

THE DETHIONATION OF
CERTAIN 2-SUBSTITUTED
PURINES AND PYRIMIDINES

by

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THE DETHIATION OF CERTAIN 2-SUBSTITUTED PURINES AND PYRIMIDINES

INTRODUCTION

The cyclization of β -ketoesters, β -diketones, β -ketonitriles, etc., with urea (16, p. 162) 25, p. 537-549) 38, p. 674-677), thiourea (1, p. 674i) 2, p. 2197-2200) 27, p. 345-355) 28, p. 364-372) and amidines (13, p. 361-366) 14, p. 163-164) 35, p. 388-390) 39, p. 2179-2184) 40, p. 61-70) has long been known to yield pyrimidines with various substituents depending upon the choice of intermediates in the 2, 4, 5 and 6 positions.

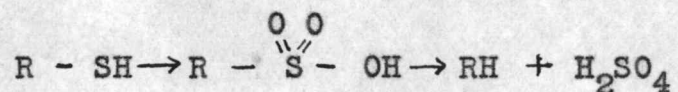
The preparation of pyrimidines with a hydrogen substituent in the 2-position however, has always presented a problem, since the necessary intermediate for such pyrimidines is formamidine which is rather hazardous as well as difficult to prepare. Furthermore it does not always cyclize in the straightforward manner of the other amidines. (10, p. 1148-1157) 11, p. 959-970) 12, p. 970-976) 15, p. 1334-1336)

There have been isolated instances, such as the preparation of pyrimidinedione-4,6 by condensation of ethyl formate with malonodiamide (22, p. 2214), in which 2-unsubstituted pyrimidines have been prepared by direct cyclization. However, it is the replacement reactions in

which the existing 2-substituent is replaced by a hydrogen atom which offers the most promise as an alternate route to such desired products.

A number of different reagents have been employed successfully for the removal of the mercapto substituent. Among those reported in the literature are hydrogen peroxide, nitric acid and Raney nickel.

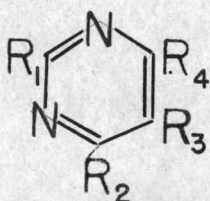
The use of nitric acid for this purpose has been limited to one isolated instance while the peroxide procedure has not been very widely adopted. The mechanism for these dethionations probably involve the oxidation of the mercapto substituent to sulfonic acid following by cleavage of the acid i.e.



That this may be the course of the reaction is supported by the reported isolation of the sulfonic acid intermediate in certain reactions of this type (23, p. 8039f). A summary of the known dethionation using peroxide is enumerated in Table I.

Table I

Dethionation of 2-thiopyrimidines and 2-thiopurines
with hydrogen peroxide

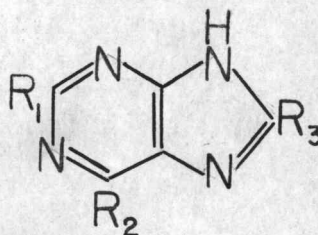


Pyrimidine Compounds

No.	R ₁	R ₂	R ₃	R ₄	%Yield	Reference
1.	SH	OH	H	H	40	44, p. 289
2.	SH	NH ₂	NH ₂	NH ₂	53-69	20, p. 4108d
3.	SH	NH ₂	p-chloro-phenyl	CH ₃	91	3, p. 135
4.	SH	NH ₂	p-chloro-phenyl	C ₂ H ₅	91	3, p. 135
5.	SH	OH	n-C ₃ H ₇	CH ₃	63	3, p. 136
6.	SH	OH	benzyl	CH ₃	82	3, p. 136

Purine Compounds

No.	R ₁	R ₂	R ₃	%Yield	Reference
1.	SH	NH ₂	H		43, p. 86-87

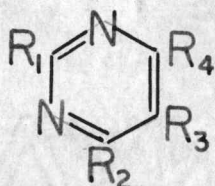


The use of Raney nickel as a dethionating agent has received more attention than the others, although this reagent has been used almost exclusively for the dethionation of thiopyrimidines. This interest has been such that it has led to the development of a Raney nickel preparation which has been recommended for dethionation purposes (6, p. 355). A summary of this work is presented in Table II.

