*p*H of blood, the degradation of pectin into smaller molecules is relatively faster, which may be of importance in promoting elimination at a satisfactory rate and preventing harmful effects.

3. The temperature coefficient of the rate of degradation at a *p*H of about 3 confirms the belief that degradation of pectin involves breaking of glycosidic bonds.

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Certain Substituted Thiobisacetamic Acids and Their Salts*

By LEWIS C. LAPPAS†, ‡ and GLENN L. JENKINS

The syntheses of the following six substituted thiobisacetamic acid derivatives and two potassium salts are described: (*a*) N-(β-benzyloxyethyl)-thiobisacetamic acid; (*b*) N-(β-benzyloxyethyl)-α,α′-thiobis-*n*-propionamic acid; (*c*) N-(β-benzyloxyethyl)-α,α′-thiobis-*n*-butyramic acid; (*d*) N-(β-benzhydryloxyethyl)-thiobisacetamic acid; (*e*) N-(β-benzhydryloxyethyl)-α,α′-thiobis-*n*-propionamic acid; (*f*) N-(-β benzhydryloxyethyl)-α,α′-thiobis-*n*-butyramic acid; (*g*) potassium N-(β-benzyloxyethyl)-thiobisacetamate; (*h*) potassium N-(β-benzyloxyethyl)-α,α′-thiobis-*n*-butyramate. The following intermediates are reported for the first time: (*a*) α,α′-thiobis-*n*-propionic anhydride; (*b*) benzyloxyethylamine; (*c*) β-(α-methylbenzyloxy)-ethylamine. Preliminary pharmacological data indicated that potassium N-(β-benzyloxyethyl)-thiobisacetamate was slightly spasmogenic and relatively nontoxic. Potassium N-(β-benzhydryloxyethyl)-thiobisacetamate did not display spasmogenic or spasmolytic activity and appeared to be nontoxic.

ANAPHYLACTIC REACTIONS have been minimized and often eliminated through the use of an antihistaminic drug which is thought to exhibit a competitive inhibitory effect against the histamine produced in allergic reactions. Of the many antihistaminic drugs produced for therapy, there is still to be found any one agent which is devoid of toxic side reactions, gives a consistent response in an individual, and has an extended duration of action.

It has been observed that the sulfur atom and the amide linkage have appeared individually in varying structural patterns of effective antihistaminic agents. It was deemed feasible to combine these groups in a common molecule, together with the ethylamine moiety which is so characteristic of many of the proved antihistaminic drugs.

This investigation consists of attempts to prepare various substituted thiobisacetamic acid derivatives. The presence of the carboxyl group in these compounds offers a means of preparing soluble salts which enhance pharmacological administration.

The substituted thiobiscarboxylic acids were synthesized by reacting the sodium salts of the α-halogenated acids with freshly prepared sodium sulfide and subsequent acidification.

The cyclization of the thiobiscarboxylic acids as the anhydrides, caused with acetyl chloride, makes possible the presence of *cis-trans* isomerism with the *trans* form existing as the dextro- or levorotatory isomer, and the *cis* form being the optically inactive or the *meso* isomer. In all instances, the mixture of isomers was used in the subsequent syntheses without attempting to isolate the individual isomers.

The aralkyl-ether-amines were prepared by reacting metallic sodium with ethanolamine and treating the formed sodium alcoholate with the α-halogenated aralkyl compound.

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The various substituted thiobisacetamic acid derivatives were synthesized by treating the corresponding thiobiscarboxylic anhydrides with the aralkyl-ether-amines under anhydrous conditions. The amic acids produced were oily to resinous in character and all of those, except N-(β-benzhydryloxyethyl)-α,α′-thiobis-*n*-butyramic acid, resisted attempts toward crystallization. Direct distillation of the oily amic acids at 8 mm., 1 mm., and 0.09 mm. resulted in decomposition.

An attempt to purify N-(β-benzyloxyethyl)-thiobisacetamic acid by preparing the ethyl ester from ethyl alcohol saturated with hydrogen chloride and subsequent distillation caused hydrolysis of the amide linkage.

The use of alcoholic potassium hydroxide for the preparation of the salts of the amic acids was inconsistent, as only two salts (Table I) could be made while the others exhibited hydrolysis of the amic acids at the amide linkage. Various attempts to prepare the salts of these amic acids with aqueous solutions of sodium carbonate and potassium carbonate produced waxy water-soluble compounds which could not be crystallized. All efforts to obtain crystalline ammonium salts from the cold ethereal solutions of the amic acids with dry ammonia gas were unsuccessful.

EXPERIMENTAL

Preparation of the Thiobiscarboxylic Acids

Preparation of Thiobisacetic Acid.—Thiobisacetic acid was synthesized according to a procedure by Loven (1) which was modified by evaporation of the acidified aqueous solution to dryness *in vacuo* (15 mm.) and extraction of the residue with ether.

