Purines. LX.[1] Dimroth Rearrangement and Concomitant Hydrolytic Deamination of 7-Alkyl-1-methyladenines

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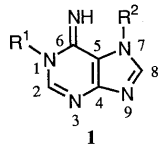
The Dimroth rearrangement of 7-alkyl-1-methyladenines (8) to produce 7-alkyl-N^6-methyladenines (9) (63—72% yield) has been found to be accompanied with unusual hydrolytic deaminations to give 7-alkyl-1-methylhypoxanthines (10) (1—3.5%) and/or 7-alkylhypoxanthines (11) (12—22%), when effected in boiling H_2O for 4—70 h. Probable pathways leading to these by-products are proposed.

Keywords Dimroth rearrangement; deamination hydrolytic; adenine 1,7-disubstituted; hypoxanthine 1,7-disubstituted; hypoxanthine 7-substituted

1,7-Dialkyladenine (type **1**) is one of the eleven theoretically possible N^x,N^y-dialkyladenines. Its chemical behavior may be characterized primarily by the susceptibility to Dimroth rearrangement[2,3] to form isomeric N^6,7-dialkyladenine (type **2**) under basic conditions or in the absence of added base. Taylor and Loeffler[4] reported that a few 1-alkyl-7-methyladenines (**1**: R^2=Me) rearranged to N^6-alkyl-7-methyladenines (**2**: R^2=Me) in essentially quantitative yields on treatment with boiling H_2O for 20 h. In the case of 1-butyl-7-methyladenine (**1**: R^1=Bu; R^2=Me), however, they observed the concomitant formation of a minute amount of 7-methylhypoxanthine (**3**), a deaminated product.[4] Leonard *et al.*[5] described the rearrangement of 1,7-dibenzyladenine (**1**: $R^1=R^2=PhCH_2$) to N^6,7-dibenzyladenine (**2**: $R^1=R^2=PhCH_2$) in boiling 2 N aqueous NaOH–EtOH for 1 h (56% yield) or in boiling 50% aqueous EtOH in the absence of added base for 30 d (75% yield), but without mention of the formation of any deaminated products. 1,9-Dialkyladenines (type **4**) usually undergo Dimroth rearrangement smoothly, producing N^6,9-dialkyladenines (type **5**), and no deaminated products are detectable,[6] with the exception of 1-(ω-hydroxyalkyl) analogues.[7] However, 1-alkyladenines (**4**: R^2=H) unsubstituted at the 9-position undergo Dimroth rearrangement more slowly than do the corresponding 9-substituted analogues,[3,6] and we have found that the rearrangement of 1-ethyladenine (**4**: R^1=Et; R^2=H) to give N^6-ethyladenine (**5**: R^1=Et; R^2=H) (90% yield) is accompanied with unusual hydrolytic deaminations to produce hypoxanthine (**6**) (6%) and 1-ethylhypoxanthine (**7**) (3.5%), when carried out in H_2O at 70 °C and pH 10.47 for 96 h.[3] This led us to check in the present work whether similar deaminations would occur in 7-alkyl-1-methyladenines (**8a—c**) under Dimroth rearrangement-inducing conditions.



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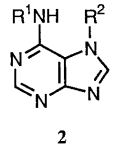

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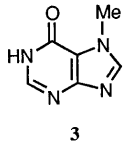

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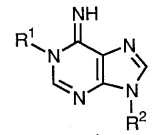

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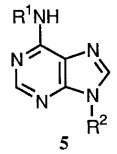

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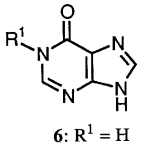

6: R^1 = H
7: R^1 = Et

Treatment of the free base[1] of 7-benzyl-1-methyladenine (**8c**) with boiling H_2O for 4 h gave the Dimroth rearrangement product 7-benzyl-N^6-methyladenine (**9c**) in 72% yield, as expected. The product was identified by direct comparison with an authentic sample.[8] On the other hand, TLC analysis of the reaction mixture indicated the presence of at least two by-products besides a small amount of the starting material (**8c**). Separation of the by-products from the reaction mixture by fractional crystallization and column chromatography resulted in the isolation of 7-benzylhypoxanthine (**11c**) and 7-benzyl-1-methylhypoxanthine (**10c**) in 12% and 1% yields, respectively. The structures of the two deaminated products were confirmed by comparison with authentic samples prepared from 7-benzyl-6-chloropurine (**15**) by alkaline hydrolysis[9] and from **11c** by methylation[10] according to the previously reported procedures.

