(1 : 1) to give 19.8 g (90%) of **3a**, mp 93—94°. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.08; H, 6.77; N, 6.30. NMR ($CDCl_3$) δ: 7.57 (1H, d, J=12.2 Hz, =CH–OEt) and 5.33 (1H, d, J=12.2 Hz, =CH–CO).

***o*-(3-Ethoxyacryloylamino)phenol (3b)**——A solution of 6.73 g (0.05 mol) of 3-ethoxyacryloyl chloride in 20 ml of AcOEt was added dropwise to a suspension of 10.9 g (0.1 mol) of *o*-aminophenol (**2b**) in 200 ml of AcOEt with stirring and cooling in ice-water. After 2 hr, the reaction mixture was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from AcOEt–petroleum ether to give 7.0 g (68%) of **3b**, mp 128—130°. *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.56; H, 6.37; N, 6.83. NMR ($CDCl_3$) δ: 7.57 (1H, d, J=12.0 Hz, =CH–OEt) and 5.37 (1H, d, J=12.0 Hz, =CH–CO).

***N*-(3,3-Di-*n*-butoxypropionyl)-*o*-anisidine (5)**——A suspension of 5.28 g (0.022 mol) of sodium 3,3-di-*n*-butoxypropionate[7] in 20 ml of $CHCl_3$ was treated dropwise with 3.39 g (0.022 mol) of phosphorus oxychloride with stirring and cooling in ice-water. After 30 min, a solution of 2.46 g (0.02 mol) of *o*-anisidine and 3.0 g of triethylamine in 20 ml of $CHCl_3$ was added in small portions to the reaction mixture. After 1 hr, the reaction mixture was washed successively with dil. HCl, dil. KOH and H_2O, dried over Na_2SO_4 and concentrated to give 6.6 g (quantitative yield) of **5** as an oil, which was used for the next procedure without further purification (the distillation of a sample of **5** was accompanied by decomposition).

8-Hydroxycarbostyril (4b)——A mixture of 5.0 g (0.0226 mol) of **3a** and 50 ml of concentrated hydrochloric acid was stirred for 24 hr at room temperature. The resulting solution was then poured into 500 ml of ice-water. The precipitate was collected, dried and recrystallized from MeOH–Et_2O to give 1.54 g (39%) of 8-methoxycarbostyril (**4a**), mp 111—113°. A suspension of 5.0 g (0.0286 mol) of **4a** in 50 ml of 47% hydrobromic acid was refluxed for 8 hr. The precipitate was collected after cooling, and washed with H_2O to give 4.6 g (quantitative yield) of **4b**, mp 301—304°. Compound **4b** was also obtained as follows. A mixture of 4.0 g (0.0193 mol) of **3b** and 40 ml of concentrated hydrochloric acid was shaken until it became a clear solution, then allowed to stand. After 24 hr, the precipitate was collected, washed with water, dried and purified with hot MeOH to give 1.03 g (33%) of **4b**.

8-Methoxycarbostyril (4a)——A solution of 5.6 g of **5** in 10 ml of MeOH was added to 50 ml of concentrated hydrochloric acid at 50—55° during 1 hr. The reaction mixture was then cooled and poured into 500 ml of ice-water. The precipitate was collected, dried and recrystallized from AcOEt–Et_2O to give 0.55 g (19%) of **4a**.

7) Sodium 3,3-di-*n*-butoxypropionate was prepared from *n*-butyl 3,3-di-*n*-butoxypropionate and sodium hydroxide in MeOH at room temperature.

[Chem. Pharm. Bull. 28(11)3443—3446(1980)]

Purines. XXI.[1] Synthesis of Adenine 1-Oxides Carrying an Allylic Side Chain at the 9-Position[2]

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(Received July 2, 1980)

9-Allyladenine 1-oxide (**3**) has been prepared from 1-ethoxyadenine (**6**) in 58% overall yield through an unequivocal synthetic route. The route consists of an initial allylation of **6** with allyl bromide and Et-O bond cleavage of the resulting 9-allyl-1-ethoxyadenine hydrobromide (**7**) by treatment with boiling pyridine. Replacement of allyl bromide by 3-methyl-2-butenyl bromide in the above reaction sequence afforded 9-(3-methyl-2-butenyl)adenine 1-oxide (**9**) in 59% overall yield through the 1-ethoxy derivative **8**.