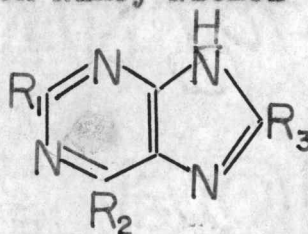
In this laboratory interest centered around the problem of dethionating the 2-thiopurines. Traube (43, p. 78, 86-87) had reported the first studies on dethionation of the thiopurines. This investigator reported the dethionation of both 2-thioadenine and 2-thioxanthine to adenine and hypoxanthine respectively using both nitric acid and hydrogen peroxide as dethionating agent. However, the repetition of this work in this laboratory indicated that the results were difficult to reproduce and the procedure did not appear practical as a synthetic method. Bendich (4, p. 3112) and coworkers had reported a 35% yield of adenine from 2-thioadenine using Raney nickel as the dethionating agent. This work has been confirmed in this laboratory and starting from this point a study was made to establish if possible conditions which would lead to more favorable yields.

Table II

Dethionation of 2-thiopyrimidines and 2-thiopurines with Raney Nickel



Pyrimidine Compounds



No.	R ₁	R ₂	R ₃	R ₄	%Yield	Media	Reference
1.	SH	OH	H	H	82	NH ₄ OH	6, p. 354; 36, p. 602
2.	SH	NH ₂	H	NH ₂	85	NH ₄ OH	6, p. 355
3.	SH	NH ₂	H	H	61	NH ₄ OH	6, p. 354
4.	SH	NH ₂	H	OH	87	NH ₄ OH	6, p. 355
5.	SH	SH	H	H	Poor		36, p. 602
6.	HOOCCH ₂ S	C ₆ H ₅ NH	H	H	60	Na ₂ CO ₃	42, p. 2281-2282
7.	SH	CH ₃	H	CH ₃	54	HCl-Ethanol	5, p. 4694
8.	SH	NH ₂	NH ₂	H	65	NH ₄ OH	7, p. 241
9.	SH	HNCH ₃	H	H	54	water	8, p. 336
10.	SH	N(CH ₃) ₂	H	H	50	water	8, p. 336

Purine Compounds

No.	R ₁	R ₂	R ₃	%Yield	Media	Reference
1.	SCH ₃ ¹	NH ₂	H	Good	Alcohol	21, p. 561
2.	SH	NH ₂	H	35	Na ₂ CO ₃	4, p. 3112

Note:

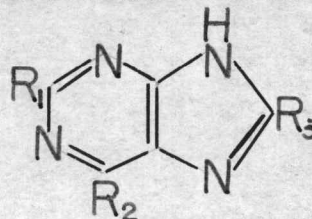
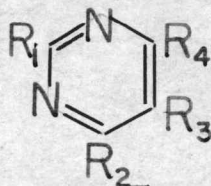
1. CH₃ also substituted in the 7-position.

Thiourea is often a much more reactive molecule than urea in cyclization reactions, yielding the 2-thioanalog of the 2-keto derivative usually more readily and in greater yield. The replacement of the thio by a keto substituent offers, therefore, another route to a desired product. Hydrochloric acid and chloroacetic acid have been used to effect these transitions. Each of the reagents operates apparently by a different mechanism. In the case of hydrochloric acid, the reaction is simply hydrolytic.

The chloroacetic acid reacts in another way yielding a carboxymethylthio substituent which often is sufficiently stable as to yield a product so substituted in the 2-position. This intermediate in turn can be hydrolyzed to the desired 2-hydroxy pyrimidines. The extension of these reactions to the 2-thiopurines has received little attention and for this reason has been made part of this current study. The known reactions of chloroacetic acid and hydrochloric acid with the thiopurines and thiopyrimidines cited in the literature are enumerated in Table III.