Similar treatment of the free base[1] of 1,7-dimethyladenine (**8a**) with boiling H_2O for 9.5 h was found to afford N^6,7-dimethyladenine (**9a**)[8] and 1,7-dimethylhypoxanthine (**10a**)[11] in 63% and 3.5% yields, respectively. In this case, however, we were unable to isolate another type of deamination product [*i.e.*, 7-methylhypoxanthine (**11a**)], if formed, from the reaction mixture.

Finally, the free base of 7-ethyl-1-methyladenine (**8b**), prepared from the corresponding perchlorate salt (**8b**·$HClO_4$)[1,12] by the use of Amberlite IRA-402 (HCO_3^-), was heated in H_2O under reflux for 70 h, and 7-ethyl-N^6-methyladenine (**9b**)[8] and 7-ethylhypoxanthine (**11b**)[1] were isolated from the reaction mixture in 67% and 22% yields, respectively. The formation of **11b** does not seem to be a result of a consecutive reaction of the main product **9b**. This is because **9b** was recovered in almost quantitative yield, with no indication of the occurrence of **11b**, even after it had been treated with boiling H_2O for 80 h.

By analogy of the previously reported case of 1-ethyl-

This paper is dedicated to Professor Yoshifumi Maki on the occasion of his retirement from Gifu Pharmaceutical University in March 1994.

