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Summary

Diglycerol has been prepared by a new series of reactions involving treatment of glycerol with calcium oxide or calcium hydroxide and carbon dioxide.

Some possible mechanisms of the reaction are suggested and experimental procedures and results obtained are reported.

CHICAGO 6, ILLINOIS RECEIVED SEPTEMBER 19, 1945

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF MINNESOTA]

4-Thio and 2,4-Dithio 5,5-Dialkylthiobarbituric Acids

BY JAMES H. BOOTHE[1] AND CHARLES O. WILSON

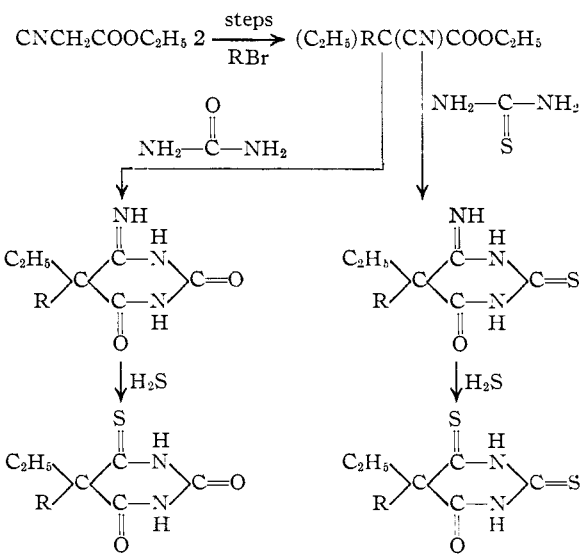
Early in the history of barbituric acid synthesis, a few 2-thiobarbiturates were prepared for the purpose of converting them into the corresponding oxygen analogs. In fact, Fischer and Dilthey[2] reported the preparation of 5,5-diethyl-2-thiobarbituric acid in their original paper in 1904. Until 1935, however, no systematic attempt was made to prepare a series of these compounds and evaluate them pharmacologically. This was probably due to the fact that Fischer and Mering[3] reported that the administration of 120 mg. per kg. of the sulfur analog of barbital to a dog produced a deep sleep, followed by death. This fact was interpreted by Fraenkel[4] as conclusive evidence that sulfur imparted a pronounced toxic character to barbital. Dox and Hjort[5] also reported in 1927 that this compound caused tremors during anesthesia as well as preanesthetic excitement and cyanosis.

In spite of these adverse indications of the toxicity of the thiobarbiturates, two separate groups of workers, namely, Volwiler and Tabern[6] and Miller, Munch and Crossley[7,8] in 1935, reported independently systematic studies of the preparation and pharmacological properties of a number of 2-thiobarbiturates. They found that these compounds had, in general, a rapid onset of action and were destroyed much more rapidly in the body than were their oxygen analogs. Because of these properties, the 2-thiobarbiturates are proving very successful as intravenous anesthetics.

Until recently, no substituted barbituric acids in which more than one of the oxygen atoms were replaced by sulfur were known, although the preparation of 2,4,6-trithiobarbituric acid by the action of potassium hydrosulfide on 2,4,6-trichloropyrimidine had been described.[9] During the course of this study, there appeared a paper by Henze and Smith[10] dealing with polythiobarbiturates in which was reported the preparation of 5,5-diethyl-2,4,6-trithiobarbiturate and 5-phenyl-5 ethyl-2,4,6-trithiobarbiturate. It was stated that these possessed no hypnotic properties. Carrington[11] has prepared the 2-thio, 2,4-dithio and 2,4,6-trithio derivatives of a series of barbiturates. He used those barbiturates that are well-known hypnotics, but reported no pharmacological data.

In view of the fact that no synthesis of 4-thiobarbiturates has been reported in the literature and that the 2,4-dithiobarbiturates reported by Carrington have not been tested pharmacologically, and since such thio compounds might exhibit interesting physiological activity, it was decided to synthesize, if possible, several typical examples of these thio compounds.

Several workers[12-16] have replaced an imino



(1) Lederle Laboratories, Inc., Research fellow, 1942–1943. Present address. Lederle Laboratories, Inc., Pearl River, New York.
(2) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).
(3) Fischer and Mering, *Therap. Gegen.*, **101**, 97 (1903).
(4) Fraenkel, "Die Arzneimittel Synthese," 6th ed., 1927, p. 510.
(5) Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927).
(6) Volwiler and Tabern, THIS JOURNAL, **57**, 1961 (1935).
(7) Miller, Munch and Crossley, *ibid.*, **58**, 1090 (1936).
(8) Miller, Munch and Crossley, *Science*, **81**, 615 (1935).
(9) Büttner, *Ber.*, **36**, 2234 (1903).
(10) Henze and Smith, THIS JOURNAL, **65**, 1090 (1943).
(11) Carrington, *J. Chem. Soc.*, 124 (1944).
(12) Hofmann, *Ber.*, **2**, 460 (1869).
(13) Hobrecker, *ibid.*, **2**, 689 (1869).
(14) Bernthsen, *ibid.*, **10**, 1240, 38 (1877).
(15) Matsui, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.*, **1**, 285 (1908).
(16) Delépine, *Comp. rend.*, **153**, 281 (1911).

group with sulfur by using carbon disulfide or hydrogen sulfide. Advantage has been taken of the fact that several iminobarbituric acid derivatives are known,[17] and the present paper describes the successful substitution of the imino group in those molecules by sulfur.

