Purines. LIV.[1] Intramolecular Cyclization of 9-Ethyl-1-(2-hydroxyethyl)adenine Caused by Nucleophiles: Formation of N^6,1-Ethanoadenine Derivatives[2]

Tohru SAITO, Miyoko MURAKAMI, Tadaaki INADA, Hiromi HAYASHIBARA, and Tozo FUJII*

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan. Received July 22, 1992

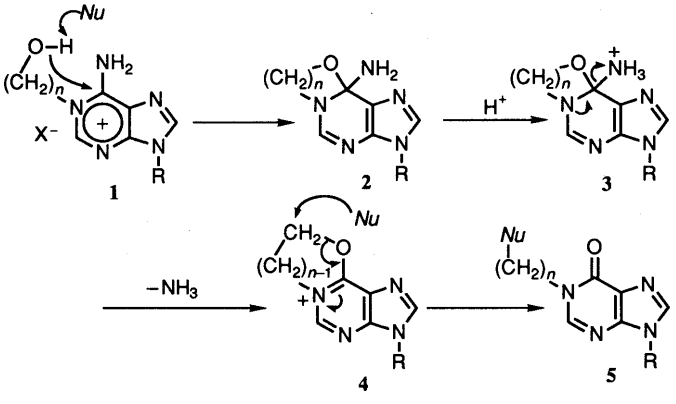
Treatment of 9-ethyl-1-(2-hydroxyethyl)adenine hydrobromide (1a) in boiling *N,N*-dimethylformamide (DMF) with an excess of thiourea for 7 h or with an excess of ammonium thiocyanate for 3 h provided 3-ethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium thiocyanate (8) in 51% or 58% yield, respectively. On treatment with an excess of triphenyl phosphite in boiling DMF for 20 min, 1a underwent a similar cyclization to form the same tricycle, which was isolated in 81% yield (from 1a) in the form of the perchlorate salt (12). A similar treatment of 1a with triethyl phosphite furnished the 9-ethyl analogue (15) in 83% yield. Conversion of 12 into the free base and oxidation of the latter with active MnO_2 in boiling CH_2Cl_2 for 16 h gave 3-ethyl-3*H*-imidazo[2,1-*i*]purine (13) (66% overall yield from 12), which was identical with a sample synthesized from 9-ethyladenine (9) and chloroacetaldehyde according to the general N^6,1-etheno bridging procedure. On treatment with methanolic ammonia at room temperature, the tricycle 15 afforded 9-ethyl-N^6-[2-(ethylamino)ethyl]adenine hydrobromide (26) in 79% yield. Mechanisms are proposed for the above intramolecular cyclizations of 1a caused by the S- and P-atom nucleophiles.

Keywords 1-(2-hydroxyethyl)adenine; nucleophile; N^6,1-ethanoadenine; cyclization; exchange amination; Dimroth rearrangement

In previous papers from this laboratory, we reported that an ω-hydroxyalkyl group at the 1-position of 9-substituted adenines (type **1**) made deamination of **1** possible, as shown in Chart 1, on treatment with hot H_2O at near neutrality[3] or with a nucleophile, such as imidazole, pyridine, or thiophenol, in boiling *N,N*-dimethylformamide (DMF).[1] The observed deamination to give the hypoxanthine derivatives (type **5**) has been assumed to proceed through the tetrahedral intermediates **2** and **3** and the oxazolinium intermediate **4** by the addition–elimination mechanism, in which the mode of intramolecular participation of the side-chain hydroxy group is nucleophilic, followed by attack on **4** by the nucleophile to cleave the oxazolinium ring.[1] For a better understanding of the key function of the ω-hydroxyalkyl group at the 1-position, we studied the behavior of 9-ethyl-1-(2-hydroxyethyl)adenine hydrobromide (**1a**) toward S- and P-atom nucleophiles (of weaker basicity relative to the above nucleophiles) in DMF in the present study.

On treatment with an excess amount (10 molar eq) of thiourea in boiling DMF for 7 h, **1a** produced the N^6,1-ethano derivative as the thiocyanate salt (**8**) in 51% yield. Conversion of **8** into the perchlorate salt **12** (79% yield) by anion exchange using $NaClO_4$ and *vice versa* (97% yield) using Amberlite IRA-402 (SCN^-) confirmed that the S-atom nucleophile had not been incorporated into the cation moiety of **8**. It has been reported that 1-butanol can alkylate thiourea in dioxane in the presence of *p*-toluenesulfonic acid at 100 °C to give *S*-butylisothiouronium *p*-toluenesulfonate.[4] An analogous reaction may occur between **1a** and thiourea, giving the isothiouronium salt **6**. Subsequent intramolecular cyclization of **6**, followed by anion exchange with ammonium thiocyanate that should have been produced by thermal decomposition of the excess thiourea,[5] would have given **8**. Interestingly, the same thiocyanate salt (**8**) was obtained in 58% yield when **1a** was treated with an excess of ammonium thiocyanate in boiling DMF for 3 h. In this case, the cyclization to **8** may be assumed to proceed through the thiocyanate ester **7**. However, differentiation between the two intermediates **6** and **7** for the reaction of **1a** with thiourea or ammonium thiocyanate leading to **8** is difficult at present because of the possible equilibration[5] between thiourea and ammonium thiocyanate at the boiling point (153 °C) of DMF.