Table III

Reactions of 2-thiopyrimidines and 2-thiopurines with
chloroacetic acid and hydrochloric acid



Pyrimidine Compounds

No.	R ₁	R ₂	R ₃	R ₄	Reagent	Conversion R ₁ to	%Yield	Reference
1.	C ₂ H ₅ S	NH ₂	H	H	HBr	OH	79	45, p. 498
2.	C ₂ H ₅ S	OH	C ₂ H ₅ OH		aniline	C ₆ H ₅ NH	59	24, p. 247
3.	CH ₃ S	OH	H	CH ₃	HCl	H		30, p. 180
4.	RS	NH ₂	H	H	HCl	OH	Quant.	17, p. 1155
5.	C ₂ H ₅ S	OH	R ¹	H	H ₂ SO ₄	OH	Good	34, p. 1140
6.	C ₂ H ₅ S	CH ₃ O	H	OH	HCl	OH		29, p. 2150-2151
7.	SR ²	NH ₂	H	NH ₂	HCl-H ₂ SO ₄	OH	68	4, p. 3112
8.	SH	SH	C ₂ H ₅	OH	NH ₃	SH ³	70	9, p. 5457b
9.	SH	OH	H	H	Chloroacetic	OH	Quant.	46, p. 552
10.	SH	OH	CH ₃	R ⁴ OCH ₂	ditto	OH	Quant.	26, p. 594

Table III
(continued)

No.	R ₁	R ₂	R ₃	R ₄	Reagent	Conversion R ₁ to	%Yield	Reference
11.	SH	H	R ⁴ O	H	Chloroacetic	SR ²	65	32, p. 2161
12.	SH	C ₆ H ₅	H	CH ₃	ditto	OH		37, p. 879
13.	SH	NH ₂	H	NH ₂	ditto	SR ²	79	4, p. 3112
14.	SH	NH ₂	H	H	ditto	SR ²	80	18, p. 358
15.	SR ²	NH ₂	H	H	HCl	OH	83	18, p. 358
16.	SH	NH ₂	CH ₃	H	Chloroacetic	SR ²	79	18, p. 359
17.	SR ²	NH ₂	CH ₃	H	HCl	OH	67	18, p. 359
18.	SH	NH ₂	C ₆ H ₅	H	Chloroacetic	SR ²		19, p. 10559g
19.	SR ²	NH ₂	C ₆ H ₅	H	NH ₄ OH	NH ₂		19, p. 10559g
20.	SH	C ₆ H ₅ NH	H	H	Chloroacetic	SR ²	Quant.	42, p. 2281
21.	SR ²	C ₆ H ₅ NH	H	H	HCl	OH	70	42, p. 2281
22.	SH	C ₆ H ₅	H	OH	Chloroacetic	OH	Quant.	31, p. 381
23.	SH	OH	R ⁵	H	ditto	OH		33, p. 2170

Table III
(continued)

Purine Compounds

1.	SH	NH ₂	H	Chloroacetic	SR ²	4, p. 3112
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Notes:

1. R = CH₂NH₂
2. R = CH₂COOH
3. SH in 4-position replaced by NH₂
4. R = C₂H₅
5. R = 3,5-dinitro-2-hydroxybenzyl

EXPERIMENTAL

The 2-thioadenine used in these studies was synthesized from 4,6-diamino-2-thiopyrimidine obtained by the cyclization of malononitrile and thiourea (4, p. 3111). 4,6-Diamino-2-thiopyrimidine was nitrosated almost quantitatively to the 5-nitroso-derivative which in turn was reduced to the 2-thio-4,5,6-triaminopyrimidine with sodium hydrosulfite in approximately 50% yield (4, p. 3111). This product in turn was cyclized to the purine by the formamide method in 68% yield (41, p. 265).

