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S-Benzylthiuronium Salts of Some Barbituric Acid Derivatives**V. Hahn, Z. Kochansky, I. Guštak-Mašek and K. Jemrić**Laboratory of Organic Chemistry, Technical Faculty, University
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Preparation and properties of the S-benzylthiuronium salts of fourteen barbituric acid derivatives are described.

The preparation of S-benzylthiuronium salts (»SBT salts«) of organic acids for identification purposes has been suggested first by Chambers and Scherer¹ and, more recently, by Donleavy², Veibel and Lillielund³, Chambers and Watts⁴ and other authors⁵. Since then, SBT salts of a large number of organic acids, especially of sulfonic and carboxylic acids, have been reported. In the course of synthetic work carried out during the last years in our laboratory, SBT salts of organic acids of different types have been prepared⁶. The purpose of this paper is to describe the preparation and properties of the SBT salts of some 5-monosubstituted, one 1,5- and several 5,5-disubstituted barbituric acids.

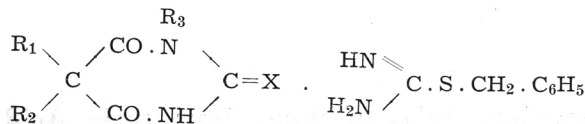
The well crystallized SBT salts I—XIV listed in table 1 have been obtained in the usual way from the corresponding sodium salts with S-benzylthiuronium chloride as reagent⁵. Whereas the SBT salts of 5-monoalkyl-(aralkyl- or aryl-) barbituric acids showed to be relatively stable compounds, the SBT salts of 5,5-disubstituted barbituric acids proved to be much less stable. During recrystallization from diluted ethanol they were partly or completely hydrolysed with liberation of benzyl mercaptan and, therefore, purification of these salts had to be limited to at most one crystallization**. Barbituric acid, contrarily to 2-thiobarbituric acid (see table 1, XII) failed to give a stable SBT salt, whether one or two equivalents of alkali and of the reagent were added. All but three of the prepared salts (V, VI and XII) showed characteristic and sharp melting points which were distributed over a wide range of temperatures.

The results obtained in this work lead to the conclusion that barbituric acid derivatives form well crystallized SBT salts which, however, are of limited value for identification purposes because of the low stability of the salts obtained from the pharmacologically important 5,5-disubstituted barbiturates.

* A part of this paper has been presented at the Meeting of Yugoslav Chemists and the First Croatian Congress of Pure and Applied Chemistry, Zagreb, October 1952.

** It was observed that after three crystallizations of some of the prepared salts (e. g. IX) the free acid was obtained in pure form.

TABLE 1

S-Benzylthiuronium Salts of Barbituric Acid Derivatives

No.	Barbituric acid	R ₁	R ₂	R ₃	X	M. P.
I	5-Methyl-	CH ₃	H	H	O	168—169 [*]
II	5-Ethyl-	C ₂ H ₅	H	H	O	178—179 ^o
III	5-n-Propyl-	CH ₃ CH ₂ CH ₂	H	H	O	182—183 ^o
IV	5-Phenyl-	C ₆ H ₅	H	H	O	240—241 ^o
V	5-Benzyl-	C ₆ H ₅ CH ₂	H	H	O	> 320 ^o (d.)
VI	5-(2'-Furfuryl)-	C ₄ H ₃ O · CH ₂	H	H	O	> 320 ^o (d.)
VII	1-Methyl-5-ethyl-	C ₂ H ₅	H	CH ₃	O	159—160 ^o
VIII	5,5-Diethyl- (VERONAL)	C ₂ H ₅	C ₂ H ₅	H	O	82—83 ^o *
IX	5,5-Diallyl- (DIAL)	CH ₂ =CHCH ₂	CH ₂ =CHCH ₂	H	O	89—90 ^o **
X	5-Ethyl-5-phenyl-					
	(LUMINAL)	C ₂ H ₅	C ₆ H ₅	H	O	134—135 ^o
XI	5-(1'-methylpropyl)- 5-(2'-bromoallyl) (PERNOCTON)	CH ₃ CH ₂ CH CH ₃	CH ₂ =CBrCH ₂	H	O	100—101 ^o
XII	2-Thio-	H	H	H	S	> 320 ^o (d.)
XIII	5-Ethyl-2-thio-	C ₂ H ₅	H	H	S	156—157 ^o *
XIV	5-Ethyl-5-(1-methyl)- butyl)-2-thio- (PENTOTHAL)	C ₂ H ₅	CH ₃ CH ₂ CH ₂ CH CH ₃	H	S	111—112 ^o

