Hydrogenation of dibenzoylethane using platinum catalyst in ethanol proceeded with absorption of 2 moles of hydrogen, giving an oil which on fractional crystallization was separated into the *dl*- and *meso*-diphenylbutane-1,4-glycols which were identified by mixed melting points with authentic samples prepared by the catalytic reduction of the acetylenic glycols.[11]

TABLE II

CATALYTIC REDUCTION OF SOME TYPICAL UNSATURATED 1,4-DIKETONES AND RELATED COMPOUNDS

Except as otherwise indicated these reductions were carried out at 25–27° and atmospheric pressure, using the platinum oxide catalyst (0.01–0.02 g. per g. of substance) in 95% ethanol as solvent (35–70 cc. per gram of substance).

Compound	Yield of monomolecular product, %
Cis-dibenzoylethylene	45–50[a]
Trans-dibenzoylmethylethylene	75
Cis-dibenzoylphenylethylene	62 (25[b])
Trans-di(2,4,6-trimethylbenzoyl)ethylene	86
Trans-di(4-chlorobenzoyl)ethylene	44
Trans-di(4-methylbenzoyl)ethylene	19
Dibenzoylmethoxyethylene	[c]
Cis-dibenzoylbromoethylene[d]	40
Cis-dibenzoyldibromoethylene[d]	84
Dibenzoylbromoethane[d]	68
dl-Dibenzoyldibromoethane[d]	44

[a] The rest of the material was accounted for as oils and small amounts of dimolecular products totaling 10–20% in yield. [b] This yield was obtained from an experiment carried out in glacial acetic acid at 100°, and triphenylfuran was obtained also in yields of 45–50%. Dibenzoylphenylethane is unaffected by these conditions and catalyst, and was recovered nearly quantitatively unchanged in a typical experiment. [c] This experiment, carried out in glacial acetic acid at 75–80°, gave largely the oily dibenzoylmethoxyethane (not identified) and a yield of 35–40% of diphenylmethoxyfuran (identified by mixed melting point with an authentic sample). [d] Palladium on barium sulfate as catalyst (0.1–0.15 g. per g. of substance).

Summary

The catalytic hydrogenation of *trans*-dibenzoylethylene under different conditions results in both mono- and dimolecular products, while other unsaturated 1,4-diketones, including *cis*-dibenzoylethylene and the halogen derivatives, undergo largely monomolecular reduction.

The striking parallelism between catalytic and zinc combination reductions is shown and is regarded as indicative of a common reaction mechanism.

The formation of furans and of cyclic dimolecular products is adduced as evidence that in these cases catalytic hydrogenation involves conjugate addition.

(11) *Cf.* Zalkind and Isakowitch, *J. Russ. Phys.-Chem. Soc.*, **45**, 1902 (1913).

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[CONTRIBUTION FROM THE ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS]

Sulfur-Containing Barbiturate Hypnotics

BY D. L. TABERN AND E. H. VOLWILER

Early in the history of barbituric acid synthesis, two or three simple 5,5-disubstituted 2-thio derivatives were made, with the aim of preparing from them by removal of the sulfur atom, the therapeutically promising oxygen analogs. Einhorn[1] and others studied the sulfur elimination through reduction, then oxidation and by the action of strong acids under pressure. They noted the comparative instability of the thiobarbituric ring, reduction of the diethyl derivative by sodium amalgam, for instance, yielding chiefly the malonic diamide.

No serious attempt at pharmacologic evaluation seems to have been reported, and no study of higher homologs has been made as in the case of the simple barbituric analogs. Fischer and Mering[2] gave a 7-kilogram dog orally a dose of one gram of diethylthiobarbituric acid with the result that "one hour later he slept, did not react to any stimulation, and died after eight hours."

Dox and Hjort[3] have included mention of the same compound in a series of simple and N-alkyl barbiturates. They state that fine and coarse tremors mask the anesthesia which is characterized by preanesthetic excitement and cyanosis.

In spite of these unfavorable pharmacologic indications, the desire to secure hypnotics more readily broken down in the body for the production of short hypnosis and even surgical anesthesia, led to the decision several years ago to make a

(1) Einhorn, *Ann.*, **359**, 145 (1908); see also German Patents 165,649, 166,266, 172,404, 182,764.

(2) Fischer and Mering, *Therapie der Gegenwart*, **44**, 100 (1903); Fränkel, "Arzneimittel Synthese," 6th ed., p. 510.