Experimental[18]

Ethyl Ethylcyanoacetate.—Cyanoacetic ester (160 g.) was added to a solution of sodium (32 g.) in absolute ethyl alcohol[19] (400 ml.) contained in a three-necked flask equipped with a mercury-seal mechanical stirrer and a reflux condenser protected from moisture by means of a calcium chloride tube. On the slow addition of ethyl bromide (152.3 g.) at about 70–80°, separation of sodium bromide took place. The next morning the mixture was refluxed briefly and the alcohol distilled. Water (approximately 250 ml.) was added to the residue in the flask to dissolve the sodium bromide. This water was shaken out twice with ether to remove the ethyl ethylcyanoacetate. The ether solution was dried over anhydrous sodium sulfate and the ether was distilled. The product was distilled through a fractionating column at ordinary pressure. The yield of ethyl ethylcyanoacetate was 183.3 g. (93.5%); b. p. 206–209°.[20]

Ethyl Diethylcyanoacetate.—Ethyl diethylcyanoacetate was prepared, as in the case of the ethyl ethylcyanoacetate. The yield of ethyl diethylcyanoacetate was 83.5%; b. p. 213–215°.[21]

Other alkyl analogs were prepared in essentially the same manner.

5,5-Diethyl-4-iminobarbituric Acid.—The condensation of the ethyl diethylcyanoacetate with urea was by a modified method of Conrad.[17] Sodium ethylate, prepared from sodium (11.6 g.) in absolute ethyl alcohol (450 ml.) was placed in the previously described three-necked flask and to it were added ethyl diethylcyanoacetate (50 g.) and urea (17.8 g.). The mixture was heated, stirred, and refluxed for eight hours. The alcohol was then distilled off and the residue dissolved in water (500 ml.). The unchanged acetate was removed by extraction of the water solution with ether. The aqueous solution was then filtered, and the product precipitated by making the solution slightly acid with hydrochloric acid. The precipitate was collected, redissolved in 10% hydrochloric acid, and reprecipitated with ammonium hydroxide. This recrystallized from alcohol; m. p. 293–294° (dec.); yield 31.5 g. (58.2%).

The other dialkyl-4-iminobarbituric acids were prepared in essentially the same manner.

All the imino compounds melted with decomposition and were very difficult to crystallize to constant melting points.

All of the imino compounds were hydrolyzed to their oxygen analog. 5,5-Diethyl-4-iminobarbituric acid was hydrolyzed by refluxing for eight hours in 10% hydrochloric acid. On cooling, the 5,5-diethylbarbituric acid crystallized out. It was recrystallized once from water, m. p. 190–191°.[17]

5,5-Diethyl-4-thiobarbituric Acid.—Absolute ethyl alcohol (1200 ml.) was saturated with hydrogen sulfide gas by placing the alcohol in a two-liter container, having a glass tube reaching to within two centimeters of the bottom of the container. The hydrogen sulfide was bubbled through the alcohol and the pressure was allowed to rise to about 10 pounds per square inch. During the period the hydrogen sulfide was being dissolved in the alcohol, the container was shaken intermittently from time to time.

To the alcoholic solution of hydrogen sulfide (1200 ml.) so prepared, there was added 5,5-diethyl-4-iminobarbituric acid (10 g.) and the mixture was sealed in a bomb which was placed in an oil-bath, heated to 140–150° for twelve hours, cooled and opened. The solution was filtered and the alcohol and excess hydrogen sulfide were evaporated off under the hood and the yellow residue was dissolved in water (200 ml.) containing sodium hydroxide (5 g.), the solution was filtered free of undissolved material and the product was precipitated by addition of hydrochloric acid. The product was collected on a Buchner funnel, stirred with 10% hydrochloric acid (200 ml.) to remove any unreacted imino compound, collected and washed again on the filter. The compound was crystallized from a mixture of alcohol and water using activated charcoal in the first crystallization. Subsequent crystallizations were continued until the melting point remained constant. The compound crystallized in lemon-yellow, rectangular platelets; yield 5 g. (45.8%); m. p. 196–197°.

