[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Direct Replacement of Oxygen in Hydantoins and Barbiturates by Sulfur

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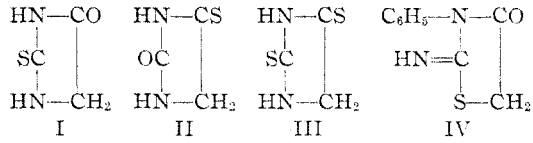
Thiohydantoins

If one considers only the replacement of oxygen atoms in hydantoin by sulfur, three thio-derivatives of hydantoin are theoretically possible, namely, 2-thiohydantoin (I), 4-thiohydantoin (II) and 2,4-dithiohydantoin (III).



I II III IV

Although Meyer[2] claimed to have synthesized a phenyl derivative of 2-thiohydantoin, it was later demonstrated that the compound is a phenylpseudothiohydantoin[3] (IV). The first preparation of the true 2-thiohydantoin (II) was that of Klason,[4] who obtained it by heating the hydrochloride of ethyl aminoacetate with potassium thiocyanate at 140–150°. In 1911, Komatsu,[5a] Wheeler, Nicolet and Johnson,[6] and Johnson and Nicolet[5b] reported new methods for synthesis of this compound. The latter workers caused hippuric acid to react with potassium thiocyanate to form 1-benzoyl-2-thiohydantoin; on subsequent hydrolysis with hydrochloric acid 2-thiohydantoin was produced.

Johnson and Chernoff[7] succeeded in preparing 4-thiohydantoin (II). In their synthesis, carbethoxyaminoacetonitrile added hydrogen sulfide to form carbethoxyaminoacetthioamide, $C_2H_5OOCNHCH_2CSNH_2$, which was condensed into the thiohydantoin by the action of exactly one molecular proportion of alkali. The structure of II was established by hydrolysis with concentrated hydrochloric acid to produce hydantoin.

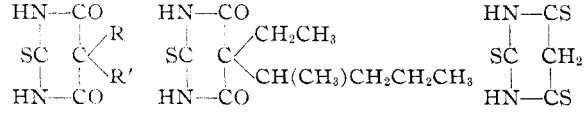
Until quite recently the dithiohydantoins were unknown. An unsuccessful attempt to introduce sulfur into a hydantoin by heating the latter with phosphorus trisulfide, or by heating with an aqueous solution of ammonium sulfide has been reported by Harries and Weiss.[8] The latter stated that as a result of lengthy heating of hydantoin with phosphorus trisulfide a viscous sirup resulted. No description was given of any procedure used in attempting to isolate a thio compound from this sirupy residue; however, failure to accomplish this end was recorded.

Bucherer and Lieb[9] tried to prepare 5,5-disubstituted 2,4-dithiohydantoins by modification of their method for obtaining hydantoins, namely, by interaction of aminonitriles with ammonia and carbon disulfide, but without success.

However, Jacobson[10] has patented a method for synthesizing 2,4-dithiohydantoin derivatives by reaction of an aminonitrile, having at least one amino hydrogen atom, with carbon disulfide. As a result of exothermic reactions "initiating at ordinary atmospheric temperature and pressure," the preparation of dithiohydantoin and 5,5-dimethyl-2,4-dithiohydantoin is claimed.

Thiobarbiturates

Numerous 5-monosubstituted 2-thiobarbiturates and 5,5-disubstituted 2-thiobarbiturates of the general type V have been prepared. The method used in their synthesis is of the ring closure type and consists of the condensation of the appropriate mono- or di-substituted malonic ester with thiourea.[11] This procedure is similar in mechanism to that used for the preparation of the oxygen analogs. At least one of these compounds, namely, 5-(1-methyl-butyl)-5-ethyl-2-thiobarbiturate[12] (VI) has found extended clinical use as a sedative or hypnotic.



V VI VII

No dithiobarbiturates are reported in the literature. Only one trithiobarbiturate has been ob-

(1) From the M.A. thesis of P. E. Smith, August, 1941. Presented before the Division of Medicinal Chemistry at the 105th meeting of The American Chemical Society at Detroit, Mich., April 12–16, 1943.

(2) Meyer, *Ber.*, **10**, 1965 (1877).

(3) Andreasch, *Monatsh.*, **2**, 775 (1881).

(4) (a) Klason, *Chem.-Ztg.*, **14**, 543 (1890); (b) Johnson, THIS JOURNAL, **35**, 780 (1913).

(5) (a) Komatsu, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.*, **3**, 1 (1911); (b) Johnson and Nicolet, THIS JOURNAL, **33**, 1975 (1911).

(6) Wheeler, Nicolet and Johnson, *Am. Chem. J.*, **46**, 456 (1911).

(7) Johnson and Chernoff, THIS JOURNAL, **34**, 1208 (1912).

(8) Harries and Weiss, *Ann.*, **327**, 372 (1903).

(9) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 21 (1934).

(10) Jacobson, U. S. Patent 2,143,816, January 10, 1939.

