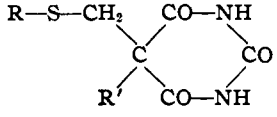
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE MALTBIE CHEMICAL CO.]

Thioether Barbiturates. I. Thiomethyl Derivatives

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

We have prepared, for pharmacological investigation, a series of barbituric acids of the structure



where R and R′ are various hydrocarbon groups. In addition, we have prepared some members of similar series of thiobarbituric and N-methylbarbituric acids. These compounds were prepared in the usual manner from the corresponding disubstituted malonic esters and urea or substituted urea. The yields were generally good with all the compounds except those where R′ was a phenyl group. One of the barbituric acids was oxidized to the sulfone and one to the sulfoxide with hydrogen peroxide in glacial acetic acid.

The intermediate malonic esters were obtained in 60–90% yields by the reaction of monosubstituted sodio-malonic esters with alkyl chloromethyl sulfides in an inert solvent such as toluene. With alcohol as the solvent the very reactive chlorides gave considerable sulfur-oxygen formal, R—S—$CH_2OC_2H_5$, even at low temperatures, and where R and R′ were large groups the formal was the major product.

When one mole of an alkyl chloromethyl sulfide reacted with one mole of sodio-malonic ester the product was almost exclusively the disubstituted malonic ester. This result was not unexpected since the great activity of the chloromethyl sulfides indicated the R—S— group was capable of a much greater degree of dynamic electron release than were the doubly bonded carbon atoms in an allyl group. In the latter case the release of electrons $\overset{H}{CH_2}=CHCH_2CH(COOC_2H_5)_2$ increased the acidity of the malonic ester to such an extent that, in its preparation by the usual procedure, 20–30% of diallylmalonic ester was obtained.

The di-alkylthiomethyl malonic ester did not give the corresponding barbituric acid when condensed with urea in the usual manner. Instead, some complex reaction took place and a sulfur-free sodium salt precipitated after a few minutes refluxing. This salt was very insoluble in water and the free acid was not precipitated by acetic acid. Analysis of the free acid gave values for nitrogen checking with that theoretically contained by two barbituric acid nuclei plus an additional methylene group. This product was not investigated further.

The alkyl chloromethyl sulfides were prepared by a slight modification of Bohme's procedure.[1a]

The pharmacology of the barbituric acids described in this and the succeeding papers of this series will be published in detail elsewhere.

Experimental

Mercaptans.—The ethyl, *n*-butyl and *t*-butyl mercaptans were Eastman Kodak Co. products. The others were prepared from alkyl bromides or chlorides and thiourea[2,3] using water as a solvent for very reactive halides, alcohol for those less reactive, and absolute alcohol for the least reactive. Where alcohol was used it was removed by distillation and the isothiourea salt dissolved in water before decomposing it with 0.9 mole of sodium hydroxide and 0.1 mole of sodium carbonate. The mercaptan was distilled from this mixture, separated from the water, dried over calcium chloride, and distilled.

TABLE I

CHLOROMETHYL SULFIDES R—S—CH_2Cl

R	B. p., °C.	mm.	Yield, %	Formula	Chlorine, % Calcd.	Found
Methyl	105–107	760	60	C_2H_5ClS	36.75	36.65
Ethyl[a]	127–129	760	60			
n-Propyl	149–150	760	93	C_4H_9ClS	28.47	28.50
Isopropyl[b]	138–139	760	85	C_4H_9ClS	28.47	28.87
Allyl[c]	52–55	15	57	C_4H_7ClS	28.92	28.82
n-Butyl	64–66	16	80	$C_5H_{11}ClS$	25.58	25.63
s-Butyl[b]	58–59	11	78	$C_5H_{11}ClS$	25.58	25.25
Isobutyl	160–161	760	75	$C_5H_{11}ClS$	25.58	25.72
t-Butyl	57–58	12	24	$C_5H_{11}ClS$	25.58	20.97[a]
n-Amyl	172–176	760	73	$C_6H_{13}ClS$	23.23	23.46
2-Pentyl[b]	73–76	13	79	$C_6H_{13}ClS$	23.23	23.19
Isoamyl	91–93	30	70	$C_6H_{13}ClS$	23.23	23.36
n-Hexyl	105–106	22	71	$C_7H_{15}ClS$	21.27	21.42
Cyclohexyl[b]	101–103	13.5	90	$C_7H_{13}ClS$	21.53	21.71
2-Ethyl)-butyl	87–88	9	74	$C_7H_{15}ClS$	21.27	21.33
1-Methyl)-heptyl-[b]	78–80	2	63	$C_9H_{19}ClS$	18.20	18.14