1) Paper XX in this series, T. Fujii, T. Itaya, T. Saito, and M. Kawanishi, *Chem. Pharm. Bull.*, **26**, 1929 (1978).
2) A part of this work was reported in a preliminary form by T. Fujii, I. Inoue, T. Itaya, and T. Saito, *Heterocycles*, **12**, 1543 (1979).
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*

Keywords——1-alkoxyadenine; allylation; nucleophilic attack; dealkylation; N-oxide; catalytic hydrogenolysis; alkylation; UV; NMR

There have been conflicting reports in the literature concerning the peracid oxidation of 9-allyladenine (**1**).[4,5] Takemoto and co-workers[4] reported that the oxidation of **1** with perbenzoic acid gave 9-(2,3-epoxypropyl)adenine (**2**) in 63% yield. However, the ultraviolet (UV) spectrum of their oxidation product was suggestive of the 1-N-oxide structure **3**. Later on, DiMenna and Piantadosi[5] reported on a similar oxidation of **1** with *m*-chloroperbenzoic acid, which furnished 9-allyladenine 1-oxide (**3**) and not the epoxypropyl derivative **2** as asserted by the Japanese group. They further stated that the decomposition point and nuclear magnetic resonance (NMR) data of their oxidation product (**3**) were consistent with those of the compound claimed[4] to be **2**. The evidence adduced by the American workers for assignment of the 1-N-oxide structure nevertheless seemed somewhat insufficient. We therefore decided to synthesize the N-oxide **3** through an unequivocal route that should consist of steps not exposing the allylic side chain to oxidation. This synthetic problem has now been solved by the following reaction sequence, which was generated on the basis of our knowledge[6] of the chemistry of 1-alkoxyadenines.

