TLC. Dry Amberlite IR-120 (H^+) resin was added and the suspension was stirred for 30 min, filtered, and the filtrate was concentrated to dryness to give an amorphous powder (60 mg, 60%), $[\alpha]_D^{26}$ +126.3° (c=0.66, H_2O). PPC: *Rf* 0.43 (solvent D), 0.25 (solvent E), 0.29 (solvent F). *Anal.* Calcd. for $C_{12}H_{22}O_{10}\cdot 2H_2O$: C, 39.77; H, 7.23. Found: C, 39.64; H, 7.03.

6-Deoxy-α-cellobiose (14)——Deacetylation of **6** (630 mg) as for **13** afforded **14** (300 mg, 91%). After recrystallization from MeOH, **15** showed mp 242—245° (dec.) and $[\alpha]_D^{28}$ +30°→+25.5° (5 hr) (c=1, H_2O). PPC: *Rf* 0.38 (solvent D), 0.27 (solvent E), 0.23 (solvent F). *Anal.* Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 43.74; H, 6.96.

4-O-α-D-Glucopyranosyl-6-deoxy-L-idopyranose (15)——Deacetylation of **10** (330 mg) as for **13** afforded **15** (121 mg, 70%), amorphous powder, $[\alpha]_D^{26}$ +91.2° (c=0.62, H_2O). PPC: *Rf* 0.42 (solvent D), 0.28 (solvent E), 0.32 (solvent F). *Anal.* Calcd. for $C_{12}H_{22}O_{10}\cdot 2H_2O$: C, 39.77; H, 7.23. Found: C, 39.48; H, 7.18.

4-O-β-D-Glucopyranosyl-6-deoxy-L-idopyranose (16)——Deacetylation of **12** (128 mg) afforded **16** (67 mg, 99%), amorphous powder, $[\alpha]_D^{16}$ −28.7° (c=0.65, H_2O). PPC: *Rf* 0.39 (solvent D), 0.24 (solvent E), 0.30 (solvent F). *Anal.* Calcd. for $C_{12}H_{22}O_{10}\cdot 2H_2O$: C, 39.77; H, 7.23. Found: C, 39.85; H, 7.13.

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Purines. XX.[1] Synthesis of 1-Substituted 5-Aminoimidazole-4-carboxamidines and Related Compounds[2]

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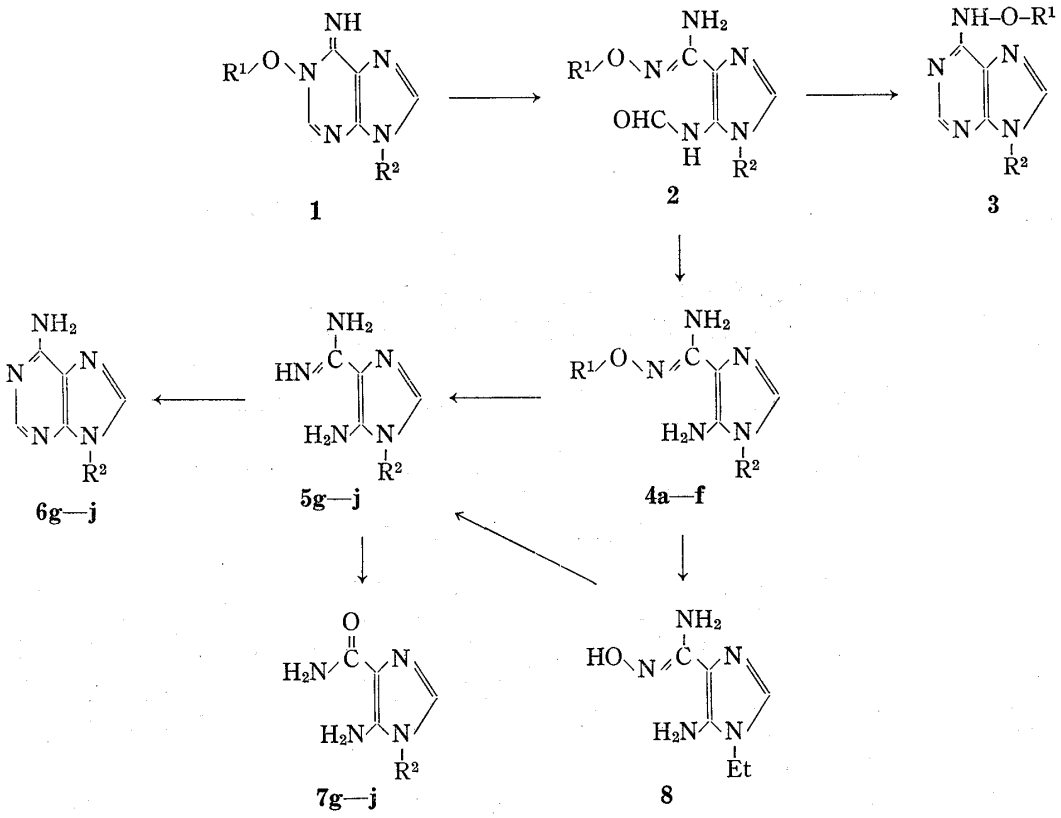
Several 1-substituted 5-aminoimidazole-4-carboxamidines (**5g—j**) have been prepared from the corresponding N′-alkoxyamidines (**4a—f**) by catalytic hydrogenolysis. In the hydrogenolysis of **4a—f** using Raney Ni catalyst, addition of one molar equivalent of hydrochloric acid accelerated the reaction to give **5g—j** in acceptable yields. The structures of **5g—j** have been confirmed by cyclization to 9-substituted adenines (**6g—j**) and by alkaline hydrolysis to 1-substituted derivatives (**7g—j**) of 5-aminoimidazole-4-carboxamide (AICA).