* Monohydrate ** Semihydrate

EXPERIMENTAL

The melting points (m. p.) are uncorrected. They were determined in capillary tubes, up to 180^o in a Thiele apparatus, above 180^o in a copper block. The analytical samples were dried *in vacuo* under phosphorus pentoxide for 2 hours.

The *barbituric acids* used in this work have all been described in the literature. While the 5-mono- and 1,5-disubstituted acids as well as 2-thiobarbituric have been prepared by known methods, samples of the pure commercial 5,5-disubstituted barbiturates were available.

Preparation of the S-benzylthiuronium salts («SBT salts»)

The barbituric acid (0.002—0.003 mole) was dissolved or suspended in 4—5 ml. of warm water and mixed with the equivalent quantity of a 15% aqueous solution of sodium hydroxyde. In some cases the sodium salt of the barbituric acid served as starting material. To the clear solution of the sodium salt 1—2 drops of *N* hydrochloric acid and then the calculated amount of *S*-benzylthiuronium chloride, dissolved in 3—5 ml. of water, were added. From the cooled mixture the SBT salt separated in form of crystals or as an oil which solidified quickly on cooling and scratching with a glass rod. Purification of the crude products, obtained in most cases in a quantitative yield, was carried out by recrystallization (usually from a mixture of equal parts of ethanol and water), taking in account the limited stability of the SBT salts of 5,5-disubstituted barbituric acids, pointed out in the first part of this paper.

SBT salt of 5-methylbarbituric acid (I)

By the above described procedure the monohydrate of I was obtained in an almost quantitative yield. Colorless prismatic crystals from aqueous ethanol (1 : 1), m. p. 168—169^o. The analytical sample was dried at room temperature.

Anal. 22.874 mg subst.: 40.1 mg. CO₂, 10.9 mg. H₂O
 3.207 mg. subst.: 0.468 ml. N₂ (21°, 759 mm)
 C₁₃H₁₆O₃N₄S · H₂O (326.37) calc'd: C 47.84; H 5.56; N 17.17%
 found: C 47.84; H 5.33; N 16.92%

When dried at 100° for 3 hours the anhydrous salt melting at 173—174° was obtained.

Anal. 18.430 mg. subst.: 34.0 mg. CO₂, 8.6 mg. H₂O
 2.575 mg. subst.: 0.419 ml N₂ (23°, 744 mm)
 C₁₃H₁₆O₃N₄S (308.35) calc'd: C 50.63; H 5.23; N 18.17%
 found: C 50.34; H 5.22; N 18.37%

SBT salt of 5-ethylbarbituric acid (II)

Almost colorless prisms from aqueous ethanol, m. p. 178—179°, yield 75%. The analytical sample was dried at 100°.

Anal. 19.498 mg. subst.: 37.5 mg. CO₂, 9.4 mg. H₂O
 3.325 mg. subst.: 0.515 ml. N₂ (27°, 751 mm)
 C₁₄H₁₈O₃N₄S (322.38) calc'd: C 52.16; H 5.63; N 17.38%
 found: C 52.48; H 5.40; N 17.41%

SBT salt of 5-n-propylbarbituric acid (III)

Colorless prisms from aqueous ethanol, m. p. 182—183°, yield 88%. The analytical sample was dried at room temperature.

Anal. 23.921 mg. subst.: 46.8 mg. CO₂, 12.3 mg. H₂O
 3.508 mg. subst.: 0.508 ml. N₂ (20°, 755 mm)
 C₁₅H₂₀O₃N₄S (336.40) calc'd: C 53.55; H 5.99; N 16.66%
 found: C 53.39; H 5.75; N 16.76%

SBT salt of 5-phenylbarbituric acid (IV)

Colorless shiny prisms from water, m. p. 240—241°, yield 70%. The analytical sample was dried at 100°.

