[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE, AND FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY, WILMINGTON, DELAWARE]

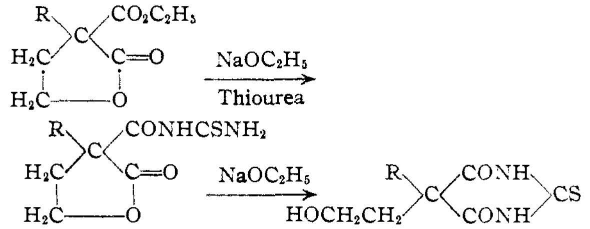
5-Alkyl-5-β-hydroxyethyl Derivatives of 2-Thiobarbituric Acid[1]

BY GLENN S. SKINNER AND JOHN MITCHELL, JR.

It was shown in earlier publications that the 5-alkyl-5-β-hydroxyethyl derivatives of barbituric acid could be prepared by the condensation of α-alkyl-α-carbethoxy-γ-butyric lactones with urea in the presence of sodium ethoxide.[2,3,4]

Recently, Heyl and Cope[5] used this reaction for the synthesis of 5-alkyl-5-(α-ethoxy-β-hydroxyethyl)-barbituric acids from the corresponding γ-butyrolactones.

In the present work, it was found that the α-alkyl-α-carboxethyl-γ-butyric lactones also condense with thiourea in the presence of sodium ethoxide to form the corresponding 5-alkyl-5-β-hydroxyethyl-2-thiobarbituric acids. The intermediate lactone thioureide has been isolated and also converted to the thiobarbiturate.



I

By substituting thiourea for urea the reaction was favored by decreased temperatures (30–35°) and smaller excesses of sodium ethoxide. The molar ratios of sodium, thiourea and lactone were 2:1·5:1, respectively. The intermediate lactone thioureide (I) was isolated and identified in two cases. During the purification of the *n*-butyl and isoamyl derivatives these compounds were recovered from the more soluble fractions.

Of the eight thiobarbituric acids recorded in Table I only one has been reported previously in the literature. Cretcher and his co-workers[6] prepared the 5-ethyl-5-β-hydroxyethyl derivative by the acid hydrolysis of 5-vinyloxyethyl-5-ethyl-2-thiobarbituric acid.

The method employed for the preparation of the first six thiobarbiturates recorded in Table I resulted from an extensive study of the condensation of the α-isoamyl-α-carboxethyl-γ-butyric lactone. Conditions varied from molar ratios of sodium, thiourea and lactone of 3:1·6:1 to 1·12:1·1:1, respectively, with maximum temperatures ranging from 8 to 55° over periods of from six to forty-eight hours. A large excess of sodium is not essential, for with the minimum quantities of ethoxide employed a yield of 70% was realized. In some cases, however, a molecular compound of the sodium thiobarbiturate with one mole of sodium ethoxide precipitated from the alcoholic solution.

TABLE I

5-ALKYL-5-β-HYDROXYETHYL-2-THIOBARBITURIC ACIDS

Alkyl group	Yield,[a] %	M. p.,[b] °C., cor.	Nitrogen, %[c] Found	Nitrogen, %[c] Calcd.	Sulfur, %[d] Found	Sulfur, %[d] Calcd.
Ethyl	93	162.9	12.85	12.96	14.90	14.82
n-Propyl	72	150.7	12.43	12.17	14.00	13.92
n-Butyl	87	161.7	11.44	11.47	13.18	13.12
n-Amyl	82	152.8	10.79	10.85	12.40	12.41
Isobutyl	94	193.2	11.50	11.47	13.22	13.12
Isoamyl	80	179.3	10.83	10.85	12.51	12.41
2-Ethylbutyl	39	164.5	10.27	10.29	11.65	11.76
2-Methylpentyl	61	173.8	10.22	10.29	11.64	11.76

[a] Calculated from purified acid recovered on basis of lactone added. [b] Melting points obtained on a carefully calibrated melting point bar. [c] By semi-micro Kjeldahl. [d] By Parr bomb peroxide procedure employing gravimetric barium sulfate precipitation.

It was evident that at least one side reaction was involved, probably between the lactone and sodium ethoxide.[7] This was demonstrated by preferential titration for free sodium ethoxide and sodium salt.[8] Indicated conversion on this basis was 7.4 to 50% greater than the yield of the thiobarbituric acid and was most evident at the higher temperatures.

The free acids are usually obtained as flat, platy or acicular crystals very lightly colored and having a very slight mercaptan-like odor. They retain liquids tenaciously, requiring vacuum drying to be completely free of the usual wash liquids. The acids are insoluble in petroleum ether, ligroin, benzene and cyclohexane and only slightly soluble in carbon tetrachloride, methylene chloride and carbon bisulfide. They are soluble in ethyl acetate and very soluble in methanol and acetone. Quantitative solubility data in water and ethanol at 25 ± 0.05° are given in Table II.

