ture refluxed 3 hr. The cooled solution was poured into a mixture of ice and water. The product was extracted with 500 ml. of ether. The ether product was washed with water and with saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the ether left an oil which was distilled *in vacuo*. The fraction distilling 160–190° at 0.15 mm. and crystallizing in the received was collected as product. The crude ester was recrystallized from a methanol–water mixture to give a yield of 4.7 g. (0.0217 mole, 7.2%) of white plates, m.p. 72–73°. Another recrystallization from the same solvent pair gave pure ester, m.p. 72.5–73°.

Ethyl 5-Chloroindole-3-butyrate (Procedure D).—A mixture of 15.8 g. (0.1 mole) of *p*-chlorophenylhydrazine hydrochloride, 360 ml. of absolute ethanol and 40 ml. of sulfuric acid was refluxed 3 hr. The cooled solution was poured into 2.5 liters of ice-water containing 300 g. of ammonium sulfate. The ester was recovered by extraction with two 250-ml. and one 100-ml. portions of ether. The combined ether extracts were dried over sodium sulfate and distilled leaving 22 g. of black oil. The oil was distilled and the fraction distilling 170–200° at 0.1 mm. collected as product. Recrystallization of the crude ester from cyclohexane gave 4.8 g. (0.018 mole, 18%) of product, m.p. 67°. After an additional recrystallization the m.p. was 69°.

Methyl 6-Chloro-7-methylindole-3-butyrate (Procedure E).—Fifty-seven grams (0.3 mole) of 3-chloro-2-methylphenylhydrazine hydrochloride was dissolved in 300 ml. of hot methanol, and 43.3 g. (0.3 mole) of methyl 5-formylvalerate was added. After gentle warming the reaction mixture refluxed spontaneously several minutes. The methanol was distilled off leaving a mixture of oil and solid materials. The residue was taken up in hot methanol, decolorized with activated charcoal and filtered. From the cooled filtrate 13.3 g. (0.05 mole, 16.7%) of ester, m.p. 140.5–141°, was obtained. After recrystallization from 210 ml. of methanol, the ester had m.p. 141°.

Methyl 5-Chloro-7-methylindole-3-butyrate (Procedure F).—A mixture of 57.8 g. (0.3 mole) of 4-chloro-2-methylphenylhydrazine hydrochloride and 300 ml. of methanol was warmed on the steam-bath to dissolve the hydrochloride. Then 43.3 g. (0.3 mole) of methyl 5-formylvalerate was added. The resulting solution was refluxed 30 minutes and saturated with anhydrous hydrogen chloride. The reaction mixture was refluxed an additional 3 hr. and left standing overnight. The reaction mixture was poured into ice and water and the product recovered by ether extraction. The ether solution was washed with water and with saturated sodium bicarbonate solution and dried over sodium sulfate. Distillation of the solvent left a sticky solid. The crude product was taken up in 100 ml. of hot methanol, treated with decolorizing charcoal and filtered. The filtrate deposited crystals on cooling. The ester was filtered off and washed with cold methanol. The yield was 10.8 g. (0.041 mole), 13.7% of product, m.p. 118.5–119°. The melting point was unchanged after recrystallization from methanol.

PEARL RIVER, N. Y.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Diuretics. III. 1,3-Dimethyl-9-alkyl- and 1,3,9-Trimethyl-8-alkylthioisoxanthines

BY F. F. BLICKE AND R. L. SCHAAF[1,2]

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1,3-Dimethyl-5,6-diaminouracil was treated with a variety of alkyl isothiocyanates to form ureido derivatives which were cyclized to 2-alkylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo-[5,4-d]pyrimidines and 1,3-dimethyl-8-thiol-9-alkylisoxanthines. The thiol group was removed from the latter with the formation of 1,3-dimethyl-9-alkylisoxanthines. 1,3,9-Trimethyl-8-alkylthioisoxanthines were prepared by alkylation of 1,3,9-trimethyl-8-thiolisoxanthine. None of the compounds tested exhibited diuretic activity.

The substituted isoxanthines described in this paper were synthesized in a search for diuretics.

Treatment of 1,3-dimethyl-5,6-diaminouracil (I)[3] with an alkyl isothiocyanate[4] yielded a 1,3-dimethyl-5-(3-alkylthioureido)-6-aminouracil (II) (Table I). In six instances we were able to cyclize the uracil II, in refluxing hydrochloric acid, to a 1,3-dimethyl-8-thiol-9-alkylisoxanthine (III) (compounds 1-6, Table II).[5] The 8-thiol compounds were converted into 1,3-dimethyl-9-alkylisoxanthines (IV) (compounds 7–11, Table II) by the action of nitrous acid[6] or Raney nickel.

Hitherto it had not been reported that 2-alkylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidines (V), compounds which are isomeric with III, are formed during the conversion of compounds of type II into III. The examples of compounds of type V (compounds 1–5, Table III) which were obtained were previously unknown. The structure of a typical representative, 2-hexahydrobenzylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (V, R = hexahydrobenzyl; XI, R = CH_3) was established by a six-step, unequivocal synthesis from butyl nitrosocyanoacetate. The acetate was reduced with aluminum amalgam to butyl aminocyanoacetate[7] which, without isolation, was converted by hexahydrobenzyl isothiocyanate into 2-hexahydrobenzylamino-4-carbobutoxy-5-aminothiazole (VII). The thiazole reacted with one molecular equivalent of methyl isocyanate to yield a monosubstituted product, 2-(1-hexahydrobenzyl-3-methylureido)-4-carbobutoxy-5-aminothiazole (VIII), and with two molecular equivalents of the same reagent to form a disubstitution product, 2-(1-hexahydrobenzyl-3-

(1) This paper represents part of a dissertation submitted by R. L. Schaaf in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1955.

(2) The Monsanto Chemical Co. Fellow.

(3) F. F. Blicke and H. C. Godt, Jr., THIS JOURNAL, **76**, 2798 (1954).

(4) The term alkyl (formulas II–V) has been used to include methyl, ethyl, propyl, isopropyl, butyl, allyl, cyclohexyl, benzyl and hexahydrobenzyl.

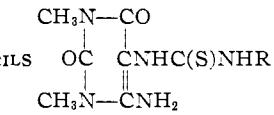
(5) Although compounds of type III are named in the literature as 8-thiouric acids, we have called them 8-thiolisoxanthines in view of their behavior with alkyl halides and other reagents. H. Biltz and J. Sauer (*Ber.*, **64**, 752 (1931)) stated that 8-thiouric acids frequently act as 8-thiolxanthines.

(6) The first use of nitrous acid to convert thiolisoxanthines (8-thiouric acids) into isoxanthines was mentioned in a German Patent (120,437; *Frdl.*, **6**, 1180 (1900–1902)). The method was used subsequently by H. Biltz, *et al.*, (*Ann.*, **423**, 200 (1921)) and by W. Traube, *et al.* (*ibid.*, **432**, 266 (1923)).

