B. Methyl Ester 4b.—By a procedure similar to that used on **4a**, the methyl ester **4b** was obtained in 72% yield upon treatment of the anhydride with methanol, mp 117–118°, $[\alpha]^{27}D$ +3.2°, $[\alpha]^{27}_{235}$ +1240° (*c* 0.63, methanol).

Anal. Calcd for $C_{14}H_{21}N_2SClO_4$ (348.9): C, 48.20; H, 6.07; N, 8.03; S, 9.19. Found: C, 48.23; H, 6.23; N, 8.16; S, 9.13.

C. Methyl Ester 4b from N^{ω}-Benzyloxycarbonyl-S-2-aminoethyl-L-cysteine.—Twelve grams of N^{ω}-benzyloxycarbonyl-S-2-aminoethyl-L-cysteine (0.04 mole), prepared according to the procedure of Lindley[5] (mp 212–213°), was esterified in 90 ml of anhydrous methanol plus 60 ml of 2.5 *N* methanolic HCl at room temperature overnight. After removing the solvent under vacuum, the product was crystallized from acetone with ether. The crystallized compound weighed 13 g (93%), mp 117°.

N^{α}-Benzoyl-N^{ω}-benzyloxycarbonyl-S-2-aminoethyl-L-cysteine Ethyl or Methyl Ester (5). A. Ethyl Ester 5a.—The hydrochloride (**4a**, 7.4 g, 0.0204 mole) was suspended in a mixture of ethyl acetate (100 ml) and ether (100 ml). A solution of 3.1 g of K_2CO_3 (0.0225 mole) in 180 ml of water was added with stirring. The organic layer containing the free base was separated and treated with 2.8 ml (0.024 mole) of benzoyl chloride and a solution of K_2CO_3 in water (2.9 g in 120 ml) with stirring for 30 min. Several drops of pyridine were added. The product in the organic layer was washed with 0.1 *N* HCl, 2% $KHCO_3$, and water. After the organic layer had been dried over anhydrous Na_2SO_4, the solvent was removed under vacuum. The product was crystallized from acetone with petroleum ether to yield 4.62 g (53%), mp 94–96°, $[\alpha]^{27}D$ −37.8° (*c* 1, ethanol).

Anal. Calcd for $C_{22}H_{26}N_2SO_5$ (430.5): C, 61.37; H, 6.09; N, 6.50; S, 7.45. Found: C, 61.11; H, 5.88; N, 6.32; S, 7.15.

B. Methyl Ester 5b.—Similar treatment of the methyl ester hydrochloride **4b** gave a syrup which failed to crystallize but which could be converted to the crystalline amide as described below.

N^{α}-Benzoyl-N^{ω}-benzyloxycarbonyl-S-2-aminoethyl-L-cysteinamide (6).—The syrupy methyl ester **5b**, prepared by benzoylation of 13 g (0.037 mole) of **4b**, was dissolved in 200 ml of anhydrous methanol, and the solution was saturated with anhydrous ammonia at 0°. After the solution had been kept overnight at room temperature, the product was obtained by evaporating the solvent and was recrystallized from methanol with ether plus a small amount of petroleum ether to yield 5.0 g (about 60% for each step; 34% over-all), mp 117–119°, $[\alpha]^{27}D$ −41.2° (*c* 0.23, methanol).

Anal. Calcd for $C_{20}H_{23}N_3SO_4$ (401.5): C, 59.83; H, 5.77; N, 10.46; S, 7.98. Found: C, 59.18; H, 5.77; N, 10.41; S, 8.04.

N^{α}-Benzoyl-S-2-aminoethyl-L-cysteinamide Hydrobromide (7).—Two grams (0.005 mole) of the benzyloxycarbonyl compound (**6**) was treated with 12 ml of 30% HBr in glacial acetic acid at room temperature.[6] After 45 min, when the evolution of CO_2 had ceased, ten volumes of dry ether was added to precipitate the hydrobromide. The product was crystallized from methanol with ether to yield 1.2 g (69%): mp 182–184°, $[\alpha]^{27}D$ −22°, $[\alpha]^{27}_{300}$ −175° (*c* 1.23 water).

Anal. Calcd for $C_{12}H_{18}N_3SBrO_2$ (348.3): C, 41.18; H, 5.20; N, 12.07; S, 9.20; Br, 22.94. Found: C, 40.88; H, 5.16; N, 12.08; S, 8.92; Br, 22.82.

