Title

SYNTHESIS OF POTENTIAL CANCER-INHIBITING AGENTS I. 2,6-DIAMINO- [3 ',2 ' -h] - THIAZOLINOPURINES

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I. 2,6-DIAMINO-[3',2'-h]-THIAZOLINOPURINES

Maxwell Gordon

June 1, 1950

Berkeley, California

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ABSTRACT

SYNTHESIS OF POTENTIAL CANCER-INHIBITING AGENTS

I. 2,6-DIAMINO-[3',2'-h]-THIAZOLINOPURINES *

by

Maxwell Gordon

Radiation Laboratory
University of California, Berkeley **

ABSTRACT

June 1, 1950

1. The following new derivatives of 2,6-diaminopurine have been prepared: 8-mercapto-, 8-acetonylmercapto-, 8-carboxymethylmercapto-, and 8-carbethoxymethylmercapto-2,6-diaminopurine.

2. The synthesis of 2,6-diamino-4'-methyl-[3',2'-h]- thiazolinopurine has been described and a route to 2,6-diamino-[3',2'-h]- thiazolinopurine has been indicated.

3. 2,6-Diamino-8-hydroxypurine has been prepared by an improved procedure.

4. Ultraviolet spectra of the above compounds have been measured in acid, neutral, and alkaline solutions.

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** The work described in this paper was sponsored by the Atomic Energy Commission.

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SYNTHESIS OF POTENTIAL CANCER-INHIBITING AGENTS

I. 2,6-DIAMINO-[3',2'-h]-THIAZOLINOPURINES *

by

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(2) Present address: Organic Chemistry Department, Imperial College of Science and Technology, London S.W. 7, England.

Various investigators[3] have reported that the concentration

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(3) Stowell, "Symposia of the Society of Experimental Biology. I. Nucleic Acids", 190 (1947). A review.

---

of nucleic acids in tumor-bearing animals is greater than in normal animals. From these results we[4], among others, postulated that

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(4) Gordon and Day, "The Chemistry of Purines and Nucleic Acids", a chapter in "Heterocyclic Compounds, Vol. III", edited by R. C. Elderfield, John Wiley and Sons, Inc., New York, in press.

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* The work described in this paper was sponsored by the Atomic Energy Commission.

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purine, specifically adenine and guanine, inhibitors could be found which would retard tumor growth. Hitchings[5] and Burchenal[6] have

(5) Hitchings, et.al., J.Biol.Chem., 174, 765 (1948).

(6) Burchenal, et.al., Cancer, 2, 119 (1949).

demonstrated the adenine inhibition of 2,6-diaminopurine, which was originally postulated by Brown[7] to be an intermediate in the

(7) Bendich and Brown, J.Biol.Chem., 176, 1471 (1948).

biosynthesis of guanine.

Hitchings[8] and Kidder[9] showed the anti-metabolite action

(8) Hitchings, et.al., Federation Proceedings, 7, 160 (1948).

(9) Kidder, et.al., Science, 109, 511 (1949).

of 8-azaguanine (called guanazolo by Kidder). From his results with mice Kidder has postulated[9] that all tumor cells may differ from ordinary cells in that the former metabolize guanine while the latter

do not[10,11]. Recent work[12], as well as earlier studies[10,11,13],

(10) Plentl and Schoenheimer, J.Biol.Chem., 153, 203 (1944).

(11) Brown, Roll, Plentl, and Cavalieri, ibid., 172, 469 (1948).

(12) Brown, et.al., Proc.Soc.Exptl.Biol., 72, 501 (1949).

(13) Kidder and Dewey, Proc.Nat.Acad.Sci., 34, 566 (1948).

shows that guanine utilization is subject to species specificity.

The only other compounds of any great promise in cancer chemotherapy are the nitrogen mustards[14] and folic acid derivatives[15],

(14) Wintrobe and Huguley, Cancer, 1, 357 (1948). A review.

(15) Law, J.Nat.Cancer Inst., 10, 179 (1949); Skipper, Cancer, 3, 348 (1950). Reviews.

both of which may act through purine inhibition[15,16].

(16) Young and Campbell, Can.J. Research, 25B, 37 (1947).

In our work it was thought to be of interest to prepare a series of purine analogs in which ribylation at the 7- and 9- positions is blocked, and in which ribylation might take place at other points in the molecule, in order to find compounds of greater cancer-inhibiting action than those described above.

