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THIOBARBITURATES. III. SOME N-SUBSTITUTED DERIVATIVES

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The synthesis of a number of 5,5-dialkyl-2-thiobarbituric acids has been described, and pharmacological and clinical evidence indicates that some of these compounds may have therapeutic value (1, 2, 3). Since the N-alkyl substituted barbituric acids, 1-methyl-5-ethyl-5-phenylbarbituric acid (Prominal) and 1,5-dimethyl-5-(1-cyclohexenyl)barbituric acid (Evipal), exhibited physiological properties that encouraged their use in medicine, it appeared worth while to prepare a series of analogous 1,5,5-trialkyl-2-thiobarbituric acids. The preparation, properties, and a preliminary study of their pharmacodynamic behavior are described in this report.

A search of the literature revealed that the following related compounds have been prepared, namely, 1-methyl-6-imino-2-thiobarbituric acid (4-oxy-6-imino-2-thio-1-methylhexahydropyrimidine)(4); 1,3-diphenyl-2-thiobarbituric acid (5), 1-allyl-5-phenylamino-2-thiobarbituric acid (1-allyl-2-thio-7-phenyluramil)(6), 1-methyl-3-phenyl-5,5-diethyl-2-thiobarbituric acid (7), and 1,3-di-*o*-tolyl-2-thiobarbituric acid (8).

Among the 5,5-disubstituted barbituric acids, certain alkyl groups may be introduced on the nitrogen by allowing the sodium salt of the acid to react with an alkyl halide. A similar procedure with analogous thiobarbituric acids, according to Tabern and Volwiler (2), forms compounds in which the third alkyl becomes attached to the sulfur, the products being semi-solids from which mercaptans are slowly evolved[2]. Consequently, the best available method for obtaining the desired products seemed to be the condensation of an appropriate dialkylmalonic or cyanoacetic ester with an N-alkylthiourea. Thus far we have examined various compounds obtained by the condensation of nine dialkyl substituted malonic or cyanoacetic esters with allyl-, methyl-, or ethyl- thiourea.

The reaction between the dialkylmalonic ester and allylthiourea proceeded quite normally when the customary ratio of reagents was used, *i.e.*, 1 mole of the malonic ester, 1.6 moles of allylthiourea, and 3 moles of metallic sodium dissolved in the required quantity of anhydrous ethanol.

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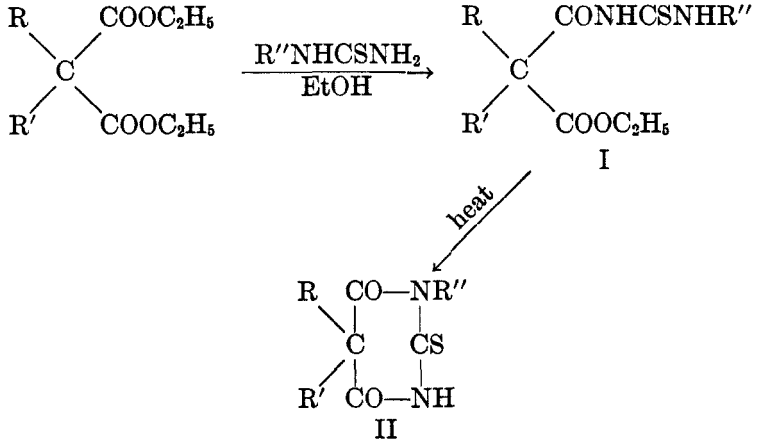
[2] These reactions were independently observed in our laboratories also. Lee, *J. Am. Chem. Soc.*, **60**, 993 (1938) observed similar reactions with 5-monoalkylthiobarbituric acids.

Satisfactory yields of 1-allyl-5,5-dialkylthiobarbituric acids were obtained. However, when methyl-, ethyl-, or phenyl- thiourea was used, a product was obtained, but it was not the desired trisubstituted thiobarbituric acid. The present evidence indicates that this product may be a dialkyl-N,N′-bis(alkylthiocarbamyl)malonamide, $R_2C(CONHCS\cdot NHR'')_2$ or, for certain derivatives, a compound derived from it by ring closure. The preparation, properties, and identification of these compounds are under investigation.

