ing, the adduct solidified, and was recrystallized from 30–60° petroleum–ether. The yield of material with the m.p. 75° was 235 mg. (86%). For analysis a sample was recrystallized from petroleum–ether, m.p. 75.0–75.6°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.51; H, 8.31.

CAMBRIDGE, MASS. RECEIVED JULY 9, 1951

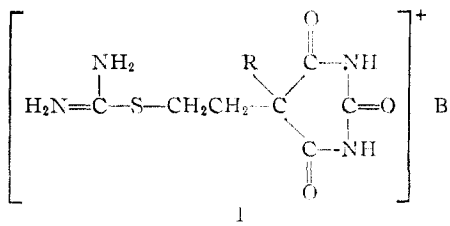
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

Thiocyanate and Isothiourea Derivatives of Barbituric Acid

BY GLENN S. SKINNER AND WILLIAM H. WAITZ, JR.

A series of thiocyanate and isothiourea derivatives of barbituric acid have been prepared and subjected to pharmacological testing. The thiocyanate resisted hydrolysis without cleavage of the ring. The isothiourea derivative was smoothly hydrolyzed to the mercaptobarbituric acid. None of the compounds gave hypnosis or anesthesia. The isothiouronium bromides showed some anticonvulsant activity.

In a previous report[1] we have described a series of 5-(β-xanthoethyl)- and 5-(β-mercaptoethyl)-barbituric acids. The establishment of the carbon–sulfur bond at this position has now been extended to include the thiocyanates and isothiouronium salts (I).



I

Both the thiocyanates and the isothiouronium salts (Table I) were easily prepared in good yields by the action of potassium thiocyanate and thiourea, respectively, on the β-bromoethylbarbituric acid derivatives in alcohol. These reagents are advantageous since they are more stable than the xanthates.

TABLE I

BARBITURIC ACIDS RR'C(CONH)$_2$CO

(R_1, $NCSCH_2CH_2$–; R_2, $(H_2N{=}C(NH_2)SCH_2CH_2{-})^+Br^-$; R_3, $HN{=}C(NH_2)SCH_2CH_2$–)

No.	R	R'	M.p., °C.	Nitrogen, % Calcd.	Found
I	C_2H_5-	R_1	193–194	17.41	17.32
II	n-C_3H_7-	R_1	203–204	16.46	16.39
III	*n*-C_4H_9-	R_1	198–199	15.60	15.53
IV	*n*-C_5H_{11}-	R_1	202–203	14.82	14.71
V	*i*-C_5H_{11}-	R_1	197–198	11.32[b]	11.41
VI	C_2H_5-	R_2	284–285[a]	23.56[c]	23.52
VII	*n*-C_3H_7-	R_2	288–289[a]	22.62[c]	22.56
VIII	*n*-C_4H_9-	R_2	302–303[a]	21.76[c]	21.70
IX	*n*-C_5H_{11}-	R_2	296–297[a]	20.96[c]	20.93
X	*i*-C_5H_{11}-	R_2	293–295[a]	20.96[c]	21.01
XI	C_2H_5-	R_3	153–155[a]	21.69	21.72
XII	*n*-C_3H_7-	R_3	148–149[a]	20.58	20.38
XIII	*n*-C_4H_9-	R_3	168–170[a]	19.56	19.46
XIV	*n*-C_5H_{11}-	R_3	169–171[a]	18.65	18.53
XV	*i*-C_5H_{11}-	R_3	187–188[a]	18.65	18.50

[a] Decomp. temp. raised 5°/min. [b] Sulfur. [c] Bromine.

The thiocyanobarbituric acid derivatives appear not to be hydrolyzed by hydrochloric acid except under conditions severe enough to rupture the ring. The isothiouronium salts are easily hydrolyzed by ice-cold alkali to the β-mercaptoethylbarbituric acids in excellent yield.

The isothiouronium salts are converted to the isothiourea derivatives by treatment of their warm aqueous solutions with a slight excess of ammonia. These isothiourea derivatives are also stable white crystalline compounds. The mercapto acid can be obtained in excellent yield by the action of cold aqueous alkali on the isothiouronium salt. This route to the mercapto acid is superior to the xanthate procedure.

