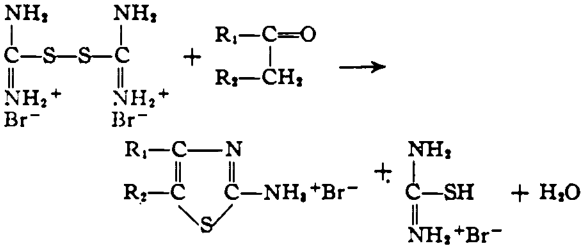
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Ketones with Formamidine Disulfide

BY L. CARROLL KING AND ISABELLE RYDEN

In recent papers from this Laboratory it was demonstrated that ketones react with thiourea and halogens,[1a] or certain oxidizing agents[1b] to give substituted 2-aminothiazoles. It has now been observed that ketones react with formamidine disulfide dihydrobromide[2] to give the corresponding substituted 2-aminothiazoles. The reaction may be formulated as



R_1 = methyl, phenyl or *m*-nitrophenyl
R_2 = H or carbethoxy

In order to determine the generality of this reaction it was used to prepare thiazoles from several ketones, namely, acetophenone, ethyl acetoacetate, acetone and *m*-nitroacetophenone. In each case the thiazole obtained from the reaction mixture agreed in chemical and physical properties with the corresponding substances as prepared previously in this Laboratory.[1a] An attempt to convert propiophenone into 2-amino-4-phenyl-5-methylthiazole by means of this reaction failed. A summary of the yield data for these syntheses is presented in Table I.

TABLE I

Thiazole	M. p., °C.	% Yield Method I^a	Method II^a	Method III^a
2-Amino-4-phenyl	149–151	32,^{b} 42^e 40,^{d} 48^e	48,^{f} 34^g	34,^{h} 2^i
2-Amino-4-methyl-5-carbethoxy	175–177	32^e	57^f	22^{i,j}
2-Amino-4-methyl	228 (dec.)^k	.....	.....	13^{c,i}
2-Amino-4-(3-nitrophenyl)	185–188	19^c	13^{l,f}	0^m
2-Amino-4-phenyl-5-methyl	.....	0	0	0

[a] See experimental part. Yields are based on the amount of formamidine disulfide used except in (ref. *e*), in which case the yield is based on the amount of ketone used. [b] Heating time, twelve hours. [c] Heating time, twenty-four hours or forty-eight hours. [d] Heated two hours at 125°. [e] Five-hundredths mole of ketone and 0.1 mole of formamidine disulfide dihydrobromide was used in the reaction. [f] Five-hundredths mole of thiourea. [g] One-tenth mole of thiourea. [h] Alcohol as solvent. [i] Alcohol-water as solvent. [j] Reaction mixture was refluxed two hours. [k] Melting point of the picrate. [l] Heated overnight on the steam-bath, then heated to 125° for ten minutes. [m] Only sulfur and starting ketone recovered.

It was further observed that addition of certain weak bases to the reaction mixture caused an increase in the yield of the thiazoles. When the mole ratio of base to formamidine disulfide dihydrobromide was 1, the maximum yield of thiazole was obtained. A strong base, such as sodium hydroxide, could not be used. The results of these experiments are listed in Tables I and II.

TABLE II^a

Base	% Yield of thiazole^b
Thiourea	57
$NaHCO_3$	60
NaO_2CCH_3	62
$HO_2CC_6H_4CO_2K$^{c}	48
NaHS	38
NaOH	0

[a] One-tenth mole of ethyl acetoacetate, 0.05 mole of formamidine disulfide was heated with 0.05 mole of the appropriate base. [b] Yields are based on the formamidine disulfide dihydrobromide used. 2-Amino-4-methyl-5-carbethoxythiazole was isolated in each case. [c] Potassium acid phthalate.

In general the best yields of thiazole were obtained when mixtures consisting of the ketone, formamidine disulfide dihydrobromide and a weak base, such as thiourea, were heated for twelve to twenty-four hours on the steam-bath in the absence of a solvent. A large excess of ketone was of no advantage except in so far as it assisted in the mixing of the reaction components. An excess of formamidine disulfide dihydrobromide caused only a slight increase in the yield of thiazole. This was probably due to the near solid nature of the reaction mixture and the resulting inefficient mixing of the components. In all the reactions carried out, sulfur was observed as a by-product.

In order to account for this sulfur it was assumed that two competing reactions take place: (1) the reaction of the ketone with the disulfide to form the thiazole, and (2) the decomposition of formamidine disulfide dihydrobromide to form sulfur, thiourea and cyanamide.[3] This view is in accord with the data which show that the best yield of thiazole is obtained when the most reactive ketone is used in the reaction. For example, ethyl acetoacetate, under the best of conditions, gave a 62% yield of thiazole, whereas acetophenone gave only a 48% yield. Ethyl acetoacetate gave 22% of thiazole when the reaction

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[1a] Dodson and King, THIS JOURNAL, 67, 2242 (1945).

[1b] Dodson and King, *ibid.*, 68, 871 (1946).

[2] It is known that certain disulfides as thiocyanogen react with double bonds and reactive hydrogen atoms. Kaufman and Oehring, *Ber.*, 59, 187 (1926); Söderbäch, *Ann.*, 443, 142 (1925); Brewster and Dains, THIS JOURNAL, 58, 1364 (1936); J. L. Wood, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 240.

[3] This decomposition is known to take place readily when water is present. Claus, *Ann.*, 179, 143 (1875); Remsen and Turner, *Am. Chem. Soc. J.*, 25, 192 (1901).

was carried out in the presence of water. Acetophenone in the presence of alcohol–water as a solvent gave only a 2% yield of the thiazole.

