stirred into the mercaptan in carbon disulfide maintained in a cooling bath below 30°. After standing for 4 hr., the solvent was evaporated under vacuum and the remaining oil was taken up in ether. The ether solution was stored in a refrigerator and white pillars were obtained from the yellow solution a few days later.

Anal. Calcd. for $C_{26}H_{22}S_4$: C, 67.49; H, 4.79; S, 27.72. Found: C, 68.00; H, 4.86; S, 27.30.

Preparation of II. Yellow needles of II were obtained by recrystallization of the white pillars from ether-petroleum ether (b.p. 33–46°). The analysis and physical properties of II, including ultraviolet spectrum, have been reported.[1,2] The ultraviolet spectrum of I was identical with that of II within experimental error.

Infrared spectra of a series of dibenzhydryl polysulfides and dibenzhydryl ether in the range of potassium bromide were determined by using a Perkin-Elmer 21. Specimens were measured in a potassium bromide disk.

X-ray diffraction patterns of single crystals of I and II were determined by the rotating crystal method. An iron target was used (λ = 1.93728 A), and the radius of the casset was 50 cm. Distances between equatorial line and first layer line and between the former and second layer line were 12 and 27.5 mm. respectively in the case of I, and those of II 18 and 46 mm. respectively.

Acknowledgment. The authors wish to express their thanks to Prof. E. E. Campaigne and Prof. M. Carmack of Indiana Univesrity for their kindness in revising the manuscript. They also are indebted to Dr. T. Imura of University of Osaka Prefecture for his kindness in determining x-ray patterns, and to Dr. T. Kanzawa of Takada Pharmaceutical Industries, Ltd. and Mr. M. Yoshida of University of Osaka Prefecture for determining infrared spectra.

SAKAI CITY, OSAKA, JAPAN

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

S-Alkylmercaptosuccinic Acids as Solid Derivatives of Olefins, Alkyl Bromides, and Mercaptans

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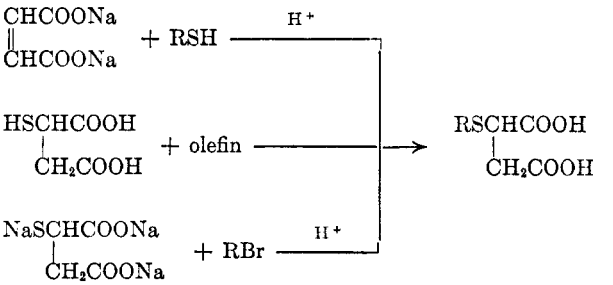
Received March 21, 1960

Solid *S*-alkylmercaptosuccinic acids have been prepared from olefins, mercaptans, and alkyl bromides and their melting points and solubilities have been studied as a function of the structure of the alkyl group. These properties vary with structure in a predictable manner. The acids are satisfactory solid derivatives for primary olefins and mercaptans and both primary and secondary alkyl bromides because of the ease with which the reaction can be effected, the good yields obtained, and the ease of purification. They have the added advantage of being acids; thus their neutralization equivalents may be obtained for confirmatory characterization.

In the present era of instrumental analyses by which compounds are characterized with scarcely a trace of chemistry, it may seem archaic to propose a new reagent for the preparation of a solid derivative to be used as an aid in compound characterization. There are times, however, when a good crystalline derivative is highly desirable, but hard to find. This is especially true with the olefins, mercaptans, and alkyl bromides.

2,4-Dinitrobenzenesulfenyl chloride[2,3] is the most generally useful reagent for olefins[4] and mercaptans.[5] Other reagents which have been proposed include nitrosyl chloride, 4-mercaptobiphenyl,[6] other sulfhydral compounds,[7] and silver 3,5-dinitrobenzoate plus iodine.[8]

The initial purpose of this investigation was to develop a satisfactory solid derivative for liquid olefins. The free radical addition of mercaptosuccinic acid to an olefin appeared to offer several desirable features. The reaction goes readily to give solid derivatives which are acids and can be titrated to confirm their identity. These derivatives also have the added advantage of ready synthesis by two independent methods. They can be formed by the free radical addition of the ap-



(1) Dow Chemical Co. Fellow, 1951–52; American Oil Co. Fellow, 1953–54. Present address: Dow Chemical Co., Freeport, Tex.