The thiocyanates, by vein in rats, gave no anesthesia and produced convulsions. The dose at which 50% of them died varied between 24 and 35 milligrams per kilogram. The isothiouronium bromides administered by mouth in cats (50 mg./kg.) gave no anticonvulsant action by the electrical method. Using the metrazol method, by mouth in rats, the relative anticonvulsant activities as compared to phenylacetylurea were as follows: VI, 1.0; VII, 0.5; VIII, none; IX, 0.5; X (cats), none. VI by vein in rats gave no hypnosis or anesthesia with doses of 50 to 600 mg./kg. None of the other bromides gave hypnosis or anesthesia; the LD_{50} values were as follows: VII, 141; VIII, 69; IX, 47; X, 49. These tests were made by Eli Lilly and Company.

Experimental

5-Alkyl-5-(β-thiocyanoethyl)-barbituric Acids.—In a typical preparation 22.4 g. (0.23 mole) of potassium thiocyanate and 52.6 g. (0.20 mole) of 5-ethyl-5-(β-bromoethyl)-barbituric acid were swirled with 125 cc. of absolute alcohol to effect partial solution. The mixture was heated under reflux (bath 95°) to give a dark red solution which slowly became yellow in the course of an hour. A white precipitate gradually separated and after four hours the contents of the flask appeared to be solid. Heating at this temperature was continued for seven hours. The solid mass was disintegrated while still hot so that it could be removed from the flask after cooling in an ice-bath. The filtered precipitate was washed separately on the buchner funnel with alcohol and with cold water until the filtrate no longer gave a test for bromide ion. The filtered alcohol solution was concentrated to yield more of the product, total yield 41.6 g. (86%). For the analysis it was crystallized from alcohol.

5-Isoamyl-5-(β-thiocyanoethyl)-barbituric acid (1.44 g.) dissolved in 4 cc. of glacial acetic containing 0.27 g. of hydrogen chloride when heated to 60°. Water (0.09 cc.) was added and the mixture was heated for five hours at 60°. The crystalline material which separated on cooling was identical with the starting material. The residue from the solvent was also identical. A similar mixture after heating two hours in a sealed tube at 150° likewise gave only the starting material. A mixture of this acid (0.2 g.), 1.0 cc. of hydrochloric acid (1.19) and 3.0 cc. of glacial

(1) G. S. Skinner and J. B. Bicking, THIS JOURNAL, 72, 1140 (1950).

acetic acid after refluxing one-half hour also gave the unchanged substance. The acid (1.0 g.) was now heated in a sealed tube with 7.0 cc. of hydrochloric acid (1.19) at 160° for two hours. Some pressure developed and hydrogen sulfide was identified among the gases evolved. No definite crystalline product was isolated from this reaction mixture.

5-Alkyl-5-(β-isothiouroniumbromidoethyl)-barbituric Acids.—In a typical experiment 15 g. (0.049 mole) of 5-isoamyl-5-(β-bromoethyl)-barbituric acid and 3.8 g. (0.050 mole) of thiourea were periodically swirled with 50 cc. of alcohol as it heated to the temperature of complete solution (80°). In five minutes at this temperature the rapid precipitation of the product began. When this had subsided the temperature of the bath was raised to 90° and the mixture was heated for five hours. After cooling in ice the solid product, obtained by filtration and concentration of the filtrate, weighed 17.8 g. (95%). It is very soluble in hot water but quite insoluble in cold water and was purified by crystallization from water.

5-Alkyl-5-(β-isothioureidoethyl)-barbituric Acids.—Five grams (0.013 mole) of 5-isoamyl-5-(β-isothiouroniumbromidoethyl)-barbituric acid was dissolved by warming in 65 cc. of water. The solution was filtered immediately and 1 cc. (0.015 mole) of aqua ammonia (0.90) was added gradually to the filtrate with stirring while it was cooled in an ice-bath. The white crystalline product obtained by filtration required no further purification, yield 4.0 g. (80%).

Mercapto Acid from the Isothiouronium Compound.—One gram (0.0026 mole) of 5-*n*-amyl-5-(β-isothiouroniumbromidoethyl)-barbituric acid was dissolved in the minimum amount (5 cc.) of ice-cold 10% sodium hydroxide. The solution was allowed to stand for an hour in an ice-bath. The 5-*n*-amyl-5-(β-mercaptoethyl)-barbituric acid was precipitated by hydrochloric acid, yield 0.6 g. (95%), m.p. 132–133.5°. It was identical with the mercapto acid prepared from the corresponding xanthate.