(11) (a) Einhorn and von Diesbach, *Ann.*, **359**, 172 (1908); (b) Miller, Munch and Crossley, *Science*, **81**, 615 (1935); (c) Tabern and Volwiler, THIS JOURNAL, **57**, 1961 (1935); (d) Miller, Munch, Crossley and Hartung, *ibid.*, **58**, 1090 (1936).

(12) Volwiler and Tabern, U. S. Patent 2,153,729, April 11, 1939.

tained, namely, 2,4,6-trithiobarbituric acid[13] (VII). The latter was prepared from trichloropyrimidine by reaction with potassium hydrosulfide. Despite a careful search of the chemical literature, no record of attempts to prepare thiobarbiturates by direct replacement of the carbonyl oxygen atoms with sulfur has been found.

In view of the fact that no successful attempts have been reported to prepare dithiohydantoins or trithiobarbiturates by methods involving the direct replacement of the oxygen atoms of these compounds with sulfur atoms, and since such thio compounds, if prepared, might exhibit interesting physiological activity, it was decided to try to prepare several typical examples of these polythio compounds.

It was visualized that the desired thio derivatives might be obtained by the interaction of 5,5-disubstituted hydantoins and 5,5-disubstituted barbiturates with phosphorus trisulfide in an appropriate solvent. Tetralin was used as the solvent since it is inert, has a high boiling temperature, and because the hydantoins and barbiturates chosen, although almost insoluble in the cold liquid, are readily soluble in it above their melting points. The phosphorus trisulfide also exhibits some solubility in hot tetralin. Attempts to use benzene or carbon disulfide, instead of tetralin, were wholly unsuccessful. By means, then, of heating with phosphorus trisulfide in an appropriate hydrocarbon solvent, four 5,5-disubstituted hydantoins (containing two alkyls, two aryls, or an alkyl and an aryl) were converted into the corresponding 5,5-disubstituted-2,4-dithiohydantoins. In a similar manner, two 5,5-disubstituted-barbiturates yielded the corresponding 5,5-disubstituted-2,4,6-trithiobarbiturates.

Through the courtesy of Parke, Davis and Company, the dithiohydantoins and trithiobarbiturates synthesized in this investigation have received testing for possible physiological activity. None of these compounds are analgesic, and only 5,5-dimethyl-2,4-dithiohydantoin and 5,5-diethyl-2,4,6-trithiobarbituric acid evidence any hypnotic activity. All six thio derivatives are without anticonvulsant activity. This lack of activity is of special interest in the case of 5,5-diphenyl-2,4-dithiohydantoin inasmuch as the oxy analog, Dilantin, is a powerful and clinically useful anticonvulsant.

(13) Büttner, *Ber.*, **36**, 2234 (1903).

Experimental

5,5-Disubstituted-2,4-dithiohydantoins.—Twenty grams of dimethylhydantoin, 40 g. of finely ground phosphorus trisulfide, and 120 cc. of tetralin were mixed and heated at 225–230° with constant stirring for two hours. Actual interaction began at about 180°, after fifteen minutes a characteristic yellow froth appeared and hydrogen sulfide was continuously evolved.

The reaction mixture was allowed to cool until yellow crystals separated from the liquid. The solid was removed and extracted with diethyl ether to dissolve the thiohydantoin, the solvent was evaporated and the residue leached with petroleum ether to remove the tetralin. The yellow crystals were dissolved in hot ethanol, the solution was filtered and diluted with hot water. The dithiohydantoin separated as a heavy, yellow liquid which, on heating over a steam cone with continual stirring, crystallized in yellow lumps. It was necessary to repeat the recrystallization from diluted alcohol. Ten and one-half grams of crude material yielded 8.0 g. (29.5% of the theoretical quantity) of purified 5,5-dimethyl-2,4-dithiohydantoin in the form of small, needle-like, faintly cream-colored crystals melting without decomposition at 147.5–148.5° (cor.).[14]

Three other dithiohydantoins were prepared in essentially the same manner. In the case of the methylphenyl and ethylphenyl derivatives it was possible to utilize decalin at 205–210° and to remove this solvent somewhat more readily than tetralin. A longer period of heating is required to form the diphenyl derivative, but too lengthy heating causes lowered yields.

The four dithiohydantoins are soluble in ether, acetone, alcohols, chloroform and dilute alkaline solutions. They are not appreciably soluble in petroleum ether, water and dilute acids. Data for these dithiohydantoins may be found in Table I.

5,5-Disubstituted-2,4,6-trithiobarbiturates.—A sample of barbital (10 g.) was converted into the corresponding trithio derivative in essentially the same manner as were the hydantoins. In this instance the characteristic yellow froth assumed an orange color after two hours of heating. Despite the fact that barbital is soluble in hot decalin, conversion of the barbiturate did not occur in this solvent.