(7) Ethyl nitrosocyanoacetate was reduced with aluminum amalgam to ethyl aminocyanoacetate by A. H. Cook, I. Heilbron and A. L. Levy (*J. Chem. Soc.*, 1594 (1947)) but the experimental details were not reported. We used the procedure described by V. Cerchez (*Bull. soc. chim.*, [4] **47**, 1282 (1930)) for the reduction of diethyl isonitrosomalonate. It might be more advantageous to employ sodium hydrosulfite (see B. F. Tullar, U. S. Patent 2,393,723; *C. A.*, **40**, 2465 (1946)).

TABLE I

1,3-DIMETHYL-5-(3-ALKYLTHIOUREIDO)-6-AMINOURACILS



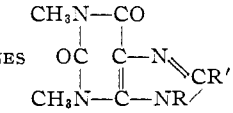
Compounds 1, 2, 3 and 4 were recrystallized from water; 5, 6, 7 and 8 from dilute ethanol.

	R	M.p., °C.[a]	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	CH_3	250	84	$C_8H_{13}O_2N_5S$	39.49	39.41	5.39	5.31	28.79	28.43	13.18	13.40
2	C_2H_5	245	90	$C_9H_{15}O_2N_5S$	42.01	42.23	5.87	5.50	27.23	27.16	12.46	12.67
3	C_4H_9	230	89	$C_{11}H_{19}O_2N_5S$	46.28	46.55	6.71	6.75	24.55	24.29	11.24	11.54
4	$CH_2{=}CHCH_2$	235	83	$C_{10}H_{15}O_2N_5S$	44.59	44.68	5.61	5.48	26.01	25.68	11.91	12.26
5	$(CH_3)_2CH$	300	87	$C_{10}H_{17}O_2N_5S$	44.26	44.34	6.32	6.49	25.81	25.87	11.81	12.02
6	C_6H_{11}[b]	240	65	$C_{13}H_{21}O_2N_5S$	50.14	50.19	6.80	6.79	22.50	22.57	10.29	10.17
7	$C_6H_5CH_2$	235	88	$C_{14}H_{17}O_2N_5S$	52.65	52.55	5.37	5.32	21.93	21.76	10.04	9.09
8	$C_6H_{11}CH_2$[c]	235	90	$C_{14}H_{23}O_2N_5S$	51.68	51.67	7.12	6.96	21.52	21.68	9.85	10.04

[a] In order to obtain the tabulated (but indefinite) melting points, the compounds were inserted into the melting point bath at temperatures 5° lower than the temperatures reported in the table. The molten compounds then evolved a gas, solidified rapidly and melted between 275 and 320° dec. [b] Cyclohexyl. [c] Hexahydrobenzyl.

TABLE II

1,3-DIMETHYL-8-THIOL-9-ALKYLISOXANTHINES AND 1,3-DIMETHYL-9-ALKYLISOXANTHINES

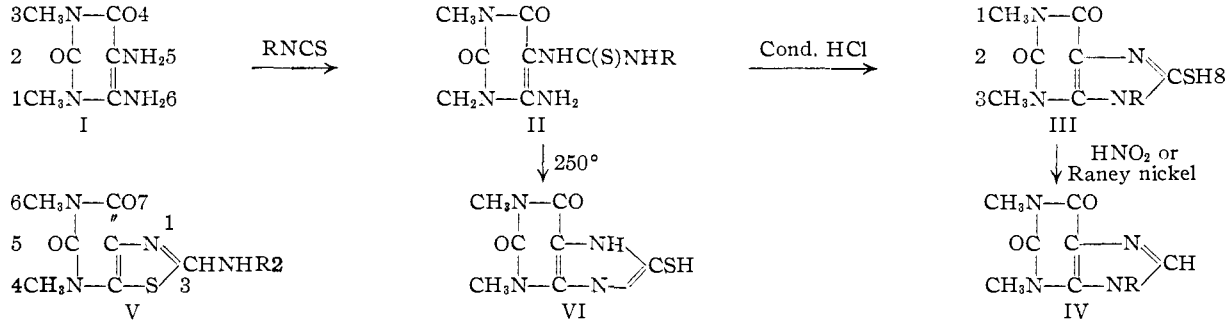


Compounds 2, 7 and 9 were recrystallized from water; 3 and 8 from dilute ethanol; 10 and 11 from 2-butanone; 4 from butanol–dimethylformamide; 5 from acetic acid; 6 from isobutyl alcohol. Compound 1 was precipitated from a dilute ammonium hydroxide solution with acetic acid. Compounds 2, 3, 5, and 6 were recrystallized from ethanol; 4 and 7 from chloroform; 1 from dilute ethanol. Compound 8 was precipitated from dilute potassium hydroxide solution with acetic acid.

	R	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	CH_3	SH	325[a,b]	70	$C_8H_{10}O_2N_4S$	42.45	42.63	4.47	4.47	24.76	24.60	14.17	14.30
2	C_2H_5	SH	275[a,c]	40	$C_9H_{12}O_2N_4S$	44.99	45.44	5.04	5.06	23.32	23.32	13.34	13.37
3	C_3H_7	SH	243–244	34	$C_{10}H_{14}O_2N_4S$	47.23	47.39	5.55	5.65	22.03	21.78	12.61	12.49
4	C_4H_9	SH	228–230	40	$C_{11}H_{16}O_2N_4S$	49.24	49.21	6.01	6.26	20.88	20.87	11.95	11.91
5	$C_6H_5CH_2$	SH	275[a]	34	$C_{14}H_{14}O_2N_4S$	55.99	56.10	4.03	4.66	18.65	18.57	10.68	10.80
6	$C_6H_{11}CH_2$[d]	SH	260[a]	9	$C_{14}H_{20}O_2N_4S$	54.54	54.40	6.51	6.40	18.17	18.03	10.40	10.65
7	CH_3	H	285–287[e]	83	$C_8H_{10}O_2N_4$	49.48	49.82	5.19	5.13	28.85	28.68	...	...
8	C_2H_5	H	233–235[f]	69	$C_9H_{12}O_2N_4$	51.91	51.85	5.81	5.88	26.91	26.83	...	...
9	C_4H_9	H	170–171	75	$C_{11}H_{16}O_2N_4$	55.91	56.00	6.83	6.91	23.72	23.76	...	...
10	$C_6H_5CH_2$	H	167–169	84	$C_{14}H_{14}O_2N_4$	62.21	62.08	5.22	5.06	20.73	20.64	...	...
11	$C_6H_{11}CH_2$[d]	H	203–205	66	$C_{14}H_{20}O_2N_4$	60.85	61.03	7.30	7.24	20.28	20.32	...	...

