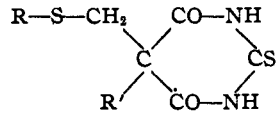
TABLE III

THIOBARBITURIC ACIDS

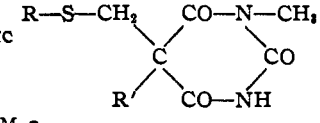


R	R'	M. p., °C., uncor.	Formula	Nitrogen, % Calcd.	Found
Methyl	Isobutyl	155–156	$C_9H_{14}O_2N_2S_2$	10.76	10.47
Ethyl	Ethyl	145–146	$C_9H_{14}O_2N_2S_2$	11.37	11.41
Ethyl	Allyl	122–123	$C_{10}H_{14}O_2N_2S_2$	10.84	10.99
Ethyl	*s*-Butyl	114–116	$C_{11}H_{18}O_2N_2S_2$	10.21	10.31
Ethyl	Isobutyl	145–147	$C_{11}H_{18}O_2N_2S_2$	10.21	9.99
Ethyl	1-Methylbutyl	97–100[a]	$C_{12}H_{20}O_2N_2S_2$	9.71	9.75
Isopropyl	Ethyl	175–176	$C_{10}H_{16}O_2N_2S_2$	10.76	10.72
Allyl	1-Methylbutyl	75–80[a]	$C_{12}H_{20}O_2N_2S_2$	9.32	9.35
n-Butyl	*n*-Butyl	90–92	$C_{12}H_{22}O_2N_2S_2$	9.26	9.27
Isoamyl	Ethyl	131.5–133	$C_{12}H_{20}O_2N_2S_2$	9.71	9.92

[a] Wax-like.

TABLE IV

N-METHYLBARBITURIC ACIDS[a]



R	R'	M. p., °C., uncor.	Formula	Nitrogen, % Calcd.	Found
Ethyl	Methyl	104–105	$C_8H_{14}O_2N_2S$	12.19	12.00
Ethyl	Ethyl	66.5–67.5	$C_{10}H_{16}O_2N_2S$	11.47	11.46
Ethyl	*n*-Propyl	102–104	$C_{11}H_{18}O_2N_2S$	10.84	10.94
Ethyl	Isopropyl	78–79	$C_{11}H_{18}O_2N_2S$	10.84	11.00
Ethyl	Allyl	63–65.5	$C_{11}H_{16}O_2N_2S$	10.93	10.86
Ethyl	Isobutyl	103–104	$C_{12}H_{20}O_2N_2S$	10.28	10.35
Ethyl	*s*-Butyl	75–79	$C_{12}H_{20}O_2N_2S$	10.28	10.07
n-Propyl	Ethyl	73–75	$C_{11}H_{18}O_2N_2S$	10.84	11.10
Isopropyl	Ethyl	87–88.5	$C_{11}H_{18}O_2N_2S$	10.84	10.72
n-Butyl	Methyl	75–77	$C_{11}H_{18}O_2N_2S$	10.84	11.01

[a] U. S. Patent 2,354,233.

The condensation of di-*n*-propylthiomethyl malonic ester with urea gave an insoluble sodium salt which was filtered from the reaction mixture and recrystallized from water. It contained no sulfur. The free acid was obtained by acidifying an aqueous solution of the salt with hydrochloric acid to congo red. It was very insoluble in all the common solvents, decomposed at 280–285°, and contained 20.22% nitrogen.

5-Ethylsulfonemethyl-5-isobutyl Barbituric Acid.—The 5-ethylthiomethyl-5-isobutylbarbituric acid was oxidized with excess hydrogen peroxide in glacial acetic acid.[4] The product decomposed at 214–215°.

Anal. Calcd. for $C_{11}H_{18}O_6N_2S$: N, 9.65. Found: N, 9.66.