Chloroform is not a particularly good solvent for these thiobarbituric acids.[9] Either ethyl acetate or possibly methylal, as suggested by Malangeau,[10] would be better suited for extraction purposes.

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(1) From the thesis submitted by John Mitchell, Jr., in partial fulfillment of the requirements for the degree of Master of Science at the University of Delaware.

(2) Rosenberg, Kneeland and Skinner, THIS JOURNAL, **56**, 1339 (1934).

(3) Skinner, *ibid.*, **59**, 322 (1937).

(4) Skinner and Stuart, *ibid.*, **63**, 2993 (1941).

(5) Heyl and Cope, *ibid.*, **65**, 669 (1943).

(6) Cretcher, Koch and Pittenger, *ibid.*, **47**, 3083 (1925).

(7) Thiourea gave no evidence of reaction with sodium under the conditions of the synthesis. It apparently was insoluble in the sodium ethoxide solution and reacted in the solid phase with the lactone.

(8) It was found that these compounds could be selectively analyzed by titration with standard acid first to thymolphthalein to determine free ethoxide and then to brom phenol blue to determine sodium salt.

(9) The solubility of the isoamyl compound in chloroform is only 0.477 g./100 ml.

(10) Malangeau, *Bull. soc. chim. biol.*, **25**, 233 (1943).

TABLE II

SOLUBILITY OF 5-ALKYL-5-β-HYDROXYETHYL-2-THIOBARBITURIC ACIDS IN WATER AND ETHANOL AT 25°

Alkyl group	Solubility (grams/100 ml. solvent) In water	In ethanol
Ethyl	0.7285	5.900
n-Propyl	.5715	14.393
n-Butyl	.1656	
n-Amyl	.1090	19.198
Isobutyl	.0584	
Isoamyl	.0716	13.640
2-Methylpentyl	.0224	3.920
2-Ethylbutyl	.0196	6.098

Experimental

The alkylmalonic esters were prepared according to the usual procedure.[11]

TABLE III

ALKYLMALONIC ESTERS

Alkyl group	Yield, %	B. p., °C.	Mm.	n^{25}_D	d^{25}_4	MR_D Found	Calcd.
Isobutyl	77	142	50[a]	1.4195	0.9677	56.4	56.1
Isoamyl	70	115.8	10[a]	1.4223	0.9580	61.1	60.7
2-Ethylbutyl	79	123	7[b]	1.4290			
2-Methylpentyl[c]	80	115	7	1.4278	0.9582	65.6	65.2

[a] Volwiler[12] reported a boiling range of 217-227° (750 mm.), for the isobutyl and 245-250 (747 mm.) for the isoamyl compound. [b] Motti[13] reported a boiling point of 145° (20 mm.) and Rothstein[14] a boiling point of 141° (16.5 mm.), n^{22}_D 1.4300. [c] % carbon, 64.02 (found), 63.93 (calcd.); % hydrogen = 9.84 (found and calcd.).

α-Alkyl-α-carboxethyl-γ-butyric Lactones.—The alkyl-β-bromoethylmalonic esters were prepared in the usual way.[2,3] After removal of the excess ethylene bromide, the excess malonic ester was distilled at 15–20 mm. and the residue placed on total reflux during the decomposition of the alkylbromoethylmalonic ester. Final distillation was made at 3-5 mm. Physical and yield data are recorded in Table IV.

TABLE IV

α-ALKYL-α-CARBOXETHYL-γ-BUTYRIC LACTONES

No.	Alkyl group	Yield, %	B. p.,[a] °C.	Mm.	n^{25}_D	n^{20}_D
1	Ethyl		116	5	1.4452	1.4473
2	Propyl		112		1.4458	1.4475
3	*n*-Butyl[b]		119		1.4467	1.4487
4	*n*-Amyl		128.5		1.4489	1.4502
5	Isobutyl	66[c]	119.5	5	1.4482	1.4499
6	Isoamyl	85–90[d]	119		1.4480	1.4498
7	2-Ethylbutyl	91	121		1.4553	
8	2-Methylpentyl	85	119–120		1.4537	

No.	d^{25}_4	d^{20}_4	MR_D Found	MR_D Calcd.	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.
1	1.1083	1.1128	44.7	44.7	58.23	58.05	7.57	7.58
2	1.0792	1.0833	49.4	49.3	59.96	59.98	8.19	8.06
3	1.059	1.063	54.0	53.9	61.1	61.66	8.40	8.47
4	1.0409	1.0447	58.8	58.5	63.36	63.13	8.79	8.83
5	1.0634	1.0781	53.95	53.9	61.41	61.66	8.50	8.47
6	1.0404	1.0443	58.7	58.5	63.37	63.13	9.06	8.83
7	1.0405		63.3	63.2	64.64	64.43	9.20	9.15
8	1.0365		63.1	63.2	64.53	64.43	9.15	9.15

[a] Boiling point at 3 mm., unless otherwise indicated. [b] Values previously reported[3] but included for comparison. [c] Minimum, some product lost during distillation. [d] Yields from two preparations.