Next we investigated the behavior of **1a** toward P-atom nucleophiles. On treatment with an excess of triphenyl phosphite in boiling DMF for 20 min, **1a** cyclized to the N^6,1-ethano derivative, which was isolated, after treatment with $NaClO_4$, in 81% overall yield in the form of the perchlorate salt (**12**). Conversion of **12** into the free base was accomplished by means of Amberlite IRA-402 (HCO_3^-), and oxidation of the free base with active MnO_2 in boiling CH_2Cl_2 for 16 h furnished the N^6,1-etheno derivative **13** in 66% overall yield (from **12**). The identity of **13** with a sample prepared in 62% yield from 9-ethyladenine (**9**) and chloroacetaldehyde according to the general N^6,1-etheno bridging procedure[6] unequivocally established the N^6,1-ethano structure of **12**, and hence



n = 2 or 3; *Nu* = OH^- or a nucleophile

Chart 1

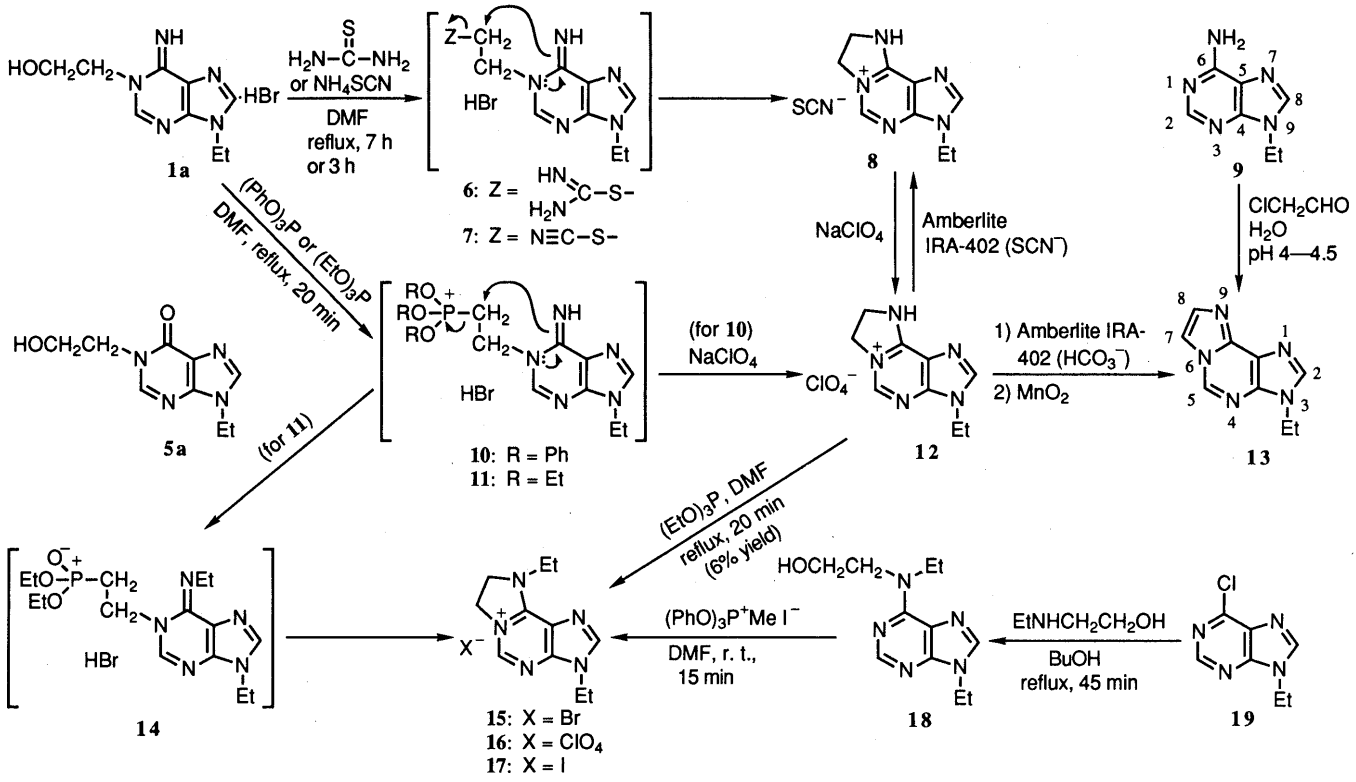


Chart 2

that of **8**. It may be assumed that the cyclization of **1a** to **12** proceeds through the quasiphosphonium intermediate **10**, but the possibility of the intermediacy of the 1-(2-bromoethyl) derivative cannot be excluded.[7]

A similar treatment of **1a** with triethyl phosphite afforded the N^6,1-ethano derivative **15**, but with N^6 ethylated, in 83% yield together with a small amount (3% yield) of the deamination product **5a**. In order to confirm the correctness of the structure of **15**, 6-chloro-9-ethylpurine (**19**) was allowed to react with 2-(ethylamino)ethanol in boiling 1-butanol for 45 min, and the amination product **18** (97% yield) was characterized as the perchlorate salt (**18**·$HClO_4$) (77% yield from **19**). Iodination of the amino alcohol **18** with methyltriphenoxyphosphonium iodide[8] in DMF at room temperature for 15 min and spontaneous cyclization of the resulting N^6-(2-iodoethyl) derivative gave the N^6,1-ethano derivative **17** in 68% yield. This iodide salt (**17**) and the bromide salt **15** derived directly from **1a** were each converted into the perchlorate salt **16**; both samples of the perchlorate were identical.