The 2-thioxanthine used in these studies was prepared from 4-amino-2-thiopyrimidone-6 obtained from the cyclization of thiourea and ethyl cyanoacetate (43, p. 71-74). The 4-amino-2-thiopyrimidone-6 was nitrosated to the 5-nitroso derivative which in turn was reduced to 4,5-diamino-2-thiopyrimidone-6 with sodium hydrosulfite in approximately 65% yield (43, p. 74-76). This product in turn was cyclized to the purine by formamide in 96% yield (41, p. 265).

Thioorotic acid was made by the cyclization of ethyl oxalacetate with thiourea. Ethyl oxalacetate: Fifty grams (0.237 moles) of sodio ethyl oxalacetate was introduced into 500 ml. separatory funnel with 20 ml. of conc. hydrochloric acid, 50 ml. of cold water and 200 ml. of

ether. This mixture is shaken until the solid disappears and two layers form. The ether layer was removed and washed with 2-50 ml. portions of cold water, and then dried with 15 g. of anhydrous sodium sulfate. The ether was removed under vacuo at room temperature.

Thioorotic acid: To 200 ml. of absolute alcohol are added 5.5 g. (0.24 mole) of sodium. To this sodium ethylate solution are added 18 g. of thiourea and then the crude ethyl oxalacetate prepared from 50 g. of sodio ethyl oxalacetate. This resultant solution was refluxed for two hours with stirring.

Upon cooling, 100 ml. of 50% aqueous alcohol containing 10 g. of sodium hydroxide was added and the mixture refluxed for 45 minutes. The alcohol was removed under vacuo from the yellow precipitate. The residue was then dissolved in 800 ml. of water which in turn was acidified with 40 ml. of 18 N sulfuric acid. The yellow precipitate was filtered, and washed well with water. Yield, 12 g. (29.5%).

Anal. calcd. for $C_5H_4N_2O_3S$: C, 34.9; H, 2.34. Found: C, 34.8; H, 2.69.

The dethionations of thioadenine were carried out in different media, for various time intervals and with different ratios of reactants. All the results of these experiments are tabulated in Table IV.

Table IV

Dethionation of 2-thiopurines and 2-thiopyrimidines
using Raney Nickel

No.	Compound	Media	Time Reflux hours	Raney Ni Ratio g/g	Yield %
1.	Thioadenine sulfate	2 g. 90 ml. 3% NH ₃	2.5	4	44
2.	ditto	2 g. 90 ml. 4.5% NH ₃	2.5	4	42
3.	Thioadenine free base	10 g. 450 ml. 3% NH ₃	2.5	4	17
4.	ditto	4.4 g. 200 ml. 3% NH ₃	2.5	4	36
5.	Thioadenine sulfate ¹	2 g. 90 ml. 3% NH ₃	2.5	4	45
6.	Thioadenine sulfate	2 g. 90 ml. 3% NH ₃	2.5	4	46
7.	ditto	2 g. ditto	2.5	1	12
8.	ditto	2 g. ditto	2.5	2	19
9.	ditto	2 g. ditto	2.5	3	33
10.	ditto	2 g. ditto	2.5	4	46
11.	ditto	2 g. ditto	2.5	5	55
12.	ditto	2 g. ditto	2.5	6	53
13.	ditto	2 g. ditto	2.5	8	13
14.	ditto	2 g. ditto	2.5	5	60
15.	ditto	2 g. ditto	0.5	5	58
16.	ditto	2 g. ditto	1	5	55
17.	ditto	2 g. ditto	2.5	5	55
18.	ditto	2 g. ditto	5	5	52
19.	Thioadenine sulfate	0.6 g. 26 ml. 0.5N NaOH	2.5	5	70

Table IV
(continued)