5-Ethylsulfoxymethyl-5-isoamyl Barbituric Acid.—Two moles of 5-ethylthiomethyl-5-isoamyl barbituric acid was oxidized with one mole of hydrogen peroxide as described above. The product was separated easily from the excess starting material by crystallization from alcohol. It decomposed at 221–223°.

Anal. Calcd. for $C_{12}H_{20}O_4N_2S$: N, 9.71. Found: N, 9.71.

Summary

Some 5-alkylthiomethyl-5-alkyl barbituric, thiobarbituric, and N-methylbarbituric acids and the intermediates used in their preparation are described. A sulfone and a sulfoxide of representative barbituric acids are also described.

NEWARK, N. J. RECEIVED NOVEMBER 4, 1944

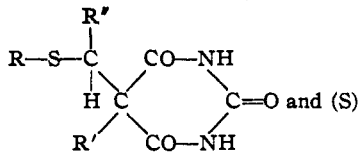
(4) Pomerantz and Connor, THIS JOURNAL, 61, 3144 (1939).

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

Thioether Barbiturates. II. α-Alkylthioalkyl 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



in which R, R′ and R″ represent primary and secondary alkyl groups. Compounds where either or both R and R′ were unsaturated were prepared but none were prepared where R″ was unsaturated. In order to avoid difficulties in purifying the products we limited the alkyl groups to those containing no asymmetric carbon atom. Compounds of the above structure where R, R′, or R″ represents a tertiary group appeared less feasible and their synthesis was not attempted.

The barbituric acids were made from the corresponding disubstituted malonic esters by the procedure given in the first paper.[2] The yields of barbituric acids varied from thirty to seventy per cent. except where R′ was a secondary group. In the latter case the yield was poor, probably due to steric effects, though the intermediate malonic ester was obtained in excellent yield.

The preparation of thiobarbituric acids where R″ was a secondary group such as isopropyl or 3-pentyl presented some difficulty as they were not obtained when the condensations were carried out in the manner described.[2] Under those conditions we were able to isolate only the monoalkyl thiobarbituric acids which resulted from the cleavage of the thioalkyl group from the desired barbituric acid and probably from the intermediate malonic ester as well. By employing the general method of Cope,[3] whereby less sodium ethoxide, more alcohol, more thiourea and a shorter reflux time were used (*i. e.*, refluxing 0.1 mole of ester, 0.15 mole of thiourea, and 0.16 mole of sodium ethoxide in 150 cc. of absolute alcohol for six hours), low yields of these thiobarbituric acids were obtained. The instability of these

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

(2) Walter, Goodson and Fosbinder, THIS JOURNAL, 67, 655 (1945).

(3) Cope and Hancock, *ibid.*, 61, 98 (1939).

compounds is shown by the fact that some decomposition of the sodium salts occurs, with the liberation of mercaptan, if they are warmed in the presence of even a trace of water.

The thiobarbituric acids represented by other variations of R, R′ and R″ within the limits first stated were obtained in fair to good yields except where R′ was a secondary group.

TABLE I

α-CHLOROETHYL SULFIDES R—S—C(CH₃)H—Cl

R	B. p. °C.	Mm.	Formula	Chlorine, % Calcd.	Found
Ethyl	42–45	18[a]			
Isopropyl	43	12.5	$C_5H_{11}ClS$	25.57	25.52
n-Butyl	43–45	3	$C_6H_{13}ClS$	23.23	22.92
n-Amyl	50–53	1.5	$C_7H_{15}ClS$	21.27	20.18

[a] Ramberg and Backlund, *Arkiv. Kemi. Mineral Geol.*, 13 A, No. 27, p. 50 (1940); *C. A.*, **34**, 4725 (1940).

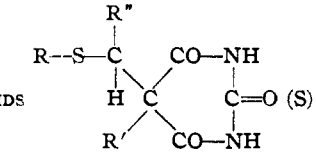
The sodium salts of all the thiobarbituric acids crystallized readily from absolute alcohol as solvates. These salts were purified readily by recrystallization from absolute alcohol and this afforded a convenient method of purifying those products which were not easily crystallized as the free acids. The alcohol-free salts were hygroscopic.

