no artifacts are formed since the rechromatographic behavior corresponds to what is expected if a real separation occurred. The electrophoretic mobility of fraction VI also remains unchanged after rechromatography on DEAE-cellulose.

Bowman[25,26] and Ham and Sandstedt[27] claim that soybeans contain at least three trypsin inhibitors on the basis of their solubility in alcohol, ammonium sulfate and trichloroacetic acid. Except for the isolation of a crystalline trypsin inhibitor by Kunitz,[28] all of these solutions containing antitryptic activity were very crude preparations. A more extensive chemical and enzymatic characterization of the whey fractions is being developed, with particular emphasis on the elucidation of the apparent presence of two trypsin inhibitors in soybean whey.

(25) D. E. Bowman, *Proc. Soc. Exptl. Biol. Med.*, **63**, 547 (1946).
(26) D. E. Bowman, *Arch. Biochem.*, **16**, 109 (1948).
(27) W. E. Ham and R. M. Sandstedt, *J. Biol. Chem.*, **154**, 505 (1944).
(28) M. Kunitz, *J. Gen. Physiol.*, **29**, 149 (1946).

Acknowledgments.—The authors are indebted to Dr. F. M. Mayer for the phosphatase and β-amylase determinations, Mr. A. M. Nash for the trypsin inhibitor assays, Mr. A. C. Eldridge for performing the hemagglutinin analyses, Mr. G. E. Babcock for carrying out the ultracentrifugal experiments and to Dr. I. E. Liener for a sample of SBH.

PEORIA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, SCHOOL OF MEDICINE, YALE UNIVERSITY]

2-Selenobarbiturates. Studies of Some Analogous Oxygen, Sulfur and Selenium Compounds[1-3]

BY HENRY G. MAUTNER AND EDWIN M. CLAYTON[4]

RECEIVED JUNE 4, 1959

2-Selenobarbituric acid and several of its derivatives were prepared by the condensation of selenourea with appropriately substituted diethyl malonates. The changes in acid dissociation constants, ultraviolet spectra and water–lipid partitions when oxygen in the 2-position of barbiturates was replaced with sulfur and selenium were determined and compared with the changes seen when sulfur and selenium were substituted for oxygen in members of the uracil and hypoxanthine series.

One of the major problems in medicinal chemistry is the frequent lack of lipid solubility of otherwise useful agents, preventing them from penetrating the blood–brain barrier.[5] The usual method of increasing fat solubility in such cases is the addition of alkyl chains. Although the introduction of such groups usually results in the desired solubility in lipids, it also modifies the steric configuration of the molecule considerably and may interfere with the ability of the modified drug to attach itself to the receptor sites on which its action is exerted.

Another method of increasing lipid solubility is the replacement of oxygen by sulfur, the classical example of such fat solubilization being the replacement of oxygen in the 2-position of pentobarbital (a short-acting hypnotic) by sulfur to yield thiopental (an ultra-fast acting anesthetic).[6-8] Here, profound changes in pharmacological action are achieved with only negligible changes in the size and configuration of the molecule.

Since selenium is related to sulfur in the same way in which sulfur is related to oxygen, it was of interest to measure water-lipid partitions in several series of isologous oxygen, sulfur and selenium compounds in order to determine whether the effect of replacement of oxygen by sulfur on solubility in lipids is a more-or-less general one, and to learn what effect the replacement of sulfur by selenium would have. 2-Selenobarbituric acid and several of its derivatives were synthesized as part of this work.

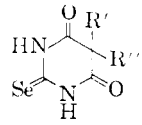
2-Selenobarbituric acid was prepared by the condensation of selenourea with diethyl malonate in the presence of sodium ethoxide, similarly to the method used previously for the synthesis of 2-selenouracil.[9] 5-Phenyl-, 5-benzyl-, and 5-pentyl-2-selenobarbituric acid could be obtained by the condensation of selenourea and the appropriately substituted diethyl malonate in the presence of sodium methoxide.

