[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

ω-Aurothio Fatty Acids and their Salts

BY E. E. MOORE AND R. T. RAPALA[1]

Many favorable reports have appeared in the recent literature on the use of gold compounds in the treatment of arthritis. Present knowledge would indicate that the ideal gold compound for this purpose should be water soluble and that its solutions should be stable and well tolerated when injected. This series of aurothio fatty acids were synthesized for this purpose. Two members of the series have been reported in the literature. Delange[2] described the insoluble calcium salt of gold thioglycolic acid. The free acid and its sodium salt were so unstable that they could not be purified. In a patent,[3] issued to Schering-Kahlbaum, β-aurothiopropionic acid is reported to be obtained as a yellow powder by the reaction of potassium gold bromide with β-mercaptopropionic acid.

The published methods require the preparation and purification of the ω-mercapto acids. Such purifications are notoriously difficult and proved so in our hands. Andreasch[4] described the preparation of β-carboxyethylisothiourea (β-guanylthiopropionic acid) and reported that it was easily hydrolyzed to β-mercaptopropionic acid. This fact proved to be the key to the problem, for these isothiourea derivatives under proper conditions react with inorganic gold salts in the same manner as the simple mercaptans, with no contamination by oxidation products. The gold compounds are thus easily prepared, analytically pure and in practically quantitative yields. Use of sulfur dioxide and an excess of the isothiourea are advantageous as shown in the experimental part.

The properties of the ω-carboxyalkylisothioureas and those of the corresponding ω-aurothio fatty acids are given in Table I.

The alkali metal and alkanolamine salts of these compounds are soluble in water except those of ω-aurothioundecylic acid whose sodium salt yields a turbid soapy product in water. The alkaline earth salts are insoluble.

The solid soluble salts are prepared by making concentrated aqueous solution and pouring into alcohol, from which the solid salt precipitates.

Experimental

δ-Bromovaleric acid was prepared by the method of Merchant, Wickert and Marvel[5]; ε-bromocaproic acid was prepared by the method of Brown and Partridge.[6] γ-Methyl-ε-bromocaproic acid was prepared from *p*-methylcyclohexanone using the same method as described for ε-bromocaproic acid.[6] ω-Bromoundecylic acid was prepared from undecylenic acid.

The ω-carboxyalkylisothioureas were prepared from the corresponding bromo acids by reaction with thiourea in aqueous solution.[4] In the case of the highest member of the series alcohol was used as the solvent. The gold compounds were all prepared by the same method, of which the following is an example.

ω-Aurothiocaproic Acid.—39.25 g. of ε-carboxyamylisothiourea was dissolved in 750 cc. of 0.65 *N* sodium hydroxide and a solution of 11.25 g. of sulfur dioxide in 150 cc. of water added. A solution of potassium gold bromide containing 16.2 g. of gold in 440 cc. of water was added slowly with stirring. The solution was acidified with concentrated hydrochloric acid and a white precipitate of ε-aurothiocaproic acid formed. This was filtered, washed with water until free of chlorides, then with alcohol and finally with ether. It was dried in a vacuum desiccator; white solid, yield 28.1 g. (99%).

Preliminary pharmacological results indicate that in this series the toxicity per unit of gold decreases with increase in molecular weight of the compounds. Complete pharmacological results will be published elsewhere by Dr. R. K. Richards.

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TABLE I

R	$NH_2C(=NH)SRCOOH$ M. p., °C.	Nitrogen, % Calcd.	Found	AuSRCOOH M. p., °C.	Gold Calcd.	Found	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found
$(CH_2)_2$[a]	183–184	18.91	18.60	218–220	65.23	65.16				
$(CH_2)_4$	197–198	15.90	15.83	227–230	59.69	59.49	18.17	18.36	2.74	2.84
$(CH_2)_5$	202–204	14.73	14.56	240–245	57.25	56.85	20.92	20.82	3.21	3.24
$CH_2CH_2CH(CH_3)CH_2CH_2$	186–189	13.72	13.50	267–270	55.02	55.54	23.45	23.74	3.65	3.53
$(CH_2)_{10}$[b]	183–185	8.21	8.08	265–275[c]	45.18[c]	45.41[c]				

[a] Andreasch[4] m. p. 172–174°. [b] Hydrobromide. [c] Sodium salt.

Summary

A series of ω-aurothioacids and their salts has been prepared by the reaction of inorganic gold salts with the corresponding ω-carboxyalkylisothioureas.

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(1) Present address: Chemistry Department, University of Wisconsin, Madison, Wisconsin.

(2) Delange, U. S. Patent 2,049,198 (1936).

(3) Schering-Kahlbaum, German Patent 544,500 (1932).

(4) Andreasch, *Monatsh.*, **6**, 882 (1885).

(5) Merchant, Wickert and Marvel, THIS JOURNAL, **49**, 1828 (1927).

(6) Brown and Partridge, *ibid.*, **66**, 839 (1945).