Keywords——imidazoles; adenines; alkoxyamidine; amidoxime; catalytic hydrogenolysis; Raney nickel catalyst; palladium-on-carbon; cyclization; hydrolysis

In previous papers[4] from this laboratory, we have already shown that the pyrimidine ring of 1-alkoxyadenines (type **1**) is easily opened under mild hydrolytic conditions to produce imidazole derivatives (types **2** and **4**), and that the formamido derivatives (type **2**) cyclize readily to N^6-alkoxyadenines (type **3**). The synthetic utility of this ring opening reaction

1) Paper XIX in this series, T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **24**, 655 (1976).
2) Presented in part at the 44th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Toyama, June 25, 1977.
3) Location: *13–1 Takara-machi, Kanazawa 920, Japan.*
4) *a*) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *b*) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1731 (1971); *c*) T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972); *d*) T. Fujii, C. C. Wu, T. Itaya, S. Moro, and T. Saito, *Chem. Pharm. Bull.* (Tokyo), **21**, 1676 (1973); *e*) T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *ibid.*, **22**, 2211 (1974); *f*) T. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *ibid.*, **23**, 2643 (1975).

has been exemplified in the recent syntheses of new N^x,N^y-disubstituted adenines by us,[5] 2-thioadenosine derivatives by Kikugawa *et al.*,[6] 2-aza-adenosine and related derivatives by Montgomery *et al.*,[7] and modified or 2-substituted derivatives of adenosine cyclic 3′,5′-phosphate by Meyer *et al.*[8] In both the last two exemplifications is included the hydrogenolysis of the N′-alkoxyamidine derivatives (type **4**) to 1-substituted 5-aminoimidazole-4-carboxamidines (type **5**) formulated as key intermediates, and it has been effected with hydrogen and Raney Ni catalyst (MeOH, 1 atm, room temp., 24 hr)[7a] or sponge Ni catalyst (H_2O, 2—3 atm, 60°, 2 hr).[8a] With a few exceptions, however, this type of hydrogenolysis appears to proceed only slowly and the yields of the amidine derivatives (type **5**) are mediocre.[7,8] Furthermore, Kikugawa *et al.*[6,9] have reported that their several attempts to convert **4f** into **5j** by catalytic reduction[7a] were unfruitful. The present paper describes our own synthetic



a : R^1=R^2=Me
b : R^1=Me; R^2=Et
c : R^1=R^2=Et
d : R^1=Et; R^2=$PhCH_2$
e : R^1=$PhCH_2$; R^2=Et
f : R^1=$PhCH_2$; R^2=β-D-ribofuranosyl
g : R^2=Me
h : R^2=Et
i : R^2=$PhCH_2$
j : R^2=β-D-ribofuranosyl

Chart 1

5) *a*) T. Fujii, F. Tanaka, K. Mohri, T. Itaya, and T. Saito, *Tetrahedron Lett.*, **1973**, 4873; *b*) T. Fujii, T. Itaya, K. Mohri, and T. Saito, *J. Chem. Soc., Chem. Commun.*, **1973**, 917; *c*) T. Fujii, T. Saito, K. Kyo, and T. Muramoto, Abstracts of Papers, 2nd Symposium on Nucleic Acids Chemistry, Tokyo, October, 1974, p. 53.
6) K. Kikugawa, H. Suehiro, R. Yanase, and A. Aoki, *Chem. Pharm. Bull.* (Tokyo), **25**, 1959 (1977).
7) *a*) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972); *b*) J. A. Montgomery, A. G. Laseter, A. T. Shortnacy, S. J. Clayton, and H. J. Thomas, *ibid.*, **18**, 564 (1975).
8) *a*) R. B. Meyer, Jr., D. A. Shuman, R. K. Robins, J. P. Miller, and L. N. Simon, *J. Med. Chem.*, **16**, 1319 (1973); *b*) R. B. Meyer, Jr., D. A. Shuman, and R. K. Robins, *J. Am. Chem. Soc.*, **96**, 4962 (1974).
9) We acknowledge with thanks several prior conversations with Dr. K. Kikugawa.

efforts, which led to improvements in the reaction conditions and yield in such a hydrogenolysis step.

Our first objective was **5h** which we hoped to prepare by catalytic hydrogenolysis of the N′-ethoxy (**4c**) or the N′-benzyloxy derivative (**4e**). Hydrogenation of **4c** in EtOH (110 atm, room temp., 8 hr) over a large excess of Raney Ni catalyst (11 parts by weight) gave **5h**, which was isolated in the form of the monopicrate in 27% overall yield. Application of heat, a lower hydrogen pressure, or a smaller amount of the catalyst was productive of poorer results. Replacement of the N′-ethoxy group of **4c** by the benzyloxy group, however, seemed to make the cleavage of the N–O bond easier, and **4e** produced **5h** in 39% yield (as the monopicrate) under similar but milder reaction conditions (1 atm, room temp., 16 hr).

