acid is prepared by refluxing the mixture of 2-chloroacetic acid and thiourea in methanol.

EXPERIMENTAL

2,2′-(Ethylenediimino)-di-1-butyric acid.——To a stirred solution of 20.4 g (0.34 mole) of purified ethylenediamine in 200 ml of ether was slowly added 56.7 g (0.34 mole) of 2-bromobutyric acid at about −5°C. The reaction mixture was refluxed on water bath with stirring for 1 hr., then cooled in ice. The precipitated product was filtered, washed with ether

and then dissolved in 50 ml of water. To this solution was slowly added sodium bicarbonate powder until it reached the neutral point to obtain the product as a solid. The solid was filtered off and washed with 25 ml of water and ether respectively. The crude product was dissolved in 100 ml of hot water and the mixture was kept in ice box overnight to obtain a crystalline colorless compound. Yield was 26.8 g, 68%, m.p. 289—290°.

Anal. Calcd for $C_{10}H_{20}N_2O_4$: C, 52.13; H, 8.67. Found: C, 51.81; H, 8.02.

2,2′-(Thioureido)-di-1-butyric acid.——68.4 g (0.41 mole) of 2-bromobutyric acid was added to a solution of 31.2 g (0.41 mole) of thiourea in 200 ml of dry methanol. The mixture was refluxed for 2 hr. and then some of the solvent was distilled off. The residual solution was cooled in ice to obtain a precipitated crude product. This product was filtered off and washed with 20 ml of methanol and then dissolved in 50 ml of water. To this solution was added, slowly, sodium bicarbonate powder until it reached the neutral point to obtain the product as a solid. The solid was filtered and washed with 25 ml of water and methanol respectively. The crude product was dissolved in 100 ml of hot water and cooled in ice box to obtain a crystalline colorless compound. The compound was filtered off and washed with two 5 ml portions of cold methanol and dried in desiccator containing anhydrous calcium chloride. Yield was 35.4 g, 71%, m.p. 189—191°.

Anal. Calcd for $C_9H_{16}N_2O_4S$: C, 43.54; H, 6.49. Found: C, 43.24; H, 6.17.

2,2′-(Thioureido)-diacetic acid.——A solution of 15.2 g (0.2 mole) of thiourea in 100 ml of dry methanol was added to 18.9 g (0.2 mole) of 2-chloroacetic acid. The mixture was refluxed for 3hr. and then some amount of the solvent was distilled off. The residual solution was cooled in ice to obtain a precipitated crude product. This product was filtered off and washed with 20 ml of methanol and then dissolved in 50ml of water. To this solution was added, slowly, sodium bicarbonate powder until it reached the neutral point to obtain the product as a solid. The solid was filtered off and washed with 20 ml of water and methanol respectively. The crude product was dissolved in 50 ml of hot water and cooled in ice box to obtain a crystalline colorless compound. The product was filtered off and washed with two 5 ml portions of cold methanol and dried in desiccator containing anhydrous calcium chloride. Yield was 11.4 g, 60%, m.p. 225—230°(dec).

Anal. Calcd for $C_5H_8N_2O_4S$: C, 30.95; H, 4.15; Found: C, 30.94; H, 4.03.

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