(3) Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927).

critical and systematic study of the higher alkyl substituted thiobarbiturates. The recent appearance of a note by Miller, Munch and Crossley[4] prompts the present publication of our earlier studies which have subsequently progressed to the stage of extensive clinical application.

Preliminary experiments demonstrated that not only could the desired compounds be synthesized by conventional methods in satisfactory yields, but that from the pharmacological and clinical side, certain members of the group were indeed powerful hypnotics of very brief action. In proper dosage, the results were frequently striking; following intravenous administration, sleep followed at once; surgical anesthesia ensued within five minutes; and not more than twenty minutes later the animal was again on its feet almost normal.

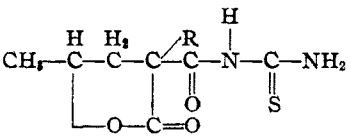
In general, the thio analogs of those disubstituted barbituric acids previously found most valuable as hypnotics, ranked highest in efficiency. Furthermore, certain thiobarbiturates were definitely more active as hypnotics than the oxygen analogs. Toxicities were not in general correspondingly higher, and it is possible to select several members of the series possessing very favorable ratios of effective to toxic doses.

The sulfur atom seemed to exert an additional influence in shortening the period of destruction within the body, and hence the duration of the hypnotic action.

Experimental

While the thiobarbituric acid derivatives may be prepared by several methods, we have found it convenient for experimental purposes to use the requisite malonic esters with somewhat more than the calculated amount of dry powdered thiourea in alcoholic sodium ethylate or its equivalent at 100–120°. Purification is best effected by dissolving in sodium hydroxide and reprecipitating by carbon dioxide followed by recrystallization from alcohol (75–90%). The pure acids are all somewhat yellowish solids that crystallize more readily than the oxygen analogs.

Johnson and Hill[5] have reported that under essentially these conditions, diallyl and benzyl allyl malonic esters yield open-chain compounds of the formula



We have repeated these experiments with much larger quantities of materials; our compounds melt somewhat higher, and both analyses and pharmacologic evaluations show that they *must be* only the normally expected thiobarbiturates.

The following example illustrates the method of preparation.

The Ethyl (1-Methylbutyl) Thiobarbituric Acid.—One hundred and thirty grams of ethyl (1-methylbutyl)-malonic ester is added to a concentrated solution of sodium ethylate prepared from 34 g. of sodium in absolute alcohol; with stirring, 60 g. of finely divided thiourea is added, and the mixture refluxed for ten hours. Most or all of the solvent is evaporated and the residual mass dissolved in cold water. The barbituric acid derivative so formed is precipitated by the addition of dilute hydrochloric acid. It may be purified by solution in dilute sodium hydroxide solution and precipitation by carbon dioxide.

Final purification is best carried out by solution in cold alcohol, heating to 50° and dilution with water to a 50% alcohol content. The ethyl (1-methylbutyl)-thiobarbituric acid so obtained is a white crystalline solid melting at 158–159° and readily forming salts with alkalies.

While the thiobarbiturates readily form stable salts, these are sometimes not easily obtained in the crystalline state. For instance, when ethyl isoamyl thiobarbituric acid in alcoholic solution is treated with one mole of alkali, the solution may be evaporated to dryness, leaving a glass which is rendered friable only by drying completely in a good vacuum.

In other instances, crystals were ultimately secured which permitted seeding of the concentrated alcoholic solutions and the separation of crystalline salts.

Such salts are hygroscopic and dissolve readily in water and alcohol to give strongly alkaline solutions. For instance, sodium ethyl (1-methylbutyl)-thiobarbiturate, in 2.5% solution, has a *p*H of approximately 10.4 to 10.6 (as determined by the glass electrode).

Another characteristic of the sodium salts is the avidity with which they hold solvents of crystallization (alcohols, chloroform, benzene, etc.) even on drying *in vacuo* at 80–100°.

Solutions of the sodium salts are rather unstable, being decomposed quite completely at the end of thirty-six hours at 60°. In the case of the ethyl *s*-butyl thiobarbituric acid, an alkali-insoluble compound, melting point about 100°, being probably the amide, was first secured; on the addition of acid, much carbon dioxide, but no hydrogen sulfide, was evolved and a compound, probably the acetyl urea, melting at 155–156°, was precipitated.

The calcium salts are best prepared by adding strong calcium chloride solution to a solution of the sodium salt in water. Mono and dialkylamine salts may be prepared

(4) Miller, Munch and Crossley, *Science*, **81**, 615 (1935).
(5) Johnson and Hill, *Am. Chem. J.*, **45**, 356 (1911).

by dissolving the thiobarbituric acid in an excess of amine and removing the excess *in vacuo*. These salts are likewise readily soluble in water, but easily hydrolyzed.