No.	Compound	Media	Time Reflux hours	Raney Ni Yield Ratio g/g %
20.	Thioadenine sulfate	2 g. 90 ml. 2.5% Ethanolamine	2.5	5 63
21.	ditto	2 g. 81 ml. 0.5N NaOH	2.5	5 80
22.	ditto	2 g. 87 ml. 0.5N KOH	2.5	5 78
23.	ditto	2 g. 84 ml. 0.3N NaOH	2.5	5 59
24.	ditto	2 g. 87 ml. 0.5N NaOH	2.5	4 65
25.	ditto	2 g. ditto	2.5	3 54
26.	ditto	2 g. ditto	0.33	5 83
27.	ditto	2 g. ditto	2	5 82
28.	ditto	2 g. ditto	2	5 81
29.	ditto	2 g. ditto	0.5	5 81
30.	ditto	2 g. ditto	0.5	6 ² 14
31.	ditto	2 g. ditto	0.5	7 ³ 8
33.	Thioadenine sulfate ⁴	0.6 g. 42 ml. 12%NH ₃	1	5 58
34.	ditto ⁵	2 g. 140 ml. 12%NH ₃	1	5 53
35.	Thioxanthine free base ⁶	2 g. 85 ml. 0.4N NaOH	2.5	5 44
36.	ditto	10 g. 425 ml. 0.4N NaOH	2.5	5 45
37.	ditto	2 g. 91 ml. 0.7N NaOH	2.5	5 55
38.	Thiouracil	2g. 35 ml. 0.9N NaOH	2	3 23
39.	ditto	2 g. 40 ml. 1.5N NaOH	2	3 50

Table IV
(continued)

No.	Compound	Media	Time Reflux hours	Raney Ni Ratio g/g	Yield %
40.	4-Amino-2-thiopyrimidine-6	2 g. 23 ml. 0.8N NaOH	0.5	4	52
41.	ditto	2 g. 26 ml. 1.4N NaOH	0.5	4	65
42.	Thiooxotic acid ⁷	2 g. 90 ml. 3%NH ₃	2	4	--

Notes:

1. added 600 mg. (NH₄)₂SO₄ to reaction mixture.
2. 5 g. was used Raney nickel.
3. 6 g. was used Raney nickel.
4. 3 ml. 28% ammonia added every 10 minutes. 6X.
5. 10 ml. 28% ammonia added every 10 minutes. 6X.
6. Product was not quite pure in case hypoxanthine experiments.
7. unable to isolate product.

Although the ammoniacal medium is quite satisfactory for the dethionation of 2-thiopyrimidines it does not work well in the case of the 2-thioadenine because of solubility characteristics. After 5 minutes of refluxing, sufficient ammonia escapes so that the remaining thio-purine precipitates, curtailing the reaction. By using a non-volatile alkali such as ethanolamine or sodium hydroxide this is corrected and better yields are obtained. The reaction of dethionation is quite rapid; this is shown by the experiment No. 15 using ammonia, as well as those involving sodium hydroxide, experiment No. 26.

Another important factor is the concentration of the base. The best results were obtained using 0.5 N sodium hydroxide while lower yields were obtained using a 0.3 N sodium hydroxide solution.

One of the very interesting facets of this study was those experiments in which previously used Raney nickel was reused. This is shown in experiments No. 30 and 31, in which it appears that the nickel becomes sufficiently poisoned so as to be almost useless after only one operation.

The ratio of Raney nickel to the thiopurine likewise affects the yields, and a 5 to 1 ratio of Raney nickel gave the best yields in this study, as shown in experiments No. 11 and 21. For the best results as far

as these studies indicate, the dethionation should be carried out as follows:

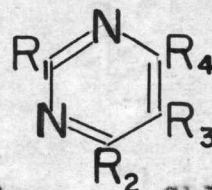
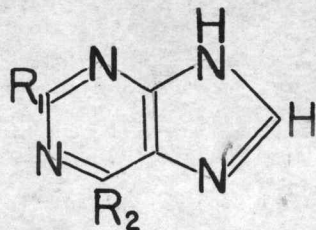
Adenine: Two grams of 2-thioadenine sulfate are dissolved in 80 ml. of boiling water containing 7 ml. of 6 N sodium hydroxide in a 300 ml. three-neck flask with a condensor and a mechanical stirrer. To this boiling solution is added 10 g. of Raney nickel (weighed wet with water). The mixture is then refluxed vigorously for two hours, filtered hot, and the Raney nickel in turn is washed with 80 ml. of boiling water. The filtrate and washings are neutralized to pH 6 with glacial acetic acid, concentrated to 80 ml., decolorized with 0.2 g. of norite, filtered, and set aside in a refrigerator overnight. The crystals which settle out are filtered and the mother liquor is again cooled overnight, which gives a second crop. Yield 0.97 g. (80%)