More difficulty was encountered in the attempts to produce a trithio derivative of phenobarbital. After heating a mixture of 30 g. of phenobarbital, 90 g. of phosphorus trisulfide and 250 cc. of tetralin at 225–230° for three and one-half hours, the mixture was cooled and the liquid portion decanted into a beaker containing 200 cc. of 10% hydrochloric acid. This mixture was boiled for one hour to decompose phosphorus trisulfide, was cooled, diluted with 50 cc. of benzene and was stirred while being heated at 100° for fifteen minutes. After cooling, the benzene layer was separated. The residue in the reaction flask also was boiled with hydrochloric acid, extracted with benzene and all benzene solutions were combined. To this benzene solution was added 400 cc. of petroleum ether and on cooling with stirring, about 15 g. of a brown-orange material separated and was filtered. This material was dissolved in 50 cc. of hot ethyl alcohol, the solution was filtered, and diluted with 150 cc. of water. After heating while stirring

(14) Jacobson, ref. 10, obtained this dithiohydantoin by a wholly different method and reported m. p. 143° (from hot water).

TABLE I

5,5-DISUBSTITUTED-2,4-DITHIOHYDANTOINS AND 5,5-DISUBSTITUTED-2,4,6-TRITHIOBARBITURATES

Substituents	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Methyl Methyl DTH[a]	147.5–148.0	30					17.48	17.30	40.01	39.93
Phenyl Methyl DTH	176.5–177.0	61	54.02	54.18	4.53	4.64	12.60	12.47	28.84	29.85
Phenyl Ethyl DTH	174.5–175.0	55	55.90	55.84	5.11	5.26	11.85	11.68	27.13	28.14
Phenyl Phenyl DTH	260.0–261.0 (dec.)	18	63.37	63.35	4.25	4.52	9.85	9.76	22.55	23.43
Phenyl Ethyl TTB[b]	175.0–177.0	22					10.00	9.81	34.30	34.45
Ethyl Ethyl TTB	196.5–197.0	56	41.34	41.25	5.20	5.49	12.05	12.28	41.39	41.77

[a] Refers to 2,4-dithiohydantoin. [b] Refers to 2,4,6-trithiobarbiturates.

for fifteen minutes, crystals formed, whereupon 200 cc. of water was added, the mixture was chilled and the crystalline material was filtered. Recrystallization was made from diluted alcohol and from benzene.

The trithiobarbiturates are more soluble in hot benzene than are the dithiohydantoins, otherwise these derivatives possess similar solubility in the usual organic solvents. Data for melting points, yields and analyses are to be found in Table I.

Hydrolysis of 5,5-Diethyl-2,4,6-trithiobarbituric Acid.—Under the conditions of the interaction of the hydantoins or barbiturates with phosphorus trisulfide, it was conceivable that structural rearrangement might have occurred. Hence, 3 g. of the trithiobarbiturate was heated under a reflux condenser with 60 cc. of a 5% solution of sodium hydroxide for twenty-four hours on a steam-bath. The solution was treated with norite, filtered and heated until ammonia ceased to be evolved. Dilute hydrochloric acid was added to cause evolution of hydrogen sulfide and the solution was evaporated to dryness. The residue was extracted with four 20-cc. portions of ether, the extract evaporated to dryness, and the residue suspended in absolute ether; the unchanged trithiobarbiturate passed into solution and was removed by filtration. The residue was again suspended in ether, filtered and dried; m. p. 222–222.5° (cor.) without decomposition. This melting point is in good agreement with that reported for the diamide of diethylmalonic acid[15]; therefore, no rearrangement had taken place during the replacement of oxygen atoms by sulfur atoms.

Summary

1. The replacement of all carbonyl oxygen atoms in certain selected 5,5-disubstituted hydantoins and barbiturates has been accomplished by heating the latter in tetralin solution with phosphorus trisulfide.

2. The six thio compounds prepared in this study do not possess analgesic, hypnotic or anticonvulsant activity.

(15) Fischer and Dilthey, *Ber.*, **35**, 854 (1902); Conrad and Zart, *Ann.*, **340**, 339 (1905).

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. XI. Some Ethers of Apocupreine

BY R. STUART TIPSON, MARY A. CLAPP AND LEONARD H. CRETCHER

In previous communications of this series, a number of ethers of apocupreine have been described. We had observed that, on passing from the methyl to the *n*-butyl ether of 6′-(β-thiolethyl)-apocupreine, there was a progressive increase[1] both in bacteriostatic activity *versus* the pneumococcus and in toxicity to mice, concomitant with a uniform change in certain physical properties. For comparison, a number of corresponding ethers of 6′-(β-hydroxyethyl)-apocupreine have now been prepared.

Some of the properties of the bases and their dihydrochlorides are given in Table I, from which it may be seen that, as the length of the aliphatic side-chain at position 6′ is increased, the melting point and specific rotation of the bases get lower, although the molecular rotations remain approximately constant. In addition, it was found that with each increase in length of the side-chain there was an increase in solubility of the resulting free base in certain organic solvents. The same general conclusions had previously been found[1] to apply to the alkylthio-ethyl ethers.

We also take this occasion to describe an improved method for the preparation of hydroxyethylapocupreine. One method described previously[2] consists in the hydrolysis of the benzyl group from benzyloxyethylapocupreine. It is

(1) Tipson and Cretcher, THIS JOURNAL, **64**, 1162 (1942).

(2) Butler and Renfrew, *ibid.*, **60**, 1473 (1938).