layer was separated and diluted with 10 ml. of concd. hydrochloric acid. The mercaptan derivative precipitated and was purified in the same manner as the products from the mercaptosuccinic acid–olefin reaction. The yield was usually in the range of 0.8 to 2.0 g.

Alkyl bromides. The following materials were placed in a 50-ml. Erlenmeyer flask: 1.00 ml. of mercaptosuccinic acid, 2 ml. of *n*-propyl alcohol, 1.00 ml. of the alkyl bromide, 25 ml. of 1.33*N* potassium hydroxide, and several boiling chips. The flask was fitted with a finger condenser and the mixture refluxed for 4 to 24 hr. If two layers were obtained upon cooling the reaction mixture, the aqueous layer was extracted with an equal volume of *n*-pentane. Ten milliliters of concd. hydrochloric acid was added to the aqueous layer and the precipitated derivative was recrystallized in the usual manner.

Neutralization equivalent. The *S*-alkylmercaptosuccinic acids were titrated with 0.07*N* potassium hydroxide to a phenolphthalein end-point in the presence of 5 ml. of ethyl alcohol and 40 ml. of water. The higher molecular weight derivatives (from 1-decene and higher) were titrated in a warm solution because of their limited solubility.

AUSTIN 12, TEX.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, THE HEBREW UNIVERSITY–HADASSAH MEDICAL SCHOOL]

Synthesis of 6-Thiouric Acid and Its Derivatives[1]

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6-Thiouric acid and its derivatives are obtained in high yield and excellent purity by direct thiation of suitable 4-oxo-5,6-diaminopyrimidines and subsequent cyclization with urea. Phosphorus pentasulfide attacks the 4-position selectively.

6-Thiouric acid (IIIa) is a substance of considerable biological interest, because it represents the main metabolite of 6-mercaptopurine,[3] a drug used for the treatment of leukemia. The synthesis of IIIa has proved a difficult task. Isolation of pure material from the reaction of uric acid with phosphorus pentasulfide required the use of anion exchangers,[4,5] because of the formation of side-products, *e.g.* the participation of the 8-position in the reaction.[5] These difficulties could be overcome if the mercapto group could be introduced at an earlier stage, *i.e.*, before the purine ring is formed. Therefore, the thiation of appropriate pyrimidines, which—as far as we are aware—has not been studied previously, was attempted.

We have found that a smooth reaction takes place at the 4-keto group of 5,6-diaminopyrimidines, when heated with phosphorus pentasulfide. The difference in reactivity of the 2- and 4-keto groups of the aforementioned compounds is similar to the differences of reactivity of keto groups in equivalent positions in xanthines.[6] Using this observation, the following syntheses were carried out: 1. 2,4-Dihydroxy-5,6-diaminopyrimidine (Ia)[7] was converted to 2-hydroxy-4-mercapto-5,6-diaminopyrimidine (IIa), the latter then being cyclized by fusion with urea to 6-thiouric acid (IIIa) in high yield. The product, as obtained, is practically pure, and can be easily recrystallized by acidification of a dilute solution of its sodium salt, without necessitating the use of an ion exchange column. 2. The same method, when applied to 1,2-dihydro-1-methyl-2-oxo-4-hydroxy-5,6-diaminopyrimidine (Ib)[8] gave 3-methyl-6-thiouric acid (IIIb) in high yield and excellent purity. 3. Because of the great difference in reactivity of the 2- and 4-keto group in I, *dithiation* of Ia or Ib in a one-step reaction with phosphorus pentasulfide is not a suitable procedure. Therefore, the following syntheses started with pyrimidines, already bearing a 2-thio group.

2-Mercapto-4-hydroxy-5,6-diaminopyrimidine (Ic)[9] reacted smoothly with phosphorus pentasulfide to give the dithio derivative (IIc).[10] The latter then was cyclized with urea to 2,6-dithiouric acid (IIIc). The spectral properties of our product are identical with those given by Elion, *et al.*,[5] who have prepared this compound by interaction of 2,6-dichloro-8-hydroxypurine with thiourea,[11] but differ from the data reported by Noell and Robins who obtained IIIc by thiation of 2-thiouric

(1) This work was supported in part by grant No. RG-6631 from the National Institutes of Health.