Considering the capability of triethyl phosphite in ethylating aromatic amines,[9] one may presume that the conversion of **1a** into **15** would have proceeded through the quasiphosphonium intermediate **11** and ethylation of the cyclized intermediate **12** (Br^- for ClO_4^-). However, treatment of **12** with triethyl phosphite under similar conditions was found to afford the *N*-ethylated product **16** in only 6% yield with 66% recovery of **12**. In addition, a similar treatment of 1,9-diethyladenine hydrobromide (**20**), a model for **12** (Br^- for ClO_4^-) or **1a** prepared from the corresponding hydriodide[10] by the use of Amberlite IRA-402 (Br^-), with triethyl phosphite failed to furnish the N^6-ethylated product (**21**). Instead, it produced the

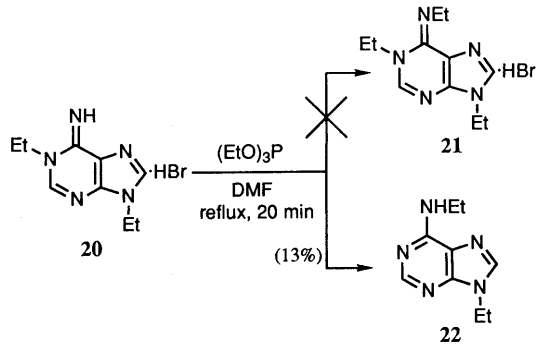


Chart 3

N^6,9-diethyl isomer (**22**),[10] a product assumed to be formed by Dimroth rearrangement,[3,10] in 13% yield with 18% recovery of **20**. This presents a contrast to the alkylations of 1,9-disubstituted adenines with common alkylating agents, in which alkylations occur predominantly at the N^6-position.[10-12] These observations led us to consider the possibility that a large portion of the quasiphosphonium intermediate **11** undergoes intramolecular ethylation at N^6 in a manner somewhat similar to that of the Michaelis–Arbusov reaction[13] and the resulting diethyl alkylphosphonate (**14**) cyclizes to **15** as in the case of **10**.

Finally, we tested the stability of the new tricycle **15**, because its UV spectrum in H_2O at pH 13 was found unstable. On treatment with methanolic ammonia at room temperature for 55 h, **15** furnished the N^6,9-disubstituted adenine derivative **26** in 79% yield. If attack on **15** by ammonia occurs at C(7), the product should be the N^6,N^6,9-trisubstituted adenine derivative **27**. However, the UV spectrum of the actual product **26** in various solvents

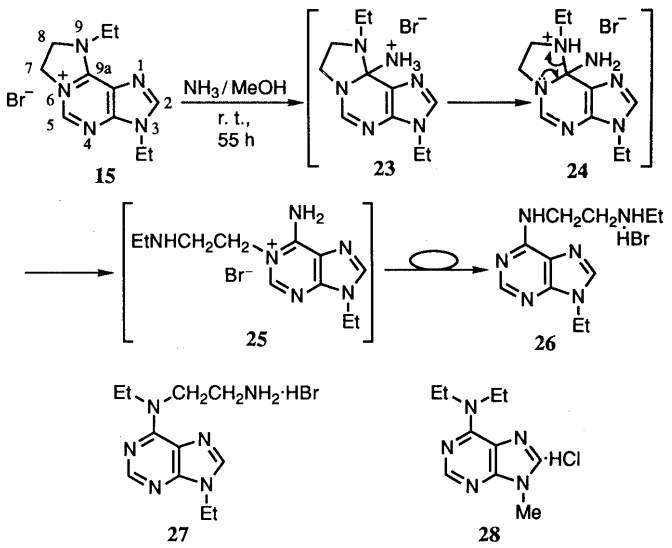


Chart 4

was different from that of **28**[14] or **18**·$HClO_4$, a model for **27**, but was similar to those[3] of N^6,9-disubstituted adenines. The ^{1}H-NMR spectrum of **26** in Me_2SO-d_6 also supported the correctness of the assigned side-chain structure. The conversion of **15** into **26** may be interpreted in terms of an initial ammonia attack at C(9a) of **15** to form **24** through **23**, subsequent ring opening of **24** in the imidazolidine moiety, and Dimroth rearrangement[3] of the resulting 1,9-disubstituted adenine derivative **25**.

In conclusion, the present results reveal that S- and P-atom nucleophiles of weak basicity, such as thiourea, thiocyanate ion, triphenyl phosphite, and triethyl phosphite, effect intramolecular cyclization of **1a** to construct an N^6,1-ethanobridge in boiling DMF. This is in sharp contrast to the cases of more basic nucleophiles,[1,3] such as hydroxide ion, imidazole, pyridine, and thiophenol,[15] in which deamination of **1a** to **5** (R = Et; n = 2) proceeds, presumably through the pathway shown in Chart 1.[1] When **1a** reacts with a less basic nucleophile, deprotonation of the hydroxy group involved in the process **1**→**2** would be less favored than the nucleophilic substitution of the hydroxy group as illustrated in Chart 2 (**1a**→**6**, **7**, **10**, or **11**). The formation of the deamination by-product **5a** to a small extent in the reaction of **1a** with triethyl phosphite would support this view, since triethyl phosphite is the most basic among the weakly basic nucleophiles tested in the present study.