By varying the relative amounts of reagents used and the conditions of the reaction, 1,5,5-trialkyl-2-thiobarbituric acids (II), together with some of the corresponding α,α-dialkyl-N-alkylthiocarbamylmalonamic acids (I), have been obtained in the condensation of dialkylmalonic esters with N-methyl- and N-ethyl- thiourea. It was found that when the proportion of malonic ester was increased, the proportion of metallic sodium decreased, and the refluxing prolonged, the yield of desired 1,5,5-trialkyl-2-thiobarbituric acid became larger. By employing 1.1 moles of ester, 1 mole of alkylthiourea, and 1.1 moles of metallic sodium (dissolved in ethanol), significant quantities of the thiobarbituric acid derivative can be obtained. Even under these conditions, however, the main product is accompanied by appreciable amounts of the other two by-products. For example, when diethylmalonic ester was condensed with methylthiourea, the following compounds were isolated: α,α-diethyl-N-methylthiocarbamylmalonamic acid,[3] and 1-methyl-5,5-diethyl-2-thiobarbituric acid. The isolation of the above products in varying amounts, as conditions were altered, indicates that the reaction parallels that suggested by Fischer and Dilthy (9) in the urea series and may be represented as follows:



[3] A similar compound, α-butyl-α-ethyl-N-*p*-ethoxyphenylcarbamylmalonamic acid, was obtained by Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929) from ethyl-*n*-

EXPERIMENTAL

The malonic and cyanoacetic esters used in this work are all described in the literature and were purchased when possible, or synthesized by well-known procedures. Allylthiourea was purchased, and the methyl- and ethyl- thioureas were prepared by a modification of the method described by Slotta and Dressler (10).

1-Allyl-5,5-dialkyl-2-thiobarbituric acids. Diethylmalonic ester was condensed with allylthiourea according to the usual procedure for barbituric acid synthesis. The desired 1-allyl-5,5-diethyl-2-thiobarbituric acid was obtained as an oil which solidified after vacuum distillation and was purified by crystallization from dilute ethanol, m.p. 97.5–98°. 1-Allyl-5-ethyl-5-isoamyl-2-thiobarbituric acid was obtained in the same manner. The physical properties of these compounds are given in Table I.

TABLE I

TRIALKYLTHIOBARBITURIC ACIDS

2-THIOBARBITURIC ACIDS			FORMULA	M.P., °C.	N ANALYSIS, %	
5-Alkyl	5-Alkyl	1-Alkyl			Calc'd	Found
Methyl	Isopropyl	Methyl	$C_9H_{14}N_2O_2S$	107–107.5	13.08	13.02
Methyl	1-Methylbutyl	Methyl	$C_{11}H_{18}N_2O_2S$	b.p. 148–150/1 mm.	11.57	11.00
Methyl	1-Cyclohexenyl	Methyl	$C_{12}H_{16}N_2O_2S$	140–141	11.11	11.19
Ethyl	Ethyl	Methyl	$C_9H_{14}N_2O_2S$	123–124	13.09	13.08
Ethyl	*n*-Propyl	Methyl	$C_{10}H_{16}N_2O_2S$	79–80	12.28	12.30
Ethyl	Isopropyl	Methyl	$C_{10}H_{16}N_2O_2S$	104–104.5	12.28	12.12
Ethyl	Isopropenyl	Methyl	$C_{10}H_{14}N_2O_2S$	94.5–95	12.38	12.64
Ethyl	Isoamyl	Methyl	$C_{12}H_{20}N_2O_2S$	84.5–85	10.94	10.98
Ethyl	Phenyl	Methyl	$C_{13}H_{14}N_2O_2S$	120–121	10.69	10.67
Ethyl	Benzyl	Methyl	$C_{14}H_{16}N_2O_2S$	119–119.5	10.15	10.11
Ethyl	Benzyl	Ethyl	$C_{15}H_{18}N_2O_2S$	b.p. 170–175/1 mm.	9.65	9.89
Ethyl	Ethyl	Allyl	$C_{11}H_{18}N_2O_2S$	97.5–98	11.66	11.75
Ethyl	Isoamyl	Allyl	$C_{14}H_{22}N_2O_2S$	b.p. 175–180/1 mm.	9.93	9.85