Anal. 20.296 mg. subst.: 43.5 mg. CO₂, 9.2 mg. H₂O
 3.922 mg. subst.: 0.532 ml. N₂ (26°, 752 mm)
 C₁₈H₁₈O₃N₄S (370.42) calc'd: C 58.36; H 4.90; N 15.13%
 found: C 58.49; H 5.07; N 15.32%

SBT salt of 5-benzylbarbituric acid (V)

Colorless needles from aqueous ethanol which darken at about 200° and decompose without melting up to 320°; yield 91%. The analytical sample was dried at 100°.

Anal. 18.381 mg. subst.: 39.8 mg. CO₂, 8.6 mg. H₂O
 2.542 mg. subst.: 0.318 ml. N₂ (22°, 752 mm)
 C₁₉H₂₀O₃N₄S (384.44) calc'd: C 59.36; H 5.25; N 14.58%
 found: C 59.09; H 5.24; N 14.32%

SBT salt of 5-(2'-furfuryl)-barbituric acid (VI)

Almost colorless prisms from aqueous ethanol which darken at about 180° and decompose without melting up to 320°; yield almost quantitative. The analytical sample was dried at 100°.

Anal. 21.894 mg. subst.: 43.4 mg. CO₂, 9.2 mg. H₂O
 2.696 mg. subst.: 0.348 ml. N₂ (20°, 763 mm)
 C₁₇H₁₈O₄N₄S (374.41) calc'd: C 54.54; H 4.85; N 14.96%
 found: C 54.11; H 4.70; N 15.10%

SBT salt of 1-methyl-5-ethylbarbituric acid (VII)

Colorless crystals from abs. ethanol + ether melting at 159—160°, yield 91%.
 Analyt. sample dried at 100°.

Anal. 4.022 mg. subst.: 0.576 ml. N₂ (19°, 750 mm)
 C₁₅H₂₀O₃N₄S (336.40) calc'd: N 16.66%
 found: N 16.52%

SBT salt of 5,5-diethylbarbituric acid (Veronal) (VIII)

The crude product, m. p. 79—80°, which was obtained in an almost quantitative yield, showed to be the monohydrate of VIII. After one crystallization from aqueous ethanol it was obtained in form of colorless crystals melting at 82—83°. The analytical sample was dried at room temperature.

Anal. 23.890 mg. subst.: 46.0 mg. CO₂, 13.7 mg. H₂O
 3.019 mg. subst.: 0.402 ml. N₂ (23°, 758 mm)
 C₁₆H₂₂O₃N₄S.H₂O (368.45) calc'd: C 52.15; H 6.57; N 15.21%
 found: C 52.54; H 6.42; N 15.32%

We were not able to obtain the anhydrous salt because heating of the monohydrate above the melting point (either at ordinary pressure or *in vacuo*) caused decomposition.

SBT salt of 5,5-diallylbarbituric acid (Dial) (IX)

The crude product, obtained in almost quantitative yield, melted unsharply at 81—85°. After crystallization from aqueous ethanol it was obtained in form of colorless crystals, m. p. 89—90°. On the basis of the obtained analytical data it was identified as the semihydrate of IX. The analytical sample was dried at room temperature.

Anal. 19.203 mg. subst.: 39.6 mg. CO₂, 10.0 mg. H₂O
 3.749 mg. subst.: 0.498 ml. N₂ (25°, 744 mm)
 C₁₈H₂₂O₃N₄S.½H₂O (383.46) calc'd: C 56.38; H 6.05; N 14.61%
 found: C 56.28; H 5.83; N 14.89%

The behavior of the semihydrate on heating was the same as of the monohydrate of VIII and no anhydrous IX could be obtained.

SBT salt of 5-ethyl-5-phenylbarbituric acid (Luminal) (X)

Colorless prisms from aqueous ethanol, m. p. 134—135°, yield almost quantitative. Analyt. sample dried at room temperature.

Anal. 23.605 mg. subst.: 51.8 mg. CO₂, 11.4 mg. H₂O
 2.618 mg. subst.: 0.312 ml. N₂ (21°, 767 mm)
 C₂₀H₂₂O₃N₄S (398.47) calc'd: C 60.28; H 5.57; N 14.06%
 found: C 59.89; H 5.40; N 13.96%

SBT salt of 5-(1'methylpropyl)-5-(2'-bromoallyl)-barbituric acid (Pernocton) (XI)

The crude product obtained in an almost quantitative yield, m. p. 96—97°, crystallized from aqueous ethanol in form of colorless crystals melting at 100—101°. The analytical sample was dried at 60°.