The intermediate malonic esters were obtained by condensing α-chloroalkyl sulfides with monosubstituted sodio-malonic esters in toluene as described in paper I.[2] The yields of esters, based on the mercaptan used in preparing the chlorosulfides, were 70–90% with α-chloroethyl sulfides, and 30–40% for those esters where R″ was larger than methyl.

When an alkyl-α-chloroethyl sulfide was condensed with sodio-malonic ester in toluene a 55% yield of about equal weights of mono and disubstituted malonic esters was obtained. Both of these esters were cleaved rapidly by sodium

TABLE II

ALKYL α-ALKYLTHIOALKYL BARBITURIC AND THIOBARBITURIC ACIDS



Malonic ester fraction used[a,b] B. p., °C.	Mm.	R	R′	R″	M. p., °C. uncor.	Formula	Nitrogen, % Calcd.	Found	M. p., °C. uncor.	Formula	Nitrogen, % Calcd.	Found
99–101	1	Methyl	*n*-Propyl	Methyl	137–138	$C_{10}H_{16}O_4N_2S$	11.47	11.48	111–114	$C_{10}H_{16}O_2N_2S_2$	10.76	10.95
120–122	3	Methyl	Allyl	Methyl	122–124	$C_{10}H_{14}O_4N_2S$	11.56	11.73	112–114	$C_{10}H_{14}O_2N_2S_2$	10.84	10.95
134–138	2	Methyl	*n*-Amyl	Methyl	107–109	$C_{12}H_{20}O_4N_2S$	10.28	10.48	88–90	$C_{12}H_{20}O_2N_2S_2$	9.71	9.68
107–110	1.5	Ethyl	Ethyl	Methyl	158–158.5	$C_{10}H_{16}O_4N_2S$	11.47	11.60	140–142	$C_{10}H_{16}O_2N_2S_2$	10.76	10.93
105–110	1	Ethyl	*n*-Propyl	Methyl	130.5–132	$C_{11}H_{18}O_4N_2S$	10.85	11.12	125–126	$C_{11}H_{18}O_2N_2S_2$	10.19	10.34
114–117	2	Ethyl	Allyl	Methyl	127–129.5	$C_{11}H_{16}O_4N_2S$	10.93	11.09	95–100	$C_{11}H_{16}O_2N_2S_2$	10.39	10.43
117–120	1.5	Ethyl	*n*-Butyl	Methyl	146–147	$C_{12}H_{20}O_4N_2S$	10.28	10.41				
114–117	1.4	Ethyl	Isobutyl	Methyl	154–154.5	$C_{12}H_{20}O_4N_2S$	10.28	10.43				
133–136	2	Ethyl	*n*-Amyl	Methyl	105–107	$C_{13}H_{22}O_4N_2S$	9.78	9.89				
140–145	2	Ethyl	*n*-Hexyl	Methyl	91–93	$C_{14}H_{24}O_4N_2S$	9.32	9.27	101–103	$C_{14}H_{24}O_2N_2S_2$	8.85	9.09
105–108	1	Ethyl	Ethyl	*n*-Propyl	115–117	$C_{12}H_{20}O_4N_2S$	10.28	10.25	146–147	$C_{12}H_{20}O_2N_2S_2$	9.71	9.61
110–112	1.2	Ethyl	Ethyl	Isopropyl	144.5–145.5	$C_{12}H_{20}O_4N_2S$	10.28	10.41	133.5–134	$C_{12}H_{20}O_2N_2S_2$	9.71	9.83
124–127	1.3	Ethyl	Ethyl	3-Pentyl	180.5–181	$C_{14}H_{24}O_4N_2S$	9.32	9.44				
129–130	1.7	*n*-Propyl	Allyl	Methyl	132–133	$C_{12}H_{18}O_4N_2S$	10.36	10.48				