All attempts to condense selenourea with diethyl diethyl malonate or with diethyl ethyl (2-methylbutyl)-malonate to obtain the selenium analogs of barbital and pentobarbital, respectively, have been unsuccessful; furthermore, these compounds could not be obtained by substituting magnesium ethoxide for sodium ethoxide. The only disubstituted selenobarbiturate which could be made is 5-phenyl-5-ethyl-2-selenobarbituric acid, the selenium analog of phenobarbital. It seems likely that the other disubstituted selenobarbiturates were too unstable to be isolated. Also, among the monosubstituted selenobarbiturates only the phenyl compound appeared to be stable, presumably due to resonance stabilization, while the pentyl compound decomposed to form a red sludge within two weeks, even when protected from light and stored in a vacuum desiccator.

(1) Presented before the Medicinal Chemistry Section at the American Chemical Society Meeting, Boston, Mass., April, 1959, p. 25-N.
(2) The material presented here is based on a thesis submitted by Edwin M. Clayton to the Yale University School of Medicine in partial fulfillment of the requirements for the M.D. degree.
(3) This work was supported, in part, by a grant (CY-3937) from the National Institutes of Health, Public Health Service.
(4) Research Fellow, summers of 1957 and 1958, Yale University Medical Student Research Program, supported by Public Health Service Training Grant, CRTY-5012.
(5) B. B. Brodie and C. A. M. Hogben, *J. Pharm. Pharmacol.*, **9**, 360 (1957).
(6) B. B. Brodie, *Fed. Proc.*, **11**, 632 (1952).
(7) J. Raventós, *J. Pharm. Pharmacol.*, **6**, 217 (1954).
(8) L. C. Mark, *et al.*, *J. Pharmacol. Expt. Therap.*, **123**, 70 (1958).
(9) H. G. Mautner, THIS JOURNAL, **78**, 5292 (1956).

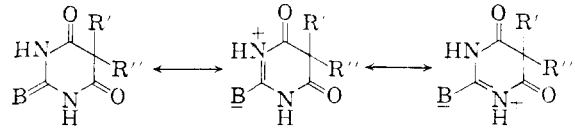
TABLE I

2-SELENOBARBITURIC ACIDS



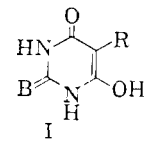
R[1]	R[2]	M.p., °C.[10]	Formula	Analyses[11] Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
H	H	195–210	$C_4H_4N_2O_2Se$	25.14	24.99	2.11	2.27	14.66	14.49
H	Phenyl	192–193	$C_{10}H_8N_2O_2Se$	44.96	44.99	3.02	3.11	10.49	10.39
H	Benzyl	125–127	$C_{11}H_{10}N_2O_2Se$	46.99	46.85	3.59	3.81	9.96	10.26
H	Pentyl	160–162	$C_9H_{14}N_2O_2Se$	41.39	41.23	5.40	5.58	10.73	11.06
Ethyl	Phenyl	209–211	$C_{12}H_{12}N_2O_2Se$	48.82	48.85	4.10	3.94	9.49	9.81

Acid Dissociation Constants.—It had been noted previously[9] that successive replacement of the oxygen in the 2-position of uracil or in the 6-position of hypoxanthine by sulfur and selenium caused a progressive increase in acidity. This was attributed to the carbon–selenium double bond being more highly polarized than the carbon–sulfur double bond which, in turn, is more highly polarized than the carbon-oxygen double bond, such polarization —Se—C=NH^{+} resulting in increased acidity. Supporting evidence for this increase in polarizability in carbamyl compounds on descending the periodic table has been obtained by means of dipole moments.[12] A similar increase in acidity was seen when the oxygen in the 2-position of phenobarbital was replaced by sulfur and selenium, the dissociating hydrogen in this case being directly affected by the polarization of the double bond in the 2-position.