An investigation of the literature showed that considerable demethylation of alkyl purines probably occurs in the metabolism of caffeine and other alkyl xanthines[17], so the use of purines for this study in

(17) Meyers and Hanzal, J.Biol.Chem., 162, 309 (1946).

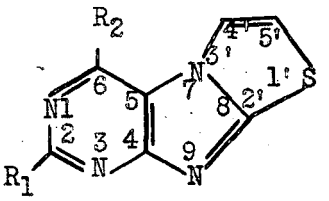
which the 7- or 9- positions was blocked by an alkyl group was ruled out.

It appeared probable that blocking could be more effectively accomplished by use of a fused ring system, and the [3',2'-h] -thiazolinopurines (I) hitherto prepared only by Todd[18], who synthesized a xanthine

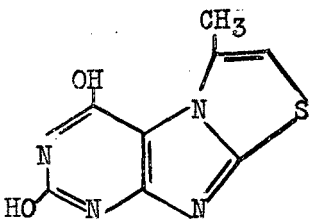
(18) Todd and Bergel, J.Chem.Soc., 1559 (1936).

homolog(II), and by Ochiai[19], who prepared a [3',2'-h] -thiazolinotheophylline (III), were thought to offer possibilities. Accordingly, a program was undertaken directed toward the synthesis of some thiazolino derivatives of 2,6-diaminopurine (I) ($R_1, R_2 = NH_2$). The results are recorded in this paper.

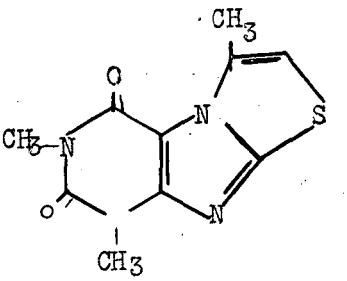
(19) Ochiai, Ber., 69B, 1650 (1936).



(I)



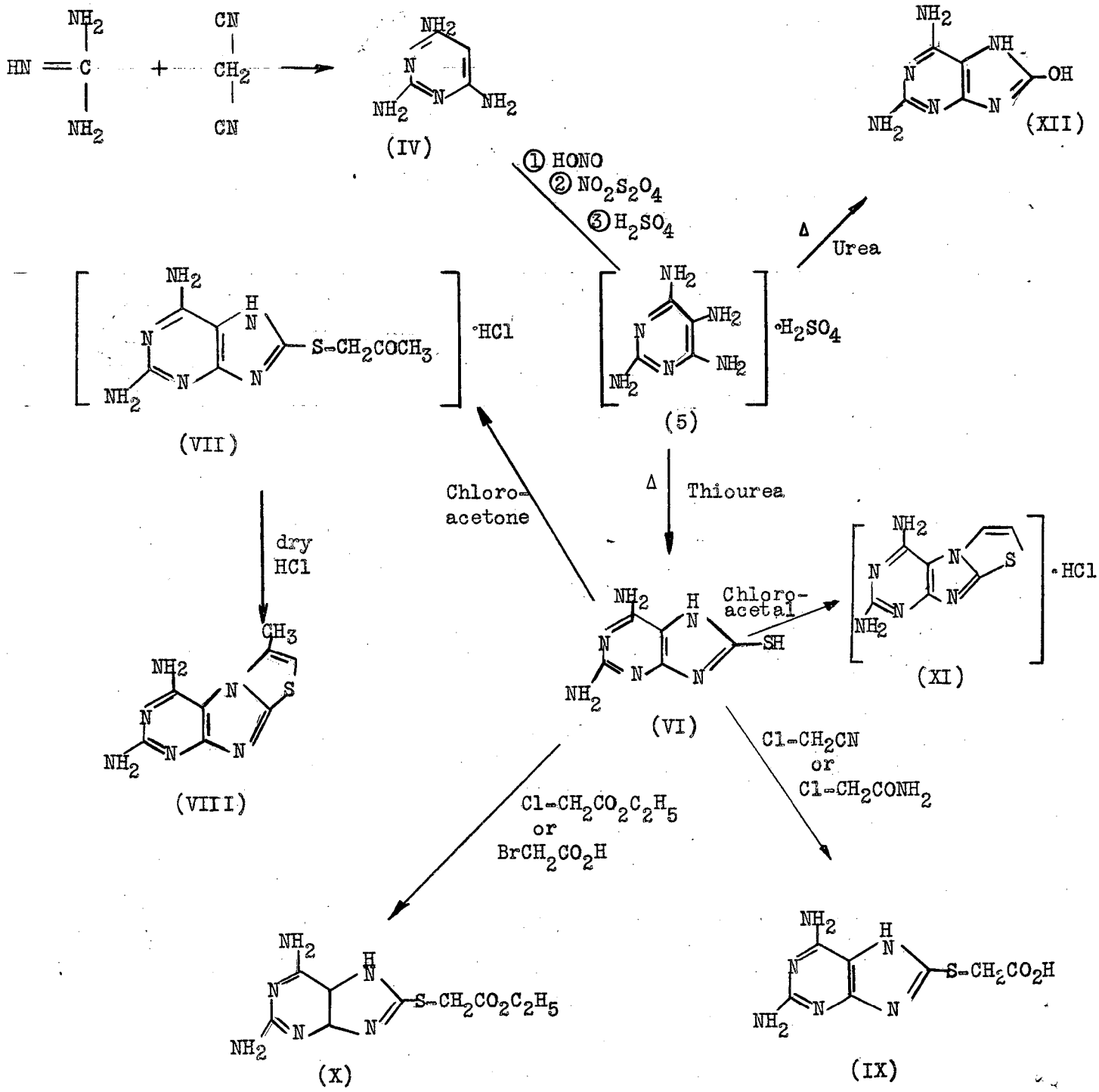
(II)