N^{α}-Benzoyl-S-2-aminoethyl-L-cysteine Ethyl or Methyl Ester Hydrobromide (8). A. Ethyl Ester 8a.—The benzyloxycarbonyl compound (**5a**, 4.3 g, 0.01 mole) was treated with 11.2 g of 30% HBr in glacial acetic acid.[6] The evolution of carbon dioxide ceased after about 15 min, at which time dry ether (120 ml) was added to precipitate the ester hydrobromide as an oily material. This ester resisted crystallization from all solvents tried. It was precipitated from ethanolic solution by dropping into a large volume of dry ether and dried under high vacuum to give a white, glassy, hygroscopic solid: 2.62 g (69.5%): mp 62–65°, $[\alpha]^{27}D$ −49.5°, $[\alpha]^{27}_{300}$ −378° (*c* 1.5, water).

Anal. Calcd for $C_{14}H_{21}N_2SBrO_3$ (377.3): C, 44.56; H, 5.61; N, 7.42; S, 8.49. Found: C, 44.31; H, 5.53; N, 7.22; S, 8.24.

B. Methyl Ester 8b.—Removal of the benzyloxycarbonyl group by similar treatment of the syrupy methyl ester **5b** gave rise to another noncrystalline compound. The latter was converted to the crystalline free acid by treatment with trypsin (see below).

N^{ω}-Benzylidine-S-2-aminoethyl-L-cysteine (9).—Five grams of AEC (**1**, 0.025 mole) was dissolved in 25 ml of ice-cold 1 *N* LiOH. To this solution, 2.75 ml of benzaldehyde (0.027 mole) was added under vigorous stirring. The product started to separate as thin plates after about 10 min of reaction. The whole mixture was kept at 4° for several hours and the product was filtered and washed with water followed by ethanol to yield 4.95 g (78.5%), mp 168–169°, $[\alpha]^{27}D$ −27.2° (*c* 0.53, 0.1 *N* NaOH).

Anal. Calcd for $C_{12}H_{16}N_2O_2S$ (252.3): C, 57.12; H, 6.39; N, 11.10; S, 12.70. Found: C, 57.26; H, 6.23; N, 11.29; S, 12.58.

N^{α}-Benzoyl-S-2-aminoethyl-L-cysteine (10).—The benzylidine derivative (**9**, 4.5 g, 0.018 mole) was benzoylated in the presence of an equivalent amount of 1 *N* NaOH at 0° with benzoyl chloride. During the reaction, it was necessary to maintain a weak basic condition with added NaOH in order to avoid the dissociation of benzaldehyde from the ω-NH_2 group. After benzoylation was complete, the benzylidine group was removed by acidification of the reaction mixture to pH 1 and warming at 55° for several minutes. The mixture was then washed four times with ether and neutralized to pH 6.2. Evaporation of the solvent to one-third of its original volume followed by refrigeration resulted in the formation of needlelike crystals. The material was recrystallized from water to yield 1.1 g (23%), mp 219–220° dec, $[\alpha]^{27}D$ −58.6° (*c* 0.67, 1 *N* HCl).

Anal. Calcd for $C_{12}H_{16}N_2SO_3$ (268.3): C, 53.71; H, 6.01; N, 10.44; S, 11.94. Found: C, 53.64; H, 6.11; N, 10.64; S, 11.75.

To establish that the benzoyl group was on the α-NH_2 rather than ω-NH_2 group, the product was allowed to react at pH 2.5 with excess ninhydrin.[9] Since there was no CO_2 formation from the product **10** in contrast to S-2-amnoethyl-L-cysteine (**1**) and DL-valine, used as controls, it could be concluded that the compound was an α-benzoyl derivative. This same observation serves to prove that **9** is an ω- rather than an α-benzylidine derivative.

Compoud **10** was also prepared by tryptic hydrolysis of N^{α}-benzoyl-S-2-aminoethyl-L-cysteine methyl ester (**8b**) at pH 8.0 in aqueous solution (enzyme–substrate, 1:3000, by weight). After the completion of the reaction, as indicated by no more comsumption of NaOH by the reaction mixture, the solvent was evaporated under vacuum. The product was taken up with a few milliliters of absolute ethanol, precipitated with ether, and finally crystallized from water as described above, mp 209–211°.

Anal. Calcd for $C_{12}H_{16}N_2SO_3$ (268.3): C, 53.71; H, 6.01; N, 10.44; S, 11.94. Found: C, 52.61; H, 6.19; N, 10.25; S, 10.96.

Registry No.—**1**, 4099-35-8; **2**, 13618-73-0; **3**, 13618-74-1; **4a**, 13618-75-2; **4b**, 13618-76-3; **5a**, 13618-77-4; **6**, 13639-91-3; **7**, 13618-78-5; **8a**, 13618-79-6; **9**, 13618-80-9; **10**, 13619-05-1.