[a] All the compounds except this one are stable when pure. The sample saved for analysis partially decomposed even though sealed in a dark glass ampule and there was insufficient material for re-purification. The freshly prepared compound was used immediately to prepare a malonic ester. The barbituric acid prepared from the ester gave a satisfactory analysis. [b] U. S. Patent 2,354,230. [c] U. S. Patent 2,354,229.

Chloromethyl Sulfides.—Bohme's procedure was used as described for the first five members of the series. The hydrogen chloride must be added carefully with runs of low boiling mercaptans larger than one mole as the initial reaction is vigorous. The higher members of the series were insoluble in concentrated hydrochloric acid and the aqueous layer was separated before drying the product by stirring it vigorously with calcium chloride for several hours at 0°. *t*-Butyl chloromethyl sulfide decomposes rapidly when impure and must be distilled immediately after drying the crude product for one hour

Malonic Esters.—Three-tenths mole of alkyl malonic ester was added to a solution of 0.3 mole of sodium in 150 cc. of absolute alcohol. As much alcohol was removed as would distill at 10–30 mm. on a water-bath, and the residue was dissolved in 300–500 cc. of dry toluene. This solution was chilled to 0° and 0.3 mole of chloromethyl sulfide slowly added. The mixture was stirred until neutral, washed with water and distilled.

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

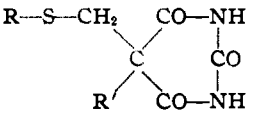
(1a) Bohme, *Ber.*, **69**, 1612 (1936).

(2) "Organic Syntheses," Vol. 21, p. 36.

(3) Backer and Dykstra, *Rec. trav. chim.*, **51**, 289 (1932).

TABLE II

BARBITURIC ACIDS[a]