Preparation of α,α′-Thiobis-*n*-propionic Acid.—Schacht (2) first reported the synthesis of α,α′-thiobis-*n*-propionic acid. The procedure used in this work was that of Loven (1) for the preparation of thiobisacetic acid with the following modification: The final acidified aqueous solution was evaporated *in vacuo* (15 mm.) until an oil layer was observed above the aqueous layer, and this mixture was subsequently extracted with ether.

Preparation of α,α′-Thiobis-*n*-butyric Acid.—Loven (3) was the first to propose a method of synthesis for α,α′-thiobis-*n*-butyric acid. The method used to prepare this acid in this work was identical to that described for the preparation of α,α′-thiobis-*n*-propionic acid.

Preparation of the Thiobiscarboxylic Anhydrides

Preparation of Thiobisacetic Anhydride.—Thiobisacetic anhydride was prepared according to the method of Anschutz and Biernaux (4) by refluxing thiobisacetic acid with an excess of acetyl chloride. The resultant anhydride was recrystallized from anhydrous chloroform in a yield of 71%. This anhydride was also obtained in a yield of 71% by direct distillation at 158–159° at 12 mm. [reported, 158° at 10 mm. (5)]; m. p. 101° [reported, 102° (4)].

Preparation of α,α′-Thiobis-*n*-propionic Anhydride.—Twenty-seven grams of dry α,α′-thiobis-*n*-propionic acid was heated at reflux temperature under anhydrous conditions with 38 cc. of acetyl chloride for a period of three hours. The resultant product was distilled *in vacuo* to remove the excess acetyl chloride and the formed acetic anhydride, and the colorless oil, distilling at 133–137° at 14 mm., was collected. The total yield was 19.8 Gm. or 81.5% of the theoretical; n_D^{25}, 1.5010.

Anal.—Calcd. for $C_6H_8O_3S$: N. E., 80.0. Found: N. E., 80.0.

Preparation of α,α′-Thiobis-*n*-butyric Anhydride.—The method of preparation for this acid was that of Rasanen and Jenkins (6). These workers prepared the anhydride from both the *meso* form and the racemic mixture of α,α′-thiobis-*n*-butyric acid with similar results, except that the anhydride from the *meso* form melted at 18–19° and that from the racemic form did not solidify even at −10°. The mixture of isomers of the acid was used in this experiment. The anhydride distilled at 149–150° at 15 mm. (reported, 149–151° at 15 mm.) in a yield of 96.2%; n_D^{25}, 1.4942 corresponded to that found in the literature. The oily anhydride solidified to a crystalline mass at 14–15° (reported, 18–19°).

Preparation of the Aralkyl-Ether-Amines

Preparation of Sodium Oxyethylamine.—To 61 Gm. (1 mole) of ethanolamine was added 21 Gm. (0.92 Gm. atom) of metallic sodium in small portions under anhydrous conditions. Gentle heat and stirring with a Hershberg stirrer were applied when the rate of reaction was noticeably decreased. Approximately 250 cc. of anhydrous toluene was added slowly to this mixture and the application of gentle heat continued until the evolution of hydrogen ceased. The gray mass of sodium oxyethylamine, which was insoluble in toluene, was used as such for the subsequent reactions with the desired α-halogenated compounds.

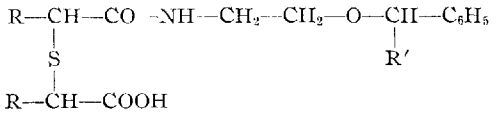
Preparation of Benzyloxyethylamine.—To the sodium oxyethylamine prepared in the previous experiment was added dropwise, under anhydrous conditions, 126 Gm. (1 mole) of benzyl chloride. Gentle heat and stirring were applied for a period of three to five hours. The mixture was allowed to cool and was filtered with suction. The precipitate was washed with several portions of anhydrous toluene and the combined washings and filtrate were distilled under vacuum. The fraction distilling at 85–125° at 1 mm. was collected. This "creeping" in the temperature range of the distillate was also observed when a second run was made at 8 mm. pressure. The latter product distilled at 109–142°. The average yield was 83 Gm. (54.3%); n_D^{25}, 1.5260.

Anal.—Calcd. for $C_9H_{13}ON$: N, 9.26%. Found: N, 9.25%.

Preparation of Benzhydryl Bromide.—The procedure followed was similar to that used by Rieveschl (7). The benzhydryl bromide, which distilled at 178–180° at 23 mm., [literature, 182° at 20 mm. (8)] was obtained in a yield of 80%.