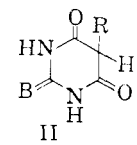


B = O, S, Se

On the other hand, when oxygen was replaced by sulfur or selenium in barbituric and in 5-phenylbarbituric acid, only slight changes in acidity were seen (Table II). It was noted long ago that introduction of one alkyl group into the 5-position of barbituric acid had little effect on the acidity of this compound, while the introduction of two groups in that position decreased acidity greatly.[13] This left some question as to whether barbituric acid and the monosubstituted barbiturates were in the 2,4-diketo-6-hydroxy form (I) or in the 2,4,6-triketo form (II), the former being considered more likely, while the disubstituted compounds must be in the triketo form.[14–16]



I



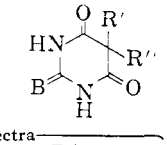
II

The lack of increase in acidity on replacing oxygen with sulfur and selenium lends support to the concept that unsubstituted and monosubstituted barbiturates exist primarily in the 2,4-diketo-6-hydroxy form (I). Since the 2-position which is being modified is *meta* to the 6-position, from which the first ionizable hydrogen is released, only minor changes in pK_a would be expected.

It seems likely that the second pK_a's of barbiturates should again be lowered, as sulfur and selenium are introduced. Unfortunately, their extreme weakness (12.5 for barbituric acid[16]) precluded titrimetric measurements.

TABLE II

ACID DISSOCIATION CONSTANTS AND ULTRAVIOLET SPECTRA OF 2-OXO, 2-THIO- AND 2-SELENOBARBITURATES



Compound B	R′	R″	pK_a	Spectra: $pH7^a$ λ_{max}, mμ	ϵ_{max}	Ethanol λ_{max}, mμ	ϵ_{max}
O	H	H	4.12	257	19,800	258	6,410
S	H	H	3.75	240[b]	7,460	235	5,480
				265	14,760	285	18,000
				280	12,600		
Se	H	H	3.74	263	10,450	269	5,480
				298	12,800	311	17,100
O	H	Phe.	3.75	266	19,700	269	11,300
S	H	Phe.	3.90	242	9,040	248	6,540
				276	14,320	298	18,400
				295	14,300		
Se	H	Phe.	4.01	273	14,700	277	7,400
				308	20,100	320	16,300
O	Et.	Phe.	7.29	<230		<215	
S	Et.	Phe.	6.30	275[b]	10,540	240	8,240
				305	11,880	292	23,300
Se	Et.	Phe.	6.02	262	6,700	243	7,360
				340	20,420	334	20,700

[a] Phosphate–citrate buffer. [b] Inflection.

Ultraviolet Absorption Spectra.—It had been noted previously that replacement of oxygen by sulfur and selenium leads to a bathochromic shift in the ultraviolet region.[9,12] This effect was seen again in the higher of the two absorption peaks exhibited by the thio- and selenobarbiturates.

(10) All m.p.'s are uncorrected.

(11) Microanalyses were performed at the Schwarzkopf Laboratories, Woodside, N. Y.

(12) H. G. Mautner and W. D. Kumler, THIS JOURNAL, **78**, 97 (1956).

(13) J. K. Wood, *J. Chem. Soc.*, **89**, 1831 (1906).

(14) G. W. Kenner and A. Todd, in Elderfield, "Heterocyclic Compounds," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1957, p. 280.

(15) F. Arndt, *Rev. fac. sci., Univ. Istanbul*, **1**, No. 4, 1 (1936).

(16) J. J. Fox and D. Shugar, *Bull. soc. chim. Belge*, **61**, 44 (1952).

Lipid Extractability.—The effect of the substitution of sulfur and selenium in the 2-position of uracil and of various barbiturates, and in the 6-position of hypoxanthine, on lipid extractability was investigated and is shown in Table III.