In view of the versatility of the N-benzyloxy group in hydrogenolytic fission,[10] we next tried to follow the two-step route to **5h** from **4e** *via* the amidoxime (**8**). Treatment of **4e** in EtOH with hydrogen and 10% Pd-C (1 atm, room temp., 2 hr) furnished **8** (82% yield), which was then hydrogenated in MeOH over Raney Ni catalyst (4 parts by weight) (1 atm, room temp., 8 hr) to give **5h** (as the monopicrate, 66% yield from **8**). When crude intermediate **8** was directly subjected to the second hydrogenolysis without purification, the overall yield of **5h**·monopicrate reached to 64%.

Having been unsatisfied with the above results, we further investigated the hydrogenolysis of **4c** in the presence of one molar equivalent of hydrochloric acid. When this hydrogenolysis was carried out in H_2O using 10% Pd-C as catalyst at atmospheric pressure and room temp. for 24 hr, **5h** was produced in 70% yield (as the monopicrate). At 50° the same hydrogenolysis proceeded faster, raising the yield of **5h** to 85%. The importance of the presence of hydrochloric acid in the reaction mixture was realized when the reaction was found not to occur at all in the absence of the acid even at 50°. A comparable result was obtained with the N′-methoxy derivative (**4b**).

Finally, we found that in the above hydrogenolysis of **4c**·HCl at room temperature replacement of the Pd catalyst by Raney Ni catalyst made the reaction rate much faster, giving **5h** in a yield of more than 71% during 1.5 hr. The N′-methoxy derivatives (**4a,b**) and the N′-benzyloxy derivatives (**4e,f**) were also hydrogenolyzed smoothly to the corresponding amidines (type **5**) under similar conditions. Table I summarizes the results thus obtained. The somewhat low yield of the ribosyl derivative (**5j**) observed for the reduction

Table I. Catalytic Hydrogenolysis of **4a**—**f**·HCl to **5g**—**j**·HCl in H_2O at Atmospheric Pressure

Starting material	Reaction conditions			Product	Yield[b] (%)
	Catalyst	Temp.[a] (°C)	Time (hr)		
4a·HCl	Raney Ni	r.t.	2	**5g**·HCl	84
4b·HCl	10% Pd-C	r.t.	16	**5h**·HCl	73
4b·HCl	Raney Ni	r.t.	2	**5h**·HCl	83
4c·HCl	10% Pd-C	r.t.	24	**5h**·HCl	70
4c·HCl	10% Pd-C	50	8	**5h**·HCl	85
4c·HCl	Raney Ni	r.t.	1.5	**5h**·HCl	71
4d·HCl	Raney Ni	r.t.	4	**5i**·HCl	91
4e·HCl	Raney Ni	r.t.	2	**5h**·HCl	86
4f·HCl	Raney Ni	r.t.	2	**5j**·HCl	45

a) The abbreviation r.t. stands for room temperature.
b) Overall yield (from the starting material) of the monopicrate derived from the product.

10) *a*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971); *b*) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **21**, 1835 (1973); *c*) T. Fujii and Y. Hatanaka, *Tetrahedron*, **29**, 3825 (1973).

Table II. Ultraviolet Spectra of Imidazole Derivatives (**5g—j**, **7g—j**)

Compound	UV spectra							
	Solvent E[a]		Solvent A[b]		Solvent N[c]		Solvent B[d]	
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
5g·monopicrate	292	17.3	282	14.1	285.5	14.1	—	—
5g (free base)[e]	—	—	283.5	10.9	285.5	11.8	267	9.11
5h·monopicrate	292	17.5	282	14.2	286	14.3	—	—
5h (free base)[e]	—	—	284	11.1	286	11.9	267	9.12
5i·monopicrate	291	18.3	282	14.9	285	15.0	—	—
5i (free base)[e]	—	—	284	11.7	285	12.6	267	9.98
5j·monopicrate	292.5	17.8	282.5	14.5	286	14.3	—	—
5j (free base)[e]	—	—	284	11.3	286	12.0	267.5	8.91
7g	268	12.3	240 268.5	7.60 10.1	267.5	12.0	267.5	11.9
7h	269	12.6	241 269	7.59 10.3	268	12.2	268	12.2
7i	270	13.7	244 269	8.43 11.1	268	13.3	268	13.3
7j	268.5	13.1	246 268.5	9.08 10.6	267	12.6	268	12.8

a) 95% (v/v) aq. EtOH. *b*) 0.1 N aq. HCl (pH 1).
c) 0.005 M phosphate buffer (pH 7). *d*) 0.1 N aq. NaOH (pH 13).
e) The spectral data were obtained as described in the text.

of **4f** may be due to an inefficiency in isolating it as the monopicrate. It seems that the function of hydrochloric acid in these hydrogenolytic reactions is to prevent the catalyst from being poisoned by the strongly basic amidines.