Experimental

General Notes All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of chromatography, instrumentation, and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

3-Ethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium Thiocyanate (8) i) By Reaction of **1a** with Thiourea: A stirred mixture of 9-ethyl-1-(2-hydroxyethyl)adenine hydrobromide (**1a**)[3] (1.01 g, 3.5 mmol) and thiourea (2.66 g, 35 mmol) in dry DMF (13 ml) was heated under reflux for 7 h. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was dissolved in EtOH (10 ml). The resulting ethanolic solution was kept in a refrigerator overnight. The precipitate that deposited was filtered off, washed with a little EtOH, and dried to give **8** (441 mg, 51%), mp 204—207 °C. Recrystallization from EtOH yielded an analytical sample of **8** as colorless prisms, mp 214—215 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 265 nm (ε 13400); $\lambda_{max}^{H_2O}$ (pH 1) 264.5 (14000); $\lambda_{max}^{H_2O}$ (pH 7) 264.5 (14000); $\lambda_{max}^{H_2O}$ (pH 13) 270.5 (15100); IR ν_{max}^{Nujol} 2040 cm^{-1} (SCN^-); ^{1}H-NMR (Me_2SO-d_6) δ: 1.44 [3H, t, J = 7 Hz, N(3)-CH_2Me], 4.09 (2H, m, NHC$\underline{H}_2$$CH_2N^+$), 4.30 [2H, q, J = 7 Hz, N(3)-C$\underline{H}_2$Me], 4.72 (2H, m, NHCH_2C$\underline{H}_2N^+$), 8.58 and 8.79 [1H each, s, C(2)-H and C(5)-H], 10.92 (1H, br, NH). *Anal.* Calcd for $C_{10}H_{12}N_6S$: C, 48.37; H, 4.87; N, 33.85. Found: C, 48.39; H, 4.89; N, 34.02.

ii) By Reaction of **1a** with Ammonium Thiocyanate: A stirred mixture of **1a**[3] (144 mg, 0.5 mmol) and ammonium thiocyanate (381 mg, 5 mmol) in dry DMF (2 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* to leave a brownish oil, which was washed with ether (20 ml) and then treated with boiling EtOH (1.5 ml). The resulting, turbid ethanolic solution was filtered while hot, and the filtrate was allowed to stand at room temperature. The crystals that deposited were filtered off, washed with a little EtOH, and dried to afford **8** (72 mg, 58%) as slightly brownish prisms, mp 209—211 °C. This sample was identical (by comparison of the TLC mobility and IR spectrum) with the one obtained by method (i).

iii) From the Perchlorate **12**: A solution of **12** (145 mg, 0.5 mmol), obtained by the reaction of **1a** with triphenyl phosphite (*vide infra*), in H_2O (25 ml) was passed through a column of Amberlite IRA-402 (SCN^-) (3 ml), and the column was eluted with H_2O. The aqueous eluate (70 ml) was concentrated to dryness *in vacuo* to leave a colorless solid (120 mg, 97%), mp 182—195 °C. Recrystallization of the solid from EtOH provided a pure sample of **8** as colorless prisms, mp 213—214 °C. This sample was identical (by comparison of the TLC mobility and IR spectrum) with the one prepared by method (i).

3-Ethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium Perchlorate (12) i) By Reaction of **1a** with Triphenyl Phosphite: A stirred mixture of **1a**[3] (1.15 g, 4 mmol) and triphenyl phosphite (2.48 g, 8 mmol) in dry DMF (20 ml) was heated under reflux for 20 min. The reaction mixture was concentrated *in vacuo* to leave an oil, which was then triturated with AcOEt (39 ml). The insoluble material that resulted was separated from the AcOEt layer by decantation, washed with AcOEt (10 ml), and dissolved in H_2O (3 ml). The resulting aqueous solution was mixed with a solution of $NaClO_4$ (588 mg, 4.8 mmol) in H_2O (1 ml), and the precipitate that resulted was filtered off, washed with H_2O, and dried to give **12** (934 mg, 81%) as a colorless solid, mp 263—264 °C. Recrystallization of the solid from H_2O furnished an analytical sample as colorless needles, mp 263—264 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 264 nm (ε 13400); $\lambda_{max}^{H_2O}$ (pH 1) 263 (13800); $\lambda_{max}^{H_2O}$ (pH 7) 263 (13800); $\lambda_{max}^{H_2O}$ (pH 13) 270 (15000); ^{1}H-NMR (Me_2SO-d_6) δ: 1.43 [3H, t, J = 7 Hz, N(3)-CH_2Me], 4.08 (2H, m, NHC$\underline{H}_2$$CH_2N^+$), 4.29 [2H, q, J = 7 Hz, N(3)-C$\underline{H}_2$Me], 4.70 (2H, m, NHCH_2C$\underline{H}_2N^+$), 8.58 and 8.78 [1H each, s, C(2)-H and C(5)-H], 10.93 (1H, br, NH). *Anal.* Calcd for $C_9H_{12}ClN_5O_4$: C, 37.32; H, 4.18; N, 24.18. Found: C, 37.47; H, 4.10; N, 23.99.

ii) From the Thiocyanate Salt **8**: The thiocyanate salt **8** (124 mg, 0.5 mmol), obtained by the reaction of **1a** with thiourea (*vide supra*), was dissolved in H_2O (1 ml), and a solution of $NaClO_4$ (73 mg, 0.6 mmol) in H_2O (0.5 ml) was added. The precipitate that resulted was filtered off, washed with a little H_2O, and dried to afford **12** (114 mg, 79%) as a colorless solid, mp 260—261 °C. Recrystallization of the solid from H_2O gave a pure sample as colorless needles, mp 263—264 °C. This sample was identical (by comparison of the TLC mobility and IR spectrum) with the one obtained by method (i).

