ethoxide in alcohol. As a result, another alkyl group could not be introduced into the monosubstituted compound, nor could the disubstituted malonic ester be condensed with urea to give the corresponding barbituric acid. Beyond ascertaining that the desired reaction had not taken place, no further study was made of the products of these reactions.

The α-chloroethyl sulfides were obtained in excellent yields from the mercaptan, paraldehyde and hydrogen chloride. However, on attempting to purify them by distillation, they usually decomposed slightly, with evolution of hydrogen chloride, even at low pressures and often the product decomposed completely. This occurred also when the product was redistilled. Some pieces of glassware appeared to catalyze this decomposition. Since the desired malonic esters were obtained in good yields from the crude product most of the chlorosulfides were not distilled.

The other α-chloroalkyl sulfides where the chloroalkyl group was larger than ethyl were prepared from mercaptans, hydrogen chloride and the appropriate aldehydes. The compounds were unstable and decomposed rapidly at room temperature.

Experimental

Alkyl α-Chloroethyl Sulfides.—A mixture of one mole of mercaptan and one-third mole of paraldehyde was chilled in an ice–salt mixture and vigorously stirred while hydrogen chloride was passed in at such a rate that the temperature was kept below 5°. The reaction proceeded smoothly and there was no highly exothermic initial reaction. When hydrogen chloride was no longer absorbed the aqueous layer was separated and the product dried by stirring it vigorously with 25 g. of calcium chloride with cooling in an ice bath. In most cases this product was filtered, aerated *in vacuo* to remove hydrogen chloride and used directly for the preparation of the malonic esters. The over-all yield of ester was usually better by this procedure than it was when the chlorosulfide was purified by distillation.

Other Alkyl α-Chloroalkyl Sulfides.—One mole of mercaptan was placed in a 3-neck flask equipped with a dropping funnel, stirrer, thermometer and gas inlet reaching to the bottom of the flask. After weighing the apparatus the flask was immersed in an ice–salt mixture and a stream of hydrogen chloride was passed into it with stirring while one mole of aldehyde was added at such a rate that the temperature was kept below 0°. When addition of the aldehyde was complete and approximately enough hydrogen chloride had been absorbed to form the desired compound and to saturate the water formed, the aqueous layer was separated. The product was dried at 0° by stirring it vigorously with 25 g. of calcium chloride for one hour. It was then filtered, aerated *in vacuo* to remove hydrogen chloride, and immediately used for the preparation of the malonic esters.

Alkyl α-Alkylthioalkyl Malonic Esters.—The above crude α-chlorosulfides were assumed to be pure and were added to the theoretical quantity of monoalkyl sodiomalonic ester in toluene as described in paper I.[2] If the reaction mixture was still basic after stirring for four or five hours at 0° it was stirred for several hours at room temperature and then acidified with acetic acid. Most of the esters were easily purified by fractionation, but in some instances the ester was contaminated with other materials which, however, did not interfere seriously with the preparation of the barbituric acids.

Summary

Some 5-alkyl-5-α-alkylthioalkylbarbituric and thiobarbituric acids and the intermediates used in their preparation are described.

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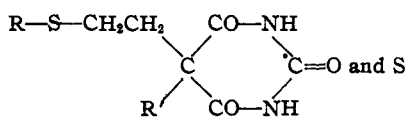
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALTBIE CHEMICAL CO.]

Thioether Barbiturates. III. β-Thioethyl Derivatives

BY L. A. WALTER, L. H. GOODSON[1] AND RUSSEL J. FOSBINDER

This paper describes a series of barbituric and thiobarbituric acids of the structure



where R and R′ represent saturated and unsaturated primary and secondary hydrocarbon groups.

The barbituric compounds were prepared from the corresponding disubstituted malonic esters and urea or thiourea by the usual procedure. The yields were good with all types except where R′ was a methyl or a phenyl group. Due to the tendency of most of the compounds to separate from solvents as oils and to their great solubility in alcohol and other solvents both the barbituric and thiobarbituric acids of this series were purified with much difficulty compared to analogous isomeric compounds described in papers I and II.[2] In several cases two or three months were required for the barbituric acids to become crystalline and then the crystals were not hard but wax-like even though they were quite pure.

As noted in papers I and II, attempts to prepare barbituric acids having an α-thioether grouping in both 5,5 substituents were unsuccessful. In this series a compound containing thioether groups in both substituents was prepared in which one group was an alkyl-β-thioethyl and the other was an alkylthiomethyl. No difficulty was encountered in introducing an alkylthiomethyl group into a monoalkyl-β-thioethylmalonic ester by the method described in paper I.

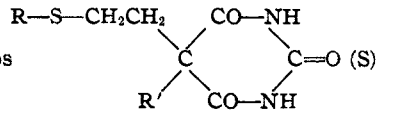
For the purposes of comparison we also prepared a barbituric and a thiobarbituric acid with an additional methylene group between the sulfur

(1) Present address: George A. Breon & Co., Kansas City, Mo.

(2) Walter, Goodson and Fosbinder, THIS JOURNAL, 67, 657 (1945).