The structures of **5g—j** were supported by elemental analyses and ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra of their monopicrates (see Experimental). Table II assembles the UV spectral data on the free bases of **5g—j**, which were obtained by subtraction of the molecular extinction coefficients of picric acid in individual solvents from those of the monopicrates of **5g—j** at the wavelengths involved. They are in general agreement with those reported[7a] for 5-amino-1-cyclopentylimidazole-4-carboxamidine. Proof of the correctness of structures **5g—j** was further provided by the following two chemical conversions. The monohydrochlorides of **5g—j** were separately heated with ethyl orthoformate and a little conc. hydrochloric acid at 80—85° for 5—24 hr to produce the corresponding 9-substituted adenines (**6g—j**) in 45—89% overall yields (from **4**). On the other hand, treatment of the hydrochlorides (**5g—j**·HCl) with hot dilute aqueous NaOH or ammonia water gave the 1-substituted derivatives (**7g—j**) of 5(4)-aminoimidazole-4(5)-carboxamide (AICA) in 34—68% overall yields (from **4**). The similarity of the UV spectra among these AICA derivatives, as shown in Table II, and identity of the ribosyl derivative (**7j**) with an authentic sample supported the assignment of their structures.

The starting N′-alkoxyamidine derivatives (**4a—f**) used in the present work were prepared from the corresponding 1-alkoxy-9-alkyladenines (**1a—f**)[10a,11] according to previously reported[4a,f] procedure, and the new compounds, **4b,d,e**, were characterized as described in Experimental section.

In conclusion, it is hoped that the above improvements in the synthesis of the amidine derivatives (type **5**) will facilitate further synthetic work using them as key intermediates, enhancing the synthetic value of the use of an alkoxyl group at the 1-position of the adenine ring as an easily removable activating group.

11) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).

Experimental[12]

5-Amino-1-ethyl-N′-methoxyimidazole-4-carboxamidine (4b)——A stirred mixture of **1b**·HI[11] (6.42 g, 20 mmol) and NaOH (5.0 g) in H_2O (100 ml) was refluxed for 15 min. After having been cooled, the mixture was extracted with $CHCl_3$ (2×100 ml, 2×50 ml). The combined extracts were dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*, leaving crude **4b** (3.03 g, 83%) as a brownish solid, mp 131—135°. Recrystallization from AcOEt gave an analytical sample as colorless prisms, mp 135.5—136.5°; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 265.5 nm (ε 11800); $\lambda_{max}^{H_2O}$ (pH 1) 282 (9740); $\lambda_{max}^{H_2O}$ (pH 7) 263.5 (9750); $\lambda_{max}^{H_2O}$ (pH 13) 263.5 (9690); IR ν_{max}^{Nujol} cm^{-1}: 3500, 3380, 3110 (NH_2's); NMR (Me_2SO-d_6) δ: 1.27 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.72 (3H, s, OMe), 3.86 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 5.37 (2H, b, NH_2), 5.53 (2H, dull s, amidine-NH_2),[13] 7.24 (1H, s, ring proton). *Anal.* Calcd. for $C_7H_{13}N_5O$: C, 45.89; H, 7.15; N, 38.23. Found: C, 45.95; H, 7.30; N, 38.12.

The aqueous layer from the above extraction was neutralized with 10% aq. HCl and extracted with $CHCl_3$ (2×100 ml, 3×50 ml). After having been dried over anhyd. Na_2SO_4, the $CHCl_3$ solution was evaporated to dryness to afford a yellowish brown solid (513 mg, 13%), which was recrystallized from EtOH to give 9-ethyl-N^6-methoxyadenine (**3b**) as slightly yellowish minute pillars, mp 204—205.5° (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 270 nm (ε 13900); $\lambda_{max}^{H_2O}$ (pH 1) 271.5 (13500); $\lambda_{max}^{H_2O}$ (pH 7) 269 (14900); $\lambda_{max}^{H_2O}$ (pH 13) 286 (11800); NMR (Me_2SO-d_6) δ: 1.38 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.79 (3H, s, OMe), 4.12 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 7.73 (1H, b) and 7.93 (1H, dull s) (purine protons), 10.5—11.4 (1H, b, NH). *Anal.* Calcd. for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.78; H, 5.83; N, 36.52.

5-Amino-1-benzyl-N′-ethoxyimidazole-4-carboxamidine (4d)——A stirred mixture of **1d**·HI[11] (1.19 g, 3 mmol) and NaOH (0.75 g) in H_2O (15 ml) was refluxed for 15 min. The mixture was cooled in a refrigerator and the precipitate that resulted was filtered off, washed with a little H_2O, and recrystallized from 33% (v/v) aq. EtOH to give **4d** (519 mg, 67%), mp 110—111°. Further recrystallization of this sample in the same manner yielded colorless pillars, mp 110—111.5°; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 266 nm (ε 12100); $\lambda_{max}^{H_2O}$ (pH 1) 283.5 (10800); $\lambda_{max}^{H_2O}$ (pH 7) 264.5 (10900); $\lambda_{max}^{H_2O}$ (pH 13) 264.5 (10900); IR ν_{max}^{Nujol} cm^{-1}: 3495, 3390, 3305 (NH_2's); NMR (Me_2SO-d_6) δ: 1.19 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.88 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 5.07 (2H, s, $C\underline{H}_2Ph$), 5.36 (2H, dull s, NH_2), 5.43 (2H, dull s, amidine-NH_2),[13] 7.13—7.45 (6H, m, Ph and imidazole proton). *Anal.* Calcd. for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60.33; H, 6.67; N, 27.12.