3-Ethyl-3*H*-imidazo[2,1-*i*]purine (13) i) From **9**: A solution of 9-ethyladenine (**9**)[16] (490 mg, 3 mmol) in 1.0 M aqueous chloroacetaldehyde (30 ml) was brought to pH 4.5 by addition of a few drops of 10% aqueous HCl and kept at room temperature at pH 4.0—4.5 by occasional addition of saturated aqueous $NaHCO_3$ for 72 h. The reaction mixture was concentrated *in vacuo* to leave a solid, which was dissolved in H_2O (3 ml). The resulting aqueous solution was brought to pH 8 by addition of 10% aqueous Na_2CO_3 and extracted with seven 15-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with saturated aqueous NaCl (5 ml), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a solid. Recrystallization of the solid from EtOH gave **13** (351 mg, 62%) as colorless needles, mp 212—214 °C. Further recrystallization in the same manner yielded an analytical sample, mp 214.5—215.5 °C; MS m/z: 187 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 259 nm (ε 4390), 266.5 (5390), 276 (5420), 297 (3340); $\lambda_{max}^{H_2O}$ (pH 1) 221 (28100), 275 (10800); $\lambda_{max}^{H_2O}$ (pH 7) 230 (31700), 260 (sh) (4450), 267 (5590), 276 (5790), 294 (3440); $\lambda_{max}^{H_2O}$ (pH 13) unstable[17]; ^{1}H-NMR (Me_2SO-d_6) δ: 1.47 [3H, t, J = 7 Hz, N(3)-CH_2Me], 4.33 [2H, q, J = 7 Hz, N(3)-C$\underline{H}_2$Me], 7.54 [1H, d, J = 1.5 Hz, C(8)-H], 8.06 [1H, d, J = 1.5 Hz, C(7)-H], 8.32 [1H, s, C(2)-H], 9.27 [1H, s, C(5)-H].[18] *Anal.* Calcd for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.63; H, 4.83; N, 37.45.

ii) From **12**: A solution of **12** (203 mg, 0.7 mmol) in H_2O (35 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (2 ml), and the column was then eluted with H_2O (90 ml). The eluate was concentrated to dryness *in vacuo* to leave a solid (142 mg), which was dried and dissolved in CH_2Cl_2 (10 ml). After addition of active MnO_2[19] (400 mg), the CH_2Cl_2 solution was heated under reflux for 6 h with stirring. At this stage, more oxidizing agent (200 mg) was added, and refluxing was continued for a further 5 h. This procedure was repeated once more, and then the excess MnO_2 was removed by filtration and washed with eight 5-ml portions of CH_2Cl_2. The filtrate and washings were combined and concentrated *in vacuo* to leave a solid, which was recrystallized from EtOH to yield **13** (86 mg, 66%) as colorless needles, mp 210—213 °C. Further recrystallization from EtOH produced a pure sample, mp 214.5—215.5 °C, which was identical (by comparison of the TLC mobility and IR spectrum) with the one obtained by method (i).

3,9-Diethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium Bromide (15) A stirred mixture of **1a**[3] (2.88 g, 10 mmol) and triethyl phosphite (3.30 g, 20 mmol) in dry DMF (50 ml) was heated under reflux for 20 min. The reaction mixture was concentrated *in vacuo*, and the residue was treated with hot AcOEt–EtOH (4 : 1, v/v) (400 ml). The resulting hot mixture was filtered to remove an insoluble material, and the filtrate was concentrated *in vacuo* to leave a pale yellowish solid. The solid was then purified by means of column chromatography [alumina (300 g), $CHCl_3$–MeOH (10 : 1, v/v)] to give a yellowish solid. Trituration of the latter solid with three 70-ml portions of AcOEt and collection of the insoluble material by filtration afforded crude **15**·1/3H_2O (2.47 g, 83%), mp 239.5—242 °C (dec.). Recrystallization from AcOEt–EtOH and drying over P_2O_5 at 2 mmHg and room temperature for 24 h yielded an analytical sample of **15**·1/3H_2O as colorless prisms, mp 255.5—256.5 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 220 nm (ε 21300), 270 (14600); $\lambda_{max}^{H_2O}$ (pH 1) 270 (15500); $\lambda_{max}^{H_2O}$ (pH 7) 270 (15500); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 1.34 [3H, t, J=7 Hz, N(9)-CH_2Me], 1.45 [3H, t, J=7 Hz, N(3)-CH_2Me], 4.05—4.3 (2H, m, NC$H_2$$CH_2N^+$), 4.08 [2H, q, J=7 Hz, N(9)-CH_2Me], 4.32 [2H, q, J=7 Hz, N(3)-CH_2Me], 4.55—4.8 (2H, m, NCH_2CH_2N^+), 8.64 and 8.78 [1H each, s, C(2)-H and C(5)-H]. *Anal.* Calcd for $C_{11}H_{16}BrN_5$·1/3H_2O: C, 43.43; H, 5.58; N, 23.02. Found: C, 43.56; H, 5.83; N, 23.10.

