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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RECEIVED MARCH 21, 1947

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

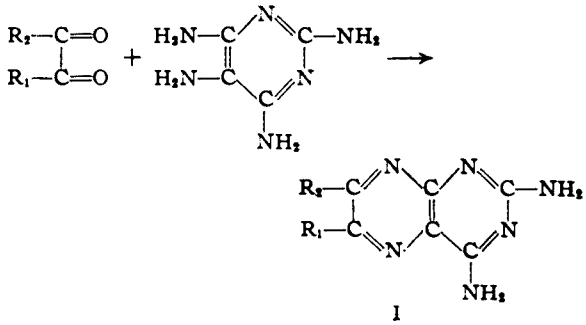
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

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

(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).

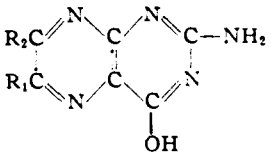
(3) Angier, *et al.*, *Science*, **103**, 667 (1946).

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

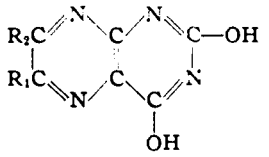
(5) Traube, *Ber.*, **37**, 4544 (1904).

of either 2,4-diamino-6-methyl- or 2,4-diamino-7-methylpyrimido[4,5-b]pyrazine. The structure of the product actually obtained under the reaction conditions employed is being investigated and will be reported in a forthcoming paper.

Table I lists the compounds prepared and studied and significant data from ultraviolet absorption spectra of solutions in 0.1 *N* hydrochloric acid. Compounds 7–10 which are represented by the general formulas II and III and which have been reported previously[2] are included for the purpose of comparing their absorption spectra in solution in 0.1 *N* hydrochloric acid.



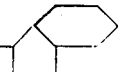
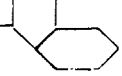
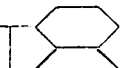
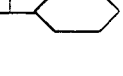
II



III

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOLUTIONS IN 0.1 *N* HYDROCHLORIC ACID

Compound	Structure	Maxima mμ	Maxima log ε	Minima mμ	Minima log ε
1	I. R_1=R_2=H	240	4.06	227	3.92
		285	3.68	262	3.57
		332	3.93	297	3.66
2	I. R_1=R_2=CH_3	242	4.14	232	4.07
		277	3.59	267	3.53
		335	4.04	290	3.54
3	I, R_1=R_2= 	267	4.25	250	4.14
		370	4.19	318	3.54
4	I. R_1=  R_2= 	263[a]	4.71	225	4.36
		287	4.29	278	4.22
		402	4.24	337	3.35
		420	4.24	410	4.21
5	I. R_1=  R_2= 	232	4.55	217	4.32
		327	4.38	272	3.75
6	I.[b]	242	4.07	230	3.97
		280	3.75	262	3.67
		330	4.03	295	3.68
7	II. R_1=R_2=H	315	3.81	270	3.15
8	II. R_1=R_2=CH_3	250	3.93	238	3.87
		320	3.97	272	3.21
9	III. R_1=R_2=H	227	3.96	216	3.87
		325	3.78	268	2.72
10	III. R_1=R_2=CH_3	(shoulder)			
		243	3.97	270	2.75
		330	4.06		
11		273	4.22	246	3.44

Because of insolubility of compound 4 in dilute aqueous acid, spectrum was measured on a solution in ethylene glycol to which concentrated hydrochloric acid had been added to make resulting solution contain 0.1 mole hydrochloric acid per liter. [b] Compound 6 is 2,4-diamino-6(or 7)-methylpyrimido[4,5-b]pyrazine. [c] Compound 11 is 2,4,5,6-tetraminopyrimidine bisulfite.

Compounds 1–6 of Table I did not exhibit satisfactory melting points for establishing purity; nor could they be analyzed for their elements by ordinary combustion procedures. Acceptable values for carbon and for nitrogen were obtained for compounds 3 and 6 by other methods as outlined in the Experimental Section. A comparison of methods of preparation, properties and ultraviolet absorption spectra of compounds 1–6 with those of compounds 7–10 allow formulas to be assigned with reasonable confidence. Evidence that pure samples were obtained was derived by recrystallizing until no change in absorption spectra could be detected.

Several derivatives of 2,4-diaminopyrimido-[4,5-b]pyrazine exhibit marked anti-folic acid activity for various bacteria. This work is being reported elsewhere.[6]

Experimental

2,4,5,6-Tetraminopyrimidine Bisulfite.—Our synthesis of this compound was a modification of that reported by Traube.[5] Since the yield was appreciably better and the method is considerably more convenient, the procedure is reported in detail.