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A Simple Method for the Synthesis of Inosine, 2-Alkylinosine, and Xanthosine from 5-Amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide[1]

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Although a number of papers have been reported on the synthesis of purines from imidazole derivatives, there are few reports[2] in which purines were prepared by the ring closure of the pyrimidine starting from

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5-amino-4-imidazolecarboxamide (AICA).[3-7] On the other hand, the only example of purine nucleoside synthesized from 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide (AICA-riboside)[8-11] is inosine (V), which was prepared by the formylation of AICA-riboside followed by cyclization.[12-14] However, the conversion of AICA-riboside to other purine nucleosides has been little investigated owing to the less availability of AICA-riboside. Since this compound, the starting material of the present investigation, became more available from the culture broth of the mutant of *Bacillus subtilis*,[15] the synthesis of various purine nucleosides by the ring closure of AICA-riboside with a suitable agent had been extensively studied.

In the previous papers,[16,17] the authors have reported the synthesis of guanosine and its derivatives from AICA-riboside by two methods, *viz.*, by using benzoyl isothiocyanate or sodium methylxanthate as ring closing agents.

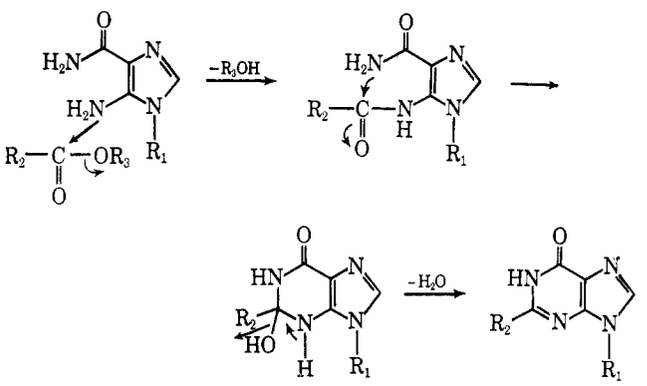
The present paper describes a simple method for the synthesis of hypoxanthine (I), 2-alkylhypoxanthine, xanthine (II), or their ribosides from AICA or AICA-riboside, respectively. We have found that AICA was condensed with ethyl formate in refluxing ethanol in the presence of sodium ethoxide to give I, although in low yield. A similar reaction[18,19] of AICA with diethyl carbonate gave II[2] in 25% yield. 2-Methylhypoxanthine[20,21] (III) and 2-ethylhypoxanthine (IV) were prepared by the reaction of AICA with ethyl acetate and ethyl propionate in 32 and 39% yields, respectively.

This procedure was successfully extended to the synthesis of inosine (V), 2-alkylinosine, and xanthosine (VI). AICA-riboside was treated with 4 equiv of ethyl formate in ethanolic sodium ethoxide solution to afford V, in 74% yield, whose ultraviolet and infrared absorption spectra were found to be identical with an authentic sample. In a similar manner, AICA-riboside reacted with diethyl carbonate to give VI in 75% yield. VI has been prepared by the deamination of guanosine with nitrous acid,[22-24] by the reaction of 1-β-D-ribofuranosylimidazole-4,5-dicarboxamide with sodium hypobromite,[25] and by the oxidation of 2-mercaptoinosine with hydrogen peroxide followed by alkaline hydrolysis.[17] However, these methods were of little preparative value. The present procedure seems to be superior for the large-scale preparation of VI since the product was isolated in good yield and by a simple procedure. Condensation of AICA-riboside with ethyl acetate afforded a good yield of 2-methylinosine (VII). The structure of VII was established by the conversion to III on treatment with 1 *N* hydrochloric acid and by the fact that its ultraviolet absorption spectra were very similar to those of V and that its nuclear magnetic resonance spectrum in pyridine showed the signal of the methyl group as a sharp singlet at τ 7.01. Similarly, reaction of AICA-riboside with ethyl propionate and ethyl *n*-butyrate gave 2-ethylinosine (VIII) and 2-(*n*-propyl)inosine (IX) in 60 and 38% yields, respectively. The nuclear magnetic resonance spectra of both the nucleosides showed the presence of ethyl and *n*-propyl groups, respectively.

When 5-amino-4-carbamoyl-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)imidazole(Ip-AICA-riboside)[26,27] was allowed to react with methyl formate, 2′,3′-*O*-isopropylideneinosine (X)[28] was obtained in 85% yield. Furthermore, the isopropylidene derivatives XI, XII, and XIII of VII, VIII, and IX were readily synthesized in good yields.