The replacement of the imino group in the other barbiturates by sulfur was accomplished by the same procedure.

5,5-Diethyl-4-imino-2-thiobarbituric Acid.—5,5-Diethyl-4-imino-2-thiobarbituric acid was prepared similar to the method of Conrad.[17] The condensation is similar to that for 5,5-diethyl-4-iminobarbituric acid. A mixture of absolute ethyl alcohol (300 ml.), sodium (18.6 g.), ethyl diethylcyanoacetate (68.1 g.) and thiourea (34 g.) was stirred and refluxed for two hours. Glacial acetic acid (46.3 ml.) was then added and the alcohol distilled. To dissolve the sodium acetate, the yellow residue was stirred with water (400 ml.). The insoluble portion was filtered off, dissolved in sufficient 10% hydrochloric acid, filtered, and reprecipitated with ammonium hydroxide. 5,5-Diethyl-4-imino-2-thiobarbituric acid was crystallized in yellow needles from alcohol; yield 60.35%; m. p. 255–256° (dec.).

5,5-Diethyl-2,4-dithiobarbituric Acid.—The 5,5-diethyl-2,4-dithiobarbituric acid and the other 2,4-dithiobarbituric acid compounds were prepared by the method given for the preparation of 5,5-diethyl-4-thiobarbituric acid. Tables I and II present the compounds prepared.

Pharmacologic Evaluation

The results reported[22] here are necessarily incomplete and should not be interpreted as conclusive results because not enough animals have been administered these compounds.

The compounds were all administered by dissolving them in a sufficient amount of 0.1 *N* sodium hydroxide solution and injecting them intravenously.

In the 5,5-dialkyl-4-thiobarbituric acid series, only two compounds have been tested, namely, 5,5-diethyl-4-thiobarbituric acid and 5-ethyl-5-isopropyl-4-thiobarbituric acid. Both of these compounds showed a marked depressant action, causing anesthesia with a rapid onset and short duration when administered to rats or rabbits. This depressant action was accompanied, however, by a stimulating or convulsant action which caused the muscles of the test animals to twitch slightly during the early stage of anesthesia.

The 5,5-diethyl, 5-ethyl-5-*n*-butyl, and 5-ethyl - 5 - isopropyl - 2,4 - dithiobarbituric acids showed much the same picture as that described in the above paragraph except that the twitching action lasted for a longer period of time.

(17) Conrad, *Ann.*, **340**, 310 (1905). German Patent, 172,980, *Friedländer*, **8**, 1068 (1905).

(18) All melting points are corrected and boiling points are uncorrected.

(19) Smith, *J. Chem. Soc.*, 1288 (1927).

(20) Hessler, *Am. Chem. J.*, **22**, 170 (1899).

(21) Hesse, *ibid.*, **18**, 747 (1896).

(22) The pharmacological work was done by Dr. James M. Dille of the University of Washington.

TABLE I

Alkyl groups	Cyanoacetic esters Yield, %	B. p. °C.	Mm.	4-Iminobarbituric acid Yield, %	M. p.[a] °C.	Oxygen analog M. p., °C.	4-Thiobarbituric acid Yield, %	M. p.[a] °C.	Formula	Nitrogen % Calcd.	Found
Ethyl	93.5	206–209[b]	Atm.								
Ethyl, ethyl	83.5	213–215[c]	Atm.	58.2	293–294[d]	190–191[e,f]	45.8	196–197	$C_8H_{12}O_2N_2S$	13.99	13.84
Ethyl, isopropyl	61.4	222–227[g]	Atm.	45.5	295–296	145[h,f]	30.4	192–193	$C_9H_{14}O_2N_2S$	13.08	12.96
Ethyl, isoamyl	68.54	90–95	1	47.1	293–293.5	153–155[i,f]	[j]				
n-Butyl	79.0	73–77	1								
Ethyl, *n*-butyl	58.69	76–79	1	37.9	285–286	127–127[k,f]	[l]				

[a] All melting points are corrected. [b] Hessler, *Am. Chem. J.*, **22**, 170 (1899), reports 206–211°. [c] Hesse, *ibid.*, **18**, 747 (1896), reports 100–101 at 14 mm. [d] Conrad, *Ann.*, **340**, 317 (1905), reports 295°. [e] Conrad (ref. d) reports 191°. [f] When mixed with an authentic sample prepared in a different manner, the melting point showed no depression. [g] Crossley and LeSueur, *J. Chem. Soc.*, **77**, 91 (1900), reported 226–227° at 756 mm. Fischer, Rode and Brauns, *Ann.*, **402**, 366 (1914), reported 233° at 760 mm. [h] Fischer and Dilthey, *ibid.*, **335**, 346 (1904), report 146°. [i] Shonle and Moment, THIS JOURNAL, **45**, 248 (1923) 150°. [j] A yellow amorphous material was obtained that could not be purified. Oxidation to oxygen analog by Conrad's method produced a compound melting at 153–155°. A mixed melting point showed no depression. [k] Dox and Yoder, THIS JOURNAL, **44**, 1580 (1922), reports 125°. [l] No identifiable product could be obtained.