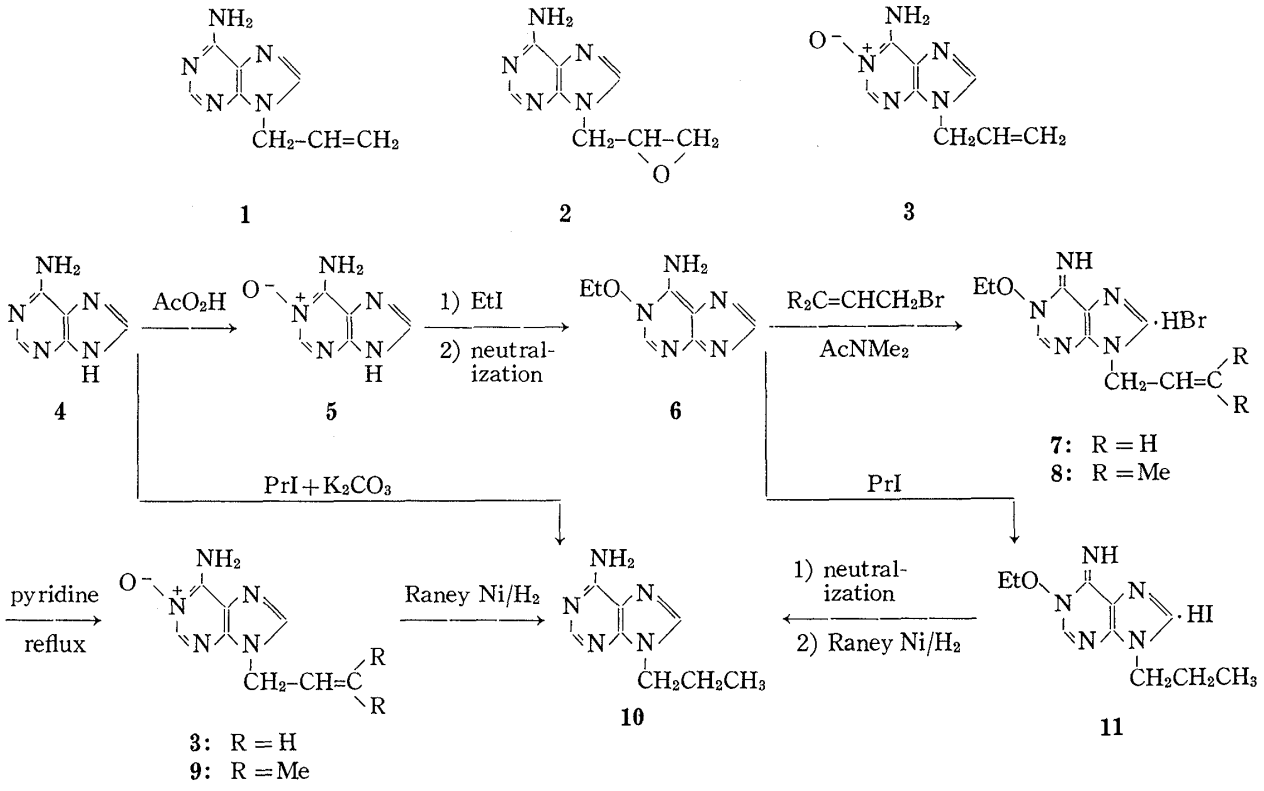

Chart 1

Allylation of 1-ethoxyadenine (**6**) [prepared from adenine (**4**) through its 1-N-oxide (**5**)[6a,7] by a method given in the literature[6a]] with allyl bromide in $AcNMe_2$ at room temperature

4) K. Kondo, K. Kuwata, and K. Takemoto, *Makromol. Chem.*, **160**, 341 (1972).
5) W. S. DiMenna and C. Piantadosi, *J. Pharm. Sci.*, **68**, 667 (1979).
6) *a*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971); *b*) T. Fujii, C. C. Wu, and T. Itaya, *Chem. Pharm. Bull.*, **19**, 1368 (1971); *c*) T. Fujii, T. Itaya, C. C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971); *d*) T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.*, **20**, 958 (1972); *e*) T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *ibid.*, **22**, 2211 (1974); *f*) T. Fujii, K. Sakamoto, S. Kawakatsu, and T. Itaya, *ibid.*, **24**, 655 (1976).
7) M. A. Stevens, D. I. Magrath, H. W. Smith, and G. B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).

for 48 hr produced the 9-allylated product **7** in 67% yield. The 9-substituted structure was assignable on the basis of the generalization[6a] that 1-alkoxyadenines undergo alkylation mainly at the 9-position as well as the observation of UV spectra similar to those[6a,b] of 1-alkoxy-9-alkyladenine salts. On treatment with boiling pyridine for 1 hr, **7** gave the desired N-oxide **3** in 86% yield. This facile fission of the Et–O bond had been expected from our previous finding[6d,e] that 9-substituted 1-alkoxyadenine salts were easily dealkylated on the attack of nucleophiles. The correctness of the structure of **3** was further supported by its UV spectra (similar to those[6b] of 9-alkyladenine 1-oxides) and by its NMR spectrum (see "Experimental"), indicating that the allylic side chain remained intact. Moreover, reduction of **3** with hydrogen activated on Raney Ni catalyst provided 9-propyladenine (**10**) (77% yield), which was identical with a sample synthesized in 44% overall yield from **6** by alkylation with propyl iodide in $AcNMe_2$ followed by hydrogenolysis (Raney Ni/H_2) of the free base of the resulting 1-ethoxy-9-propyl derivative **11**. An alternative synthetic route to **10** from **4** was an application of the previously reported, general 9-alkylation procedure;[8] **4** was alkylated with propyl iodide in $AcNMe_2$ in the presence of anhydrous K_2CO_3 to produce **10** in 33% yield. It should be noted that the Fourier transform NMR data of **3** in Me_2SO-d_6 were consistent with those[5] reported for the *m*-chloroperbenzoic acid oxidation product from **1**.

With a view to checking the generality and utility of the present synthetic route to **3**, we next carried out a parallel synthesis of 9-(3-methyl-2-butenyl)adenine 1-oxide (**9**), the 1-N-oxide of one of the positional isomers of triacanthine.[9] Treatment of **6** with 3-methyl-2-butenyl bromide ($AcNMe_2$, 29—33°, 12 hr) furnished the 9-substituted product **8** in 67% yield. Removal of the ethyl group from **8** was effected with boiling pyridine (1 hr), giving the N-oxide **9** in 88% yield. The UV and NMR spectral data for **8** and **9** were consistent with the structures assigned.