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[CONTRIBUTION FROM THE RADIOCHEMISTRY LABORATORY, DEPARTMENT OF CHEMISTRY, WASHINGTON UNIVERSITY]

The Reaction of D-Glucose, D-Mannose and D-Fructose in 0.035 *N* Sodium Hydroxide at 35°

BY JOHN C. SOWDEN AND ROBERT SCHAFFER[1]

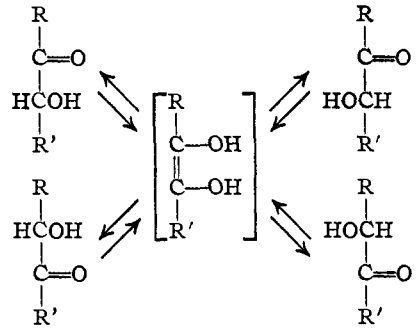
The reactions of individual molar solutions of D-glucose, D-mannose and D-fructose in 0.035 *N* sodium hydroxide at 35° have been studied using radioisotopic dilution analysis for D-glucose and D-fructose in the reaction mixtures and a corrected phenylhydrazone precipitation procedure for D-mannose. After reaction times of four to eight weeks, summation of the analyses for these three isomeric sugars accounted in each instance for only 77–80% of the starting carbohydrate. The remainder was shown, by fermentation experiments, to have been converted nearly quantitatively to a mixture of non-fermentable sugar products. Some exploratory experiments were performed concerning the nature of these non-fermentable substances.

The complex reaction sequence promoted by the action of aqueous alkali on reducing sugars includes isomerization, fragmentation and fragment recombination. Two kinds of isomeric products form: carbohydrates[2] and saccharinic acids.[3,4,5] The products of fragmentation are themselves at the oxidation level of carbohydrate and they also may isomerize[6] or recombine to larger molecules.[7] In addition, there are formed colored products of high molecular weight and undetermined structure.

Lobry de Bruyn and Alberda van Ekenstein demonstrated the interconvertibility of D-glucose, D-mannose and D-fructose in aqueous alkali. They also isolated fractions from the reaction which they considered to be, respectively, the 3-epimer of D-fructose ("pseudo-fructose," "psicose," D-ribohexulose) and a mixture of 3-ketohexoses. However, the former material does not conform in its properties to synthetic D-ribohexulose[8,9] and their "3-ketohexose" mixture ("glutose") is now considered to be a complex mixture containing fructosans.[10]

Conclusive evidence for the presence of material epimeric with D-glucose at carbon-3 has been obtained recently, however, by characterization of the products obtained by electroreduction of the mixture that results from the interaction of D-glucose and aqueous alkali.[11]

The generally accepted mechanism of the Lobry de Bruyn–Alberda van Ekenstein isomerization reaction postulates enediol intermediates, as illustrated in the scheme



(R = H, CH_2OH, etc.; R′ = H, CH_2OH, etc.)

Observations, based on the measurement of deuterium exchange when the reaction was conducted in heavy water, apparently in conflict with the enediol mechanism have been recorded.[12,13] These objections to the mechanism, however, have not been sustained in more recent studies with heavy

(1) Abstracted from the thesis of Robert Schaffer presented in partial fulfillment for the degree Doctor of Philosophy, Washington University, October, 1950.

(2) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **14**, 203 (1895); **15**, 92 (1896); **16**, 257, 262, 274, 282 (1897); **18**, 147 (1899); **19**, 5 (1900).

(3) E. Peligot, *Ann. chim. et phys.*, [2] **67**, 154 (1839).

(4) C. Schiebler, *Ber.*, **13**, 2212 (1880).

(5) H. Kiliani, *ibid.*, **15**, 701, 2953 (1882).

(6) J. U. Nef, *Ann.*, **357**, 294 (1907); **376**, 1 (1910); **403**, 204 (1913).

(7) E. Fischer and J. Tafel, *Ber.*, **20**, 2566 (1887).

(8) Marguerite Steiger and T. Reichstein, *Helv. Chim. Acta*, **19**, 187 (1936).

(9) M. L. Wolfrom and E. F. Evans, THIS JOURNAL, **67**, 1793 (1945).

(10) L. Sattler and F. W. Zerban, *Ind. Eng. Chem.*, **37**, 1133 (1945).

(11) M. L. Wolfrom and co-workers, THIS JOURNAL, **68**, 122, 578, 1443, 2342 (1946).

(12) H. Fredenhagen and K. F. Bonhoeffer, *Z. physik. Chem.*, **A181**, 392 (1938).

(13) K. Goto, *J. Chem. Soc. Japan*, **63**, 217 (1942).