5-Alkyl-5-β-hydroxyethyl-2-thiobarbituric Acids.—Since the technique must be followed closely for maximum yields, the method used for the preparation of most of the derivatives is given in detail.

Into a 0.5-liter three-necked distillation flask was placed 0.20 atom of sodium and 92 ml. of absolute ethanol. After all of the sodium had reacted, the flask was surrounded with an ice-bath and the contents cooled to 2–3°. Then, while stirring, 0.15 mole of dry powdered thiourea was added, followed immediately by 0.10 mole of α-alkyl-α-carboxethyl-γ-butyric lactone. The temperature was allowed to rise to 25° in approximately one and half hours and then to 35° in the next one and half hours, where it was maintained for about three hours.

The butyl and amyl acids[15] were recovered almost quantitatively by the following new method: after the condensation was complete the alcoholic solution was washed into a two-liter beaker with about one liter of ice water. The beaker was placed in ice and then, with mechanical stirring, the solution was acidified to congo red paper with 6 *N* hydrochloric acid. The mixture was filtered cold and the acid was washed with cold water, then triturated alternately with cold water and petroleum ether. The acid was transferred to a tared beaker, vacuum dried and weighed. In all cases the acid thus obtained was pure.

An additional 0.5–0.6 g. of acid was found in a chloroform extract of the filtrate.

The ethyl and propyl derivatives, because of increased water solubility, could not be recovered in this way. In these cases the alcohol was removed at reduced pressure and the acids were isolated in the usual manner.

The degree of conversion of the lactone to the thiobarbiturate was determined by titration of 5 or 10 ml. portions of the alkaline solution with 0.5 *N* hydrochloric acid, first to thymolphthalein and then to brom phenol blue. The validity of this method was verified by potentiometric titration of known mixtures.

A molecular compound of the sodium *n*-butylthiobarbiturate with sodium ethoxide was precipitated soon after adding the thiourea and lactone to the alcoholic solution of sodium ethoxide. A portion of this finely divided white solid was recovered and vacuum dried. A portion was titrated, requiring 5.8 ml. of 0.5 *N* hydrochloric acid to thymolphthalein and an additional 5.7 ml. to brom phenol blue, indicating equivalent quantities of thiobarbiturate salt and strong base. The acid which precipitated was vacuum dried. It melted at 193° and gave no depression when mixed with the *n*-butyl compound.

Anal. Calcd. for $C_{10}H_{16}O_3N_2SNa \cdot C_2H_5ONa$: Na, 13.77. Found: Na, 13.92.

An analogous compound has been obtained from the lactone esters and urea.[16]

Lactone Thioureides.—In two experiments where the *n*-butyl and isoamyl acids were recovered in the usual way, the lactone thioureides were isolated. They remained in solution during recrystallization of the acids from butanol–toluene and isoamyl alcohol–toluene, respectively. When the filtrates were concentrated and chilled, the lactone thioureides precipitated. They were recrystallized from hot ethanol. Significant data are given.

Alkyl group	M. p., °C.	Nitrogen, % Found	Nitrogen, % Calcd.	Sulfur, % Found	Sulfur, % Calcd.
n-Butyl	125.0			13.07	13.12
Isoamyl	113–114	10.72	10.85	12.55	12.41

The *n*-butyl lactone thioureide (0.005 mole) was allowed to react for two and one-half hours at 35° with a solution of 0.010 mole of sodium ethoxide in 4.6 ml. of ethanol. The yield of *n*-butyl-β-hydroxyethyl-2-thiobarbiturate was 91% of the theoretical, m. p. 161.5°. There was no de-

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[11] "Organic Syntheses," **4**, 11–12 (1924).

[12] Volwiler, THIS JOURNAL, **47**, 2236 (1925).

[13] Motti, *Anesthesie and Analgesie*, **2**, 52 (1936).

[14] Rothstein, *Bull. soc. chim.*, [5] **2**, 80 (1935).

[15] The 2-ethylbutyl and 2-methylpentyl derivatives could also be recovered in this way. However, they were prepared before this technique was developed.

[16] Unpublished work done at the University of Delaware.

pression of the melting point when mixed with an authentic specimen.

Physical Measurements.—For the determination of solubilities an excess of the acid was placed in a glass-stoppered graduated cylinder to which a known volume of solvent had been added. The mixture was placed in a thermostatically controlled water-bath at 25 ± 0.05° and left for several hours, shaking periodically. Filtered samples were titrated with standard sodium hydroxide to thymolphthalein.