In conclusion, the above results together with those reported in the literature[4,5] confirm that the peracid oxidation product obtained from **1** has the 1-N-oxide structure (**3**) and not the epoxypropyl structure (**2**). They also exemplify the synthetic utility of the 1-ethoxy group for the preparation of adenine 1-oxides with unsaturated side chains at the 9-position.

Experimental

General Notes——All melting points were determined with a Yamato MP-1 capillary melting point apparatus and are corrected. NMR spectra were recorded on a JEOL JNM-FX-100 spectrometer at 24° with Me_4Si as an internal standard. See ref. 1 for other instrumentation and measurements. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

9-Allyl-1-ethoxyadenine Hydrobromide (**7**)——A mixture of **6**[6a] (630 mg, 3.5 mmol) and allyl bromide (1.27 g, 10.5 mmol) in $AcNMe_2$ (10.5 ml) was stirred at room temperature (26—32°) for 48 hr. The mixture was concentrated *in vacuo*, and the oily residue was triturated with ether. The crystals that resulted were filtered off, washed with ether, and recrystallized from 90% aq. EtOH to provide **7** (710 mg, 67%), mp 198—205° (dec.). Further recrystallizations from 90% aq. EtOH yielded an analytical sample as colorless needles, mp 204—208° (dec.); $\lambda_{max}^{95\%\ aq.\ EtOH}$ 259 nm (ε 12700); $\lambda_{max}^{H_2O}$ (pH 1) 260 (12900); $\lambda_{max}^{H_2O}$ (pH 7) 260 (12800); $\lambda_{max}^{H_2O}$ (pH 13)[10] 258 (13400), 265 (sh) (12000); NMR (Me_2SO-d_6) δ: 1.43 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 4.43 (2H, q, J=7 Hz, $O\underline{CH_2}Me$), 4.88 (2H, d, J=5 Hz, $N\underline{CH_2}CH$), 5.10 (1H, d-d, J=1.5 and 17.5 Hz, *trans* $CH{=}C\underline{H_2}$), 5.24 (1H, d-d, J=1.5 and 10.5 Hz, *cis* $CH{=}C\underline{H_2}$), 5.80—6.25 (1H, m, $CH_2\underline{CH}{=}CH_2$), 8.56 and 9.13 (1H each, s, purine protons), 9.95 (b, $=NH_2^+$ or $2\times NH$). *Anal.* Calcd for $C_{10}H_{14}BrN_5O$: C, 40.02; H, 4.70; N, 23.33. Found: C, 39.72; H, 4.79; N, 23.29.

9-Allyladenine 1-Oxide (**3**)——A stirred mixture of **7** (600 mg, 2 mmol) and pyridine (18 ml) was heated under reflux for 1 hr, and then cooled in an ice bath for 2 hr. The precipitate that formed was filtered off,

8) *a*) J. A. Montgomery and H. J. Thomas, *J. Heterocyclic Chem.*, **1**, 115 (1964); *b*) T. Fujii, S. Sakurai, and T. Uematsu, *Chem. Pharm. Bull.*, **20**, 1334 (1972).

9) *a*) N. J. Leonard and J. A. Deyrup, *J. Am. Chem. Soc.*, **84**, 2148 (1962); *b*) A. Cavé, J. A. Deyrup, R. Goutarel, N. J. Leonard, and X. G. Monseur, *Ann. Pharm. Franc.*, **20**, 285 (1962); *c*) H. Morimoto and H. Oshio, *Chem. Pharm. Bull.*, **11**, 1320 (1963).