A mechanism for the formation of 2-alkylhypoxanthine derivatives is postulated in Chart I, in which the ring closure appears to proceed *via* the N^5-acyl derivative. Attempts to convert AICA-riboside into 2-phenylinosine by means of methyl benzoate resulted in failure, giving starting material.

CHART I



The two 2-alkylinosines and their isopropylidene derivatives thus obtained may be converted to some biologically interesting purine nucleosides and nucleotides. Details of the results will be reported later.

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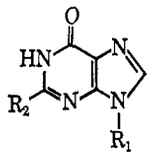
TABLE I



Compd No.	R_1	R_2	Mp, °C	$[\alpha]^{26}D$, deg	R_f values in solvents[c] A	B	Yield, %	Empirical formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
IV	H	C_2H_5	>250		0.76	0.63	39	$C_7H_8ON_4 \cdot 1/3H_2O$	49.41	49.89	5.06	5.48	32.94	32.92
VII	Rf[a]	CH_3	165–166	−50.0 (*c* 1, H_2O)	0.57	0.35	78	$C_{11}H_{14}O_5N_4 \cdot 1/2H_2O$	45.36	45.29	5.19	5.05	19.24	19.21
VIII	Rf	C_2H_5	179–181	−42.2 (*c* 1, H_2O)	0.63	0.46	60	$C_{12}H_{16}O_5N_4 \cdot 1/4H_2O$	47.91	48.06	5.53	5.58	18.63	18.44
IX	Rf	*n*-C_3H_7	150–151	−48.8 (*c* 1, H_2O)	0.70	0.59	38	$C_{13}H_{18}O_5N_4 \cdot 1/2H_2O$	48.99	48.93	5.98	5.70	17.56	17.66
XI	Ip-Rf[b]	CH_3	>240	−84.5 (*c* 2, 0.1 *N* NaOH)	0.85	0.69	88	$C_{14}H_{18}O_5N_4$	52.17	51.80	5.63	5.74	17.38	17.20
XII	Ip-Rf	C_2H_5	212 dec	−80.5 (*c* 2, 0.1 *N* NaOH)	0.89	0.77	68	$C_{15}H_{20}O_5N_4 \cdot 1/2H_2O$	52.17	52.37	6.09	6.16	16.23	15.81
XIII	Ip-Rf	*n*-C_3H_7	215–216	−79.0 (*c* 2, 0.1 *N* NaOH)	0.90	0.83	60	$C_{16}H_{22}O_5N_4$	54.85	54.84	6.33	6.39	15.99	15.84

[a] Rf = β-D-ribofuranosyl. [b] Ip-Rf = 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl. [c] Paper chromatography was carried out on Toyo No. 51 filter paper by the ascending method. Solvent systems: A, *n*-propyl alcohol–ammonia (28%)–water, 20:12:3 (v/v); B, *n*-butyl alcohol–acetic acid–water 4:1:1 (v/v).

Experimental Section[29]

General Procedure.—The starting material and the ethyl ester of aliphatic carboxylic acid (5–10 equiv) were added to a stirred solution of ethanolic sodium ethoxide (prepared from 7–10 equiv of metallic sodium and ethanol), and the mixture was refluxed for 2–3 hr. The product solution was diluted with water and neutralized with Amberlite IR-120 (H^+ form). In the cases of VI, VII, VIII, and IX, the pH of the solutions must be adjusted to 3. Paper chromatography showed a single spot in the synthesis of purine nucleosides. After the resin was removed by filtration, the filtrate was concentrated under reduced pressure. The crude product was recrystallized from water (except for compound II). Yields, properties, and analyses of the new compounds are summarized in Tables I and II.

TABLE II

ULTRAVIOLET SPECTRA

No.	λ_{max} mμ (s) pH 1	pH 7	pH 13
IV	252 (10,100)	252 (10,400)	266 (10,300)
VII	253 (11,900)	251.5 (12,700)	258 (13,100)
VIII	252 (8,400)	251.5 (9,800)	258 (10,600)
IX	253 (12,300)	251.5 (12,900)	258 (15,200)
XI	252 (12,200)	251 (13,000)	257 (14,200)
XII	253 (12,400)	251 (14,800)	257 (13 600)
XIII	254 (12,600)	252 (13,700)	258 (13,600)

5-Amino-4-imidazolecarboxamide (AICA).—5-Amino-4-imidazolecarboxamide hydrochloride[7] (16.2 g, 0.1 mole) was dissolved in 150 ml of water, and to this stirred solution was added portionwise 8.4 g (0.1 mole) of sodium hydrogen carbonate. The solution was evaporated to dryness under reduced pressure below 40°. The resulting free base of AICA was extracted with hot ethanol, and the extracts were evaporated *in vacuo* to give 10 g of crude product. Crystallization from ethanol with charcoal afforded 6.6 g (52%) of white crystals, mp 168–169°.