(2) Part of a Ph.D. thesis, submitted to the Faculty of Science, The Hebrew University, Jerusalem, 1960.

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(9) (a) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952); (b) W. Traube, *Ann.*, **331**, 71 (1904).

(10) K. L. Dille and B. E. Christensen, *J. Am. Chem. Soc.*, **76**, 5087 (1954).

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TABLE I

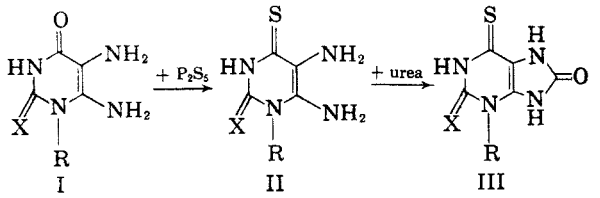
PHYSICAL PROPERTIES OF 6-THIOURIC ACID AND ITS DERIVATIVES

Compound	λ_{max}, mμ, pH 1	ϵ_m	λ_{max}, mμ, pH 8	ϵ_m	λ_{max}, mμ, pH 11	ϵ_m	R_F[a]	Fluorescence[b]
6-Thiouric acid (IIIa)	260	8,550	244	10,700	235	17,980	0.28	Blue
	355	28,730	347	27,270	344	22,000		
3-Methyl-6-thiouric acid (IIIb)	258	5,940	247	10,230	266	9,900	0.40	Blue
	358	23,960	357	26,730	344	20,990		
2,6-Dithiouric acid (IIIc)	261	9,100	245	23,450	252	26,000	0.44	Blue
	298	21,100	283	20,100				
	366	17,800	357	19,000	352	13,200		
3-Methyl-2,6-dithiouric acid (IIId)	262	11,030	255	24,180	241	13,420	0.57	Violet
	296	23,640	281	16,480	285	25,640		
	366	19,520	363	26,420	351	24,500		

[a] Descending method. Solvent used: isopropyl alcohol, 65 vol.; dimethylformamide, 25 vol.; water, 10 vol. [b] Observed under a Mineralight ultraviolet lamp, emitting light of about 255 mμ.

acid[12,13] (see Table I). 4. The same series of reactions, when applied to 1,2-dihydro-1-methyl-2-thio-4-hydroxy-5,6-diaminopyrimidine (Id),[14] led to 3-methyl-2,6-dithiouric acid (IIId) in 75% yield.

The spectral data and the R_f values of the uric acid derivatives described are summarized in Table I.



a. X = O; R = H
b. X = O; R = CH_3
c. X = S; R = H
d. X = S; R = CH_3

EXPERIMENTAL

2-Hydroxy-4-mercapto-5,6-diaminopyrimidine (IIa). Crude 2,4-dihydroxy-5,6-diaminopyrimidine (Ia), as obtained by reduction of the corresponding crude 5-nitroso derivative,[7] (2.0 g.), and phosphorus pentasulfide[15] (6.0 g.) in pyridine (100 ml.) were refluxed for 2.5 hr. with continuous stirring. The solvent was removed under reduced pressure and the residue decomposed by heating with water (50 ml.) during 40 min. Upon standing overnight in the refrigerator, brown crystals (1.5 g.) precipitated. By recrystallization from dilute sulfuric acid, yellow prisms of the neutral sulfate of IIa were obtained, which decomposed slowly above 270°. For cyclization, however, the crude precipitate is suitable.

Anal. Calcd. for $C_4H_6N_4OS \cdot {}^1/_2H_2SO_4 \cdot {}^1/_2H_2O$: C, 22.2; H, 3.7. Found: C, 22.5; H, 3.6.