(III)

The thiazolino derivatives of adenine (R_1 = H; R_2 = NH_2), guanine (R_1 = NH_2; R_2 = OH), and isoguanine (R_1 = OH; R_2 = NH_2) are also being synthesized in this laboratory and will be made the subject of later communications.

The syntheses recored in this paper were carried out according to the scheme recorded below. All purines shown, with the exception of the 8-hydroxy compound, are believed to be hitherto unreported in the literature.


(IV)
(XII)
① HONO
② $NO_2S_2O_4$
③ H_2SO_4
Δ Urea
(5)
(VII)
·HCl
·H_2SO_4
Chloro-acetone
Δ Thiourea
dry HCl
(VIII)
(VI)
Chloro-acetal
(XI)
·HCl
$Cl-CH_2CN$ or $Cl-CH_2CONH_2$
$Cl-CH_2CO_2C_2H_5$ or $BrCH_2CO_2H$
(X)
(IX)

It is apparent that in the cyclization of VII ring closure may take place to either the 7- or 9-positions of the purine. Todd[18] and Ochiai[19] both reported their thiazolino compounds to be 7,8-derivatives, without giving any evidence for this structure. Based on the u/v spectrum, we have also made the 7,8- (or h-) thiazolinopurine assignment. Gulland and Story[20] determined the position of attachment of the sugar in

(20) Gulland and Story, J.Chem.Soc., 692 (1938).

nucleosides on the basis of the similarity of their u/v spectrum to that of 9-methylxanthine, in contrast to 7-methylxanthine. In a like manner it can be seen from our ultraviolet data of VIII that the alkaline spectrum has two peaks, like 9-methylxanthine, whereas 7-methylxanthine has only one peak in the ultraviolet.

Experimental[21]

(21) All melting points are corrected.

2,4,6-Triaminopyrimidine (IV). - This compound was prepared by the Mallette, Taylor, and Cain[22] modification of the Traube[23] synthesis.

(22) Mallette, Taylor, and Cain, J.Am.Chem.Soc., 69, 1814 (1947).

(23) Traube, Ann., 331, 64 (1904).

The sulfate was isolated in white prisms by crystallizing the crude product from 2N sulfuric acid, m.p. 263-265°. It is soluble in water and insoluble in organic solvents. The acetate has a m.p. of 216-218° and is unstable.

Anal. Calcd. for $C_4H_7N_5 \cdot H_2SO_4$: C, 21.52; H, 4.06; N, 31.38; S, 14.36. Found: C, 21.75; H, 4.01; N, 31.27; S, 14.58.

Ultraviolet Spectrum. ($c = 5.2 \times 10^{-5}$ moles/l.)

		Min.	Max.	
pH = 2.0	mμ	236-248 (Infl.)	273	
	ϵ	2500	18,900	
pH = 6.5	mμ	248	272	
	ϵ	2790	15,100	
pH = 9.2	mμ	247	267	Infl. at 235-239
	ϵ	2980	10,500	3270

2,4,5,6-Tetraaminopyrimidine Sulfate (V). - This compound was prepared according to previously published directions[22], except that only about one-eighth of the amount of sodium hydrosulfite reported was required to reduce the nitroso compound. The sulfate was obtained by recrystallizing the reduction product from 2N sulfuric acid, giving white plates or prisms, depending on the concentration, no m.p. $< 300^{\circ}$. The sulfate is soluble in hot water and relatively insoluble in cold water and organic solvents. The hydrochloride separates in nearly colorless needles from 2N hydrochloric acid and it is quite soluble in water and alcohol, no m.p. $< 300^{\circ}$. A picrate forms with equal amounts of picric acid in the form of yellow needles, no m.p. $< 300^{\circ}$.