TABLE I

ALKYL β-ALKYLTHIOETHYL BARBITURIC AND THIOBARBITURIC ACIDS



Malonic ester fraction used B. p., °C.	Mm.	R	R	M. p., °C., uncor.	Formula	Nitrogen, % Calcd.	Found	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
135–140	2.5	Ethyl	Allyl	96.5–98	$C_{11}H_{16}O_2N_2S$	10.93	11.11	101–103	$C_{11}H_{16}O_2N_2S_2$	10.32	10.41
130–131	1	Ethyl	Isoamyl	116–117	$C_{13}H_{22}O_2N_2S$	9.78	10.05	111–113	$C_{13}H_{22}O_2N_2S_2$	9.26	9.25
149–151	1.2	Ethyl	Phenyl	143.5–144	$C_{14}H_{16}O_2N_2S$	9.59	9.80				
110–115	1	*n*-Propyl	Allyl	83–85	$C_{12}H_{18}O_2N_2S$	10.36	10.55	78–80	$C_{12}H_{18}O_2N_2S_2$	9.78	10.07
105–110	1	Isopropyl	Allyl	93–95	$C_{12}H_{18}O_2N_2S$	10.36	10.60	87–89	$C_{12}H_{18}O_2N_2S_2$	9.78	9.81
129–131	1.3	Allyl	*n*-Butyl	101.5–102.5	$C_{13}H_{20}O_2N_2S$	9.85	10.00	109.5–110	$C_{13}H_{20}O_2N_2S_2$	9.32	9.56
114–117	1	*n*-Butyl	Methyl	124.5–126	$C_{11}H_{16}O_2N_2S$	10.84	10.76				
135–140	2	*n*-Butyl	Ethyl	86–87.5	$C_{12}H_{20}O_2N_2S$	10.28	10.33	64–66	$C_{12}H_{20}O_2N_2S_2$	9.71	9.77
131–133	1.3	*n*-Butyl	Isopropyl	89–90	$C_{13}H_{22}O_2N_2S$	9.78	10.05	68–70	$C_{13}H_{22}O_2N_2S_2$	9.26	9.42
130–131	1	*n*-Butyl	Allyl	40–50[a]	$C_{13}H_{20}O_2N_2S$	9.85	9.97		$C_{13}H_{20}O_2N_2S_2$[c]	9.32	9.00
132–134	1	*n*-Amyl	Ethyl	83–84	$C_{13}H_{22}O_2N_2S$	9.78	9.84		$C_{13}H_{21}O_2N_2S_2Na$[b]	8.64	8.62
138–140	1.5	1-Methylbutyl	Ethyl	91–94	$C_{13}H_{22}O_2N_2S$	9.78	9.84		$C_{13}H_{21}O_2N_2S_2Na$[b]	8.64	8.42
140–145	1.5	Ethyl	Ethylthiomethyl[d]	111–113	$C_{11}H_{18}O_2N_2S_2$	9.71	9.75				
130–132	1.5	*n*-$C_3H_7S(CH_2)_2$[c]	Ethyl	109–111	$C_{13}H_{20}O_2N_2S_2$	10.28	10.22	71–73	$C_{13}H_{20}O_2N_2S_2$	9.71	9.73

[a] Wax-like. [b] Free acid not obtained as a solid. [c] Not R, but the entire group. [d] The β-ethylthioethyl malonic ester used to prepare this ester has a b. p. of 110–112° at 1.1 mm.

atom and the barbituric acid nucleus. These alkyl-γ-thiopropyl compounds resembled the isomeric β-thioethyl derivatives in their physical properties and are included in Table I.

The malonic esters were obtained in 70–90% yields by the reaction of alkyl-β-chloroethyl sulfides with alkyl sodio-malonic esters in toluene at 100°. With alcohol as the reaction medium the yields were poor.

Experimental

Alkyl β-Chloroethyl Sulfides.—One mole of alkyl β-hydroxyethyl sulfide, obtained by adding ethylene chlorohydrin to the sodium mercaptide in absolute alcohol, was added slowly with stirring to 1.3 moles of thionyl chloride in 600 cc. of chloroform. The temperature was kept below 5° during the addition and for several hours thereafter. The mixture was then kept at room temperature for twenty-four hours and the chloroform and excess thionyl chloride removed *in vacuo* with a water aspirator. The remaining oil was fractionated in a good vacuum to give 90–95% yields of the chloride. Better yields of the chlorosulfides and less tar were obtained by this procedure than by that described in "Organic Syntheses," Coll. Vol. II, p. 136.

Alkyl β-Alkylthioethyl Thiobarbituric Acids.—The crude thiobarbituric acid prepared as described[1] was dissolved in a small quantity of ether and filtered to remove the yellow jelly-like impurity. The solution was then well washed with saturated sodium bicarbonate solution. After distilling the ether the residue was dried to constant weight *in vacuo* on a steam-bath and dissolved in hot absolute alcohol containing (1 g. of sodium per 20 cc. of alcohol) the amount of sodium ethoxide necessary to form the sodium salt. On cooling, large crystals of solvated salt separated and these were filtered off and washed with a little cold absolute alcohol in the funnel. This salt was crystallized several times from a small quantity of absolute alcohol with washing each time. It was then dissolved in water and the thiobarbituric acid precipitated with acetic acid. Where possible this acid was crystallized from alcohol to constant melting point. In those cases where the purified acid did not crystallize it was found advantageous to wash the ether solution with successive portions of 5% sodium carbonate until very little material, as shown by acidification of the extract, was removed. The sodium salts were then prepared as before and crystallized until a sample, dried to constant weight *in vacuo* over sulfuric acid, analyzed correctly. The alcohol-free salts were very hygroscopic.

Summary

Some 5-alkyl-5-β-alkylthioethylbarbituric and thiobarbituric acids and the intermediate malonic esters used in their preparation are described. One 5-ethyl-5-γ-*n*-propylthiopropyl acid of each type and also a barbituric acid containing thioether groups in both 5,5-substituents is included.

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