6-Thiouric acid (IIIa). An intimate mixture of the diamine IIa (1.0 g.) and urea (1.5 g.) was heated for 20 min. at 180–200°. The solid cake was dissolved in 5% sodium hydroxide, treated with Norit, and the filtrate acidified with dilute sulfuric acid. 6-Thiouric acid was obtained as yellow, microcrystalline precipitate (1.0 g.; 90%). When a very dilute solution of this material in 5% sodium hydroxide was acidified with dilute sulfuric acid, slow crystallization took place, yielding analytically pure IIIa as yellowish plates, dec. >300°. The product showed properties identical with those reported in the literature.[4,5]

1,2-Dihydro-1-methyl-2-oxo-4-mercapto-5,6-diaminopyrimidine (IIb). Crude 1,2-dihydro-1-methyl-2-oxo-4-hydroxy-5,6-diaminopyrimidine (Ib)[8] (1.5 g.), phosphorus pentasulfide (5.0 g.) and pyridine (75 ml.) were refluxed for 4 hr. under continuous stirring. The starting material dissolved completely in the beginning and somewhat later the product (IIb) started to precipitate. After cooling, the crystals were filtered and boiled with water (30 ml.) for 15 min. Finally, the mercapto derivative was dissolved in 5% sodium hydroxide and precipitated with glacial acetic acid: yield 1.0 g. (60%). For analysis the product was recrystallized from dilute ethanol to give yellowish prisms, dec. >300°.

Anal. Calcd. for $C_5H_8N_4OS$: C, 34.9; H, 4.7. Found: C, 35.2; H, 4.7.

3-Methyl-6-thiouric acid (IIIb). An intimate mixture of the diamine (IIb) (0.3 g.) with urea (0.45 g.), was heated to 180–195° for 20 min. The solid cake was dissolved in 5% sodium hydroxide, treated with charcoal, and the product precipitated by acidification with hydrochloric acid. Purification was effected by redissolving in sodium hydroxide and acidification with glacial acetic acid. Pure IIIb consists of yellowish needles, which decompose >300°; yield 0.3 g. (75%).

Anal. Calcd. for $C_6H_6N_4O_2S$: C, 36.3; H, 3.0; N, 28.3. Found: C, 36.2; H, 3.1; N, 28.4.

2,4-Dithio-5,6-diaminopyrimidine (IIc). 2-Mercapto-4-hydroxy-5,6-diaminopyrimidine (Ic)[9] (3.0 g.) and phosphorus pentasulfide (9.0 g.) in pyridine (150 ml.) were heated as described for IIa. Acidification of a solution of crude IIc in 5% sodium hydroxide with glacial acetic acid gave golden prismatic needles; yield 2.4 g. (73%). The product proved identical with the product obtained from 2,4-dichloro-5-nitro-6-aminopyrimidine.[10]

2,6-Dithiouric acid (IIIc). Cyclization of IIc (0.5 g.) with urea (0.75 g.), as described above, gave 0.4 g. (69%) of yellow needles, dec. >300° The product was identical in every respect with the one described by Elion, *et al.*[5]

1,2-Dihydro-1-methyl-2-thio-4-hydroxy-5,6-diaminopyrimidine (Id).[14] The method used deviates from the original procedure of Traube and Winter,[14] but gives better yields. 1,2-Dihydro-1-methyl-2-thio-4-hydroxy-6-aminopyrimidine (4.2 g.) was dissolved in 5% sodium hydroxide (42 ml.), then sodium nitrite (2.3 g.) was added, and the mixture heated to 40°. Under continuous stirring, glacial acetic acid (45 ml.) was added slowly, the bath temperature raised to 75° for 2

(12) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

(13) We have observed that aqueous solutions of IIIc decompose, when standing at room temperature for about half an hour, as recognized by increasing turbidity. Therefore, spectral measurements require always the use of freshly prepared solutions.

(14) W. Traube and F. Winter, *Arch. Pharm.*, **244**, 11 (1906).

(15) A gift of Oldbury Electro-Chemical Co., Niagara Falls, N. Y.

hr. and to 100° for 10 min. After cooling, the greenish-violet 5-nitroso derivative was filtered and, while still wet, was added portionwise with stirring to 80 ml. of water, kept at 60–70°. Alternating with the nitroso compound, portions of sodium hydrosulfite were added in such a manner that complete reduction of each charge was effected before introduction of a fresh lot of nitroso derivative. Upon cooling, the yellowish diamine (Id) crystallized in polyhedric prisms, m.p. 278–280°; yield 3.5 g. (76%).

1,2-Dihydro-1-methyl-2,4-dithio-5,6-diaminopyrimidine (IId). Thiation of Id (2.0 g.) with phosphorus pentasulfide (7.0 g.) in pyridine (100 ml.) was carried out by the method described above. IId was obtained in yellow, prismatic needles, which decomposed above 300°; yield 1.9 g. (87%).