In view of the establishment of the present reaction, formamidine disulfide can be considered as one of the intermediate substances formed in the thiazole synthesis reported by Dodson and King.[1b]

Experimental

Formamidine Disulfide Dihydrobromide.[4]—To 1.0 mole of thiourea dissolved in a minimum volume of boiling absolute alcohol 100 g. of bromine was added. The product which crystallized from the hot solution was separated, dried at 50° for eight hours, and used without further purification.

Preparation of Thiazoles.—These preparations were varied widely in an attempt to study reaction conditions.

Method I.—A mixture of the appropriate ketone and formamidine disulfide dihydrobromide was heated on the steam-bath or as specified otherwise in Table I. Except where noted in the table, 0.1 mole of ketone and 0.05 mole of formamidine disulfide dihydrobromide was used. At the end of the heating period the reaction mixture was acidified with 2 cc. of concentrated hydrochloric acid and thoroughly extracted with ether. The crude thiazole was then recovered from the reaction mixture as described in previous papers.[1a] This crude thiazole was dissolved in hot water–alcohol and the solution was treated with norit, filtered and cooled. The crystals which separated from the cooled solution were used as the basis for the yields reported in Table I.

Method II was similar to I except the reaction mixture consisted of the appropriate ketone, formamidine disulfide dihydrobromide and thiourea or other base.

Method III was similar to I except a solvent was added to a mixture of the appropriate ketone and formamidine disulfide dihydrobromide. The following examples will illustrate Method III.

2-Amino-4-methyl-5-carbethoxythiazole.—One-tenth mole of ethyl acetoacetate was added to a solution of 0.05 mole of formamidine disulfide dihydrobromide in 50 cc. of water and the mixture was refluxed for two hours. A small amount of sulfur was filtered from the solution and the thiazole recovered by precipitating with concentrated ammonia. The product was purified in a manner similar to that described above; yield 22%; m. p. 175–177°.

2-Amino-4-methylthiazole.—Five-hundredths mole of formamidine disulfide dihydrobromide was refluxed in 50 cc. of acetone and 50 cc. of water. After twelve hours the reflux condenser was removed and the excess acetone distilled out. The reaction mixture was then made strongly alkaline with sodium hydroxide and the thiazole extracted with ether. The thiazole was determined by converting to the picrate; m. p. 228–230° (dec.).

Summary

1. It has been demonstrated that methyl ketones react with formamidine disulfide dihydrobromide to give substituted 2-aminothiazoles.

2. The conditions for effecting this reaction were studied.

3. It is suggested that formamidine disulfide may be an intermediate, when thiazoles are synthesized by direct action of oxidizing agents with ketones and thiourea.

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[4] Formamidine disulfide dihydrobromide was prepared in this manner by Claus (*Ann.*, **179**, 138 (1875)).

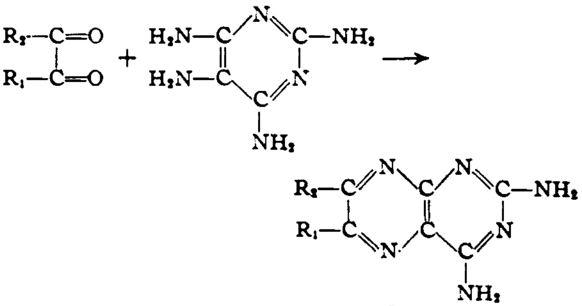
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Pyrimido[4,5-b]pyrazines. II. 2,4-Diaminopyrimido[4,5-b]pyrazine and Derivatives[1]

BY M. F. MALLETTE, E. C. TAYLOR, JR., AND C. K. CAIN

A previous paper[2] reported the preparation and properties of 2,4-dihydroxypyrimido[4,5-b]pyrazine (Lumazine) and several of its derivatives as well as 2-amino-4-hydroxypyrimido[4,5-b]pyrazine and several of its derivatives. The recent synthesis of folic acid[3] confirmed the previously reported evidence[4] that the pyrimido[4,5-b]pyrazine nucleus is present in the molecule. Moreover, the substituents in the 2 and 4 positions (amino and hydroxyl, respectively) are the same as those present in xanthopterin.

It seemed of interest to prepare 2,4-diaminopyrimido[4,5-b]pyrazine and several of its derivatives. Traube[5] described the preparation of 2,4,5,6-tetraminopyrimidine from guanidine and malononitrile. Condensation of the bisulfite salt of this compound with 1,2-dicarbonyl compounds has resulted in the production of molecules having the general structure shown in Formula I.



I

By the use of the appropriate symmetrical dicarbonyl compounds, five substances of this type (1–5 of Table I) were prepared.

Condensation of methylglyoxal with the tetraminopyrimidine should result in the formation

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[1] The work presented in this paper was undertaken in collaboration with the Office of Naval Research, Navy Department, Washington, D. C., and was aided by a grant to Cornell University by the Nutrition Foundation, Inc., New York City. It represents a part of a collaborative project on "Newer Members of the B Group of Vitamins."

[2] Cain, Mallette and Taylor, THIS JOURNAL, **68**, 1996 (1946).

[3] Angier, *et al.*, *Science*, **103**, 667 (1946).

[4] Mitchell, THIS JOURNAL, **66**, 274 (1944); Bloom, Vandenbelt, Binkley, O'Dell and Pfiffner, *Science*, **100**, 295 (1944).

[5] Traube, *Ber.*, **37**, 4544 (1904).