TABLE II

Alkyl groups	4-Imino-2-thiobarbituric acid Yield, %	M. p., °C.	4-Oxygen analog m. p.,[a] °C.	2-4-Dithiobarbituric acid Yield, %	M. p., °C.	Formula	Nitrogen % Calcd.	Found
Ethyl, ethyl	60.35	255–256[b]	173[c]	47.2	210–210.5[d]	$C_8H_{12}ON_2S_2$	12.95	13.01
Ethyl, isopropyl	44.5	241–242	192[e,f]	31.5	179.5–180.5[g]	$C_9H_{14}ON_2S_2$	12.17	12.21
Ethyl, isoamyl	37.1	260.5–261.5	168[h,f]	36.45	161–162	$C_{11}H_{18}ON_2S_2$	10.84	10.96
Ethyl, *n*-butyl	66.1	263–264	142–144[i,f]	56.75	130.5–131[j]	$C_{10}H_{16}ON_2S_2$	26.24[k]	26.29[k]

[a] All melting points are corrected. [b] Conrad, *Ann.*, **340**, 325 (1905), reports 255°. [c] Miller, Munch, Crossley and Hartung, THIS JOURNAL, **58**, 1090 (1936), report 174.5°. [d] Carrington, *J. Chem. Soc.*, 126 (1944), reports 205–206°. [e] Tabern and Volwiler, THIS JOURNAL, **57**, 1961 (1935), report 192°. [f] When mixed with an authentic sample prepared in a different manner, the melting point showed no depression. [g] Carrington (ref. d) reports 173°. [h] Tabern and Volwiler (ref. e) report 167–169°. [i] Tabern and Volwiler (ref. e) report 144–145°. [j] Carrington (ref. d) reports 127°. [k] Figures represent analyses based on sulfur content.

The 5-ethyl-5-isoamyl-2,4-dithiobarbituric acid showed the most promising indications. It was administered to fifteen rats, only two of which showed signs of twitching and this was very mild. Upon intravenous injection of 20-30 mg. per kg., rabbits slept instantly, recovered the righting reflex in about twelve minutes and the placing reaction in fifteen to twenty minutes. The animals suffered no ill effects; however, 80 mg. per kg. has caused death. A few experiments on cats showed the same effect as in rabbits.

Summary

A method is described wherein, by using hydrogen sulfide under pressure, the imino group of dialkyl-4-iminobarbituric acids or dialkyl-4-imino-2-thiobarbituric acids may be replaced by sulfur.

The preparation of two dialkyl-4-thiobarbituric acids and four dialkyl-2,4-dithiobarbituric acids is reported.

A brief summary of the pharmacological action of these compounds is included.

MINNEAPOLIS, MINNESOTA RECEIVED DECEMBER 3, 1945

[CONTRIBUTION FROM THE LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

The Synthesis of Amino Acids from Ethyl Acetamidomalonate and Ethyl Acetamidocyanoacetate. III. The Use of Primary Halides[1]

BY NOEL F. ALBERTSON

During the last few years there has been a rapid development in the preparation of amino acids by various modifications of the original Sörensen method in which phthalimidomalonic ester is alkylated and degraded to the amino acid. Although aminomalonic ester itself may be used to prepare amino acids,[2] this intermediate has several disadvantages the most important of which is its tendency to undergo N-alkylation as well as C-alkylation. The protection of the amino group by benzoylation enabled Redemann and Dunn[3] to eliminate this disadvantage. The next advance was the use of acetamidomalonic ester.[4] The acetyl group is more readily intro-

(1) For the first two papers in this series see references 4d and 5.

(2) Putochin, *Ber.*, **56**, 2213 (1923); Keimatsu and Kato, *J. Pharm. Soc. Japan*, **49**, 731 (1929); Locquin and Cerchez, *Bull. soc. chim.*, (4) **47**, 1386 (1930).

(3) Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939); see also Painter, THIS JOURNAL, **62**, 232 (1940).

(4) (a) For a summary of literature references see Snyder, Shekleton and Lewis, *ibid.*, **67**, 310 (1945); see also (b) Albertson, Archer and Suter, *ibid.*, **67**, 36 (1945); (c) Howe, Zambito, Snyder and Tishler, *ibid.*, **67**, 38 (1945); (d) Albertson and Archer, *ibid.*, **67**, 308 (1945); (e) Albertson and Archer, *ibid.*, **67**, 2043 (1945).