Malonic ester Fraction used[b,c,d] B. p., °C.	Mm.	R	R′	M. p., °C., uncor.	Formula	Nitrogen, % Calcd.	Found
104–106	1	Methyl	Isobutyl	118–120	$C_{10}H_{16}O_3N_2S$	11.47	11.51
102–105	1	Methyl	*s*-Butyl	133.5–135	$C_{10}H_{16}O_3N_2S$	11.47	11.53
114–116	2	Methyl	β-Methallyl	180–181.5	$C_{10}H_{14}O_3N_2S$	11.56	11.52
107–109	1.5	Methyl	1-Methylbutyl	124–127	$C_{11}H_{18}O_3N_2S$	10.84	10.93
94–96	1.2	Ethyl	Methyl	149.5–151	$C_8H_{12}O_3N_2S$	12.96	12.92
104–107	2	Ethyl	Ethyl	161–162	$C_9H_{14}O_3N_2S$	12.16	12.20
118–119	2	Ethyl	*n*-Propyl	169–170	$C_{10}H_{16}O_3N_2S$	11.47	11.61
108–109	1.8	Ethyl	Isopropyl	138–139	$C_{10}H_{16}O_3N_2S$	11.47	11.47
113–114	2.5	Ethyl	Allyl	131–132	$C_{10}H_{14}O_3N_2S$	11.56	11.67
125–127	2	Ethyl	*n*-butyl	151–152	$C_{11}H_{18}O_3N_2S$	10.84	10.90
107–109	0.8	Ethyl	Isobutyl	146.5–147	$C_{11}H_{18}O_3N_2S$	10.84	11.04
114–116	1.5	Ethyl	*s*-Butyl	128–131	$C_{11}H_{18}O_3N_2S$	10.84	11.03
115–117	1	Ethyl	β-Methallyl	133–133.5	$C_{11}H_{16}O_3N_2S$	10.93	10.97
123–126	1.7	Ethyl	Isoamyl	121–122	$C_{12}H_{20}O_3N_2S$	10.29	10.17
123–125	1	Ethyl	1-Methylbutyl	103–106[e]	$C_{12}H_{20}O_3N_2S$	10.29	10.30
120–124	1.5	Ethyl	Δ-1-(1-Methylbutenyl)	111–113	$C_{12}H_{18}O_3N_2S$	10.36	10.66
149–151	1.2	Ethyl	Phenyl	205.5–206	$C_{12}H_{14}O_3N_2S$	10.07	10.21
124–126	0.8	Ethyl	*n*-Hexyl	110.5–111	$C_{13}H_{22}O_3N_2S$	9.79	10.00
142–146	1	Ethyl	Δ-1-Cyclohexenyl	170–171.5	$C_{13}H_{18}O_3N_2S$	9.92	9.93
105–107	1	*n*-Propyl	Ethyl	131–132	$C_{10}H_{16}O_3N_2S$	11.48	11.43
121–122	1.2	*n*-Propyl	Allyl	105.5–106.5	$C_{11}H_{16}O_3N_2S$	10.93	10.66
105–106	2	Isopropyl	Ethyl	152–153	$C_{10}H_{16}O_3N_2S$	11.48	11.48
107–109	1.4	Isopropyl	Isopropyl	133.5–134.5	$C_{11}H_{18}O_3N_2S$	10.84	10.85
110–112	0.5	Allyl	Ethyl	165–166	$C_{10}H_{14}O_3N_2S$	11.56	11.76
135–140	1.8	Allyl	1-Methylbutyl	89–92[e]	$C_{13}H_{20}O_3N_2S$	9.85	10.08
114–117	2	*n*-Butyl	Methyl	144–146	$C_{10}H_{16}O_3N_2S$	11.48	11.46
121–122	1	*n*-Butyl	Ethyl	106.5–107.5	$C_{11}H_{18}O_3N_2S$	10.84	10.87
133–136	2	*n*-Butyl	*n*-Propyl	129–130.5	$C_{12}H_{20}O_3N_2S$	10.29	10.44
125–128	1	*n*-Butyl	Isopropyl	129–129.5	$C_{12}H_{20}O_3N_2S$	10.29	10.31
142–145	3	*n*-Butyl	Allyl	99–100	$C_{12}H_{18}O_3N_2S$	10.37	10.29
142–145	2	*n*-Butyl	*n*-Butyl	106–108	$C_{13}H_{22}O_3N_2S$	9.79	9.76
135–138	1	*n*-Butyl	Isobutyl	112–113	$C_{13}H_{22}O_3N_2S$	9.79	9.77
128–130	0.8	*n*-Butyl	*s*-Butyl	121–122	$C_{13}H_{22}O_3N_2S$	9.79	9.50
112–115	1.5	Isobutyl	Ethyl	154.5–155.5	$C_{11}H_{18}O_3N_2S$	10.84	11.06
114–115	1.5	*s*-Butyl	Ethyl	130–130.5	$C_{11}H_{18}O_3N_2S$	10.84	11.03
103–104	1.5	*t*-Butyl	Ethyl	186.7–187	$C_{11}H_{18}O_3N_2S$	10.84	11.03
134–135	1.1	*n*-Amyl	Ethyl	107.5–108.5	$C_{12}H_{20}O_3N_2S$	10.29	10.10
118–120	0.5	Isoamyl	Ethyl	120–121	$C_{12}H_{20}O_3N_2S$	10.29	10.22
118–124	1.2	1-Methylbutyl	Ethyl	106.5–107.5	$C_{12}H_{20}O_3N_2S$	10.29	10.13
138–140	0.5	*n*-Hexyl	Ethyl	103.5–104.5	$C_{13}H_{22}O_3N_2S$	9.79	9.70
133–135	0.8	2-Ethylbutyl	Ethyl	127–128	$C_{13}H_{22}O_3N_2S$	9.79	10.01
144–147	1	Cyclohexyl	Ethyl	162–163	$C_{13}H_{20}O_3N_2S$	9.86	9.96

[a] U. S. Patent, 2,354,232. [b] Several of the malonic esters were analyzed for sulfur and without exception gave values checking with the theoretical. The authors are reasonably certain all were of 95% purity or better. [c] U. S. Patent 2,354,231. [d] The di-alkylthiomethyl malonic ester prepared was $(n\text{-}C_3H_7SCH_2)_2C(COOC_2H_5)_2$, b. p. 147–149°, at 1.2 mm. [e] Wax-like.