The experiments with thioxanthine were not quite as good yieldwise as those with thioadenine (see experiments No. 35-37) but the yields did increase significantly as the concentration of the alkali was raised. Similar results were also obtained with thiouracil and 4-amino-2-thiopyrimidone-6.

Although the sodium hydroxide media give much better results than in the case of aqueous ammonia, this is not true of the thiopyrimidines investigated in which

Table V

Reactions of chloroacetic acid with 2-substituted purines and pyrimidines and hydrolysis of resultant products



No.	Compound		Media		Time Reflux hours	Chloroacetic acid Ratio	Yield
	Purines R ₁	R ₂					
1.	SH	NH ₂	1 g ¹	30 ml. 0.3% NH ₃	2	0.8	77%
2.	SH	NH ₂	1 g ¹	30 ml. 0.3% NH ₃	2	0.8	79%
3.	SH	NH ₂	1 g ¹	30 ml. H ₂ O	5 ²	1.0	51%
4.	SH	NH ₂	1 g ¹	15 ml. 1.4% NH ₃	2 ³	1.0	83%
5.	R ¹ ₄	NH ₂	1 g.	10 ml. 12N HCl	2	---	mixture ⁹
6.	R ¹ ₄	NH ₂	0.5 g.	10 ml. 2.5N H ₂ SO ₄	2 ⁵	---	ditto ⁹
7.	R ¹ ₄	NH ₂	0.5 g.	10 ml. 34% HBr	2	---	ditto ⁹
8.	R ¹ ₄	NH ₂	0.5 g.	10 ml. 6N H ₂ SO ₄	3 ⁶	---	ditto ⁹
9.	R ¹ ₄	NH ₂	0.5 g.	10 ml. 12N HCl	8	---	ditto ⁹
10.	R ¹ ₄	NH ₂	0.3 g.	10 ml. 12N HCl	36	---	ditto ⁹
11.	SH	OH	1 g.	60 ml. H ₂ O	2.5	1.0	49%

Table V
(continued)

No.	Compound		Media	Time Reflux hours	Chloroacetic acid Ratio	Yield
	Purines R ₁ R ₂					
12.	R' ⁴ OH	1 g.	20 ml. 2N H ₂ SO ₄	1.0 ⁸	---	mixture ⁹
Pyrimidines						
	R ₁ R ₂ R ₃ R ₄					
13.	SH OH H COOH	1 g.	30 ml. H ₂ O	7	1.0	35%
14.	SH OH H COOH	1 g.	30 ml. 0.02% NH ₃ ⁷	2	1.0	
15.	Reaction Product Exp't. 14.		10 ml. 2N H ₂ SO ₄	3 ⁸	---	mixture ⁹

Notes:

1. Compound used was the sulfate.
2. Reaction product treated with 5 ml. of conc. HCl and refluxed for 2 hours longer.
3. Reaction product treated with 27 ml. of 2 N sulfuric acid and refluxed for 2 hours and then retreated with 2.7 ml. of 2 N HCl and again refluxed for 30 minutes additional.
4. R' = -SCH₂COOH
5. One ml. of 2.5N HCl added and mixture refluxed an

Table V
(continued)

additional 30 minutes.

6. One ml. of 6N HCl added and mixture refluxed an additional 30 minutes.
7. Product was not isolated.
8. One ml. of 2.5N HCl added and mixture refluxed an additional hour.
9. Hydrolysis reactions.

the results were just the reverse.