Densities were determined with Reischauer pyknometers and refractive indices with a Bausch and Lomb Abbe refractometer which had been calibrated at the D line with Bureau of Standards certified test prisms.

Melting points were determined with the aid of a carefully calibrated Dennis–Parr melting point bar. Temperatures were measured thermoelectrically using a special Leeds and Northrup portable potentiometer reading directly in degrees centigrade for copper–constantan thermocouples and graduated in units of 0.5°.

Summary

1. Eight 5-alkyl-5-β-hydroxyethyl-2-thiobarbituric acids have been prepared by the condensation of α-alkyl-α-carboxethyl-γ-butyric lactones with thiourea in the presence of sodium ethoxide.

2. High yields were obtained using molar ratios of sodium, thiourea and lactone of 2:1·5:1, respectively, at maximum temperatures of 35°. These conditions are considerably less drastic than those for the synthesis of the corresponding barbiturates.

3. In two cases the intermediate lactone thioureides have been isolated.

4. A molecular compound of the sodium n-butylthiobarbiturate with sodium ethoxide was obtained.

5. A rapid and simple method for the estimation of conversion is illustrated and a new technique by which six of the eight thiobarbituric acids can be recovered nearly quantitatively is described.

6. Physical properties studied include melting points and solubility in common solvents.

7. Modifications of existing methods of preparation and physical properties of the intermediates are discussed. These include alkylmalonic esters and α-alkyl-α-carboxethyl-γ-butyric lactones.

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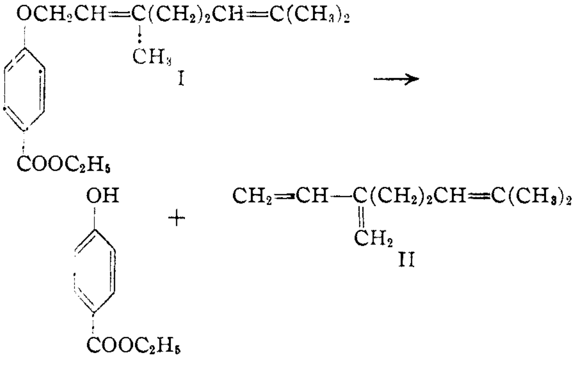
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Pyrolysis of Ethyl *p*-Geranyloxybenzoate[1]

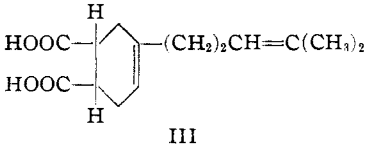
BY WALTER M. LAUER AND RAFAEL LABRIOLA[2]

The pyrolysis of only a few γ,γ-disubstituted allyl phenyl ethers has been studied. Claisen reported, but without experimental detail, that the pyrolysis of γ,γ-dimethylallyl phenyl ether yields isoprene and phenol[3] and Hurd and Cohen[4] showed that $\alpha,\alpha,\gamma,\gamma$-tetramethylallyl phenyl ether likewise gave cleavage products, in this case hexadiene and phenol. Lauer and Moe[5] studied the pyrolysis of ethyl p-(γ,γ-dimethylallyloxy)-benzoate; the cleavage products, isoprene and ethyl p-hydroxybenzoate were obtained together with 2,2,3-trimethylcoumaran. The formation of 2,2,-3-trimethylcoumaran was accounted for on the basis of an abnormal rearrangement followed by ring closure. The geranyl, farnesyl and phytyl radicals are γ,γ-disubstituted allyl radicals. In view of their importance in the field of natural products, it was considered of interest to extend the aforementioned pyrolysis studies to the next higher isoprenolog, ethyl p-geranyloxybenzoate.

The results of the present study show that pyrolysis of ethyl p-geranyloxybenzoate (I) at temperatures approximating 200° yields the unsaturated hydrocarbon myrcene (II) and ethyl p-hydroxybenzoate. There was no evidence indicating the formation of either an abnormal or normal rearrangement product; consequently the behavior of this ester on heating is represented by the equation



The unsaturated hydrocarbon produced in this pyrolysis formed an addition product with maleic anhydride. The dibasic acid III, prepared by hydrolysis of this addition product, melted at the temperature reported by Diels and Alder.



III

Experimental

Geranyl bromide (b. p. 109° at 20 mm.; n^{15}_{D} 1.5005) was prepared from geraniol (b. p. 104–110° at 9 mm.;

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(1) Paper X in series on the Phenyl Allyl Ethers.

(2) Professor of Organic Chemistry, The University of Buenos Aires, Argentina, and Fellow of the Guggenheim Foundation.

(3) Claisen and Tietze, *Ber.*, **59B**, 2344 (1926).

(4) Hurd and Cohen, THIS JOURNAL, **53**, 1917 (1931).

(5) Lauer and Moe, *ibid.*, **65**, 291 (1943).