On the other hand, the AcOEt extracts, obtained in the above trituration with AcOEt, were concentrated *in vacuo*, and the residue was chromatographed [alumina (9 g), $CHCl_3$–MeOH (10 : 1, v/v)] to give a pale yellowish solid. Recrystallization of the solid from AcOEt yielded 9-ethyl-1-(2-hydroxyethyl)hypoxanthine hydrate (**5a**·H_2O) (65 mg, 3%) as pale yellowish needles, mp 164—168 °C. This sample was identical (by comparison of the paper chromatographic (PPC) and TLC mobilities and IR spectrum) with authentic **5a**·H_2O.[3]

3,9-Diethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium Perchlorate (16) i) From **15**: The bromide salt **15**·1/3H_2O (152 mg, 0.5 mmol) was dissolved in H_2O (0.2 ml), and a solution of $NaClO_4$·H_2O (105 mg, 0.75 mmol) in H_2O (0.1 ml) was added. The precipitate that resulted was filtered off, washed with a little H_2O, and dried to give the perchlorate salt **16** (111 mg, 70%) as colorless needles, mp 172—174 °C. Recrystallization from EtOH furnished an analytical sample, mp 172—174.5 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 220 nm (ε 21300), 270 (14700); $\lambda_{max}^{H_2O}$ (pH 1) 270 (15400); $\lambda_{max}^{H_2O}$ (pH 7) 270 (15400); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 1.32 [3H, t, J=7 Hz, N(9)-CH_2Me], 1.43 [3H, t, J=7 Hz, N(3)-CH_2Me], 4.05—4.3 (2H, m, NC$H_2$$CH_2N^+$), 4.06 [2H, q, J=7 Hz, N(9)-CH_2Me], 4.30 [2H, q, J=7 Hz, N(3)-CH_2Me], 4.55—4.8 (2H, m, NCH_2CH_2N^+), 8.61 and 8.73 [1H each, s, C(2)-H and C(5)-H]. *Anal.* Calcd for $C_{11}H_{16}ClN_5O_4$: C, 41.58; H, 5.08; N, 22.04. Found: C, 41.49; H, 5.09; N, 22.16.

ii) By Reaction of **12** with Triethyl Phosphite: A stirred mixture of **12** (145 mg, 0.5 mmol) and triethyl phosphite (166 mg, 1 mmol) in dry DMF (2.5 ml) was heated under reflux for 20 min. The reaction mixture was concentrated *in vacuo*, and the residual solid was washed with two 5-ml portions of ether and recrystallized from H_2O (*ca.* 1 ml) to recover **12** (96 mg, 66%), mp 261—263 °C. The mother liquor from this recrystallization was concentrated *in vacuo* to leave a glass. Purification of the glass by means of preparative TLC [Merck aluminum oxide 150 F_{254} (type T) (1.5-mm thickness), $CHCl_3$–EtOH (8 : 1, v/v)], followed by recrystallization from EtOH, furnished **16** (9 mg, 6%) as colorless needles, mp 172—173.5 °C. This sample was identical (by comparison of the TLC mobility and IR spectrum) with the one prepared by method (i).

iii) From **17**: The iodide salt **17** (180 mg, 0.52 mmol) was dissolved in a small amount of EtOH, and 70% aqueous $HClO_4$ (120 mg, 0.84 mmol) was added. The colorless needles that deposited were filtered off, washed with EtOH (15 ml), and dried to give the perchlorate salt **16** (91 mg, 55%), which was identical (by comparison of the PPC mobility and IR spectrum) with the one obtained by method (i).

***N*^{6},9-Diethyl-*N*^{6}-(2-hydroxyethyl)adenine (18)** A stirred solution of 6-chloro-9-ethylpurine (**19**)[20] (1.28 g, 7 mmol) and 2-(ethylamino)ethanol (3.12 g, 35 mmol) in 1-butanol (35 ml) was heated under reflux for 45 min. The reaction mixture was concentrated *in vacuo*, and the residual oil was purified by means of column chromatography [silica gel (83 g), $CHCl_3$–EtOH (15 : 1, v/v)], giving **18** (1.60 g, 97%) as a colorless solid, mp 56.5—59 °C.

A portion (300 mg) of the solid was dissolved in EtOH (1 ml), and 70% aqueous $HClO_4$ (220 mg) was added. The precipitate that resulted was filtered off, washed with a little EtOH, and dried to give the perchlorate salt **18**·$HClO_4$ (341 mg, 77% from **19**), mp 115.5—120.5 °C. Recrystallization from EtOH yielded an analytical sample of **18**·$HClO_4$ as colorless prisms, mp 115.5—118.5 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 280 nm (ε 19400); $\lambda_{max}^{H_2O}$ (pH 1) 273 (18400); $\lambda_{max}^{H_2O}$ (pH 7) 279 (20000); $\lambda_{max}^{H_2O}$ (pH 13) 279 (20000); ^{1}H-NMR (Me_2SO-d_6) (at 80 °C) δ: 1.27 [3H, t, J=7 Hz, NCH_2Me], 1.44 [3H, t, J=7 Hz, N(9)-CH_2Me], 3.75 (2H, m, NCH_2CH_2OH), 4.05 (2H, m, NCH_2CH_2OH), 4.12 [2H, q, J=7 Hz, NCH_2Me], 4.26 [2H, q, J=7 Hz, N(9)-CH_2Me], 5.13 (s, OH), 8.34 and 8.35 [1H each, s, purine protons]. *Anal.* Calcd for $C_{11}H_{18}ClN_5O_5$: C, 39.35; H, 5.40; N, 20.86. Found: C, 39.51; H, 5.60; N, 21.12.