TABLE III

PARTITION OF ISOLOGOUS OXYGEN, SULFUR AND SELENIUM COMPOUNDS BETWEEN BUFFERS AND ORGANIC SOLVENTS

Compound	Fraction dissolved in ethyl acetate after extraction of buffer solution *p*H 7.4	*p*H 3.0	*p*H 1.2
Hypoxanthine	0.000	0.002	
6-Mercaptopurine	.168	.165	
6-Selenopurine	.195	.242	
Uracil	.000	.006	
2-Thiouracil	.375	.416	
2-Selenouracil	.215	.432	
Barbituric acid	.000	.000	0.000
2-Thiobarbituric acid	.010	.188	.612
2-Selenobarbituric acid	.005	.040	.529
	Fraction dissolved in chloroform after extraction of buffer solution		
5-Phenyl-5-ethylbarbituric acid	0.600[a]	[a]	
2-Thio-5-phenyl-5-ethylbarbituric acid	.950	0.900	
2-Seleno-5-phenyl-5-ethylbarbituric acid	.905	.980	

[a] Due to the steep slope of the end absorption, accurate readings could not be made at this *p*H.

The compounds were dissolved in buffer previously saturated with the organic solvent and then shaken mechanically with ethyl acetate or with chloroform which had previously been saturated with buffer. The amount of solute lost from the aqueous phase was determined spectrophotometrically.

It can be seen that with the exception of phenobarbital the lipid solubility of the oxygen compounds investigated was negligible at physiological *p*H (7.4).

The hypoxanthine series was of interest since 6-mercaptopurine is a clinically used antileukemic agent,[17] while selenopurine shows activity against both microbial and tumor systems.[18,19] It was found that the lipid solubility of selenopurine is slightly greater than that of its thio-analog. On the other hand, at physiological *p*H, 2-thiouracil was more soluble in ethyl acetate than was 2-selenouracil, while the solubilities of these compounds were almost identical at *p*H 3. This is attributed to the pK_a values of thiouracil (7.75) and selenouracil (7.18) being such that at physiological *p*H the selenium compound is ionized to an appreciably greater extent than its sulfur analog.

Being strong acids, the members of the unsubstituted and monosubstituted barbituric acid series are fully ionized at *p*H 7.4 and show negligible solubility in organic solvents. It is believed that this circumstance accounts for their complete lack of physiological activity.[20]

(17) G. H. Hitchings and C. P. Rhoads, *Ann. N. Y. Acad. Sci.*, **60**, 183 (1954).

(18) H. G. Mautner, *Biochem. Pharmacol.*, **1**, 169 (1958).

(19) H. G. Mautner and J. J. Jaffe, *Cancer Res.*, **18**, 294 (1958).

(20) A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 121.

However, in the phenobarbital series, in which one deals with much weaker acids, even the oxygen compound showed such high solubility in ethyl acetate, that to differentiate between the oxygen, sulfur and selenium analogs, chloroform had to be used as an extracting solvent. For all the barbiturates investigated the lipid solubilities of the sulfur and selenium analogs were very similar.

Accordingly, it appears that replacing oxygen with sulfur, at least in carbamyl compounds of the type investigated here, is a good way of increasing lipid solubility with only slight changes in the steric configuration of the molecule. Further replacement of sulfur with selenium does not reduce solubility in organic solvents even though this involves the substitution of an essentially non-metallic by an essentially metallic element. It can be expected, therefore, that lack of lipid solubility will not be a major problem in synthesizing selenium analogs of physiologically active oxygen and sulfur compounds.

Acknowledgments.—We are indebted to Mrs. Joyce Briggs and to Miss Barbara Sheldon for obtaining the spectroscopic, potentiometric and partition data, and to Dr. Arnold D. Welch for his encouragement during the course of this investigation. We should like to thank Dr. Richard U. Schock of the Abbott Laboratories, North Chicago, Ill., for generously supplying several of the malonic esters used.

Experimental

2-Selenobarbituric Acid.—Diethylmalonic ester (2.3 g., 0.015 mole) and 2.7 g. (0.022 mole) of selenourea[9] were placed in 40 ml. of absolute ethanol. The stirred mixture was heated to reflux and a solution of 0.7 g. (0.03 mole) of sodium in 12 cc. of ethyl alcohol slowly added through a dropping funnel. The solution was stirred at reflux temperature for 45 minutes. After chilling, a white precipitate was filtered off; a second crop could be obtained by adding ether to the filtrate. The combined material was dissolved in 5 cc. of ice-cold water and the solution carefully acidified with hydrochloric acid. A creamy-white precipitate weighing 1.5 g. (52%) and decomposing over a range of 193–210° was obtained.