To a solution of sodium ethoxide prepared by dissolving 200 g. (8.7 moles) of sodium in 6 liters of absolute ethanol, 600 g. (6.25 moles) of guanidine hydrochloride[7] and 450 g. (6.8 moles) of malononitrile were added. The mixture was refluxed on a water-bath for six hours while being stirred by means of a stream of dry air. The mixture was then cooled to room temperature and the solid, which consisted of sodium chloride and 2,4,6-triaminopyrimidine, was collected by filtration and washed with absolute ethanol. The solid was divided into two approximately equal parts for convenience in handling. Each portion was placed in a 4-liter beaker and 1 liter of water added. After vigorous mechanical stirring had resulted in a homogeneous suspension, glacial acetic acid was added until the mixture was neutral to litmus. Further addition of 200 ml. of glacial acetic acid resulted in complete solution. A solution of 220 g. (3.2 moles) of sodium nitrite in 500 ml. of water was added while vigorous stirring was continued. The bright red solid which had formed was filtered as quickly as possible to avoid continued contact with excess nitrous acid, washed with water and pressed to drain off most of the water. The partially dried solid, 2,4,6-triamino-5-nitrosopyrimidine, was again divided into two parts for convenience in handling. Each portion was suspended in 1 liter of water and heated to 60–70° with mechanical stirring. Solid sodium hydrosulfite was added slowly until the red color disappeared, each portion of the pyrimidine requiring approximately 2175 g. (12.5 moles). The mixture was then heated to boiling and filtered through a steam-jacketed Büchner funnel. The filtrate, on standing in the refrigerator, deposited 755 g. (54%) of a yellow product which was sufficiently pure to be used without further purification. For the determination of the ultraviolet absorption spectrum, a sample was recrystallized five times from water to yield well-defined orange needles exhibiting parallel extinction. Upon heating, the crystals progressively darkened without melting.

2,4-Diaminopyrimido[4,5-b]pyrazine.—A mixture of 15.0 g. (0.068 mole) of 2,4,5,6-tetraminopyrimidine bisulfite, 20 g. (0.077 mole) of glyoxal bisulfite and 250 ml. of water was heated to boiling, acidified to *p*H 3 with dilute

(6) Biological testing of these compounds was done by Daniel, Norris, Scott and Heuser of the School of Nutrition of Cornell University. A report of this work has been submitted to the *Journal of Biological Chemistry*.

(7) The authors wish to express their thanks to the New York Color and Chemical Co., Belleville, N. J., for this material.

hydrochloric acid and boiled gently for twenty minutes. The solid which separated on cooling was filtered and dried. The product weighed 9.5 g. (88%). Recrystallization from 2% formic acid gave small needles exhibiting parallel extinction and decomposing upon heating.

2,4-Diamino-6,7-dimethylpyrimido[4,5-b]pyrazine.—This compound was prepared in 85% yield by warming a mixture of 50 g. of 2,4,5,6-tetraminopyrimidine bisulfite, 20 ml. of biacetyl and 300 ml. of water to approximately 80° for one hour. Recrystallization from 0.1 *N* hydrochloric acid gave small prisms exhibiting parallel extinction and progressively darkening without melting upon heating.

2,4-Diamino-6,7-diphenylpyrimido[4,5-b]pyrazine.—A mixture of 5 g. of benzil, 5 g. of 2,4,5,6-tetraminopyrimidine bisulfite, 3 ml. of concentrated hydrochloric acid, 50 ml. of ethanol, 50 ml. of methyl ethyl ketone and 100 ml. of water was refluxed for two hours. The solid which separated on changing the *p*H to 6 and cooling was recrystallized from 80% formic acid to give small elongated prisms in 84% yield. The crystals exhibited parallel extinction and melted with decomposition at 280–283° (cor.).

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.77; N, 26.74. Found: C, 68.89, 69.12; N, 26.74, 26.96.

2,4-Diaminoacenaphtho[1,2-e]pyrimido[4,5-b]pyrazine.—A solution of 1.0 g. of acenaphthenequinone in 25 ml. of dimethylformamide was added to a mixture of 4.5 g. of 2,4,5,6-tetraminopyrimidine bisulfite, 50 ml. of water and 5 ml. of concentrated hydrochloric acid. After heating for four hours on the steam-bath, the mixture was adjusted to *p*H 6 and cooled. The solid obtained in 90% yield was recrystallized from 80% formic acid to give small needles which showed parallel extinction and which progressively darkened without melting upon heating.