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TABLE I

S-ALKYLMERCAPTOSUCCINIC ACIDS

$$R{-}SCHCOOH$$
$$\quad\quad|$$
$$\quad\quad CH_2COOH$$

			Source													
			Olefin		Mercaptan		Bromide			Neut. Equiv.		Analyses				
												Found		Calcd.		
	R	Olefin	Yield, %	M.P.	Yield, %	M.P.	Yield, %	M.P.	Lit., M.P.	Found	Calcd.	C	H	C	H	
C_1	Methyl								133[a]							
C_2	Ethyl								119.5[a]							
									126–128[b]							
C_3	1-Propyl						78	118.4–118.8	118–119[c]							
									112[a]							
C_4	1-Butyl				43	103.7–104.0			144.5[a]			46.45	6.83	46.58	6.84	
	2-Butyl						60	134.9–135.1				46.59	6.86			
	Isobutyl						41	120.9–121.4		102.8	103.1	46.76	6.79			
	tert-Butyl								164[a]							
C_5	1-Pentyl	1-Pentene	85	107.3–107.6	100	107.7–108.0	60	107.0–107.6	99.5[a]			48.86	7.26	49.06	7.32	
	2-Pentyl						50	134.8–135.4		110.0	110.1	49.09	7.09			
	3-Pentyl						39	153.8–154.1				48.84	7.22			
	2-Methylbutyl	2-Methyl-1-butene	85	122.3–122.6								49.18	7.20			
	Isopentyl						65	115.6–116.0	215[a]			48.89	7.13			
	1,2-Dimethylpropyl	2-Methyl-2-butene	75	153.7–154.0								48.87	7.11			
C_6	1-Hexyl	1-Hexene	100	95.4–95.7	79	96.0–96.2	91	96.3–96.5		117.8	117.1	51.41	7.62	51.25	7.74	
	2-Hexyl						31	123.9–125.0				51.53	7.65			
	3-Hexyl						24	143.4–143.5		118.0		51.01	7.78			
	3-Methylpentyl						84	111.9–112.3		117.0		51.01	7.52			
	4-Methylpentyl	4-Methyl-1-pentene	92	102.6–102.9								51.08	7.43			
	1-Isopropylpropyl	2-Methyl-2-pentene	60	152.1–152.6								51.36	7.58			
	2-Ethylbutyl						75	132.4–132.8		117.9		50.15	7.74			
C_7	1-Heptyl	1-Heptene	88	103.4–103.9	82	105.8–106.2				124.2	124.1	52.89	7.99	53.20	8.12	
	2-Heptyl						31	128.0–129.1				52.93	8.11			
	3-Heptyl						21	144.9–145.4				52.37	8.05			
	4,4-Dimethylpentyl	4,4-Dimethyl-1-pentene	90	119.0–119.5								53.22	8.13			
	1-Methyl-2-ethylbutyl	3-Ethyl-2-pentene	45	148.9–149.9								53.14	7.84			
C_8	1-Octyl	1-Octene	96	96.1–96.6					81[a]	133.1	131.2	54.98	8.36	54.93	8.45	
	2-Octyl						50	128.0–129.0				54.68	8.19			
	3-Octyl	2-Octene	94	142.9–143.5						131.7		54.58	8.17			
	2-Ethylhexyl	2-Ethyl-1-hexene	81	101.9–102.7			59	103.7–104.2		128.5		54.66	8.37			

TABLE I (*Continued*)

	R	Olefin	Source: Olefin Yield, %	Source: Olefin M.P.	Source: Mercaptan Yield, %	Source: Mercaptan M.P.	Source: Bromide Yield, %	Source: Bromide M.P.	Lit., M.P.	Neut. Equiv. Found	Neut. Equiv. Calcd.	Analyses Found C	Analyses Found H	Analyses Calcd. C	Analyses Calcd. H
	2-Cyclohexylethyl						47	126.3–126.8		130.4	130.1	55.21	7.71	55.37	7.74
C_9	1-Nonyl				85	105.0–106.0	43	105.0–105.5	103–105[d]	137.0	138.1	56.55	8.54	56.47	8.75
	3-Phenylpropyl				98	114.9–115.7				133.6	134.1	57.89	5.87	57.76	5.78
C_{10}	1-Decyl	1-Decene	82	93.5–93.8						145.5	145.2				
C_{11}	1-Undecyl						37	110.4–110.6	104–105[d]			58.99	9.13	59.18	9.27
C_{12}	1-Dodecyl								97.5[a] 102–103[d]						
C_{14}	1-Tetradecyl	1-Tetradecene	76	104.0–104.8					103–104[d]	174.8	173.5				
C_{16}	1-Hexadecyl	1-Hexadecene	84	105.0–105.8					105–106.5[d]	188.6	187.0				
C_{18}	1-Octadecyl				100	102–103			103–104[d]						
Cyclic Compounds															
C_5	Cyclopentyl	Cyclopentene	75	142.8–143.1						110.2	109.3	49.03	5.91	49.51	6.46
C_6	Cyclohexyl	Cyclohexene	83	150.5–151.1			9	149.0–149.9	148.0–148.5[e]	116.5	116.1				
C_7	2-Methylcyclohexyl	2-Methylcyclohexene	73	187.0–187.3								53.66	7.27	53.63	7.36
	4-Methylcyclohexyl				6	148.7–149.3						53.43	7.10		
Miscellaneous Compounds															
	Benzyl				97	188.4–188.9			189–190[f] 192[g]	115.2	113.0				
	p-Chlorophenyl								163–164[h]						
	3-Thienyl								130–131[i]						
	3-Chloropropyl	Allyl chloride	35	108.5–108.8						113.6	113.3	37.37	4.80	37.09	4.89