5-Monosubstituted Selenobarbiturates.—Selenourea (1.85 g. 0.015 mole) and 0.0075 mole of monosubstituted diethylmalonic ester in 15 cc. of absolute methanol were heated to reflux. A solution of 0.7 g. (0.03 mole) of sodium in 15 cc. of methyl alcohol was added slowly and the mixture permitted to reflux for one hour. The solution was poured into ten volumes of ice-cold ether. A grayish-white precipitate separated, was filtered off, and dissolved in a small volume of water. Acidification with hydrochloric acid yielded 5-phenyl-, 5-benzyl- and 5-pentyl-2-selenobarbituric acid, respectively, in 25–30% yield.

5-Phenyl-5-ethyl-2-selenobarbituric Acid.—Selenourea (1.85 g., 0.015 mole) and 1.97 g. (0.0075 mole) of diethyl-5-phenyl-5-ethylmalonic ester were dissolved in 15 cc. of refluxing absolute methanol. A solution of 0.7 g. (0.03 mole) of sodium in 10 cc. of absolute methanol was added dropwise. After one hour of reflux the clear, yellow solution was added to 15 volumes of ether. A dark precipitate was filtered off and the filtrate extracted with 15-cc. portions of water. The aqueous extracts were combined and filtered. After the clear, yellow solution was acidified with acetic acid, a light yellow precipitate appeared. It was dissolved in 5 cc. of cold 5% sodium carbonate, filtered and acidified with acetic acid to a *p*H of 5. The light yellow product weighed 0.05 g.

Ultraviolet Spectra.—A Beckman model DU spectrophotometer with quartz cells was used. Solutions were made up in volumetric flasks from weighed quantities of the compounds.

Acid Dissociation Constants.—All pK_a values were determined by potentiometric titration using a Photovolt model

110 *p*H meter. The 5-phenyl and 5-phenyl-5-ethyl derivatives of 2-thio- and 2-selenobarbituric acid, which were very insoluble in water, were dissolved in an equivalent amount of sodium hydroxide and back-titrated with hydrochloric acid. All determinations were made in duplicate.

Partition Studies.—Solutions containing 1 mg. per 100 cc. of the compounds investigated were prepared in buffer previously saturated with ethyl acetate and their spectra determined. The solutions were then shaken mechanically for 30 minutes with an equal volume of ethyl acetate previously saturated with buffer, the aqueous layer was separated, and the spectra were measured again. From the decrease in the extinction coefficient the solubility in the organic layer was determined. The chloroform studies were carried out in an analogous fashion. Phosphate–citrate buffer was used for the *p*H 3 and *p*H 7.4 studies, hydrochloric acid for the *p*H of 1.2.

No decrease in extinction coefficient was observed when the selenium compounds were shaken for 30 minutes in buffer saturated with ethyl acetate or chloroform; therefore, decomposition must have been negligible.

All determinations were made in duplicate.

NEW HAVEN, CONN.

[CONTRIBUTION NO. 552 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND CO.]

Synthesis of Alkylsilylphosphines

BY G. W. PARSHALL AND R. V. LINDSEY, JR.

RECEIVED MAY 14, 1959

Alkylsilylphosphines have been synthesized by reaction of alkylchlorosilanes with lithium derivatives of phosphine and substituted phosphines. For example, tris-(trimethylsilyl)-phosphine was prepared by reaction of trimethylchlorosilane with trilithium phosphide obtained by absorbing phosphine in butyllithium solution. Cyclic derivatives were obtained from dilithium phosphides and diethyldichlorosilane.

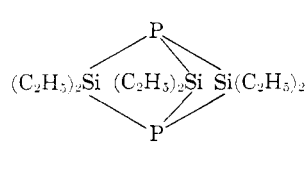
Prior to the inception of the work described herein, only two silylphosphines had been reported, *i.e.*, SiH_3PH_2 and $(SiH_3)_3P$, described by Fritz and Emeleus,[1] respectively. Quite recently, trimethylsilyldiphenylphosphine, the first reported organosilylphosphine, was obtained by Kuchen and Buchwald[2] by reaction of trimethylchlorosilane with the sodium cleavage product of tetraphenylbiphosphine.