The filtrate and washings from the above filtration of the reaction mixture were combined and the pH of the solution was adjusted to 7 with 10% aq. HCl. The precipitate that resulted was filtered off, washed with a little H_2O, and recrystallized from EtOH to produce 9-benzyl-N^6-ethoxyadenine (**3d**) (89 mg, 11%), mp 234—234.5° (dec.) [lit.[4d] mp 227—228° (dec.)]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 271 nm (ε 14400); $\lambda_{max}^{H_2O}$ (pH 1) 270 (17400); $\lambda_{max}^{H_2O}$ (pH 7) 270.5 (16300); $\lambda_{max}^{H_2O}$ (pH 13) 287 (12200); NMR (Me_2SO-d_6) δ: 1.26 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.98 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 5.29 (2H, s, $C\underline{H}_2Ph$), 7.29 (5H, s, Ph), 7.47—7.78 and 7.78—8.16 (1H each, b, purine protons), 10.75—11.19 (1H, b, NH). *Anal.* Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.41; H, 5.81; N, 26.03. This sample was identical [by thin-layer chromatography (TLC), mixed melting-point test, and IR spectrum] with authentic **3d**.[4d]

5-Amino-N′-benzyloxy-1-ethylimidazole-4-carboxamidine (4e)——Compound **1e**·HBr[11] was treated in a manner similar to that described above for **4d**, and **4e** (84% yield) and 9-ethyl-N^6-benzyloxyadenine (**3e**) (13% yield) were obtained.

Compound **4e**: colorless prisms (from AcOEt), mp 109.5 —110.5°; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 265.5 nm (ε 12300); $\lambda_{max}^{H_2O}$ (pH 1) 281.5 (9550); $\lambda_{max}^{H_2O}$ (pH 7) 264 (10500); $\lambda_{max}^{H_2O}$ (pH 13) 264 (10400); NMR (Me_2SO-d_6) δ: 1.25 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.85 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 4.97 (2H, s, $C\underline{H}_2Ph$), 5.34 (2H, b, NH_2), 5.62 (2H, dull s, amidine-NH_2),[13] 7.24 (1H, s, imidazole proton), 7.32—7.60 (5H, m, Ph). *Anal.* Calcd. for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.61; N, 27.01. Found: C, 60 50; H, 6.52; N, 26.76.

Compound **3e**: colorless plates (from AcOEt), mp 187.5—189° [lit.[4d] mp 154—155° (dec.)]; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 270.5 nm (ε 15600); $\lambda_{max}^{H_2O}$ (pH 1) 273.5 (14200); $\lambda_{max}^{H_2O}$ (pH 7) 270.5 (16500); $\lambda_{max}^{H_2O}$ (pH 13) 286.5 (12900); NMR (Me_2SO-d_6) δ: 1.36 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 4.09 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 5.02 (2H, s, $C\underline{H}_2Ph$, 7.35 (5H, m, Ph), 7.60 and 7.84 (1H each, b, purine protons), 11.14 (1H, b, NH). *Anal.* Calcd. for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.18; H, 5.62; N, 25.85. This specimen was identical [by paper chromatography (PPC), TLC, mixed melting-point test, and IR spectrum] with authentic **3e**.[4d,14]

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12) All melting points are corrected. Spectra reported herein were measured with a Hitachi Model 323 UV spectrophotometer, a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-PS-100 NMR spectrometer at 23° using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet.

13) The assignment of the NH_2 and the amidine-NH_2 signals was based on comparison of these with the MeNH and the amidine-NH_2 signals of N′-alkoxy-1-alkyl-5-methylaminoimidazole-4-carboxamidines.[5b]

14) We observed that a previously reported[4d] sample of **3e**, mp 154—155° (dec.), has been stable on storage at room temperature for 10 years but its melting point has been raised to 187 —189°.

5-Amino-1-ethylimidazole-4-carboxamidoxime (8)——A solution of **4e** (778 mg, 3 mmol) in EtOH (150 ml) was hydrogenated over 10% Pd-C[15] (600 mg) at atmospheric pressure and room temp. for 2 hr. The catalyst was removed by filtration and washed with hot EtOH (300 ml). The combined filtrate and washings were evaporated to dryness *in vacuo* to leave a grey solid (495 mg), which was recrystallized from EtOH to afford **8** (415 mg, 82%) as colorless pillars, mp 174—175° (dec.); MS *m/e*: 169 (M^+); UV $\lambda_{max}^{95\%\ aq.EtOH}$ 258.5 nm (ε 10700); $\lambda_{max}^{H_2O}$ (pH 1) 279 (9330); $\lambda_{max}^{H_2O}$ (pH 7) 257.5 (9240); $\lambda_{max}^{H_2O}$ (pH 13) 260 5 (10100); IR ν_{max}^{Nujol} cm^{-1}: 3485, 3455, 3375, 3145—3070 (b) (NH_2's, OH); NMR (Me_2SO-d_6) δ: 1.24 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.77 (2H, q J=7 Hz, $C\underline{H}_2Me$), 5.18 and 5.24 (4H, b, NH_2's), 7.06 (1H, s, ring proton), 8.73 (1H, dull s, OH). *Anal.* Calcd. for $C_6H_{11}N_5O$: C, 42.59; H, 6.55; N, 41.40. Found: C, 42.57; H, 6.65; N, 41.36.