Anal. Calcd for $C_4H_6ON_4$: C, 38.10; H, 4.76; N, 44.44. Found: C, 38.45; H, 4.51; N, 44.78.

Hypoxanthine (I).—To a solution of ethanolic sodium ethoxide (prepared from 1 g (43 mg-atoms) of metallic sodium and 25 ml of ethanol) was added 1 g (7.9 mmoles) of AICA. Ethyl formate (2.96 g, 40 mmoles) was then added, and the mixture was refluxed for 3 hr. After 50 ml of water was added to the reaction mixture, the resulted clear solution was neutralized by adding portionwise Amberlite IR-120 (H^+ form). The resin was removed by filtration, and the filtrate was concentrated *in vacuo* to precipitate crude crystals, which were recrystallized from water to give 0.59 g (42%) of pure sample. This compound was confirmed to be identical with an authentic I by comparison of their ultraviolet and infrared absorption spectra.

Xanthine (II).—One gram of AICA was treated with diethyl carbonate in a manner similar to that described for I. Purification of the crude product was accomplished by reprecipitation from aqueous sodium hydroxide with dilute acetic acid: yield 0.3 g (25%).

Inosine (V).—To a solution of ethanolic sodium ethoxide (prepared from 0.8 g (34.9 mg-atoms) of metallic sodium and 40 ml of ethanol) was added 2 g (7.74 mmoles) of 5-amino-1-β-D-ribofuranosyl-4-imidazolecarboxamide (AICA-riboside), followed by the addition of 2.29 g (31.1 mmoles) of ethyl formate to the clear solution with stirring. When the mixture was refluxed, a precipitate soon formed. After 3 hr, it was diluted with 50 ml of water. Examination of this solution by paper chromatography showed a single spot, the starting material no longer being present. The solution was neutralized to pH 7 by adding portionwise Amberlite IR-120 (H^+ form). The resin was removed by filtration and washed with water. The filtrate and washings were combined and concentrated to dryness *in vacuo*. The residue was crystallized from water to give 1.55 g (74%) of an analytically pure material, which was identified by direct comparison of ultraviolet and infrared spectra with those of an authentic sample.

Xanthosine (VI).—Two grams (7.74 mmoles) of AICA-riboside was dissolved in a solution of ethanolic sodium ethoxide (prepared from 1.2 g (52.3 mg-atoms) of metallic sodium and 40 ml of ethanol), and to this solution was added 4.57 g (38.7 mmoles) of diethyl carbonate with stirring. The mixture was then heated in an autoclave at 120° for 2 hr. At the end of the reaction, the precipitate was formed. After 100 ml of water was added, the clear solution was adjusted to pH 4 with Amberlite IR-120 (H^+ form). The filtrate, after removal of the resin, was concentrated *in vacuo* to afford a crude product, which was crystallized from water, yielding 1.68 g (74%) of a pure sample. This compound was shown to be in good agreement with an authentic sample by comparison of physical properties.

2′,3′-*O*-Isopropylideneinosine (X).—A solution of 5-amino-4-carbamoyl-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)imidazole (Ip-AICA-riboside, 5 g), ethyl formate, and metallic sodium in ethanol was refluxed and worked up in the usual manner, yielding 4.4 g (85%) of pure material. This compound was proved to be identical with an authentic sample[29] in all physical properties.

Registry No.—IV, 13591-88-3; V, 58-63-9; VI, 146-80-5; VII, 13591-89-4; VIII, 13591-90-7; IX, 13591-91-8; XI, 6670-90-2; XII, 13591-93-0; XIII, 13591-94-1; AICA, 932-15-0; AICA-riboside, 2627-69-2.

Acknowledgment.—The authors wish to express their gratitude to Professor M. Ikehara of the Hokkaido University and Dr. H. Oeda of Ajinomoto Co., Inc., for their encouragement throughout the course of this work.

(29) All melting points are uncorrected. Ultraviolet absorption spectra were taken with a Hitachi EPS-2 automatic recording spectrophotometer, and infrared absorption spectra were measured with a Jasco Model IR-S spectrophotometer. The nmr spectra were measured with a Varian A-60 using tetramethylsilane as an internal standard.