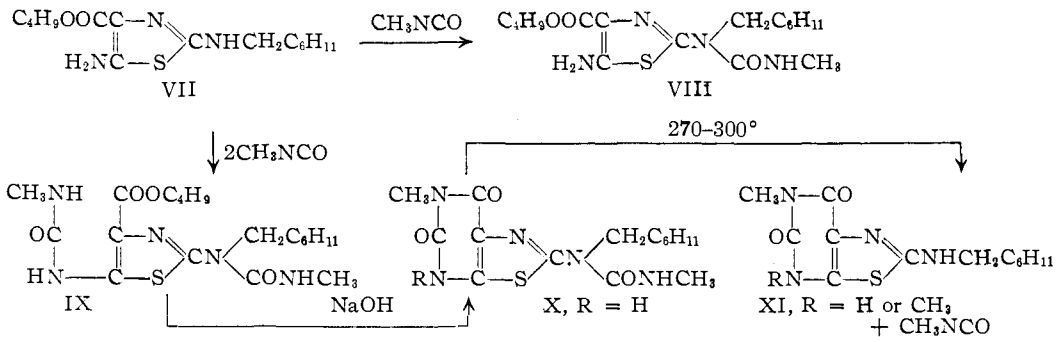
[a] Melted with decomposition. [b] Ref. 20, m.p. 335° dec. [c] Ref. 20, m.p. 277° dec. [d] Hexahydrobenzyl. [e] Ref. 20, m.p. 285–287°. [f] Ref. 20, m.p. 227–228°.

methylureido)-4-carbobutoxy-5-(3-methylureido)-thiazole (IX).[8] In conformity with its structure, VIII reacted with benzaldehyde to produce a 5-benzalamino derivative, and upon treatment with alkali it did not cyclize to form a thiazolopyrimidine. Compound IX was treated with sodium hydroxide in the manner used by Cook, *et al.*,[9] to obtain thiazolopyrimidines. The product, X (R = H) (compound 6, Table III), was alkylated with methyl iodide to form 2-(1-hexahydrobenzyl-3-methylureido)-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]-pyrimidine (X, R = CH_3; compound 7, Table III).



(8) It seems strange that A. H. Cook, J. D. Downer and I. Heilbron (*J. Chem. Soc.*, 1069 (1949)) obtained only a monosubstitution product 2-methylamino-5-N'-methylureido-4-carbethoxythiazole, by interaction of 2-methylamino-5-amino-4-carbethoxythiazole with about two molecular equivalents of methyl isocyanate.

(9) A. H. Cook, J. D. Downer and I. Heilbron, *J. Chem. Soc.*, 1069 (1949).



It was found that compounds of type X (R = H or CH_3), when heated at 270–300°, decomposed with the formation of methyl isocyanate and a compound of type XI (R = H or CH_3). The melting points and the mixed melting point of compound XI (R = CH_3) and compound V (R = $CH_2C_6H_{11}$) were practically identical.

Compound V (R = $CH_2C_6H_{11}$) reacted with methyl isocyanate to produce a methylureido derivative (X, R = CH_3); the infrared spectrum of the last mentioned compound was identical with that of compound X (R = CH_3).

Incidentally, it was found that butyl nitrosocyanoacetate was reduced by hydrogen, in the presence of platinum oxide catalyst and hydrochloric acid, to butyl 2,3-diaminopropionate dihydrochloride.

Heated at 250°, 1,3-dimethyl-5-(3-ethylthioureido)-6-aminouracil (II, R = C_2H_5) decomposed with the formation of 8-thioltheophylline (VI).

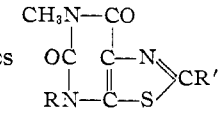
1,3-Dimethyl-5-nitroso-6-aminouracil[3] was hydrolyzed with dilute hydrochloric acid to 1,3-dimethyl-5-nitroso-6-hydroxyuracil which was reduced to 1,3-dimethyl-5-amino-6-hydroxyuracil with sodium hydrosulfite. The 5-amino compound yielded 1,3-dimethyl-8-thiol-9-butylisoxanthine when treated successively with butyl isothiocyanate and hydrochloric acid.

The effect of hydrochloric acid on the 3-isopropylthioureido derivatives of two other diamines, namely 5-(3-isopropylthioureido)-6-aminouracil and *o*-amino-(3-isopropylthioureido)-benzene, was determined. When the thioureidouracil was refluxed with hydrochloric acid, 9-isopropyl-8-thiolisoxanthine precipitated from the reaction mixture. The possibility that the product was the isomeric 2-isopropylamino-5,7-diketo-4,5,6,7-tetrahydrothiazolo-[5,4-d]pyrimidine was eliminated when the product was shown to yield a sulfur-free compound, undoubtedly 9-isopropylisoxanthine, when treated with nitrous acid. The thioureidobenzene and hydrochloric acid yielded *o*-phenylenediamine dihydrochloride.

1,3,9-Trimethyl-8-alkylthioisoxanthines (XIII) (Table IV) were obtained by alkylation of 1,3,9-trimethyl-8-thiolisoxanthine (XII)[10] with alkyl halides.[11] In ten instances a mercaptan odor was noticed after samples of the products had been fused with potassium hydroxide and the mixture acidified. This test has been used[12] as proof for the presence of a thio ether radical in the original compound. Although this test was negative in the case of two compounds (10 and 12, Table IV), the ultra-

TABLE III

2,4-DISUBSTITUTED-6-METHYL-5,7-DIKETO-4,5,6,7-TETRAHYDROTHIAZOLO[5,4-d]PYRIMIDINES



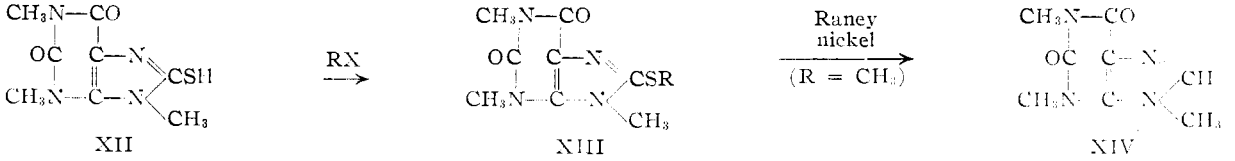
	R	R'	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	CH_3	NHC_2H_5	241–243	21	$C_9H_{12}O_2N_4S$	44.99	45.19	5.04	4.34	23.32	23.09	13.34	13.60
2	CH_3	NHC_4H_9[a]	202–204	22	$C_{11}H_{16}O_2N_4S$	49.24	49.34	6.01	5.88	20.88	20.79	11.95	12.28
3	CH_3	NHC_6H_{11}[b]	206–207[c]	70	$C_{13}H_{18}O_2N_4S$	53.04	52.86	6.16	5.92	19.03	19.04	10.89	11.08
4	CH_3	$NHCH_2C_6H_5$	223–226	31	$C_{14}H_{14}O_2N_4S$	55.99	56.12	4.03	4.73	18.65	18.48	10.68	10.82
5	CH_3	$NHCH_2C_6H_{11}$[d]	214–216	59	$C_{14}H_{20}O_2N_4S$	54.53	54.64	6.51	6.45	18.17	17.91	10.40	10.28
			213–215[e]	92[e]			54.42[e]		6.47[e]		17.93[e]		10.38[e]
6	H	$N(CH_2C_6H_{11})(CONHCH_3)$	270[f]	86	$C_{15}H_{21}O_3N_5S$	51.26	51.38	6.02	6.17	19.94	19.85	9.12	9.34
7	CH_3	$N(CH_2C_6H_{11})(CONHCH_3)$	235[g]	97	$C_{16}H_{23}O_3N_5S$	52.59	52.66	6.34	6.54	19.17	18.88	8.77	8.57
			235[g,h]	70[h]			52.79[h]		6.39[h]		19.16[h]		8.88[h]
8	H	$NHCH_2C_6H_{11}$	335[g]	98	$C_{13}H_{18}O_3N_4S$	53.04	53.29	6.16	6.13	19.03	18.87	10.89	10.81