Anal. Calcd. for $C_4H_8N_6 \cdot H_2SO_4 \cdot 2H_2O$: C, 17.53; H, 5.15; N, 30.67; S, 11.67. Found: C, 17.76; H, 5.07; N, 30.83; S. 11.97.

Ultraviolet Spectrum. ($c = 5.04 \times 10^{-5}$ moles/l.)

		Min.	Max.	
pH = 1.9	mμ	243	271	
	ϵ	4760	18,800	
pH = 6.6	mμ	235	279	Infl. at 252
	ϵ	5480	13,300	7150

2,6-Diamino-8-mercaptopurine (VI). - 5.0 G. of V (0.0275 moles) and 8.0 g. of thiourea (0.105 moles) were powdered together and heated in an open ignition tube in an oil bath under a carbon dioxide atmosphere for 25 minutes at a bath temperature of 190-195°. The reaction mixture was stirred occasionally. After five minutes of heating the

reaction mixture melted to a clear amber fluid and copious evolution of ammonia began. At the end of 20 minutes of heating the mixture resolidified to a brownish-yellow paste. After cooling, the product was boiled with 25 cc. of water to remove unreacted thiourea, then filtered. The yield of crude product was quantitative and it was pure enough to be used for the next step in the synthesis. For analysis the product was dissolved in the minimum amount of dilute ammonia and reprecipitated with acetic acid to give pale yellowish-brown masses which charred without melting when heated on a spatula. The product is insoluble in organic solvents. VI-Hydrochloride was obtained in white microcrystals by dissolving 1.0 g. of free base in 100 cc. of hot 2N hydrochloric acid and decolorizing with charcoal; the hydrochloride did not melt on a spatula.

Anal. Calcd. for $C_5H_6N_6S$: C, 32.96; H, 3.32; N, 46.13; X, 17.59. Found: C, 33.04; H, 3.25; N, 46.35; S, 17.34.

Ultraviolet Spectrum. ($c = 2.29 \times 10^{-5}$ moles/l.) (hydrochloride)

		Min.	Max.	Min.	Max.	
pH = 2.2	mμ	227	265	291	326	
	ϵ	6770	15,900	4800	19,700	
pH = 7.1	mμ	250	261	278	310	Infl. at 227
	ϵ	7640	8730	4590	20,100	and 240 mμ.
pH = 9.6	mμ	215	218	278	308	
	ϵ	17,200	17,900	6110	17,500	

2,6-Diamino-8-acetonylmercaptopurine Hydrochloride (VII). - 10.0 G. of VI (0.0556 moles), well powdered, was suspended in 250 cc. of 95% ethanol, 5.2 cc. (0.065 moles) of chloroacetone was added and the

mixture was refluxed for 24 hours. The volume was gradually increased to 700 cc. with ethanol and an additional gram of chloroacetone was added after 24 hours. After a total of 43 hours of refluxing only a few white lumps remained out of solution. The pale brown solution was decolorized with charcoal to give a nearly colorless solution which deposited masses of white ill-defined plates, 8.1 g., m.p. 204-205° (d.) with frothing. The melting point varies somewhat with the rate of heating, but it is constant in a sealed evacuated capillary. Recrystallization from water or alcohol does not alter the m.p.

Evaporation and prolonged cooling of the mother liquor produced an additional 4.5 g. of VII. The total yield was 84%. The product is quite soluble in water and alcohol, and insoluble in ether, acetone, benzene, ethyl acetate, hexane, carbon tetrachloride, chloroform, and dioxane. It formed a dinitrophenylhydrazone, m.p. 235-236° (d.).

Reaction of chloroacetone with VI-hydrochloride, instead of with the free base, gives a slightly higher yield of product which needs no purification.

Anal. Calcd. for $C_8H_{10}ON_6S \cdot HCl$: C, 34.97; H, 4.04; N, 30.59; S, 11.67. Found: C, 34.66; H, 3.86; N, 30.27; S, 11.74.