[a] W. B. Chilcote, U. S. Patent **2,481,514** (1952). [b] P. Fitger, *Ber.*, **54B**, 2945 (1921). [c] M. Mantell, *Arkiv Kemi*, **3**, 129 (1951). [d] V. C. Berry, L. O'Rourke, and D. Towmey, *Proc. Roy. Irish Acad.*, **51B**, 223 (1947). [e] B. Weibull, *Arkiv Kemi, Mineral. Geol.*, **23-A**, No. 18, 1947, 25 pp. [f] K. D. Gundermann, *Chem. Ber.*, **90**, 72 (1957). [g] J. L. Szabo and E. T. Stiller, *J. Am. Chem. Soc.*, **70**, 3667 (1948). [h] E. W. Bousquet, U. S. Patent **2,434,100** (1948). [i] J. W. Brooks, E. G. Howard, and J. J. Wehrle, *J. Am. Chem. Soc.*, **72**, 1289 (1950).

propriate mercaptan to disodium maleate and by the reaction of an alkyl bromide and the trisodium salt of mercaptosuccinic acid. These same reactions are also useful for the preparation of solid derivatives of alkyl bromides and mercaptans.

The various *S*-alkylmercaptosuccinic acids prepared during this investigation and their physical properties are given in Table I.

Olefins. Prior to this work, cyclohexylmercaptosuccinic acid was the only olefin derivative of mercaptosuccinic acid obtained directly from the olefin.[9] This derivative was prepared by refluxing the olefin and mercaptosuccinic acid dissolved in acetic acid for ten hours or by irradiating the mixture for 117 hours using ultraviolet light. This did not appear to be a promising method for routine work.

The thermal addition of thioglycolic acid to olefins has been studied by Hoog and Eichwald.[10] The reaction was quantitative with primary olefins but low yields were obtained with highly hindered olefins. The free radical addition of thiolacetic acid to cyclic olefins has been reported by Bordwell and Hewett.[11]

The addition of mercaptosuccinic acid to olefins was initiated by various compounds capable of furnishing free radicals under the prevailing reaction conditions. The reaction rates as a function of the catalyst were in the order: benzoyl peroxide > ascardole > α,α'-bisisobutyronitrile > peracetic acid. Benzoyl peroxide was used because of its greater catalytic activity. Methanol was the best reaction medium due to the solubility of the reactants in it and its ease of removal from the reaction product.

Good yields of pure adducts were obtained with primary olefins. The 2-alkenes gave a mixture of two products which melted over a range of 5 to 10° between the melting points of the 2-alkyl- and 3-alkylmercaptosuccinic acids. With 2-octene it was possible to isolate the 3-octyl isomer by recrystallization. The more highly hindered olefins such as 2,6-dimethyl-2-heptene and 2,4,4-trimethyl-2-pentene did not react; yet 2-methyl-2-pentene and 3-ethyl-2-pentene gave satisfactory yields. A mixture of equal amounts of 1-octene and 2,4,4-trimethyl-2-pentene gave a good yield of the *n*-octyl derivative. Polymers were formed with styrene, indene, and 2-phenyl-2-butene. Butyl vinyl ether and allyl alcohol apparently reacted, but solid derivatives could not be isolated. The following vinyl halides did not react: 2-chloro-2-butene, 2-bromo-2-butene, 1,3-dichloro-2-butene, and β-bromostyrene. Allyl bromide apparently did not react, but allyl chloride gave a useful product in low yield (35%).