5-Amino-1-methylimidazole-4-carboxamidine (5g)——Compound **4a**[4a] was hydrogenolyzed as described below under method-(i) in the synthesis of **5h**, and crude product (**5g**·HCl) was similarly converted into the monopicrate (see Table I), yellow pillars, mp 237—239° (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 3.44 (3H, s, Me), 6.46 (2H, b, NH_2), 7.36 (1H, s, imidazole proton), 7.77 (4H, dull s, protonated amidine), 8.55 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{11}H_{12}N_8O_7$: C, 35.87; H, 3.28; N, 30.43. Found: C, 35.88; H, 3.37; N, 30.28.

5-Amino-1-ethylimidazole-4-carboxamidine (5h)——i) Hydrogenolysis of **4c**·HCl over Raney Ni: A solution of **4c**[4a] (197 mg, 1 mmol) in a mixture of H_2O (24 ml) and 1 N aq. HCl (1 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (*ca.* 180 mg) at atmospheric pressure and room temp. for 1.5 hr. The catalyst was removed by filtration and washed with hot (*ca.* 80°) H_2O (100 ml). The combined filtrate and washings were evaporated to dryness *in vacuo* to leave a pinkish solid (**5h**·HCl) (184 mg). The solid was dissolved in H_2O (10 ml) and to this solution was added a saturated solution (*ca.* 40 ml) of picric acid in H_2O. The yellow precipitate that resulted was filtered off, washed with a little H_2O, and recrystallized from 0.1 M phosphate buffer (pH 6.0), yielding **5h**·monopicrate hemihydrate (278 mg, 71%) as yellowish brown needles, mp 204—206° (dec.) (dried over P_2O_5 at room temp. and 1 mmHg for 24 hr); UV (Table II); NMR (Me_2SO-d_6) δ: 1.26 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.88 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 6.47 (2H, dull s, NH_2), 7.45 (1H, s, imidazole proton), 7.79 (4H, dull s, protonated amidine), 8.57 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{12}H_{14}N_8O_7 \cdot 1/2H_2O$: C, 36.83; H, 3.86; N, 28.64. Found: C, 37.04; H, 3.82; N, 28.76. When dried over P_2O_5 at 50° and 1 mmHg for 14 hr, the hemihydrate afforded an anhydrous sample, mp 204—206° (dec.). *Anal.* Calcd. for $C_{12}H_{14}N_8O_7$: C, 37.70; H, 3.69; N, 29.31. Found: C, 37.71; H, 3.62; N, 29.40.

Recrystallization of the monopicrate hemihydrate from a 9: 1 (v/v) mixture of a saturated aq. picric acid solution and H_2O provided **5h**·dipicrate as yellow needles, mp 183.5—185° (dec.); NMR (Me_2SO-d_6) δ: 1.28 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.93 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 6.34 (dull s, protonated amidine), 7.85 (1H, s, imidazole proton), 8 02 (3H, dull s, NH_3^+), 8 60 (4H, s, aromatic protons). *Anal.* Calcd. for $C_{18}H_{17}N_{11}O_{14}$: C, 35.36; H, 2.80; N, 25.20. Found: C, 35.34; H, 2.66; N, 25.29.

ii) Hydrogenolysis of **4b**·HCl or **4e**·HCl over Raney Ni: Compounds **4b** and **4e** were separately treated in a manner similar to that described under method-(i). The results are summarized in Table I.

iii) Hydrogenolysis of **4b**·HCl or **4c**·HCl over Pd-C: A solution of **4b** (183 mg, 1 mmol) or **4c**[4a] (197 mg, 1 mmol) in H_2O (24 ml) containing 1 N aq. HCl (1 ml) was hydrogenated over 10% Pd-C[15] (1—3 parts by weight) under the conditions specified in Table I. The results are also shown in Table I.

iv) Reduction of **8**: A solution of the amidoxime (**8**) (150 mg, 0.887 mmol) in MeOH (40 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (600 mg) at atmospheric pressure and room temp. for 8 hr. The catalyst was filtered off and washed with hot MeOH (160 ml). The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was treated with a saturated solution of picric acid in H_2O as described under method-(i) to give **5h**·monopicrate hemihydrate (230 mg, 66%), identical (by mixed melting-point test and IR spectrum) with an authentic sample.

When a crude sample of **8**, obtained by the debenzylation (Pd/H_2) of **4e**, was directly hydrogenolyzed as above, the reaction also proceeded smoothly and **5h** was isolated in the form of the monopicrate hemihydrate in 64% overall yield from **4e**.

v) Hydrogenolysis of **4c** over Raney Ni: A solution of **4c**[4a] (500 mg, 2.53 mmol) in EtOH (30 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (5.4 g) at 110 atm and room temp. for 8 hr. The reaction mixture was worked up as described under method-(i) and **5h**·monopicrate hemihydrate was obtained in 27% yield.

vi) Hydrogenolysis of **4e** over Raney Ni: A solution of **4e** (260 mg, 1 mmol) in MeOH (60 ml) was hydrogenated over Raney Ni W-2 catalyst[16] (2.6 g) at atmospheric pressure and room temp. for 16 hr. From this reaction mixture was isolated **5h**·monopicrate hemihydrate in 39% yield by following a similar after-treatment to that described under method-(i).