1,5,5-Trialkyl-2-thiobarbituric acids. The reaction of ethylisopropenylmalonic ester with N-methylthiourea will serve as an example of the best conditions employed in preparing the trialkylthiobarbituric acids described in Table I from malonic esters and methyl- or ethyl- thiourea. While the procedure still leaves much to be desired, it served to provide sufficient amounts of the thiobarbituric acids for identification and pharmacological examination. Least satisfactory was the condensation with diethylmalonic ester, because of the difficulty encountered in separating the thiobarbituric acid from its by-products.

In 102 ml. of anhydrous ethanol was dissolved 5.06 g. of sodium (0.22 mole); the solution was cooled to room temperature and 50.2 g. of ethylisopropenylmalonic ester (0.22 mole) and 18 g. of methylthiourea (0.2 mole) were added. The mixture

butylmalonic ester and *p*-ethoxyphenylurea. This compound is erroneously listed in *Chem. Abstr.*, **23**, 3024 (1929) as α-butyl-α-ethyl-N-*p*-phenethylcarbamylmalonamic acid.

was stirred at room temperature for one hour and then refluxed from twelve to fifteen hours. It was then diluted to 500 ml. with water and extracted with benzene to remove alkali-insoluble matter. Acidification of the aqueous solution gave an oil which was extracted from the mixture with benzene. The benzene solution was washed twice with water and extracted with sodium bicarbonate solution to remove any α,α-ethyl-α-isopropenyl-N-methylthiocarbamylmalonamic acid present. The sodium bicarbonate extract yielded 2 g. of an oily product on acidification.

The residual benzene solution was then extracted with 2% sodium hydroxide solution. Acidification of the sodium hydroxide extract gave 22 g. of an oil which solidified upon long standing. 1-Methyl-5-ethyl-5-isopropenyl-2-thiobarbituric acid, 10 g., melting at 94.5–95°, was separated from an unidentified by-product contained in the crude material, by four recrystallizations from dilute ethanol.

Condensation of (1-cyclohexenyl)methylcyanoacetic ester with N-methylthiourea. (1-Cyclohexenyl)methylcyanoacetic ester (42 g.) was condensed with methylthiourea under the same experimental conditions as above, to give 18 g. of the iminothio-

TABLE II

DIALKYL-N-METHYLTHIOCARBAMYLMALONAMIC ACIDS

N-METHYLTHIOCARBAMYL-MALONAMIC ACIDS		FORMULA	M.P., °C. (DECOMP. WITH EVOLUTION OF GAS)	N ANALYSIS, %	
α-Alkyl	α-Alkyl			Calc'd	Found
Methyl	*n*-Propyl	$C_9H_{16}N_2O_3S$	109–109.5	12.07	12.28
Ethyl	Ethyl	$C_9H_{16}N_2O_3S$	132.5–133	12.07	12.09
Ethyl	*n*-Propyl	$C_{10}H_{18}N_2O_3S$	120.5–121	11.38	11.48
Ethyl	Phenyl	$C_{13}H_{16}N_2O_3S$	131–132[a]	10.00	10.36
n-Propyl	Allyl	$C_{11}H_{16}N_2O_3S$	97–98	10.85	10.99

[a] After standing for approximately two years, this sample was found to melt at 107.5°, without effervescence, and the nitrogen content had risen to 12.09%, which corresponds closely to the theory for phenylethylacetylmethylthiourea, 11.86%. The identity was established by synthesis of phenylethylacetylmethylthiourea, m.p. 107–107.5°. *Anal.* Found: N, 11.85%.

barbituric acid, which upon hydrolysis with dilute hydrochloric acid (1:2) gave 15 g. of 1,5-dimethyl-5-(1-cyclohexenyl)-2-thiobarbituric acid, melting at 140–141° after recrystallization from anhydrous ethanol.

α,α-Dialkyl-N-methylthiocarbamylmalonamic acids. An increase in the molecular proportion of sodium and dialkylmalonic ester in the above procedure for the preparation of 1-methyl-5,5-dialkyl-2-thiobarbituric acids led to the production of a significant quantity of α,α-dialkyl-N-methylthiocarbamylmalonamic acids.