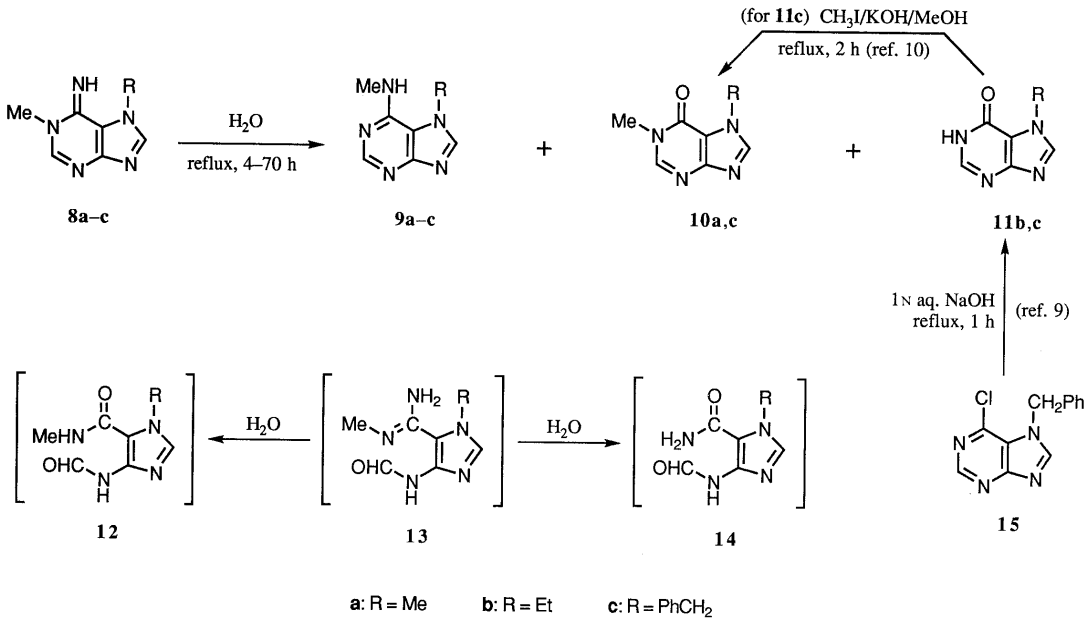

Chart 1

adenine (**4**: $R^1 = Et$; $R^2 = H$),[3] we assume that the reaction of 7-alkyl-1-methyladenine (**8**) in boiling H_2O would first form the monocyclic intermediate **13** (Chart 1), which may cyclize to **9** (thus concluding a Dimroth rearrangement) and to **10** and **11** through **12** and **14** (both would be formed by hydrolysis of the unsymmetrical amidine moiety of **13**), respectively. Thus, the occurrence of the unusual hydrolytic deaminations observed in the above Dimroth rearrangement of **8** may be rationalized by assuming the cyclization of the putative common intermediate **13** to **9** to be sufficiently slow, owing to steric repulsion between the N(1)-alkyl and the neighboring methylimino groups in **13**. In the case of the formation of **10**, however, the possibility of a direct hydrolytic deamination of **8** *via* an addition–elimination mechanism may not necessarily be excluded.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of instrumentation and measurements. The solvents used for measurements of UV spectra were 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13). Elemental analyses and MS measurements were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, q = quartet, s = singlet, t = triplet.

Conversion of 1,7-Dimethyladenine (8a) into N^6,7-Dimethyladenine (9a) and 1,7-Dimethylhypoxanthine (10a) A stirred solution of **8a**·$3/5H_2O$[1] (179 mg, 1.03 mmol) in H_2O (10 ml) was heated under reflux for 9.5 h. The reaction mixture was concentrated *in vacuo* to leave a solid. The solid was dried and recrystallized from EtOH to afford a first crop (69 mg, 41%) of **9a** as colorless prisms, mp 307.5—308 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9a** (mp 309—310 °C).[8] The mother liquor of the above recrystallization was then concentrated *in vacuo*, and the residual solid was subjected to column chromatography [alumina (15 g), $CHCl_3$–EtOH (20 : 1, v/v)]. Earlier fractions gave **10a** (6.0 mg, 3.5%) as a colorless solid, mp 248.5—249 °C (lit.[11b] mp 251—253 °C); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 257 nm (ε 7690); IR ν_{max}^{Nujol} 1685 cm^{-1} (CO) [lit.[11c] ν_{max}^{KBr} 1683 cm^{-1} (CO)]; ^{1}H-NMR (Me_2SO-d_6) δ: 3.48 [3H, s, N(1)-Me], 3.97 [3H, s, N(7)-Me], 8.15 and 8.26 (2H, s each, purine protons).

Later fractions collected from the above chromatography yielded a second crop (36.1 mg, 22%) of **9a** as a colorless solid, mp 306—308 °C, which was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9a**.[8] The total yield of **9a** was 105 mg (63%).

Conversion of 7-Ethyl-1-methyladenine (8b) into 7-Ethyl-N^6-methyladenine (9b) and 7-Ethylhypoxanthine (11b) A solution of **8b**·$HClO_4$[1,12] (162 mg, 0.583 mmol) in H_2O (*ca.* 40 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (3 ml), and the column was eluted with H_2O (40 ml). The combined eluates were concentrated *in vacuo* to a volume of *ca.* 20 ml and then heated under reflux for 70 h. The reaction mixture was concentrated to dryness *in vacuo* to leave a colorless solid. After having been dried, the solid was chromatographed on silica gel (10 g) using $CHCl_3$–EtOH (8 : 1, v/v) as the eluent. Earlier fractions furnished **11b** (21 mg, 22%) as a colorless solid, mp > 300 °C; MS *m/z*: 164 (M^+); UV $\lambda_{max}^{95\%\,aq.\,EtOH}$ 255 nm (ε 8930); $\lambda_{max}^{H_2O}$ (pH 1) 250 (10200); $\lambda_{max}^{H_2O}$ (pH 7) 256 (9440); $\lambda_{max}^{H_2O}$ (pH 13) 262 (10400); ^{1}H-NMR (Me_2SO-d_6) δ: 1.41 [3H, t, J = 7 Hz, N(7)-CH_2<u>Me</u>], 4.34 [2H, q, J = 7 Hz, N(7)-<u>CH_2</u>Me], 7.96 [1H, slightly dull s, C(2)-H], 8.23 [1H, s, C(8)-H], 12.3 [1H, br, N(1)-H]. The ^{1}H-NMR spectrum of this sample was superimposable on that of **11b** obtained previously[1] as a by-product from the reaction of 4-amino-1-ethyl-1*H*-imidazole-5-carboxamide perchlorate with Vilsmeier reagent.