[a] Mol. wt. (camphor), 275; calcd., 268. [b] Cyclohexylamino. [c] This melting point was taken with material which had been dried *in vacuo* at 65°; material which had not been dried melted at about 110° with the loss of one molecular equivalent of ethanol. [d] Hexahydrobenzylamino. [e] Found for material obtained from compound 7. [f] The compound melted with liberation of a gas, resolidified and melted at 335° dec. [g] Melted with decomposition. [h] Found for material prepared from compound 6.

(10) The term alkyl has been used (formula XIII) to include methyl, ethyl, propyl, isopropyl, allyl, butyl, cyclohexyl, benzyl, β-hydroxyethyl, β-methoxyethyl, β-acetoxyethyl, carboxymethyl and β-diethylaminoethyl.

(11) Compound 11 (Table IV) was prepared by acetylation of 9.

(12) H. Blitz and H. Bülow, *Ann.*, **426**, 306 (1922).



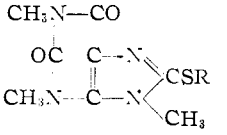
violet spectra of these products were essentially identical with that obtained from the thioether, compound 2, Table IV.[13]

250° or when boiled with water; in the former reaction ethylene sulfide[14] was isolated.

Some of the products were tested for diuretic activity in the Eli Lilly and Co. laboratories. The following compounds were inactive when administered orally in 500-mg. doses to dogs: compounds 1, 5 and 6, Table I, compounds 1, 2, 3, 9, 10 and 11, Table II, and compounds 1, 5, 6, 7, 8 and 9, Table IV.

TABLE IV

1,3,9-TRIMETHYL-8-ALKYLTHIOISOXANTHINES



Compounds 1, 9, 10 and 12 were recrystallized from water; 3, 4, 6 and 7 from ethanol; 2, 5, 8 and 13 from dilute ethanol; 11 from 2-butanone.

	R	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	CH_3	240–242	56	$C_9H_{12}O_2N_4S$	44.98	45.15	5.04	5.17	23.32	23.46	13.34	13.33
2	C_2H_5[a]	220–222	84	$C_{10}H_{14}O_2N_4S$	47.22	47.35	5.55	5.63	22.03	22.01	12.61	12.54
3	C_3H_7	203	73	$C_{11}H_{16}O_2N_4S$	49.24	49.39	6.01	6.05	20.88	20.85	11.95	12.26
4	C_4H_9	171–172	71	$C_{12}H_{18}O_2N_4S$	51.03	51.18	6.43	6.38	19.84	19.66	11.36	11.42
5	CH_2=$CHCH_2$	199	88	$C_{11}H_{14}O_2N_4S$	49.60	49.60	5.30	5.25	21.04	21.28	12.04	12.36
6	$(CH_3)_2CH$	182	51	$C_{11}H_{16}O_2N_4S$	49.24	49.63	6.01	6.21	20.88	20.72	11.95	11.70
7	C_6H_{11}[b]	222–223	15	$C_{14}H_{20}O_2N_4S$	54.52	54.35	6.54	6.31	18.17	18.23	10.40	10.68
8	$C_6H_5CH_2$	200–201	45	$C_{15}H_{16}O_2N_4S$	56.94	57.14	5.10	5.19	17.71	17.67	10.13	10.26
9	$HOCH_2CH_2$	250[c]	91	$C_{10}H_{14}O_3N_4S$	44.42	44.66	5.22	5.46	20.73	20.75	11.87	12.18
10	$CH_3OCH_2CH_2$[d]	169–171	74	$C_{11}H_{16}O_3N_4S$	46.46	46.49	5.67	5.79	19.71	19.69	11.28	11.58
11	$CH_3COOCH_2CH_2$	159–161	12	$C_{12}H_{16}O_4N_4S$	46.14	46.12	5.16	5.03	17.94	17.90	10.27	10.28
12	$HOOCCH_2$[e]	275[f]	84	$C_{10}H_{12}O_4N_4S$	42.24	42.48	4.26	4.07	19.71	19.70	11.28	11.41
13	$HCl\cdot(C_2H_5)_2NCH_2CH_2$	260[f]	31	$C_{14}H_{24}O_2H_5SCl$					19.36	19.35	Cl, 9.80	9.64

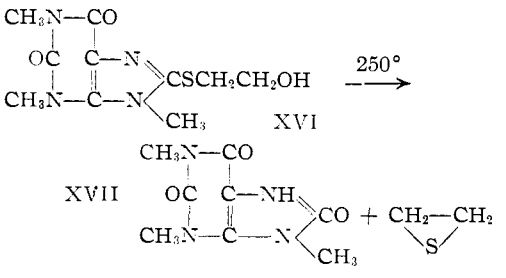
[a] λ_{max} 260 mμ (log ε 4.09), 281 mμ (log ε 4.11). [b] Cyclohexyl. [c] Decomposed with gas evolution to a solid which melted at about 320° dec. [d] λ_{max} 260 mμ (log ε 4.09), 281 mμ (log ε 4.11). [e] λ_{max} 230 mμ (log ε 4.08), 283 mμ (log ε 4.10). [f] Melted with decomposition.

When benzyl bromide was used as the alkylating agent 1,3,9-trimethyl-7-benzyl-8-thiouric acid (XV) was isolated in addition to the desired 8-benzylthio derivative.

In conformity with its isoxanthine structure 1,3,9-trimethyl-8-methylthioiosoxanthine (XIII, R = CH_3), when refluxed in water with Raney nickel, yielded 1,3,9-trimethylisoxanthine (XIV); a strong mercaptan odor was noticed in the reaction mixture.

Acetylation of 1,3,9-trimethyl-8-β-hydroxyethylthioisoxanthine (XVI) yielded the 8β-acetoxyethylthio derivative (11, Table IV).