In a typical reaction, 18.4 g. of sodium in 370 ml. of anhydrous ethanol, 69.1 g. of diethylmalonic ester, and 18 g. of methylthiourea (molar ratio—Na:ester:thiourea:: 4:1. 6:1) were refluxed for seven and one-half hours. The solution was concentrated to one-third its volume on the steam-bath and then acidified with concentrated hydrochloric acid, whereupon an oil separated. This oil was dissolved in benzene and the solution extracted with sodium bicarbonate. The bicarbonate extract was acidified and an oil, which slowly crystallized, was obtained. Yield, 9 g. The product melted with effervescence at 132.5–133° after several recrystallizations from a mixture of solvent naptha and benzene. These crystals were identified as α,α-

diethyl-N-methylthiocarbamylmalonamic acid. Its properties, with those of its homologs, are summarized in Table II.

A sodium hydroxide extract of the residual benzene solution, on acidification with hydrochloric acid, gave 8 g. of an oil which crystallized rapidly on stirring, and upon recrystallization from benzene melted at 142.5–143°. The identity and reactions of this compound are being investigated.

Synthesis of phenylethylacetylmethylthiourea. In a one-liter three-necked flask, equipped with reflux condenser and mechanical stirrer, were placed 22.5 g. (0.25 mole) of methylthiourea, 45.6 g. (0.25 mole) of phenylethylacetyl chloride, and 250 ml. of toluene. This mixture was refluxed with stirring for fifteen hours. The toluene was removed by evaporation on a steam-bath and the residue purified by

TABLE III

TRIALKYLTHIOBARBITURIC ACIDS

Results of Pharmacological Tests in White Mice[a, b]

2-THIOBARBITURIC ACIDS			AD 50 MG/KG	AD 100 MG/KG	LD 50 MG/KG	RATIO LD 50/AD 50	DURATION AT AD 100	
5-Alkyl	5-Alkyl	1-Alkyl					Induction Minutes	Anesthesia Hours
Methyl	1-Methylbutyl	Methyl	45	60	190	4.2	1	0.3
Methyl	1-Cyclohexenyl	Methyl	100	125	600	6.0	4	1.3
Ethyl	Isopropyl	Methyl	85	100	270	3.2	2	0.5
Ethyl	Isopropenyl	Methyl	85	90	320	3.7	3	2.0
Ethyl	Isoamyl	Methyl	125	150	290	2.3	5	0.3
Ethyl	Benzyl	Methyl	Convulsions		15			
Ethyl	Benzyl	Ethyl	Convulsions		100			
Ethyl	Ethyl	Allyl	250	300	700	2.8	4	0.2
Ethyl	Isoamyl	Allyl	300		500	1.7	11	0.3–1.0

[a] We are indebted to Mr. H. J. Pratt for technical assistance in the pharmacological testing of these compounds.

[b] We have followed the method of testing described by Cope and Hancock, *J. Am. Chem. Soc.*, **61**, 96 (1939), and the terms and symbols used herein have the meaning defined by them.

crystallization from boiling anhydrous alcohol, yield 38 g. (65% of the theoretical), m.p. 107–107.5°.

Anal. Calc'd for $C_{13}H_{16}N_2OS$: N, 11.86. Found: N, 11.85.

Pharmacological data. Pharmacological data obtained by the intraperitoneal injection into white mice of the sodium salt of the thiobarbituric acids are summarized in Table III. In general, it can be said that all of the compounds are active as hypnotics, having short induction periods and producing anesthesia of short duration, except the two containing a benzyl group, which were convulsant, rather than hypnotic in action. The effective and lethal doses, as well as the therapeutic ratios, varied widely within the group.

SUMMARY

The preparation, properties, and preliminary pharmacological data of several new 1,5,5-trialkyl-2-thiobarbituric acids are described.

The condensation of dialkylmalonic esters with N-methyl- and N-ethylthiourea gives rise to a series of α,α-dialkyl-N-alkylthiocarbamylmalonamic acids, and products as yet unidentified, as well as of thiobarbituric acids.

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