Mercaptans. The formation of *S*-alkylmercaptosuccinic acids by the addition of a mercaptan to disodium maleate followed the general procedure described by Chilcote[12] and Bousquet.[13]

The present study was limited to the primary mercaptans between C_4 and C_7, and nonyl, benzyl, and 3-phenylpropyl mercaptan. The yields were uniformly high. Suitable derivatives could not be obtained from higher molecular weight mercaptans because of emulsion formation. Tertiary mercaptans did not react.

Alkyl bromides. *S*-Alkylmercaptosuccinic acids were obtained from twenty-one primary and secondary alkyl bromides and from two cyclohexyl bromides by reaction with trisodium mercaptosuccinate. The highest yields were obtained from the primary bromides, but satisfactory yields were also obtained from the secondary bromides. Tertiary bromides did not produce products which could be isolated. The two cyclohexyl bromides gave low yields (6% and 9%). The reaction mixtures were refluxed from four to twenty-four hours and the free acid was liberated by concentrated hydrochloric acid.

Recrystallization. The solubility of a number of *S*-alkylmercaptosuccinic acids was determined in toluene at 50°. Some of these solubilities are given in Table II and others are in Fig. 1. The data in Fig. 1 show that the solubility of the *S*-alkylmercaptosuccinic acids is dependent upon the nature of the group attached to the sulfur atom forming the sulfide linkage. The 1-alkyl compounds are about twice as soluble as the 2-alkyl and several times more soluble than the 3-alkyl isomer. This difference in solubility has made it possible to separate 3-octylmercaptosuccinic acid from its mixture with 2-octylmercaptosuccinic acid.

TABLE II

THE SOLUBILITY OF S-ALKYLMERCAPTOSUCCINIC ACIDS IN TOLUENE AT 50.0°

RSCHCOOH
|
CH_2COOH

R	Grams per 100 G. Toluene
1-Propyl	0.30
2-Butyl	0.46
Isobutyl	0.87
2-Methylbutyl	4.00
2-Methyl-2-butyl	0.14
2-Ethylbutyl	2.59
Octadecyl	3.70
Cyclohexyl	0.25
2-Cyclohexylethyl	1.90
3-Chloropropyl	0.67

(9) B. Weibull, *Arkiv. Kemi, Minerali., Geol.*, **23-A**, No. 18, 1947, p. 25.

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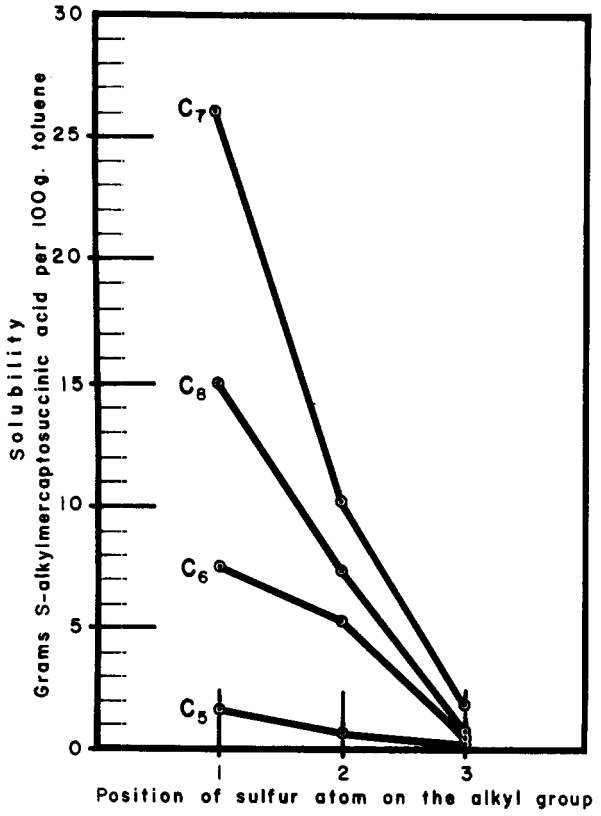

Fig. 1. Influence of the type of alkyl group on the solubility of *s*-alkylmercaptosuccinic acid in toluene at 50.0°C.

The *S*-alkylmercaptosuccinic acids retain both polar and nonpolar solvents very tenaciously. The best results were obtained by dissolving the derivative in diethyl ether and precipitating it with *n*-pentane. Usually one crystallization was sufficient to give an acceptable product, and the overall recovery was about 70%. Compounds with a C_{12} or higher alkyl group were recrystallized from acetic acid. About twenty milliliters of solvent was used per gram of solid.