Preparation of Benzhydryloxyethylamine.—The procedure of Sutherland, *et al.* (9), was followed for

TABLE I.—SUBSTITUTED THIOBISACETAMIC ACID DERIVATIVES[a]



R	R′	Yield, %	n_D^{20}	M. P., °C.	Formula	N Analysis, % Calcd.	N Analysis, % Found	N. E. Calcd.	N. E. Found
H	H	63.5	1.5592	...	$C_{13}H_{17}O_4NS$	4.95	4.54	283	284.9
CH_3	H	74.3	1.5427	...	$C_{15}H_{21}O_4NS$	4.5	4.26	311	303
C_2H_5	H	84.0	1.5364	...	$C_{17}H_{25}O_4NS$	4.13	3.82	339	335.2
H	C_6H_5	49.5	1.5698[b]	...	$C_{19}H_{21}O_4NS$	3.9	3.79	359	368.9
CH_3	C_6H_5	71.0	1.5630[c]	...	$C_{21}H_{23}O_4NS$	3.62	3.33	387	388
C_2H_5[d]	C_6H_5[d]	61.0	...	114[e]	$C_{23}H_{29}O_4NS$	3.38	3.39	415	416
H (K salt)[f]	H	52.4	...	204[e, g]	$C_{13}H_{16}O_4NSK$	4.36	4.49	...	...
C_2H_5 (K salt)[f]	H	53.0	...	160–162[e, g]	$C_{17}H_{24}O_4NSK$	3.71	3.88	...	...

[a] The attempts to prepare a series of the amic acids from the thiobiscarboxylic anhydrides and β-(α-methylbenzyloxy)-ethylamine, using the general procedure, yielded oily products, the analyses of which did not compare favorably for the desired compounds.
[b] n_D^{38}.
[c] $n_D^{39.5}$.
[d] Crystallized from ethereal solution in the cold (0° C.) after six days.
[e] Recrystallized from absolute alcohol.
[f] Cold alcoholic solution of the corresponding acid neutralized with cold alcoholic potassium hydroxide solution of known strength.
[g] Melted with decomposition.

the preparation of benzhydryloxyethylamine. The viscid colorless oil, distilling at 185–186° at 4 mm. (reported, 150–153° at 0.3 mm.), crystallized on cooling; and the product which was recrystallized from ether melted at 74–75° (reported, 73–74°); yield, 95.5 Gm. (42%).

Preparation of β-(α-Methylbenzyloxy)-ethylamine.—This compound was synthesized in the same manner as that previously described for the preparation of benzyloxyethylamine using one mole of α-phenylethyl bromide. The colorless oil, distilling at 105–108° at 2 mm., was collected in a yield of 40.6%; n_D^{20}, 1.5290.

Anal.—Calcd. for $C_{10}H_{15}ON$: N, 8.49%. Found: N, 8.03%.

Preparation of the Substituted Thiobisacetamic Acid Derivatives (Table I)

General Procedure.—A definite amount of the thiobiscarboxylic acid anhydride (8–12 Gm.) was placed in a 250-cc. three-neck flask equipped with reflux condenser, calcium chloride drying tube, dropping funnel, and mercury seal stirrer. To this was added, under anhydrous conditions, 50 cc. of anhydrous benzene with subsequent heating on a steam bath for five minutes. An equimolar amount of the aralkyloxyethylamine was dissolved in 50 cc. of anhydrous benzene and added dropwise to the anhydride with constant stirring. This mixture was heated at reflux temperature for a period of one-half hour. The excess benzene was removed at reduced pressure (15 mm.) and the residue was neutralized with a saturated solution of sodium carbonate until a *p*H of 9.0 was attained. The alkaline solution was diluted to five times its volume with distilled water. This mixture was then extracted with three 200-cc. portions of ether and the ether extractions were discarded. The aqueous layer was treated with activated charcoal and heated on a steam bath for five minutes. This mixture was filtered through Filter-Cel with suction until the filtrate was clear. The filtrate was acidified with a 3.5% solution of hydrochloric acid to a *p*H of 5.0. The resultant mixture was extracted with ether until the aqueous layer was clear. The aqueous layer was discarded and the ether layer was dried over Drierite. The ether was removed by distillation and the remaining oil was redissolved in acetone and treated with activated charcoal and heated over a steam bath for five minutes. This mixture was then filtered and the Drierite was washed with anhydrous acetone with subsequent evaporation of the acetone *in vacuo* (15 mm.). The final product, which was oily to resinous in character, was subjected to analysis.

SUMMARY

1. The syntheses of six substituted thiobisacetamic acid derivatives and two potassium salts are described.

2. Preliminary pharmacological tests indicated that potassium N-(β-benzyloxyethyl)-thiobisacetamate was slightly spasmogenic and relatively nontoxic. Potassium N-(β-benzhydryloxyethyl)-thiobisacetamate did not display spasmogenic or spasmolytic activity and appeared to be nontoxic.

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