The reactions with chloroacetic acid were quite straightforward with thioadenine and thioxanthine yielding a product with a SCH_2COOH substituent in the 2-position in fair yield (see experiments No. 2 and 11 of Table V). The hydrolyses of these reaction products were incomplete yielding mixtures which were not isolated in view of the incompleteness of the reaction.

The directions for the preparation as developed in this investigation of the 2-carboxymethylthio derivatives are as follows.

6-Amino-2-carboxymethylthiopurine:

1.00 g. of 6-Amino-2-thiopurine sulfate was suspended into 30 ml. of hot water and 0.3 ml. of 28% ammonium hydroxide. To the suspension was added 0.8 g. of monochloroacetic acid and the mixture refluxed for 2 hours. Upon cooling, the mixture was neutralized with 7 ml. of 2.5N sodium hydroxide, norited, filtered, acidified with acetic acid, and allowed to stand in a refrigerator. Yield: 0.77 g. (77%). An analytical sample of the sulfate was obtained on recrystallization from 34 ml. of 5% sulfuric acid.

Anal. Calcd. for $(\text{C}_7\text{H}_7\text{O}_2\text{N}_5\text{S})_2 \cdot \text{H}_2\text{SO}_4 \cdot 2\text{H}_2\text{O}$: C, 28.86; H, 3.11 Found: C, 28.54; H, 3.52. The ultraviolet absorption was determined: 7.63 mg/l in 0.1 M phosphate

buffer pH 6.5

	max. 232	min. 216
	275	250
Reported:	max. 232	min. 217
	275	251

6-hydroxy-2-carboxymethylthiopurine:

1.00 g. of 2-thiohypoxanthine was suspended into 60 ml. water. To the suspension was added 1 g. of monochloroacetic acid and the mixture refluxed for 2.5 hours. Upon cooling, the mixture was neutralized with 2.5N sodium hydroxide, norited, filtered, acidified with acetic acid, and then allowed to stand in a refrigerator. The yellow solid was filtered, washed with water, and dried over P_2O_5 .

Yield: 0.59 g. (48.8%)

Anal. Calcd. for $C_7H_6N_4O_3S$: H, 2.65; C, 37.2.

Found: H, 3.57; C, 37.4.

SUMMARY

Dethionations of the thiopurines and thiopyrimidines have been investigated. The effects of varying the media, ratios of reactants, time, etc., have been studied.

The dethionations of thioadenine by Raney nickel were carried out in ammonia. After 5 minutes of refluxing, sufficient ammonia escapes so that the remaining thiopurine precipitates, curtailing the reaction. By using a non-volatile alkali such as ethanolamine or sodium hydroxide this is corrected and better yields are obtained. The reaction of dethionation is quite rapid.

The best results were obtained using a 0.5 normal sodium hydroxide solution.

One of the very interesting facts of this study was those experiments in which previously used Raney nickel was reused. It would appear that the nickel became sufficiently poisoned as to be almost useless after only one operation.

The dethionations of thioxanthine by Raney nickel were carried out in sodium hydroxide media, but the experiments were not quite as good yieldwise as those with thioadenine. The yields did increase significantly as the concentration of alkali was raised. Similar results were also obtained with thiouracil and 4-amino-2-thiopyrimidone-6.

The ratio of Raney nickel to the thiopurine likewise affects the yields and a 5 to 1 ratio of Raney nickel gave the best yields reported in this study.

Although the sodium hydroxide media give much better results than in the case of aqueous ammonia, this is not true of the thiopyrimidines investigated in which the results were just the reverse.

The reactions with chloroacetic acid were quite straightforward with thioadenine and thioxanthine yielding a product with a SCH_2COOH substituent in the 2-position in fair yield. The hydrolyses of these reaction products were incomplete yielding mixtures which were not isolated in view of the incompleteness of the reaction.

Thioorotic acid was made by the cyclization of ethyl oxalacetate with thiourea and the dethionation by Raney nickel was unable to isolate product.

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