Melting points. The melting point of an *S*-alkylmercaptosuccinic acid is a function of the position of the substitution on the alkyl group (Fig. 2). The *n*-alkyl compounds have a melting point range of about 95° to 110°; the 2-alkyl isomers have a melting point range between 125° and 135° and the 3-alkyl isomers have a melting point range between 142 and 153°. There is the expected variation in melting points of the straight-chain alkyl compounds with change in carbon content. Those with odd number of carbon atoms melt higher than the next higher, even numbered, homologue. There is also a correlation between melting point and the position of a methyl group on the alkyl group. There is a decrease of 7 to 10° in melting point as the methyl group moves from the 2 to 3 to 4 positions in respect to the carbon-sulfur linkage.

The cycloalkylmercaptosuccinic acids have a melting point range of 142 to 153° when there are no alkyl groups adjacent to the carbon-sulfur linkage. 2-Methylcyclohexylmercaptosuccinic acid has a melting point of 181°. 2-Cyclohexylethylmercaptosuccinic acid, however, melts at 117°.

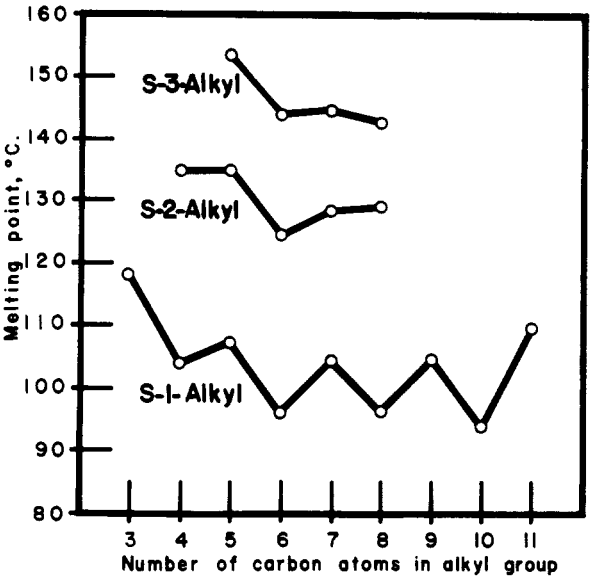

Fig. 2. Melting points of homologous *S*-alkylmercaptosuccinic acids

Many of the melting points of the *S*-alkylmercaptosuccinic acids reported by Chilcote[12] are incorrect (Table I).

EXPERIMENTAL

All melting points were taken using conventional melting point apparatus with calibrated Anschutz thermometers. All the reagents were commercial grade and used without further purification.

Olefins. Two grams of mercaptosuccinic acid and 3 ml. of methanol were heated in a 10 × 75 mm. test tube until the acid had completely dissolved. The solution was cooled and 1.00 ml. of olefin plus 0.10 g. of benzoyl peroxide were added. The test tube was tightly stoppered with a cork and shaken vigorously for 5 min. Because the olefin and methanol solution initially formed a two phase system, it was necessary to use vigorous shaking to insure a high yield of derivative. The test tube was then allowed to stand at room temperature until the desired amount of product had been formed. The crude crystals were washed into a 4 oz. bottle with 25 ml. of water and then treated with 25 ml. of 6*N* hydrochloric acid. The yield of product from this initial isolation was 1.3 to 1.9 g.

The crystals were recovered by vacuum filtration and washed with 25 ml. of 3*N* hydrochloric acid. They were dried for 15 min. on the filter and then for 12 hr. at room temperature. One gram of the derivative was dissolved at room temperature in 10 to 15 ml. of diethyl ether; then, *n*-pentane was added until turbidity resulted. After approximately 10% of the anticipated total amount of derivative had crystallized, the material was filtered and the crystals discarded. *n*-Pentane was then added to the filtrate until essentially all of the derivative had crystallized. These crystals were filtered and were sufficiently pure for melting point determinations and analyses.

Mercaptans. The following materials were placed in a 50 ml. Erlenmeyer flask: 20 ml. of 1.0*M* disodium maleate, 2.0 ml. of ethyl alcohol, 1.00 ml. of the mercaptan, and three or four boiling chips. The flask was equipped with a snugly fitting finger condenser and the contents were refluxed for 2 to 4 hr. After the reaction mixture was cooled, the lower

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]

GERSHON LEVIN,[2] ABRAHAM KALMUS, AND FELIX BERGMANN

Received February 15, 1960

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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