Anal. 22.581 mg. subst.: 40.2 mg. CO₂, 10.6 mg. H₂O
 2.167 mg. subst.: 0.221 ml. N₂ (19°, 752 mm)
 C₁₉H₂₅O₃N₄SBr (469.40) calc'd: C 48.61; H 5.37; N 11.94%
 found: C 48.58; H 5.25; N 11.80%

SBT salt of 2-thiobarbituric acid (XII)

Almost colorless prisms from aqueous ethanol which darken at about 210° and decompose without melting up to 320°; yield 80—90%. The analytical sample was dried at 100°.

Anal. 21.299 mg. subst.: 36.3 mg. CO₂, 8.2 mg. H₂O
 2.606 mg. subst.: 0.418 ml. N₂ (27°, 753 mm)
 C₁₂H₁₄O₂N₄S₂ (310.38) calc'd: C 46.43; H 4.55; N 18.05%
 found: C 46.51; H 4.31; N 18.08%

SBT salt of 5-ethyl-2-thiobarbituric acid (XIII)

The monohydrate, obtained in an almost quantitative yield, melted after recrystallization from aqueous ethanol at 156—157°. The analytical sample was dried at room temperature.

Anal. 18.048 mg. subst.: 31.0 mg. CO₂, 9.2 mg. H₂O
 2.225 mg. subst.: 0.310 ml. N₂ (24°, 748 mm)
 C₁₄H₁₈O₂N₄S₂.H₂O (356.46) calc'd: C 47.17; H 5.66; N 15.72%
 found: C 46.87; H 5.70; N 15.76%

When a sample of the monohydrate was dried *in vacuo* at 100° for 3 hours, the anhydrous salt, m. p. 180—181°, was obtained.

Anal. 21.834 mg. subst.: 39.6 mg. CO₂, 10.2 mg. H₂O
 3.697 mg. subst.: 0.512 ml. N₂ (18°, 771 mm)
 C₁₄H₁₈O₂N₄S₂ (338.44) calc'd: C 49.68; H 5.36; N 16.56%
 found: C 49.49; H 5.23; N 16.48%

SBT salt of 5-ethyl-5-(1-methylbutyl)-2-thio-barbituric acid (Pentothal) (XIV)

Almost colorless crystals from aqueous ethanol, m. p. 111—112°, yield 60%. The analytical sample was dried at 60°.

Anal. 20.895 mg. subst.: 42.8 mg. CO₂, 12.6 mg. H₂O
 3.189 mg. subst.: 0.374 ml. N₂ (21°, 767 mm)
 C₁₉H₂₈O₂N₄S₂ (408.57) calc'd: C 55.85; H 6.91; N 13.71%
 found: C 55.90; H 6.75; N 13.74%

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IZVOD

S-Benziltiuronijeve soli nekih derivata barbiturne kiseline

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Pripravljene su lijepo kristalizirane S-benziltiuronijeve soli (»SBT soli«) četrnaest različitih derivata barbiturne kiseline (I—XIV), prikazane u tabeli 1. Dok su se SBT soli 5-monosupstituiranih barbiturnih kiselina pokazale relativno stabilnim spojevima, SBT soli dobivene iz 5,5-disupstituiranih barbiturata mnogo su manje stabilne, pa se već nakon nekoliko prekrizalizacija iz razređenog etanola hidrolitički cijepaju uz stvaranje benzilmerkaptana i ishodne kiseline. Kako je iz tabele 1 vidljivo, pripravljene SBT soli pokazuju karakteristična tališta, koja leže u širokom temperaturnom intervalu. Izuzetak su soli V, VI i XII, koje se kod ca. 200° C mijenjaju uz potamnjenje, ali se ne rastale do 320°.

Na osnovu dobivenih rezultata može se zaključiti da derivati barbiturne kiseline daju lijepo kristalizirane SBT soli, koje međutim nisu podesne za svrhe identifikacije zbog ograničene stabilnosti SBT soli farmakološki važnih 5,5-disupstituiranih barbiturata.

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