Our own work has led to the discovery of a general synthesis of alkylsilylphosphines that involves the metathesis of alkylchlorosilanes with the lithium phosphides obtained by interaction of alkyllithium compounds and phosphines. For example, reaction of trimethylchlorosilane with monolithium phosphide ($LiPH_2$)[3] has given trimethylsilylphosphine (I) in about 30% yield. When phosphine was rapidly bubbled into a butyllithium solution,

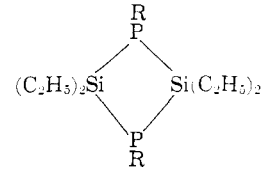
$(CH_3)_3SiPH_2$ (I) $\quad$ $[(CH_3)_3Si]_2PH$ (II) $\quad$ $[(CH_3)_3Si]_3P$ (III)

a mixture of di- and trilithium phosphides was formed. Reaction of the mixture with trimethylchlorosilane gave as major products, bis-(trimethylsilyl)-phosphine (II) in 35% yield and tris-(trimethylsilyl)-phosphine (III) in 24% yield. Tris-(trimethylsilyl)-phosphine predominated when trimethylchlorosilane was added to a suspension of trilithium phosphide prepared by passing phosphine over the surface of a butyllithium solution. Tris-(trimethylsilyl)-phosphine was also obtained by treating the lithium derivative of II with trimethylchlorosilane.

The novel cyclic silylphosphines IV and V have been obtained by treating a mixture of di- and trilithium phosphides with diethyldichlorosilane. The cyclic compounds VI and VII which bear substituents on the phosphorus atoms were obtained by reaction of diethyldichlorosilane with the dilithium derivatives of phenylphosphine and trimethylsilylphosphine, respectively.



IV



V, R = H
VI, R = C_6H_5
VII, R = $(CH_3)_3Si$

The alkylsilylphosphines are colorless liquids or low-melting solids which are extremely sensitive to oxygen and water.[4] The compounds containing phosphorus–hydrogen bonds (as determined by proton magnetic resonance) are spontaneously flammable in air. Despite their sensitivity to air and moisture, these compounds are thermally stable. For example, tris-(trimethylsilyl)-phosphine was refluxed in an inert atmosphere at 243° for eight hours without appreciable decomposition.

The structure of tris-(trimethylsilyl)-phosphine has been established by elemental analysis and by preparation of a crystalline borane complex VIII and by oxidation to the known tris-(trimethylsilyl) phosphate (IX).[5] The oxidation of the phosphine

$[(CH_3)_3Si]_3P\cdot BH_3$ (VIII) $\quad$ $[(CH_3)_3SiO]_3PO$ (IX)

to the phosphate with nitrogen dioxide is unusual, since this reagent is known to convert trialkylphosphines to the corresponding phosphine oxides.[6] The cyclic compounds IV–VII were characterized by elemental analyses, molecular weight and proton magnetic resonance. Molecular models of

(1) (a) G. Fritz, *Z. Naturforsch.*, **8b**, 776 (1953); *Z. anorg. allgem. Chem.*, **280**, 332 (1955); (b) B. J. Aylett, H. J. Emeleus and A. Maddock, *Research*, **6**, 30S (1953); *J. Inorg. Nucl. Chem.*, **1**, 187 (1955).

(2) W. Kuchen and H. Buchwald, *Ber.*, **92**, 227 (1959).

(3) N. Kreutzkamp, *ibid.*, **87**, 919 (1954).

(4) The authors wish to acknowledge the efforts of the Physical and Analytical Division of this Department in developing techniques for analyzing these compounds.

(5) F. Feher, G. Kuhlbörsch, A. Blümcke, H. Keller and K. Lippert, *Ber.*, **90**, 134 (1957).

(6) C. C. Addison and J. C. Sheldon, *J. Chem. Soc.*, 1705 (1956).