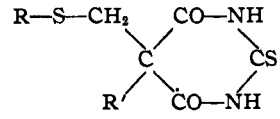
Barbituric Acids.—Two-tenths mole of malonic ester and 0.24 mole of urea were refluxed for twelve to eighteen hours with a solution of 0.42 mole of sodium in 150 cc. of absolute alcohol. The alcohol was removed *in vacuo* on a water-bath and the residue dissolved in 150–200 cc. of water. This solution was extracted with ether and then acidified with acetic acid. The crude product was purified by crystallization from alcohol or alcohol–water mixture. The yields were good.

The thiobarbituric acids were prepared from thiourea in the same manner. They were usually contaminated with a jelly-like impurity which was removed by filtering a concentrated ether solution of the crude product. The sodium salts of all the thiobarbituric acids crystallized readily from absolute alcohol as solvates containing two molecules of alcohol. In those cases where the free acid was not easily purified it was first purified as the sodium salt by several crystallizations from absolute alcohol. The alcohol-free salts were hygroscopic.

The N-methyl barbiturates were prepared from the same proportions of ester and methyl urea with 0.22 mole of sodium in 75 cc. of absolute alcohol.

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	$C_8H_{12}O_2N_2S_2$	11.37	11.41
Ethyl	Allyl	122–123	$C_9H_{12}O_2N_2S_2$	10.84	10.99
Ethyl	*s*-Butyl	114–116	$C_{10}H_{16}O_2N_2S_2$	10.21	10.31
Ethyl	Isobutyl	145–147	$C_{10}H_{16}O_2N_2S_2$	10.21	9.99
Ethyl	1-Methylbutyl	97–100[a]	$C_{11}H_{18}O_2N_2S_2$	9.71	9.75
Isopropyl	Ethyl	175–176	$C_9H_{14}O_2N_2S_2$	10.76	10.72
Allyl	1-Methylbutyl	75–80[a]	$C_{11}H_{18}O_2N_2S_2$	9.32	9.35
n-Butyl	*n*-Butyl	90–92	$C_{11}H_{22}O_2N_2S_2$	9.26	9.27
Isoamyl	Ethyl	131.5–133	$C_{11}H_{18}O_2N_2S_2$	9.71	9.92

[a] Wax-like.

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.

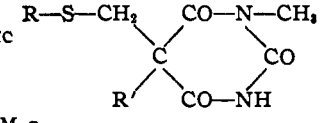
5-Ethylsulfonemethyl-5-isobutyl Barbituric Acid.—The 5-ethylthiomethyl-5-isobutylbarbituric acid was oxidized with excess hydrogen peroxide in glacial acetic acid.[4] The product decomposed at 214–215°.

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

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

TABLE IV

N-METHYLBARBITURIC ACIDS[a]



R	R'	M. p., °C., uncor.	Formula	Nitrogen, % Calcd.	Found
Ethyl	Methyl	104–105	$C_8H_{14}O_4N_2S$	12.19	12.00
Ethyl	Ethyl	66.5–67.5	$C_{10}H_{16}O_4N_2S$	11.47	11.46
Ethyl	*n*-Propyl	102–104	$C_{11}H_{18}O_4N_2S$	10.84	10.94
Ethyl	Isopropyl	78–79	$C_{11}H_{18}O_4N_2S$	10.84	11.00
Ethyl	Allyl	63–65.5	$C_{11}H_{16}O_4N_2S$	10.93	10.86
Ethyl	Isobutyl	103–104	$C_{12}H_{20}O_4N_2S$	10.28	10.35
Ethyl	*s*-Butyl	75–79	$C_{12}H_{20}O_4N_2S$	10.28	10.07
n-Propyl	Ethyl	73–75	$C_{11}H_{18}O_4N_2S$	10.84	11.10
Isopropyl	Ethyl	87–88.5	$C_{11}H_{18}O_4N_2S$	10.84	10.72
n-Butyl	Methyl	75–77	$C_{11}H_{18}O_4N_2S$	10.84	11.01

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

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.

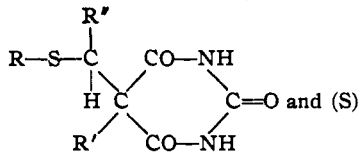
NEWARK, N. J. RECEIVED NOVEMBER 4, 1944

[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).