5-Amino-1-benzylimidazole-4-carboxamidine (5i)——Compound **4d** was hydrogenated as described above under method-(i) in the synthesis of **5h**, and the product (**5i**·HCl) was similarly converted into the mono-

15) R. Mozingo, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 685.

16) R. Mozingo, in the reference 15 book, p. 181.

picrate (see Table I) as yellow needles, mp 237.5—239.5° (dec.); UV (Table II); NMR (Me_2SO-d_6) δ: 5.14 (2H, s, $C\underline{H}_2Ph$), 6.53 (2H, b, NH_2), 7.13—7.40 (5H, m, Ph), 7.55 (1H, s, imidazole proton), 7.83 (4H, dull s, protonated amidine), 8.56 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{17}H_{16}N_8O_7$: C, 45.95; H, 3.63; N, 25.22. Found: C, 45.92; H, 3.58; N, 24.97.

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamidine (5j)——Treatment of **4f**[4f] in a manner similar to that described under method-(i) in the synthesis of **5h** gave **5j** as the monopicrate monohydrate (Table I), yellowish brown plates, mp 177.5—180.5° (dec.) (dried over P_2O_5 at room temp. and 1 mmHg for 24 hr) (lit.[7a] mp 192—194° for an anhydrous sample); UV (Table II); NMR (Me_2SO-d_6) δ: 3.61 (2H, b, $H_{(5')}$'s), 3.83—4.14 (2H, m, $H_{(4')}$ and $H_{(3')}$), 4.14—4.44 (1H, m, $H_{(2')}$), 5.08—5.48 (3H, m, OH's), 5.54 (1H, d, J= 6.5 Hz, $H_{(1')}$), 6.66 (2H, dull s, NH_2), 7.63 (1H, s, imidazole proton), 7.86 (4H, dull s, protonated amidine), 8.58 (2H, s, aromatic protons). *Anal.* Calcd. for $C_{15}H_{18}N_8O_{11}\cdot H_2O$: C, 35.72; H, 4.00; N, 22.22. Found: C, 35.42; H, 3.93; N, 22.43.

Cyclization of 1-Substituted 5-Aminoimidazole-4-carboxamidines (5g—j) to 9-Substituted Adenines (6g—j)——The cyclization of **5h** is described in detail as a typical example.

A stirred mixture of ethyl orthoformate (20 ml) and crude **5h**·HCl (185 mg), obtained from **4c** (197 mg, 1 mmol) in a manner described under method-(i) in the synthesis of **5h**, was heated at 80—85° for 16 hr. After addition of three drops of conc. aq. HCl, the mixture was further stirred at 80—85° for 8 hr. The precipitate that resulted was filtered off and combined with the residual solid which had been obtained by evaporation of the filtrate *in vacuo*. The combined solids were dissolved in 1 N aq. HCl (4 ml) and the solution was evaporated to dryness *in vacuo*. The resulting solid was dissolved in H_2O (20 ml) and the solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (6 ml). Elution with H_2O and evaporation of the eluate (60 ml) *in vacuo* left a colorless solid (122 mg, 75% from **4c**), mp 194.5—197°, which was recrystallized from benzene to give **6h** as colorless needles, mp 196.5—197.5° (lit.[17] mp 194—195°), identical (by TLC, mixed melting-point test, and IR spectrum) with authentic 9-ethyladenine. When **5h**·monopicrate hemihydrate was converted into the free base by the use of Amberlite IRA-402 (HCO_3^-) and the free base was cyclized for 5 hr in a similar manner, **6h** was obtained in 94% yield.

In similar cyclizations, **5g**·HCl, **5i**·HCl, and **5j**·HCl gave 9-methyladenine (**6g**), 9-benzyladenine (**6i**), and adenosine (**6j**) in 68%, 89%, and 45% overall yields (from **4a,d,f**), respectively.

5-Amino-1-methylimidazole-4-carboxamide (7g)——A mixture of 1 N aq. NaOH (50 ml) and crude **5g**·HCl, obtained from **4a** (169 mg, 1 mmol) in a manner described under the synthesis of **5g**, was heated at reflux for 4 hr with stirring. A small amount of an insoluble material was removed by filtration and washed with a little H_2O. The pH of the combined filtrate and washings was adjusted to 7—8 with 10% aq. HCl. The resulting solution was salted out with anhyd. K_2CO_3 and extracted with $CHCl_3$ (5×100 ml). The $CHCl_3$ extracts were dried over anhyd. K_2CO_3 and evaporated to dryness *in vacuo*, leaving **7g** (83 mg, 59% yield from **4a**). Recrystallization from EtOH produced an analytical sample as slightly pinkish pillars, mp 251.5—253.5° (dec.) [lit. mp 260°;[18] mp 254° (dec.)[19]]; UV (Table II); IR ν_{max}^{Nujol} cm^{-1}: 3375, 3205 (b), 3105 (NH_2, $CONH_2$), 1665, 1633 ($CONH_2$, C=N), 1562 ($CONH_2$); NMR (Me_2SO-d_6) δ: 3.40 (3H, s, Me), 5.68 (2H, dull s, NH_2), 6.60 (2H, dull s, $CONH_2$),[20] 7.03 (1H, s, ring proton). *Anal.* Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.73; H, 5.96; N, 39.85.