Later fractions of the above chromatography gave **9b** (69.3 mg, 67%) as a colorless solid, mp 246.5—249 °C. Recrystallization from EtOH yielded a pure sample as colorless pillars, mp 251—252.5 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9b** (mp 254—255 °C).[8]

Conversion of 7-Benzyl-1-methyladenine (8c) into 7-Benzyl-N^6-methyladenine (9c), 7-Benzyl-1-methylhypoxanthine (10c), and 7-Benzylhypoxanthine (11c) A stirred solution of **8c**[1] (1.20 g, 5.02 mmol) in H_2O (45 ml) was heated under reflux for 4 h. The reaction mixture was concentrated to a small volume *in vacuo*, and the colorless precipitate that resulted was filtered off and dried to afford **9c** (867 mg, 72%) as a colorless solid, mp 178—180 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9c** (mp 181—182 °C).[8] The filtrate was then concentrated to dryness *in vacuo*, and the residual solid was dried and washed repeatedly with hot benzene to leave a first crop (102 mg, 9%) of **11c** as a benzene-insoluble colorless solid, mp 267—269 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **11c** [colorless plates (from H_2O), mp 272—274 °C (lit.[9] mp > 260 °C); ^{1}H-NMR (Me_2SO-d_6) δ: 5.56 [2H, s, N(7)-C<u>H</u>$_2$Ph], 7.33 [5H, s, N(7)-CH_2<u>Ph</u>], 7.98 [1H, slightly dull s, C(2)-H], 8.39 [1H, s, C(8)-H], 12.31 [1H, br, N(1)-H]. *Anal.* Calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.48; H, 4.43; N, 24.86], prepared from 7-benzyl-6-chloropurine (**15**) according to the literature procedure.[9]

The benzene extracts described above were combined and concen-

trated *in vacuo*, and the residue was chromatographed on silica gel (45 g) using CH_2Cl_2–EtOH (15 : 1, v/v; 10 : 1, v/v; and then 6.6 : 1, v/v) as the eluent. Earlier fractions gave **10c** (12.2 mg, 1%) as a yellowish solid, mp 152—155.5°C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **10c** [colorless prisms (from benzene–hexane), mp 157—161 °C (lit.[10] mp 159—160 °C); UV $\lambda_{max}^{95\%\,aq.EtOH}$ 258 nm (ε 7770); ^{1}H-NMR (Me_2SO-d_6) δ: 3.49 [3H, s, N(1)-Me], 5.58 [2H, s, N(7)-C$\underline{H}_2$Ph], 7.33 [5H, s, N(7)-CH$_2$$\underline{Ph}$], 8.29 and 8.41 (2H, s each, purine protons). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.08; H, 5.07; N, 23.32], prepared from **11c** by methylation according to the literature.[10] Later fractions of the chromatography yielded a second crop (34 mg, 3%) of **11c** as a yellowish solid, mp 268—277 °C, which was identical (by comparison of the IR spectrum and TLC mobility) with anthentic **11c**.[9] The total yield of **11c** was 136 mg (12%).

Stability of 7-Ethyl-N^6-methyladenine (9b) in Boiling H_2O A solution of **9b** (20 mg) in H_2O (4 ml) was heated under reflux for 80 h. The reaction was monitored by TLC, but there was no indication of the formation of any products. The reaction mixture was concentrated to dryness *in vacuo*, recovering **9b** in almost quantitative yield as a colorless solid, mp 253.5—255 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with authentic **9b** (mp 254—255 °C).[8]

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