Anal. Calcd. for $C_5H_8N_4S_2$: C, 31.9; H, 4.3. Found: C, 32.4; H, 4.5.

3-Methyl-2,6-dithiouric acid (IIId). Ring closure with urea was carried out as described above. By reprecipitation with 5% sodium hydroxide and acetic acid, yellow plates decomposing above 300° were obtained; yield 85%.

Anal. Calcd. for $C_6H_6N_4OS_2$: N, 26.2. Found: N, 26.1.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE DIVISION OF PHYSICAL SCIENCES, UNIVERSITY OF CALIFORNIA AT RIVERSIDE]

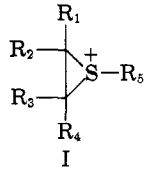
Stereochemistry of the Desulfurization of Thiiranes with Methyl Iodide[1]

GEORGE K. HELMKAMP AND DAVID J. PETTITT[2]

Received April 11, 1960

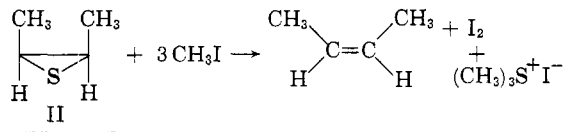
The reaction of isomers of 2,3-dimethylthiirane with methyl iodide results in the formation of 2-butene, with greater than 97% stereoselective desulfurization.

The reaction of thiiranes with methyl iodide leads to the formation of trimethylsulfonium iodide,[3,4] but little information has been given in literature concerning the olefin formed in the reaction.[5] This desulfurization has been investigated with regard to its stereochemistry, since a probable cyclic sulfonium intermediate (I) was of interest for studying generalized thiirane ring-openings.



I

When *cis*-2,3-dimethylthiirane (II) was treated with methyl iodide in refluxing acetone, *cis*-2-butene, iodine, and trimethylsulfonium iodide were formed in approximately equivalent amounts. The progress of such reactions was usually determined by gravimetric analysis of the sulfonium halide which precipitated from solution. Although yields of butene and iodine were occasionally higher than that of the salt, measurements of butene were limited to volume estimations, and titration or photometric methods for iodine were somewhat unsatisfactory because of chemical instability of the acetone solutions. Yields of sulfonium iodide varied from about 15% to 40%, the higher values arising from low methyl iodide/thiirane ratios in the reaction mixtures.



II

The entire reaction sequence involved the conversions *cis*-2-butene→*meso*-2,3-dimethyloxirane (*meso*-2,3-epoxybutane)→*cis*-2,3-dimethylthiirane →*cis*-2-butene. Trace chromatographic analysis showed less than 0.2% *trans*-2-butene in the starting olefin and only 1.6% in the final product. In a somewhat parallel synthetic sequence, the *meso*-epoxide was prepared from recrystallized *meso*-2,3-butanediol, and the final olefin was found to contain 3.0% *trans*-2-butene. The results of reactions of *meso*- and DL-isomers are given in Table I. The processes appear to have a high degree of stereospecificity, for the small amount of con-

TABLE I

PRODUCTS OF DESULFURIZATION OF 2,3-DIMETHYLTHIIRANES

Thiirane Isomer	Source of Thiirane	Composition of Butenes, %[a] 1-	*cis*-2-	*trans*-2-
meso	*cis*-2-Butene	0	98.4	1.6
meso	*meso*-2,3-Butanediol	0	97.0	3.0
DL	Epoxide distilled from mixed isomers[b]	1.0	0.6	98.4

[a] Infrared spectra of the butenes showed no trace of isobutylene. [b] Low-boiling fraction of Dow Chemical Co's Butylene Oxides S.

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund.

(2) Taken in part from the B.A. thesis of David J. Pettitt, University of California at Riverside.

(3) M. Delépine and P. Jaffeux, *Compt. rend.*, **172**, 158 (1921).

(4) C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, **1949**, 284.

(5) R. D. Schuetz and R. L. Jacobs, Abstracts of Papers of the Division of Organic Chemistry, April, 1960. Mention is made of the fact that 2-alkoxymethylthiiranes react with methyl iodide to yield an olefinic compound corresponding to the thiirane employed.