5-Amino-1-ethylimidazole-4-carboxamide (7h)——Crude **5h**·HCl, prepared from **4c** (197 mg, 1 mmol) in a manner described under method-(i) in the synthesis of **5h**, was hydrolyzed as described above for **7g**, giving **7h** in 68% overall yield from **4c**. Recrystallization from AcOEt provided an analytical sample as almost colorless needles, mp 223.5—226° (dec.)(lit.[18] mp 230—232°); UV (Table II); IR ν_{max}^{Nujol} cm^{-1}: 3390, 3220 (b), 3100 (NH_2, $CONH_2$), 1663, 1633 ($CONH_2$, C=N), 1563 ($CONH_2$); NMR (Me_2SO-d_6) δ: 1.24 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 3.79 (2H, q, J=7 Hz, $C\underline{H}_2Me$), 5.72 (2H, dull s, NH_2), 6.62 (2H, b, $CONH_2$),[20] 7.09 (1H, s, ring proton). *Anal.* Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.62; H, 6.62; N, 36.46.

5-Amino-1-benzylimidazole-4-carboxamide (7i)——A stirred mixture of NaOH (2 g), 50% (v/v) aq. EtOH (50 ml), and crude **5i**·HCl, prepared from **4d** (259 mg, 1 mmol) according to the procedure described under the synthesis of **5i**, was refluxed for 2 hr. The mixture was filtered and the pH of the filtrate was adjusted to 8 with 10% aq. HCl. The resulting solution was evaporated to dryness *in vacuo*. The residual solid was extracted with hot $CHCl_3$ (1×100 ml, 2×50 ml) and the $CHCl_3$ extracts were evaporated to dryness *in vacuo* to leave crude **7i**. Recrystallization from MeOH furnished almost colorless plates (74 mg,

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18) G. Shaw, R. N. Warrener, D. N. Butler, and R. K. Ralph, *J. Chem. Soc.*, **1959**, 1648.
19) A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, **1948**, 2028.
20) Comparison of the NMR spectra of **7g—i** with those of 1-alkyl-5-alkylaminoimidazole-4-carboxamides [T. Itaya and K. Ogawa, *Heterocycles*, **6**, 965 (1977); J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, *J. Org. Chem.*, **31**, 2202 (1966)] made the differentiation between the NH_2 and the $CONH_2$ signal.

34% yield from **4d**), mp 254—257° (dec.) (lit.[21] mp 249—251°); UV (Table II); IR ν_{max}^{Nujol} cm^{-1}: 3385, 3280 (b), 3205 (b), 3095 (NH_2, $CONH_2$), 1663, 1632 ($CONH_2$, C=N), 1556 ($CONH_2$); NMR (Me_2SO-d_6) δ: 5.05 (2H, s, CH_2Ph), 5.78 (2H, dull s, NH_2), 6.64 (2H, dull s, $CONH_2$),[20] 7.08—7.36 (6H, Ph, imidazole proton). *Anal.* Calcd. for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 60.81; H, 5.61; N, 25.92.

5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide (7j)——A mixture of conc. aq. NH_3 (8 ml) and crude **5j**·HCl, prepared from **4f** (290 mg, 0.8 mmol) according to the procedure described under the synthesis of **5j**, was heated in a sealed tube at 100° for 16 hr. A small amount of an insoluble material was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (5 ml) and a saturated solution (15 ml) of picric acid in H_2O was added. The yellow precipitate (269 mg) that resulted was filtered off, washed with a little H_2O, and dissolved in H_2O (400 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (4.5 ml). Elution with H_2O and evaporation of the eluate (500 ml) *in vacuo* left crude **7j** (155 mg), mp 207—209° (dec.). Recrystallization from 90% (v/v) aq. EtOH gave almost colorless prisms (98 mg, 47% yield from **4f**), mp 213—214.5° (dec.) (lit. mp 213—214°;[22] mp 218°[23]); UV (Table II). This sample was identical (by PPC, mixed melting-point test, and IR spectrum) with an authentic sample of AICA riboside.

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Studies on the Constituents of Useful Plants. VI.[1] Constituents of the Calyx of *Diospyros kaki* (2), and Carbon-13 Nuclear Magnetic Resonance Spectra of Flavonol Glycosides

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Structure of substances XIV and XVIII, obtained previously among the constituents of the calyx of persimmons (*Diospyros kaki*, Ebenaceae), was examined, and XIV was determined as astragalin (kaempferol 3-β-D-glucopyranoside) and XVIII as *n*-butyl-β-D-fructopyranoside, although the latter was considered to be an artifact. Carbon-13 NMR spectra of kaempferol, quercetin, trifolin, astragalin, and hyperin were measured and their structure was proved from the assignment of NMR signals.

Keywords——Ebenaceae; *Diospyros kaki* Thunb.; astragalin; hyperin; trifolin; *n*-butyl-β-D-fructopyranoside; carbon-13 nuclear magnetic resonance spectra

Our previous report[3] described the isolation of higher fatty acids, aromatic acids, flavonols and their glycosides, steroids, and triterpenoids as a constituent of the calyx of persimmons (*Diospyros kaki*, Ebenaceae). In the present series of work, structure of substances XIV

1) A part of this work was presented at the Osaka Meeting of Japanese Pharmacognostic Society, October 1974 and at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya 1976.
2) Location: *Mitahora-Higashi, Gifu, 502, Japan.*
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