3,9-Diethyl-7,8-dihydro-3*H*-imidazo[2,1-*i*]purinium Iodide (17) A solution of **18** (600 mg, 2.55 mmol) and methyltriphenoxyphosphonium iodide[8] (2.31 g, 5.1 mmol) in dry DMF (10 ml) was stirred at room temperature for 15 min. After addition of MeOH (0.5 ml), the reaction mixture was concentrated *in vacuo*, and the residue was chromatographed on an alumina (88 g) column using $CHCl_3$ and $CHCl_3$–EtOH (8 : 1, v/v) as the eluents. Fractions containing the major product were collected and concentrated *in vacuo* to leave a solid, which was then washed with benzene (10 ml) and dried to yield crude **17** (601 mg, 68%), mp 216—217 °C (dec.). Recrystallization from AcOEt–EtOH produced an analytical sample as colorless needles, mp 217—219 °C (dec.); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 219 nm (ε 34400), 270 (14800); $\lambda_{max}^{H_2O}$ (pH 1) 222 (30700), 270 (15400); $\lambda_{max}^{H_2O}$ (pH 7) 222 (30700), 270 (15400); $\lambda_{max}^{H_2O}$ (pH 13) unstable; ^{1}H-NMR (Me_2SO-d_6) δ: 1.32 [3H, t, J=7 Hz, N(9)-CH_2Me], 1.42 [3H, t, J=7 Hz, N(3)-CH_2Me], 4.05—4.3 (2H, m, NC$H_2$$CH_2N^+$), 4.07 [2H, q, J=7 Hz, N(9)-CH_2Me], 4.30 [2H, q, J=7 Hz, N(3)-CH_2Me], 4.55—4.8 (2H, m, NCH_2CH_2N^+), 8.62 and 8.75 [1H each, s, C(2)-H and C(5)-H. *Anal.* Calcd for $C_{11}H_{16}IN_5$: C, 38.28; H, 4.67; N, 20.29. Found: C, 38.33; H, 4.78; N, 20.11.

1,9-Diethyladenine Hydrobromide (20) A solution of 1,9-diethyladenine hydriodide[10] (638 mg, 2 mmol) in H_2O (30 ml) was passed through a column of Amberlite IRA-402 (Br^-) (10 ml), and the column was then eluted with H_2O (60 ml). Concentration of the aqueous eluate under reduced pressure and drying of the residue gave **20**·2/3H_2O (529 mg, 93%) as a colorless solid, mp 278—279 °C (dec.). Recrystallization of the solid from EtOH and drying over P_2O_5 at 2 mmHg and room temperature for 24 h furnished an analytical sample of **20**·2/3H_2O as colorless needles, mp 285—286 °C (dec.); ^{1}H-NMR (Me_2SO-d_6) δ: 1.34 [3H, t, J=7 Hz, N(1)-CH_2Me], 1.44 [3H, t, J=7 Hz, N(9)-CH_2Me], 4.28 [2H, q, J=7 Hz, N(1)-CH_2Me or N(9)-CH_2Me], 4.32 [2H, q, J=7 Hz, N(9)-CH_2Me or N(1)-CH_2Me], 8.57 and 8.74 (1H each, s, purine protons), 9.18 and 9.85 (1H each, br, NH's). *Anal.* Calcd for $C_9H_{14}BrN_5$·2/3H_2O: C, 38.04; H, 5.44; N, 24.65. Found: C, 38.13; H, 5.28; N, 24.73.

Reaction of 1,9-Diethyladenine Hydrobromide (20) with Triethyl Phosphite A stirred mixture of **20**·2/3H_2O (82 mg, 0.29 mmol) and triethyl phosphite (100 mg, 0.6 mmol) in dry DMF (1.5 ml) was heated under reflux for 20 min. The reaction mixture was concentrated *in vacuo* to leave a mixture of a colorless solid and an oil. The residue was triturated with AcOEt–EtOH (1 : 1, v/v) (2 ml), and the insoluble solid was filtered off, washed with a little EtOH, and dried to recover **20**·2/3H_2O (15 mg, 18%), mp 272—273 °C.