The 8β-hydroxyethylthio derivative XVI decomposed into 1,3,9-trimethyluric acid (XVII) at



Experimental

Alkyl Isothiocyanates.—The ethyl and allyl esters were purchased. The methyl[15] and cyclohexyl[16] esters were prepared by known methods. Propyl, isopropyl, butyl, benzyl and hexahydrobenzyl isothiocyanates were obtained by the described general procedure[15] except that the amine was introduced during a period of 1.5 hours, the reaction mixture was not heated but was stirred for 2 hours at room temperature and the ethyl chlorocarbonate was then added over a period of 2 hours. The yield of the isopropyl ester was 45%; the other yields were 74–87%.

The hexahydrobenzyl ester boiled at 123–126° (17 mm.).

Anal. Calcd. for $C_8H_{13}NS$: N, 9.03. Found: N, 9.09.

1,3-Dimethyl-5-(3-alkylthioureido)-6-aminouracils (II) (Table I).—1,3-Dimethyl-5,6-diaminouracil[3] (I, 0.30 mole), 0.33 mole of the required isothiocyanate and about 300 cc. of 95% ethanol were stirred and heated on a steam-bath for 6 hours. The cooled mixture was filtered and the product was washed successively with water, ethanol and ether.

1,3-Dimethyl-8-thiol-9-alkylisoxanthines (III) (1–6, Table II) and 2-Alkylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-*d*]pyrimidines (V) (1–5, Table III) from

(13) The differences in the ultraviolet spectra of methoxycaffeine and tetramethyluric acid can be seen in curves published by H. Fromherz and A. Hartmann (*Ber.*, **69**, 2420 (1936)).

(14) It had been found by F. G. Bordwell and H. M. Andersen (THIS JOURNAL, **75**, 4959 (1953)) that pyrolysis of 2-hydroxy-1-propylthiouronium benzoate yielded propylene sulfide.

(15) M. L. Moore and F. S. Crossley, *Org. Syntheses*, **21**, 81 (1941).

(16) A. Skita and H. Rolfes, *Ber.*, **53**, 1242 (1920).

1,3-Dimethyl-5-(3-alkylthioureido)-6-aminouracils (II).—The required uracil (II, 0.05 mole), dissolved in concentrated hydrochloric acid,[17] was refluxed vigorously for 6 hours.[18] The precipitate (III) was filtered from the hot mixture and was washed with concentrated hydrochloric acid. The acidic wash solution and the filtrate were combined, evaporated to dryness and the residue (A) was treated in the manner described below. The product (III) was washed successively with water, ethanol and ether.

Eight uracils (Table I, compounds 1, 2, 3, 5, 6, 7 and 8 and also an impure sample of 1,3-dimethyl-5-(3-propylthioureido)-6-aminouracil)[19] were treated with acid in the manner mentioned above or by modifications of this process. In six instances, the isoxanthines (III) (1–6, Table II) precipitated from the reaction mixture.

In four of the eight instances, it was shown that the reaction mixture also contained thiazolopyrimidines (V) (Table III); in another instance we were able to isolate only the thiazolopyrimidine (3, Table III) from the reaction mixture.

In order to isolate the thiazolopyrimidine, the residue (A) was extracted with dilute ammonia water and the extract was discarded. The insoluble material was then extracted first with hot ethanol and finally, if any solid remained, with hot chloroform. Upon concentration of the solutions, the thiazolopyrimidine V precipitated.

In the preparation of 8-thiol-1,3,9-trimethylisoxanthine (1, Table II) it was necessary to remove the precipitated product by filtration after the reaction mixture had been heated for 15 minutes in order to avoid excessive frothing. The filtrate was then refluxed for 45 minutes and the product was again removed by filtration. In this instance, further heating was unnecessary.

1,3-Dimethyl-8-thiol-9-butylisoxanthine (4, Table II) was precipitated with acid from a dilute ammoniacal solution before recrystallization.

In order to obtain 1,3-dimethyl-8-thiol-9-ethylisoxanthine (2, Table II) and 2-ethylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo-[5,4-d]pyrimidine (1, Table III), the reaction mixture was evaporated to dryness, the residue was recrystallized from water and the crystalline material was extracted with dilute ammonia water. The insoluble material was compound 1 (Table III); acidification of the ammoniacal extract yielded compound 2 (Table II).

When compound II, R = isopropyl, was refluxed with hydrochloric acid, neither III nor V, R = isopropyl, could be isolated; the general procedure was employed.

1,3-Dimethyl-9-alkylisoxanthines (IV) (7–11, Table II) from 1,3-Dimethyl-8-thiol-9-alkylisoxanthines (III).—Compounds 8–11 (Table II) were prepared by treatment of the required thiolisoxanthine with nitrous acid according to the procedure which H. Biltz, *et al.*,[20] used to obtain 1,3-dimethyl-9-ethylisoxanthine (IV, R = C_2H_5). Compound 7 was prepared by a known procedure[20] and also by the following method.

A mixture of 16.0 g. of 8-thiol-1,3,9-trimethylisoxanthine (III, R = CH_3), 50 g. of Raney nickel[21] and 150 cc. of water was refluxed for 1 hour. The hot mixture was filtered, the nickel was washed with 300 cc. of hot water and the combined filtrate and wash water was evaporated to a volume of 30 cc. The product was precipitated with 450 cc. of ethanol, and recrystallized from dilute ethanol; yield 7.3 g. (53%), m.p. 284–286°, mixed m.p. with IV (R = CH_3), obtained by the use of nitrous acid, 285–287°.

Proof of Structure of 2-Hexahydrobenzylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]-pyrimidine (V, R = $CH_2C_6H_{11}$). 2-Hexahydrobenzylamino-4-carbobutoxy-5-aminothiazole (VII).—Twenty grams of butyl nitrosocyanoacetate was reduced with aluminum amalgam in the manner in which Cerchez[22] reduced 25 g. of diethyl isonitrosomalonate. The ether extract of the reaction mixture was evaporated to a volume of 75 cc. Hexahydrobenzyl isothiocyanate (8.0 g.) was added and after 12 hours the mixture was evaporated to a small volume. The precipitate was filtered and washed with a small amount of ether; yield 8.0 g. (22% based on butyl nitrosocyanoacetate), m.p. 142–143° after recrystallization from benzene.

Anal. Calcd. for $C_{15}H_{25}O_2N_3S$: C, 57.85; H, 8.09; N, 13.49; S, 10.30. Found: C, 57.65; H, 8.05; N, 13.47; S, 10.43.

2-(1-Hexahydrobenzyl-3-methylureido)-4-carbobutoxy-5-aminothiazole (VIII).—Compound VII (4.0 g., 0.013 mole), 0.7 g. (0.013 mole) of methyl isocyanate[23] and 20 cc. of anhydrous pyridine were heated on a steam-bath for 1 hour. The pyridine was removed, the oily residue was triturated with water and crystallized from methanol; yield 46%, m.p. 135–137°.