106–108	1.4	Isopropyl	*n*-Propyl	Methyl	172–173	$C_{12}H_{20}O_4N_2S$	10.28	10.38				
104–106	1.2	Isopropyl	Ethyl	Ethyl	171–171.5	$C_{12}H_{20}O_4N_2S$	10.28	10.45	142–143	$C_{12}H_{20}O_2N_2S_2$	9.71	9.75
129–130	2	Allyl	Allyl	Methyl	115–116.5	$C_{12}H_{18}O_4N_2S$	10.44	10.43				
110–112	1	Allyl	Isobutyl	Methyl	157.5–159	$C_{13}H_{22}O_4N_2S$	9.85	9.92	153–154	$C_{11}H_{20}O_2N_2S_2$	9.32	9.14
117–120	1	Allyl	β-Methallyl	Methyl	154.5–156	$C_{13}H_{18}O_4N_2S$	9.92	9.90				
116–117	0.6	*n*-Butyl	Ethyl	Methyl	138–139.5	$C_{12}H_{20}O_4N_2S$	10.28	10.31	111–113	$C_{12}H_{20}O_2N_2S_2$	9.71	9.90
127–129	1	*n*-Butyl	*n*-Propyl	Methyl	102–104	$C_{13}H_{22}O_4N_2S$	9.78	9.95	104–106	$C_{13}H_{22}O_2N_2S_2$	9.26	9.41
119–120	1.4	*n*-Butyl	Isopropyl	Methyl	113–114	$C_{13}H_{22}O_4N_2S$	9.78	9.79				
135–137	1.5	*n*-Butyl	Allyl	Methyl	120–122	$C_{13}H_{20}O_4N_2S$	9.85	9.95	79–81	$C_{13}H_{20}O_2N_2S_2$	9.33	9.35
126–129	1.2	*n*-Butyl	Ethyl	Ethyl	134–135	$C_{13}H_{22}O_4N_2S$	9.78	9.91	107–108.5	$C_{13}H_{22}O_2N_2S_2$	9.26	9.38
121–122	1.2	Isobutyl	Allyl	Methyl	143–144	$C_{13}H_{20}O_4N_2S$	9.85	9.97				
129–130	1	*n*-Amyl	Ethyl	Methyl	127–129	$C_{13}H_{22}O_4N_2S$	9.78	9.81	106–107	$C_{13}H_{22}O_2N_2S_2$	9.26	9.32
124–126	1	Isoamyl	Ethyl	Methyl	130–131	$C_{13}H_{22}O_4N_2S$	9.78	9.77	108–110	$C_{13}H_{22}O_2N_2S_2$	9.26	9.42
139–141	1.3	Cyclohexyl	Methyl	Methyl	176–176.5	$C_{13}H_{20}O_4N_2S$	9.85	9.94	150.5–151.5	$C_{13}H_{20}O_2N_2S_2$	9.33	9.28

[a] U. S. Patent, 2,354,234. [b] Several of the malonic esters R″ = Methyl were analyzed for sulfur and gave values checking with the theoretical. However, where R was allyl the esters were contaminated with a small amount of colored, odoriferous impurity, probably polymeric allyl mercaptan. Esters where R″ was larger than methyl were contaminated with a small amount of non-saponifiable impurity, but the authors are reasonably certain all the esters were at least 95% pure. The esters obtained from ethyl α-chloroethyl sulfide and sodio-malonic ester were $C_2H_5S—C(CH_3)H—CH(COOC_2H_5)_2$, b. p. 109–110° at 2 mm. and $(C_2H_5S—C(CH_3)H)_2C(COOC_2H_5)$: b. p. 140–144 at 1.1 mm.

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.

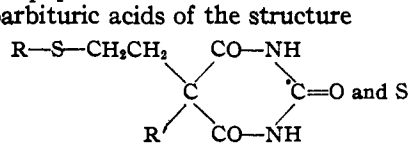
NEWARK, N. J. RECEIVED NOVEMBER 4, 1944

[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).