On the other hand, the filtrate from the above trituration was concentrated *in vacuo*, and the residue was purified by preparative TLC [Merck aluminum oxide 150 F_{254} (type T) (1.5-mm thickness), benzene–EtOH (10 : 1, v/v)] to provide *N*^{6},9-diethyladenine (**22**) (7 mg, 13%) as a colorless solid, mp 103.5—105 °C. This sample was identical (by comparison of the TLC mobility and IR spectrum) with authentic **22**.[10]

9-Ethyl-*N*^{6}-[2-(ethylamino)ethyl]adenine Hydrobromide (26) A mixture of **15**·1/3H_2O (363 mg, 1.19 mmol) and a saturated solution of NH_3 in MeOH (3 ml) was stirred at room temperature. At 24 h and 52 h after the start of the reaction, more methanolic NH_3 (3 ml each) was added. At 55 h after the start, the reaction mixture was concentrated *in vacuo*, and the residue was washed with acetone (5 ml) and dried to give **26** (299 mg, 79%), mp 208—213 °C. Recrystallization from EtOH furnished an analytical sample as colorless prisms, mp 212.5—214 °C; UV $\lambda_{max}^{95\%\,aq.\,EtOH}$

269 nm (ε 17600); $\lambda_{max}^{H_2O}$ (pH 1) 269 (15700); $\lambda_{max}^{H_2O}$ (pH 7) 268 (17500); $\lambda_{max}^{H_2O}$ (pH 13) 270 (17500); ^{1}H-NMR (Me_2SO-d_6) δ: 1.18 (3H, t, J=7 Hz, $N^+H_2CH_2\underline{Me}$), 1.40 [3H, t, J=7 Hz, N(9)-$CH_2\underline{Me}$], 3.01 (2H, m, $N^+H_2C\underline{H}_2Me$), 3.18 (2H, m, $NCH_2C\underline{H}_2N^+H_2Et$), 3.78 (2H, br, $NC\underline{H}_2CH_2N^+H_2Et$), 4.20 [2H, q, J=7 Hz, N(9)-$C\underline{H}_2Me$], 7.86 [1H, br, C(6)-NH], 8.24 and 8.27 (1H each, s, purine protons), 8.44 (2H, br, $N^+\underline{H}_2Et$). *Anal.* Calcd for $C_{11}H_{19}BrN_6$: C, 41.91; H, 6.08; N, 26.66. Found: C, 41.93; H, 6.22; N, 26.64.

References and Notes

1) Paper LIII in this series, T. Saito, M. Murakami, T. Inada, H. Hayashibara, and T. Fujii, *Chem. Pharm. Bull.*, **40**, 3201 (1992).
2) A part of this work was presented in a preliminary form: T. Saito, M. Murakami, T. Inada, H. Hayashibara, and T. Fujii, Abstracts of Papers, 18th Congress of Heterocyclic Chemistry, Fukuoka (Japan), October 1986, pp. 197—200.
3) T. Fujii, T. Saito, and N. Terahara, *Chem. Pharm. Bull.*, **34**, 1094 (1986).
4) K. Nakano, T. Takido, and K. Itabashi, *Yuki Gosei Kagaku Kyokai Shi*, **30**, 63 (1972).
5) *a*) Beilstein's "Handbuch der Organischen Chemie," Vol. 3, EIII, 293; *b*) E. Jona and T. Sramko, *Chem. Zvesti.*, **20**, 569 (1966) [*Chem. Abstr.*, **65**, 16856*h* (1966)].
6) *a*) N. K. Kochetkov, V. N. Shibaev, and A. A. Kost, *Tetrahedron Lett.*, **1971**, 1993; *b*) J. A. Secrist III, J. R. Barrio, N. J. Leonard, and G. Weber, *Biochemistry*, **11**, 3499 (1972).
7) P. Beck, "Organic Phosphorus Compounds," Vol. 2, ed. by G. M. Kosolapoff and L. Maier, Wiley–Interscience, New York, 1972, pp. 191 and 207.
8) *a*) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970); *b*) H. N. Rydon, "Organic Syntheses," Coll. Vol. 6, ed. by W. E. Noland, John Wiley & Sons, New York, 1988, pp. 830—832.
9) *a*) R. B. Crawford, U. S. Patent 3253036 (1966) [*Chem. Abstr.*, **65**, 5397*h* (1966)]; *b*) D. Amos and R. G. Gillis, *Aust. J. Chem.*, **22**, 1555 (1969).
10) T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *Chem. Pharm. Bull.*, **24**, 655 (1976).
11) B. Singer, L. Sun, and H. Fraenkel-Conrat, *Biochemistry*, **13**, 1913 (1974).
12) T. Fujii, T. Itaya, F. Tanaka, T. Saito, K. Mohri, and K. Yamamoto, *Chem. Pharm. Bull.*, **31**, 3149 (1983).
13) *a*) K. H. Worms and M. Schmidt-Dunker, "Organic Phosphorus Compounds," Vol. 7, ed. by G. M. Kosolapoff and L. Maier, John Wiley & Sons, New York, 1976, pp. 23—27; *b*) J. I. G. Cadogan, "Organophosphorus Reagents in Organic Synthesis," ed. by J. I. G. Cadogan, Academic Press, London, 1979, pp. 4—5.
14) T. Itaya, H. Matsumoto, and K. Ogawa, *Chem. Pharm. Bull.*, **28**, 1920 (1980).
15) Considering the resonance stabilization of *O*-protonated DMF, we tentatively assume that the reacting species of thiophenol in DMF would be thiophenolate ion in this case.
16) T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.*, **20**, 1334 (1972).
17) This instability may be attributable to ring fission at the C(5)–N(6) bond similar to that reported for N^6,1-ethenoadenosine derivatives in 0.1 N NaOH at room temperature: K. F. Yip and K. C. Tsou, *Tetrahedron Lett.*, **1973**, 3087.
18) The assignments of the ring proton signals were made on the basis of those reported[6b] for N^6,1-ethenoadenosine hydrochloride in D_2O.
19) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).
20) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).