Anal. Calcd. for $C_{17}H_{28}O_3N_4S$: C, 55.41; H, 7.66; N, 15.21; S, 8.70. Found: C, 55.77; H, 7.57; N, 15.20; S, 8.97.

The benzal derivative was obtained when 1.0 g. of VIII, 15 cc. of ethanol and 2 cc. of benzaldehyde were refluxed for 12 hours, the mixture evaporated to dryness and the residue triturated with petroleum ether (30–40°); yield 1.3 g., m.p. 156–158° after recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{32}O_3N_4S$: C, 63.14; H, 7.06; N, 12.27; S, 7.02. Found: C, 63.22; H, 7.08; N, 12.31; S, 6.75.

2-(1-Hexahydrobenzyl-3-methylureido)-4-carbobutoxy-5-(3-methylureido)-thiazole (IX).—This compound was prepared by the procedure used to obtain VIII except that 1.7 g. (0.03 mole) of methyl isocyanate was employed and the reaction mixture was heated 2 hours; the yield 61%, m.p. 167–169°.

Anal. Calcd. for $C_{19}H_{31}O_4N_5S$: C, 53.63; H, 7.35; N, 16.46; S, 7.53. Found: C, 53.85; H, 7.26; N, 16.46; S, 7.86.

2-(1-Hexahydrobenzyl-3-methylureido)-6-methyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (X, R = H) (6, Table III).—Compound IX (20.4 g.) and 12 g. of sodium hydroxide, dissolved in a mixture of 100 cc. of water and 100 cc. of ethanol, were refluxed vigorously for 5 minutes over a free flame. A hot mixture of 70 cc. of acetic acid and 600 cc. of water was added and the reaction mixture was cooled. The precipitate was dissolved in aqueous potassium hydroxide solution, the product was precipitated with acetic acid and washed successively with water, ethanol and ether.

2-(1-Hexahydrobenzyl-3-methylureido)-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (X, R = CH_3) (7, Table III). (A) From X, R = H.—Compound X, R = H (14.6 g.), 2.7 g. of potassium hydroxide, dissolved in 50 cc. of water and 2.6 cc. of methyl iodide were heated for 20 hours at 100° in a pressure bottle. A concentrated aqueous solution of 2.7 g. of potassium hydroxide was added, the precipitate was filtered and washed successively with water, ethanol and ether.

(B) From V, R = Hexahydrobenzyl.—Four grams (0.013 mole) of V, 20 cc. of pyridine and 1.6 cc. (0.026 mole) of methyl isocyanate were heated on a steam-bath for 2 hours. The solvent was removed and the residue was washed with ether.

The infrared spectra of X, R = CH_3, prepared by methods A and B, were identical.

2-Hexahydrobenzylamino-6-methyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (XI, R = H) (8, Table III).—Compound X, R = H (4.0 g.), was heated (bath temperature 300°) in a nitrogen stream for 1 hour. The effluent nitrogen was passed into anhydrous benzene in order to collect the methyl isocyanate which was evolved. The residue was purified for analysis. The benzene solution was treated with dry methylamine and then evaporated to dryness; a mixed m.p. of the residue (m.p. 104–107°) with 1,3-dimethylurea (m.p. 105–108°) was 104–107°.

2-Hexahydrobenzylamino-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]pyrimidine (XI, R = CH_3) (5, Table III) from 2-(1-Hexahydrobenzyl-3-methylureido)-4,6-dimethyl-5,7-diketo-4,5,6,7-tetrahydrothiazolo[5,4-d]-pyrimidine (X, R = CH_3) (7, Table III).—Compound X, R = CH_3, prepared from V, R = hexahydrobenzyl, was treated as described above for the preparation of XI, R =

(17) The quantity of acid employed for the uracil (Table I) was as follows: for 1, 75 cc.; for 2, 100 cc.; for 3 and 5, 150 cc.; for 7, 400 cc.; for 6, 500 cc.; for 8, 650 cc. and for the propyluracil, 65 cc.

(18) In a number of instances precipitation of the product was completed after about 2 hours.

(19) Obtained by the general procedure described above.

(20) H. Biltz, K. Strufe, E. Topp, M. Heyn and R. Robl, *Ann.*, **423**, 200 (1921).

(21) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(22) V. Cerchez, *Bull. soc. chim.*, [4] **47**, 1282 (1930).

(23) J. Colucci, *Can. J. Research*, **23B**, 111 (1945).

H, except that the bath temperature was 270°. The residue was dissolved in chloroform and the product (XI, R = CH_3) was precipitated with petroleum ether (30–40°); a mixed m.p. of this product with V, R = hexahydrobenzyl (m.p. 214–216°), was found to be 213–216°. The benzene solution upon treatment with methylamine yielded 1,3-dimethylurea.

A sample of X, R = CH_3, which had been prepared from X, R = H, was heated at 270° for 1 hour, the residue was dissolved in chloroform and the product was precipitated with petroleum ether (30–40°). After recrystallization from ethanol, the product (XI, R = CH_3) melted at 212–215°; a mixed m.p. with V, R = hexahydrobenzyl (m.p. 214–216°) was 212–215°.

Butyl 2,3-Diaminopropionate Dihydrochloride.—A mixture of butyl nitrosocyanoacetate (10.0 g.), 0.2 g. of platinum oxide catalyst, 50 cc. of ethanol and 5.0 cc. of concentrated hydrochloric acid was hydrogenated under an initial pressure of 50 pounds for 40 hours. Ether was added, the precipitate (3.7 g.) was dissolved in boiling dilute ethanol, the solution was treated with charcoal, filtered and the filtrate was cooled. The precipitate was recrystallized from dilute ethanol; m.p. 205° dec.

Anal. Calcd. for $C_7H_{18}O_2N_2Cl_2$: N, 12.02; Cl, 30.42. Found: N, 12.04; Cl, 30.55.

Thermal Decomposition of 1,3-Dimethyl-5-(3-ethylthioureido)-6-aminouracil (II, R = C_2H_5).—Twelve grams of II was heated at 240–250° for 25 minutes. The residue (9.7 g.) was dissolved in dilute ammonia water, the solution was heated with charcoal, filtered and the filtrate was acidified with acetic acid. The precipitated 8-thioltheophylline (VI) was washed successively with water, ethanol and ether; yield 8.7 g. (89%), m.p. 320° dec.[24] after recrystallization from water.

Anal. Calcd. for $C_7H_8O_2N_4S$: C, 39.61; H, 3.80; N, 26.40; S, 15.11. Found: C, 39.70; H, 3.63; N, 26.37; S, 15.13.

