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Preparation of Thiocarbanilides as Antituberculosis and Antileprosy Agents

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鞠埰豪：抗結核 및 治癩劑로서의 Thiocarbanilide類의 合成

抗結核劑 或은 治癩劑로써 脚光을 받고 있는 Carbanilide 類中 臨床試驗에 있어 往往 其効果가 期待에 어긋나는 點이 있음을 勘案하건데 그들 藥品의 물에 對한 溶解度가 매우 나쁘며 따라서 經口投與時 吸收가 잘안되는데에 緣由하는게 아닌가하는 假想下에 —OH 基(化合物Ⅰ) 或은 —COOH基(化合物 Ⅱ, Ⅲ)를 갖는 構造의 物質과 I N A H의 構造를 一邊에 갖는(化合物Ⅳ) thiosemicarbazide 를 合成하였기에 여기 報告한다. Carboxy 基를 갖는 化合物Ⅱ는 300° 까지로는 融點을 얻을 수 없었으나 窒素分析値와 I R分析의 結果로 記載名稱의 構造가 合成되었다고 生覺된다.

4, 4′-Diisoamyloxythiocarbanilide[1] and 4, 4′-Diethoxythiocarbanilide[2] are already known as an antituberculosis agent. 4-*N*-butoxy-4′-dimethylaminothiocarbanilide[3] is known as an antileprosy agent with a brand of "ciba.-1690". Youmans, Youmans, and Doub reported several thiocarbanilides[4] as an antituberculosis agent.

These thiocarbanilides show less antibacterial activity *in vivo* than *vitro*. Sometimes it is reported that the clinical results with these compounds are inconsistent. It is supposed that the extreme insolubility of these chemicals in water hempers the absorption into blood stream through intestinal system.

From this point of view, the author prepared several thiocarbanilides having a hydroxy(4-hydroxy -4′-ethoxythiocarbanilide-compound I) or carboxy(4- carboxyphenyl -4′- ethoxy-thiocarbaniilde-compound II) radical considering increase in the solubility, and also prepared δ-4-ethoxyisonicotinylthiosemicarbanilide (compound IV) which is supposed to be considerably soluble in hot water. Compounds III (3-hydroxy-4- carboxy-4′-ethoxy thiocarbanilide) and IV and thiocarbanilides derived respectively, from PAS and INAH which are well known conventional antituberculosis agent.

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On the IR(Nujol inspection of compound I, II, III, IV), absorption peaks at 2130~2040 cm^{-1} (aromaticiso thio cyanate) and 3400 cm^{-1}(aromatic amine) included in starting materials were disappeared. Instead, absorption peak at 1050 cm^{-1}(ethoxy) was appeared in compound 1—IV, and a new absorption peak at 3200 cm^{-1}(phenolic OH) was appeared in compound I and III, and not in compound II and IV.

Absorption peak at 1690 cm^{-1}(carboxyl carbonyl) was also appeared in compound II, III, IV and not in compound I.

EXPERIMENTAL

Preparation of 4-hydroxy-4′-ethoxyhtiocarbanilide (Compound I). —1.99 g (0.01 mol) of *p*-aminophenol and 1.79g(0.01 mol) of 4-ethoxyphenylisothiocyante[5] were dissolved into 100 ml of methylthylketone(MEK)* and heated in sealed tube in xylene bath for 10 hrs. Almost of solvent was distilled off after reaction, and crystalized in methanol, then, washed with dilute acetic acid in order to remove unreacted aminophenol, and then recrystalized in methanol again. Obtained 1.37 g(Yield 47.5%) of white crystal, m.p. 186~187°. *Anal.* Calcd. for C_{25} H_{16} O_2 N_2 S: N, 9.37. Found: N, 9.39

Preparation of 4-carboxy -4′-ethoxythiocarbanilide(Compound II). —1.37 g(0.01 mol) of *p*-aminobenzoic acid and 1.79 g(0.01 mol) of *p*-ethoxyphenylisothiocyanate were heated in MEK in xylene bath for 10 hrs., as same as experiment I. After the reaction crystalied in MEK and methanol. Obtained yellowish powder 1.8 g(Yield 56.9%), m.p.> 300°. *Anal.* Calcd. for C_{16} H_{16} O_3 N_2 S: N, 8.85 Found: N, 8.81.

Preparation of 3-hydroxy -4-carboxy -4′-ethoxythiocarbanilide (Compound III). —1.53 g(0.01 mol) of PAS and 1.79 g(0.01 mol) of 4-ethoxyphenylisothiocyanate were heated in MEK in xylene bath for 10 hrs. After the reaction solvent was distilled off, and crystalized in 60% methanol. Obtained 1.2 g(Yield 36.3%) of white crystal, m.p. 161—162°. *Anal.* Calcd. for C_{16} H_{16} O_4 N_2 S: N, 8.43 Found: N, 8.40.

Preparation of δ-4-ethoxyisonicotinylthiosemicarbazide(Compound IV).—2.6 g (0.02 mol) of INAH and 3.58 g(0.02 mol) of *p*-ethoxyphenylisothiocyanate were reacted in MEK in xylene bath for 10 hrs. After the reaction, almost of solvent was distilled off, and crystalized in 70% methanol and boiled with 200 ml of water in order to remove INAH and by-producted water soluble compounds. Obtained 2.7 g(Yield 41.7%) of yellow crystal m.p. 126~165°.

* The abbreviation used is: MEK, methylethylketone.

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