Ultraviolet Spectrum. ($c = 1.67 \times 10^{-5}$ moles/l.)

		Min.	Max.	Min.	Max.	Min.	Max.
pH = 2.3	mμ	215	220	254	264	276	302
	ϵ	19,200	20,500	7780	8080	7490	18,000
pH = 7.1	mμ	216	220	244	257	271	296
	ϵ	25,700	26,600	7180	8380	7780	16,200
pH = 9.6	mμ	214	221			268	297
	ϵ	24,600	26,400			6290	16,200

2,6-Diamino-4'-methyl-[3',2'-h] - thiazolinopurine (VIII). - 1.0 G. of VII (0.00365 moles) was refluxed with 100 cc. of absolute ethanol with exclusion of water, then dry hydrogen chloride was passed in for five minutes, at the end of which time total solution had been effected. The hydrogen chloride was then turned off and the solution was refluxed for 3.5 hours. A turbidity developed at the end of 0.5 hour and continued to increase on heating. The suspension was filtered hot to give 0.8 g. of white solid (VIII-hydrochloride), m.p. 291-293° (d.). The product is soluble in ethanol and water, and insoluble in acetone, benzene, and dry ether. An additional 100 mg. of product was isolated from the mother liquor; total yield 95%. 100 Mg. of the product was recrystallized from 10 cc. of hot water to give, after a few hours of standing, a quantitative recovery of fine needles, m.p. 288-290° (d.). Analysis shows the hydrochloride to contain between one and two moles of acid. Dissolving VIII-hydrochloride in hot water and making it alkaline with ammonia results in precipitation of the free base VIII in pearly microcrystals, m.p. 288-289° (d.).

Anal. Calcd. for $C_8H_8N_6S$: C, 43.62; H, 3.66; N, 38.16; S, 14.56. Found: C, 43.64; H, 3.49; N, 38.06; S, 14.80.

Ultraviolet Spectrum. ($c = 2.72 \times 10^{-5}$ moles/l.)

		Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
pH = 1.7	mμ	227	253	268	281	286	290	302	318
	ε	9000	28,900	9930	12,700	12,100	12,500	7900	9560
pH = 6.7	mμ	228	240	260	285				
	ε	20,800	23,000	8460	15,300				
pH = 9.2	mμ	228	239	259	285				
	ε	21,300	23,200	8090	15,300				

Attempts to cyclize VII by means of phosphorus oxychloride or thionyl chloride, or by means of heat alone, were unsuccessful, resulting in destruction of the product in the first and third cases and recovery of some unreacted starting material in the second.

2,6-Diamino-8-carboxymethylmercaptopurine (IX). -

(a) 1.0G. of VI (0.00556 moles) was suspended in 50cc. of 95% ethanol and 0.76 cc. of chloroacetonitrile (0.012 moles) was added and the mixture refluxed for 88 hours. The brown product obtained was recrystallized from dilute hydrochloric acid and decolorized with charcoal. 350 Mg. of a white powder was obtained which did not melt $< 300^{\circ}$ and was insoluble in water and organic solvents, but soluble in alkali.

(b) 1.0 G. of VI and 1.22 g. (0.0130 moles of chloroacetamide were refluxed together for 96 hours in 50 cc. of 95% ethanol. The suspended matter was filtered off to give 0.9 g. of a dirty white product. This was dissolved in dilute ammonia and reprecipitated with acetic acid to give 0.75 g. of IX.

Anal. Calcd. for $C_7H_8O_2N_6S$: S, 13.34. Found: S, 13.56.

Ultraviolet Spectrum. ($c = 2.37 \times 10^{-5}$ moles/l.)

	Min.	Max.	Min.	Max.	Min.	Max.
pH = 2.0 mμ	214	220	Infl. 241-264		277	301
ϵ	17,900	19,000	9280		8220	17,100
pH = 6.9 mμ	216	218	244	257	272	297
ϵ	26,200	26,400	8440	9280	8230	16,200
pH = 9.3 mμ	214	220			270	298
ϵ	22,800	24,100			6540	16,000

Attempts to cyclize IX by means of refluxing with phosphorus oxychloride or with dry hydrogen chloride in ethanol resulted in isolation of unreacted starting material in every case.