For further identification, the product was converted into theophylline in the following manner. A mixture of 1.0 g. of the material, 20 cc. of ethanol, 5 cc. of water and 5 g. of Raney nickel[21] was refluxed for 2 hours. The hot mixture was filtered, the nickel was washed with hot ethanol, and the combined filtrates were evaporated to dryness. The residue was recrystallized from ethanol (yield 0.5 g., 60%) and then from water; m.p. 263–265°; a mixed m.p. with an authentic sample of theophylline (m.p. 264–266°) was 263–266°.

1,3-Dimethyl-5-nitroso-6-hydroxyuracil.—Fifty grams of 1,3-dimethyl-5-nitroso-6-aminouracil[3] and 250 cc. of water were stirred and refluxed while 25 cc. of concentrated hydrochloric acid was added during a two-minute period. The mixture was refluxed until the original red-violet color became pale green (20 minutes) and then it was immediately cooled with ice. The precipitate, the monohydrate, was washed with water; yield 43.0 g. (85%). The material was recrystallized from ethanol and then, for analysis, it was dehydrated at 65° *in vacuo;* m.p. 144–147°.[25]

Anal. Calcd. for $C_6H_7O_4N_3$: C, 38.92; H, 3.81. Found: C, 38.82; H, 3.95.

1,3-Dimethyl-5-amino-6-hydroxyuracil.—1,3-Dimethyl-5-nitroso-6-hydroxyuracil monohydrate (6.0 g.), 30 cc. of concentrated ammonia water and a solution of 16.5 g. of sodium hydrosulfite in 75 cc. of water were heated on a steam-bath until the red-violet solution became colorless (3 minutes). Concentrated hydrochloric acid (about 30 cc.) was added to the cold solution until the product had precipitated completely and the mixture had darkened slightly; concentrated ammonia water was then added until the mixture became colorless. The filtered precipitate was washed successively with water, ethanol and ether; yield 4.8 g. (95%), m.p. about 300° dec.[26]

The 5-(3-ethylthioureido) derivative melted at 195° dec.[27] and the 5-(3-allylthioureido) derivative at 186–187°.[28]

(24) E. Ochiai (*Ber.*, **69**, 1650 (1936)), reported m.p. 320–321° dec.

(25) M. A. Whiteley (*J. Chem. Soc.*, **83**, 18 (1903)), reported m.p. 141°.

(26) H. Biltz and P. Damm (*Ber.*, **46**, 3662 (1913)), m.p. about 300° dec.

(27) Ref. 20, gave m.p. 195° dec.

(28) H. Biltz and J. Sauer (*Ber.*, **64**, 752 (1931)), m.p. 192°.

1,3-Dimethyl-8-thiol-9-butylisoxanthine (III, R = C_4H_9).—Five grams of 1,3-dimethyl-5-amino-6-hydroxyuracil, 2.6 g. of potassium hydroxide, dissolved in 20 cc. of water, and 4.1 cc. of butyl isothiocyanate were stirred at room temperature for 15 hours. Concentrated hydrochloric acid (70 cc.) was then added, and the mixture was refluxed vigorously for 2 hours. After refrigeration, the precipitate was filtered and washed with ethanol and then with ether; yield 3.2 g. (41%), m.p. 226–228°. A mixed m.p. with III, R = C_4H_9, which had been prepared from II, R = C_4H_9, was 226–228°.

Effect of Hydrochloric Acid on Mono-(3-isopropylthioureido) Derivatives of 5,6-Diaminouracil and *o*-Phenylenediamine. 5-(3-Isopropylthioureido)-6-aminouracil and Monohydrate.—5,6-Diaminouracil (15.0 g.), 3.2 g. of sodium hydroxide, dissolved in 100 cc. of water, and 7.0 g. of isopropyl isothiocyanate were stirred on a steam-bath for 3 hours. The cold mixture was acidified with concentrated hydrochloric acid, the precipitate was filtered and washed successively with water, ethanol and ether. The product was purified by precipitation from a potassium hydroxide solution with concentrated hydrochloric acid; yield of monohydrate, 12.5 g. (74% based on the isothiocyanate); it melted at about 275° where it decomposed with gas evolution to a solid which melted above 335°. It was dehydrated at 110°.

Anal. Calcd. for $C_8H_{13}O_2N_5S$: C, 39.49; H, 5.39; N, 28.79; S, 13.18. Found: C, 39.37; H, 5.54; N, 28.79; S, 12.91.

After exposure to moist air, the analytical data corresponded to that calculated for a monohydrate.

Anal. Calcd. for $C_8H_{15}O_3N_5S$: C, 36.77; H, 5.79; N, 26.81; S, 12.27. Found: C, 36.73; H, 5.67; N, 27.01; S, 12.73.

8-Thiol-9-isopropylisoxanthine.—5-(3-Isopropylthioureido)-6-aminouracil monohydrate (24.0 g.), dissolved in 900 cc. of concentrated hydrochloric acid, was refluxed vigorously for 4 hours. The precipitate was filtered from the hot mixture and washed successively with concentrated hydrochloric acid, water, ethanol and ether; yield 8.0 g. (38%). It was purified by precipitation from a dilute ammonium hydroxide solution with concentrated hydrochloric acid; m.p. above 335°.

Anal. Calcd. for $C_8H_{10}O_2N_4S$: C, 42.46; H, 4.46; N, 24.76; S, 14.17. Found: C, 42.38; H, 4.32; N, 24.88; S, 14.17.

The thiol compound was converted into 9-isopropylisoxanthine in the following manner. To a stirred mixture of 4.0 g. of 8-thiol-9-isopropylisoxanthine, 15 cc. of concentrated hydrochloric acid and 15 cc. of water, there was added 10 g. of sodium nitrite during a 3-hour period. After stirring for 30 minutes, 30 cc. of water was added, the mixture was filtered and concentrated ammonia water was added to the filtrate until the *p*H was 2. The sulfur-free solid (1.8 g.) which precipitated gradually was recrystallized from water; m.p. 325° dec.

Anal. Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.76; H, 5.38; N, 28.74.

***o*-Amino-(3-isopropylthioureido)-benzene.**—*o*-Phenylenediamine (8.1 g.), dissolved in 300 cc. of anhydrous ether, was stirred while a solution of 7.6 g. of isopropyl isothiocyanate in 100 cc. of ether was added, dropwise, during a 1.5-hour period. After 24 hours, the solution was evaporated to a small volume, petroleum ether (30–40°) was added, and the precipitate was recrystallized first from carbon tetrachloride and then from benzene–petroleum ether; yield 9.4 g. (60%), m.p. 109–111°.

Anal. Calcd. for $C_{10}H_{15}N_3S$: C, 57.37; H, 7.22; N, 20.08; S, 15.33. Found: C, 57.38; H, 6.96; N, 20.23; S, 15.61.