2,4-Diaminophenanthro[9,10-e]pyrimido[4,5-b]pyrazine.—A mixture of 2 g. of 2,4,5,6-tetraminopyrimidine bisulfite, 1.5 g. of phenanthrenequinone, 250 ml. of 95% ethanol and 5 ml. of 10% aqueous sodium hydroxide was refluxed for six hours. The solid which separated on cooling was crystallized from 80% formic acid to give an 84% yield of sheaves of small needles exhibiting parallel extinction. Upon heating, the crystals began to sinter at approximately 340° and progessively darkened without melting.

2,4-Diamino-6(or 7)methylpyrimido[4,5-b]pyrazine.—This compound resulted in 90% yield from a mixture of 6 g. of methyl glyoxal, 15 g. of 2,4,5,6-tetraminopyrimidine bisulfite and 200 ml. of boiling water. Recrystallization from 0.1 *N* hydrochloric acid gave prisms showing parallel extinction and darkening without melting upon heating.

Anal. Calcd. for $C_7H_8N_6$: C, 47.72; N, 47.71. Found: C, 47.65, 48.11; N, 47.73, 47.85.

Elementary Analysis of Compounds.—Compounds 3 and 6 of Table I were analyzed for carbon by a modification of the method of Parr.[8] The combustion mixture consisted of 2.5 g. of sodium peroxide, 0.5 g. of potassium perchlorate and 0.2 g. of powdered aluminum for a sample of approximately 50 mg.

The same two compounds were analyzed for nitrogen by the method of Friedrich[9] using a mixture of copper sulfate, potassium sulfate and powdered selenium as catalyst for the digestion.

Summary

2,4-Diaminopyrimido[4,5-b]pyrazine and several of its derivatives have been synthesized. Ultraviolet absorption spectra of solutions of the compounds in dilute acid have been determined.

(8) Parr, THIS JOURNAL, **29**, 1606 (1907).

(9) Pregl-Grant, "Quantitative Organic Microanalysis," The Blakiston Co., Philadelphia, Pa., 1946, p. 82.

ITHACA, N. Y. RECEIVED APRIL 8, 1947

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF STANFORD UNIVERSITY, NORTHWESTERN UNIVERSITY, AND CORN PRODUCTS REFINING COMPANY]

Crystalline 2,3,4,6-Tetrapropionyl-β-D-glucose

BY WILLIAM A. BONNER, CHARLES D. HURD AND SIDNEY M. CANTOR

A large-scale propionylation of α-D-glucose at 100°, using propionic anhydride and sodium acetate, was performed with the assistance of R. J. Smith and E. A. Cleveland, Jr. On subsequent processing, the volatile materials were removed by steam distillation. A sirupy propionate was obtained which crystallized to the extent of about 5% of the weight of the sirup after standing four months at room temperature. The white crystals, which were isolated by centrifuging and purified by washing with petroleum ether, melted at 111–112°, $[\alpha]^{28}D$ 21.8° (*c*, 1.42; ethanol). Preliminary work on the characterization of this crystalline product yielded results suggesting 2,3,4,6-tetrapropionyl-β-D-glucose as a probable structure. Accordingly, synthesis of this substance was undertaken.

Sirupy D-glucose pentapropionate was converted into tetrapropionyl-α-D-glucosyl bromide by action of hydrogen bromide in propionic acid. The resulting bromo compound was a strongly dextro-rotatory liquid. Since it decomposed rapidly, it was converted immediately into 2,3,4,6-tetrapropionyl-β-D-glucose. This material was crystalline, identical with the material above. Although several crystalline aryl tetrapropionyl-D-aldohexosides have been reported earlier,[1] all of the previously reported[2] hexose propionates have been sirups. This crystalline propionate is, therefore, unusual.

2,3,4,6-Tetrapropionyl-β-D-glucose shows marked reducing properties and mutarotates in alcohol. It was quantitatively propionylated in pyridine at −10° to give β-D-glucose pentapropionate, a sirup, $[\alpha]^{25}D$ 14.29°. This latter compound showed no mutarotation in alcohol. Another sirupy pentapropionate was obtained, $[\alpha]^{25}D$ 64.5°, by propionylating a mutarotated sample of the tetrapropionylglucose at room temperature. From these specific rotations and the

(1) Oden, *Arkiv. Kemi, Min. Geol.*, **6**, 18 (1917); *C. A.*, **12**, 581 (1918); Hurd and Bonner, THIS JOURNAL, **67**, 1764 (1945); *J. Org. Chem.*, **10**, 603 (1945); **11**, 50 (1946).

(2) Hess and Messmer, *Ber.*, **54**, 511 (1921); Hurd and Gordon, THIS JOURNAL, **63**, 2657 (1941).