The salts give intense green or brown solutions or precipitates with compounds of copper, iron, nickel, cobalt, etc. These appear to be analogous to the colored cobalt salts which Koppanyi[6] and others have employed for the colorimetric estimation of simple barbiturates. Here, however, the greater residual valence of the sulfur permits the use of aqueous rather than anhydrous media.

On attempting to prepare the N-(or S)-allyl derivatives by the method normally used for the synthesis of N-alkyl barbiturates, that is the reaction of allyl bromide with the sodium salts in aqueous or alcoholic solutions, unstable semi-solids gradually evolving allyl mercaptan were secured. Synthesis through the use of the N-alkyl thioureas is being studied.

The action of potassium permanganate on ethyl-(1-methylbutyl)-thiobarbituric acid in alkaline solution, yielded the oxygen analog (Nembutal); when an unsaturated group was present, however, extensive change of a still undetermined nature took place. Hydrogen peroxide in alkaline solution either left the acid unchanged or, if used in sufficient excess, led to poorly defined products. Freshly precipitated silver oxide formed a complex addition product soluble in sodium hydroxide, but insoluble in ammonium hydroxide, water, alcohol, and acids.

TABLE I

THIOBARBITURATES

	M. p., °C.	Nitrogen Calcd.	Found
Ethyl allyl	172–173	13.2	13.1
Ethyl isopropyl	192	13.1	12.76
Ethyl *n*-butyl	144–145	12.3	12.07
Ethyl *s*-butyl	163–165	12.3	12.4
Ethyl (2-methylallyl)	160–161	12.3	12.4
Ethyl isoamyl	167–169	11.6	11.52
Ethyl (1-methylbutyl)	158–159	11.6	11.7
Ethyl *n*-hexyl	136–137	10.9	11.1
Ethyl 2-ethylbutyl	137–138	10.9	10.8
Ethyl cyclohexyl	205–207	11.03	11.1
Ethyl phenyl	215–217	11.3	11.2
Methyl (2-methylallyl)	128–130	13.2	13.45
Diallyl	134	12.5	12.5
Allyl 2-methyl allyl	180–182	11.7	11.67
Allyl *s*-butyl	142–143	11.7	11.83
Allyl (1-methylbutyl)	127–129	11.0	11.04
Allyl benzyl	140–150	10.2	10.38
Ethyl (3-chloro-2-butenyl)	128–130	10.7	10.85

Pharmacologic

We are indebted to Mr. H. C. Spruth of the Pharmacologic Department, Abbott Laboratories, for the pharmacologic investigation of the thiobarbiturates, which will be reported in detail elsewhere. It is of interest, however, to record here preliminary data regarding certain of the most promising compounds. Intravenous injection into rabbits has been found to be the method of choice because it is thus possible to evaluate not only the effective and toxic doses, but also gain some information regarding relative depths of depression and sleeping times. The latter point is important since for compounds designed for the production of brief surgical anesthesia the sleeping time must be as brief as is consistent with proper depth of hypnosis and recovery must be rapid.

TABLE II

THIOBARBITURATES

	Minimum effective dose mg./kg.	Minimum lethal dose, mg./kg.	Sleeping time min.	at mg./kg.
Diethyl	75	>200	64	at 100
Ethyl isopropyl	30	80–100	97	at 40
Ethyl *n*-butyl	20	90–100	22	at 40
Ethyl *s*-butyl	15	>50	15	at 25
Ethyl (2-methylallyl)	30			
Ethyl isoamyl	30	55–60	78	at 40
Ethyl (1-methylbutyl)	10	35–40	14	at 20
Ethyl (2-ethylbutyl)	10	40		
Diallyl	30	>125		
Allyl (2-methylallyl)	20			
Allyl *s*-butyl	10	50	13	at 20
Ethyl (3-chloro-2-butenyl)	Convulsions 20 mg./kg.			

It will be seen that several of the compounds indicated fulfil to a considerable degree the properties desired. In clinical experience they have also proved of practical value.

Summary

A series of disubstituted thiobarbituric acids has been synthesized and characterized. Several of these compounds are powerful hypnotics. When injected intravenously into animals, they produce very prompt sleep, from which the animals recover rapidly. The sulfur in these compounds appears to accelerate their destruction in the body.

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(6) Koppanyi, *J. Am. Pharm. Assoc.*, **23**, 1074 (1934).