When this compound was refluxed in hydrochloric acid as described above for the thioureidouracil, *o*-phenylenediamine dihydrochloride was obtained; yield 78%, m.p. 250° dec.; the product was identified by conversion into *o*-phenylenediamine.

1,3,9-Trimethyl-8-alkylthioisoxanthines (XIII) (Table IV). General Procedure.—1,3,9-Trimethyl-8-thiolisoxanthine (XII) (7.5 g., 0.033 mole), 2.4 g. (0.043 mole) of potassium hydroxide dissolved in 75 cc. of water, and the required

alkyl halide[29] (0.043 mole) were heated at 100–110° in a pressure bottle for 20 hours. A solution of 2.4 g. (0.043 mole) of potassium hydroxide in 10 cc. of water was added to the cooled, stirred mixture. The product was filtered and washed successively with water, ethanol and ether.

In the preparation of compound 7, 50% ethanol was used as a solvent. To isolate the product, the reaction mixture, after addition of the potassium hydroxide solution, was extracted with chloroform, the extract was evaporated to dryness and the residue was washed with ether.

To prepare compound 9 (XVI), the reaction mixture was merely heated on a steam-bath for 5 minutes.

In the preparation of compound 13, twice the usual quantity of potassium hydroxide was used, and the basic halide was added as the hydrochloride. After heating for 1 hour, the precipitated basic thio ether was filtered and washed, successively, with isopropyl alcohol and ether; yield 3.7 g., m.p. 182–183°. A filtered chloroform solution was treated with hydrogen chloride, the solvent was removed and the oily residue was solidified by rubbing it with ether and then with ethanol.

When the preparation of compound 8 was carried out by the general procedure, a mixture (8.4 g.) of compound 8 and 1,3,9-trimethyl-7-benzyl-8-thiouric acid (XV) was obtained. In order to separate the two isomers, the mixture was extracted with concentrated hydrochloric acid and the insoluble solid (A) was treated as described below. The acidic extract was diluted with water and then neutralized with potassium carbonate to precipitate compound 8.

To obtain XV, the insoluble material (A) was washed with ethanol and ether (yield 1.1 g., 10%) and recrystallized from 2-butanone; m.p. 190–191°.

Anal. Calcd. for $C_{15}H_{16}O_2N_4S$: C, 56.94; H, 5.10; N, 17.71; S, 10.13. Found: C, 56.80; H, 5.08; N, 17.92; S, 10.27.

A mixed melting point of compound 8 with XV was found to be 165–190°. A qualitative test for a thio ether linkage[12] was positive for compound 8 but negative for XV.

Compound 11 was obtained when 6.0 g. of compound 9 and 50 cc. of acetic anhydride were heated for 4 hours on a steam-bath. The excess anhydride was removed *in vacuo*, the residue was washed successively with water, ethanol and ether, and the material was then extracted with chloroform. The extract was evaporated to dryness and the residue was recrystallized from 2-butanone. When the preparation of 11 was attempted by the general procedure described above, compound 9 was obtained.

(29) The iodide was used for the preparation of compound 1, the bromide for compounds 2–10 and the chloride for compounds 12 and 13. Compound 11 was prepared by acetylation of 9.

Four grams of compound XII, 3.0 g. of chloroacetic acid and 10 cc. of water were refluxed for 48 hours, and the precipitate was washed successively with water, ethanol and ether. The product was the 8-carboxymethyl derivative (compound 12).[30]

1,3,9-Trimethylisoxanthine (XIV).—One gram of 1,3,9-trimethyl-8-methylthioisoxanthine (XIII, R = CH_3), 10 cc. of water and 3.3 g. of Raney nickel[21] were refluxed for 1 hour. The hot mixture, which smelled strongly of methyl mercaptan, was filtered, the nickel was washed with hot water, and the filtrate and wash water were combined and evaporated to dryness. The residue was extracted with chloroform and the insoluble material was recrystallized twice from dilute ethanol; yield 0.2 g. (25%), m.p. 285–286°. A mixed melting point with XIV (m.p. 285–287°), which had been prepared from III (R = CH_3), was 285–287°.

Decomposition of XVI. (A).—Ten grams of XVI was heated at 240–260° in a nitrogen stream for 30–60 minutes and the evolved ethylene sulfide (1 cc., micro b.p. 55°)[31] was condensed in an ice-cold receiver. The residue was extracted with chloroform and the extract was discarded. The insoluble material was dissolved in dilute potassium hydroxide solution, the solution was extracted with chloroform, and the water layer was acidified. The precipitate, 1,3,9-trimethyluric acid (XVII), was washed with ethanol and ether (yield 5.0 g., 64%) and recrystallized from water; m.p. 340° dec.[32]

Anal. Calcd. for $C_8H_{10}O_3N_4$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.96; H, 4.63; N, 26.70.

The acetyl derivative melted at 230–236°.[33]

(B).—Three grams of XVI and 150 cc. of water were refluxed for 80 hours. The hot mixture was filtered, the filtrate was cooled and made basic with dilute potassium hydroxide solution. The filtered solution was acidified with concentrated hydrochloric acid and evaporated to a small volume. The precipitate (XVII) was washed with water, ethanol and then with ether; yield 1.9 g. (81%), m.p. 340° dec.

(30) In some instances, thio compounds have been converted into corresponding hydroxy compounds by the action of chloroacetic acid (W. J. Croxall, C. Lo and E. Y. Shropshire, THIS JOURNAL, **75**, 5419 (1953)).

(31) This compound exhibited the properties described by M. Delepine (*Bull. soc. chim.*, [4] **27**, 740 (1920)).

(32) H. Biltz and H. Pardon (*Ber.*, **63**, 2876 (1930)) reported m.p. 340° dec.

(33) H. Biltz and H. Pardon (*J. prakt. Chem.*, [2] **134**, 310 (1932)), m.p. 235°.

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Some Reactions of 3-Substituted Hydantoins

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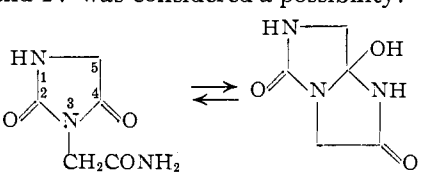
A variety of chemical methods have been used to search for amine–carbonyl interaction in hydantoinacetamides (III). Such interaction was not observed. Improved methods for the cyclization of carbobenzyloxydipeptide derivatives to the corresponding hydantoins are described as well as some novel transformations of hydantoinacetonitriles.

The facile interaction of a peptide nitrogen with a ketonic carbonyl has been reported recently from this Laboratory.[1] As part of a study of peptide bond reactivity, we have investigated the possibility of NH· · ·CO interaction in hydantoin-3-acetamides (for example, III ⇄ IV). Since the reactivity of the 4-carbonyl of hydantoins may be considered intermediate between that of an amide and a ketone,[2] the existence of an equilibrium mixture of III and IV was considered a possibility.



III IV

Among the numerous methods available for the

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