2,6-Diamino-8-carbethoxymethylmercaptopurine (X). -

(a) 1.0G. of VI (0.00556 moles) was refluxed with 2.4 g. of ethyl chloroacetate (0.0195 moles) for 85 hours in 50 cc. of 95% ethanol. Solution was effected and the color was a clear amber at the end of that time, so the solution was decolorized and allowed to cool. 0.85 G. of pearly white masses with a slight mercaptan odor were filtered off, X-hydrochloride, m.p. 222-224° (d.) with rapid heating. The mother liquor gave an additional 150 mg. of product, giving a total yield of about 60%.

(b) 1.0 G. of VI was refluxed with 0.9 g. of bromoacetic acid (0.0065 moles) in 80 cc. of 95% ethanol for 43 hours and then filtered hot. The filtrate was reduced in volume to 40 cc. and on standing several hours 0.5 g. of pearly white masses deposited, X-hydrobromide, m.p. 222-224° (d.). Esterification had obviously taken place in the course of the coupling reaction. The product is soluble in alcohol and water and insoluble in benzene.

Anal. Calcd. for $C_9H_{12}O_2N_6S \cdot HBr$: C, 30.95; H, 3.75; N, 24.07; S, 9.18. Found: C, 31.17; H, 3.85; N, 24.45; S, 9.28.

Calcd. for $C_9H_{12}O_2N_6S \cdot HCl$: C, 35.48; H, 4.27; Cl, 11.64. Found: C, 35.15; H, 4.13; Cl, 11.78.

The ultraviolet spectrum of X-hydrochloride is identical with that of IX. The spectrum of the X-hydrobromide is qualitatively also identical; the extinction coefficients of the maxima of the hydrobromide are slightly higher than those of the hydrochloride.

Attempts to cyclize these esters by the methods described under IX above were likewise unsuccessful.

2,6-Diamino-[3',2'-h]-thiazolinopurine (XI). - Reaction of chloroacetal with VI results in a yellow product whose ultraviolet spectrum is different from that of VI. Its spectrum has the double peak noted in the case of VIII, and the peak in the neighborhood of 260 mμ is much higher than that at about 325 mμ. This compound could not be purified sufficiently to give a satisfactory analysis, despite repeated attempts. No intermediate thioglycolaldehyde could be isolated.

Attempts to form thiazolinopurines by the reaction of VI with 1,2-dibromoethylene or with phenacyl chloride were unsuccessful.

2,6-Diamino-8-hydroxypurine (XII). - This compound was originally prepared by Fischer[24] from uric acid by treatment with phosphorus

(24) Fischer and Ach, Ber., 30, 2208 (1897).

oxychloride and then aqueous ammonia. It is obtained in better yield in the following procedure:

3.0 G. of V was ground with 5.0 g. of urea and heated in an ignition tube, under a stream of carbon dioxide, immersed in an oil bath at 150-155° for 20 minutes. The mixture melted at the end of five minutes and resolidified after 20 minutes. The melt was boiled with 25cc of water and filtered and washed with alcohol to give 0.85 g. of XII. Additional product can be obtained from the mother liquor by precipitation with alcohol. XII was recrystallized from 2N hydrochloric acid to give long colorless needles of XII-hydrochloride which decomposed on heating without melting.

Anal. Calcd. for $C_5H_6ON_6 \cdot HCl \cdot 1/2H_2O$: N, 39.68; Cl, 16.73.
Found: N, 39.88; Cl, 16.77.

Ultraviolet Spectrum. ($c = 5.33 \times 10^{-5}$ moles/l.)

		Min.	Max.	Min.	Max.
pH = 2.1	mμ	230	247	272	305
	ε	3750	7880	1400	11,100
pH = 6.8	mμ	233	244	265	290
	ε	5910	7600	3280	9600
pH = 9.1	mμ	235	244	265	291
	ε	6570	7040	3940	10,100

Acknowledgement. - The author is grateful to Prof. Melvin Calvin for his kind encouragement and interest in this project, as well as for providing the facilities for this work. Elemental analyses were performed

by the microanalytical laboratory of the Chemistry Department, University of California.

SUMMARY

1. The following new derivatives of 2,6-diaminopurine have been prepared: 8-mercapto-, 8-acetonylmercapto-, 8-carboxymethylmercapto-, and 8-carbethoxymethylmercapto-2,6-diaminopurine.

2. The synthesis of 2,6-diamino-4'-methyl-[3',2'-h]- thiazolinopurine has been described and a route to 2,6-diamino-[3',2'-h-] thiazolinopurine has been indicated.

3. 2,6-Diamino-8-hydroxypurine has been prepared by an improved procedure.

4. Ultraviolet spectra of the above compounds have been measured in acid, neutral, and alkaline solutions.