washed successively with a little pyridine and EtOH, and dried to give **3** (330 mg, 86%), mp 259—265° (dec.). Recrystallization from 30% aq. EtOH produced an analytical sample as slightly brownish prisms, mp 265—269° (dec.); MS *m/e*: 191 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 42300), 263 (8000), 300 (2100); $\lambda_{max}^{H_2O}$ (pH 1) 259 (12300); $\lambda_{max}^{H_2O}$ (pH 7) 232 (45300), 262 (8100), 292 (2100); $\lambda_{max}^{H_2O}$ (pH 13) 232 (28500), 269 (8700), 305 (4100); NMR (CF_3CO_2D) δ: 5.16 (2H, d, J=6 Hz, $NC\underline{H}_2CH$), 5.62 (1H, d, J=17.5 Hz, *trans* $CH=C\underline{H}_2$), 5.66 (1H, d, J=9 Hz, *cis* $CH=C\underline{H}_2$), 5.80—6.32 (1H, m, $CH_2C\underline{H}=CH_2$), 8.92 and 9.17 (1H each, s, purine protons); NMR (Me_2SO-d_6) δ: 4.70—4.90 (2H, m, $NC\underline{H}_2CH$), 4.90—5.30 (2H, m, *trans* and *cis* $CH=C\underline{H}_2$), 5.85—6.30 (1H, m, $CH_2C\underline{H}=CH_2$), 8.29 and 8.58 (1H each, s, purine protons). *Anal.* Calcd for $C_8H_9N_5O$: C, 50.26; H, 4.74; N, 36.63. Found: C, 50.06; H, 4.71; N, 36.59.

1-Ethoxy-9-(3-methyl-2-butenyl)adenine Hydrobromide (8)——A mixture of **6**[6a] (2.87 g, 16 mmol) and 3-methyl-2-butenyl bromide (7.54 g, 51 mmol) in $AcNMe_2$ (48 ml) was stirred at 29—33° for 12 hr. The reaction mixture was worked up in a manner similar to that described above for **7**, affording **8** (3.51 g, 67%), mp 200—206° (dec.). For analysis this sample was recrystallized from EtOH to give colorless needles, mp 207.5—210.5° (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 260 nm (ε 13200); $\lambda_{max}^{H_2O}$ (pH 1) 261 (13300); $\lambda_{max}^{H_2O}$ (pH 7) 261 (13200); $\lambda_{max}^{H_2O}$ (pH 13)[10] 259 (14100), 266 (sh) (12700); NMR (Me_2SO-d_6) δ: 1.43 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.73 and 1.83 (3H each, s, $CH=C\underline{Me}_2$), 4.42 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.86 (2H, d, J=7.5 Hz, $NC\underline{H}_2CH$), 5.42 (1H, b, $NCH_2C\underline{H}$), 8.56 and 9.12 (1H each, s, purine protons), 9.97 (b, $=NH_2^+$ or $2\times NH$). *Anal.* Calcd for $C_{12}H_{18}BrN_5O$: C, 43.91; H, 5.52; N, 21.34. Found: C, 43.97; H, 5.66; N, 21.29.

9-(3-Methyl-2-butenyl)adenine 1-Oxide (9)——Compound **8** was treated with pyridine as described above for **3**, giving **9**, mp 255—265° (dec.), in 88% yield. Recrystallization of this material from 30% aq. EtOH yielded an analytical sample as colorless needles, mp 266.5—268.5° (dec.); MS *m/e*: 219 (M^+); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 235 nm (ε 46400), 266 (7800), 300 (2500); $\lambda_{max}^{H_2O}$ (pH 1) 260 (13000); $\lambda_{max}^{H_2O}$ (pH 7) 232 (47900), 262 (8600), 290 (2400); $\lambda_{max}^{H_2O}$ (pH 13) 232 (32500), 268 (9200), 303 (4200); NMR (CF_3CO_2D) δ: 1.96 (6H, s, $CH=C\underline{Me}_2$), 5.15 (2H, d, J=8 Hz, $NC\underline{H}_2CH$), 5.59 (1H, t, J=8 Hz, $NCH_2C\underline{H}$), 8.94 and 9.24 (1H each, s, purine protons). *Anal.* Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.70; H, 5.89; N, 31.84.

1-Ethoxy-9-propyladenine Hydriodide (11)——A mixture of **6**[6a] (1.79 g, 10 mmol) and PrI (4.25 g, 25 mmol) in $AcNMe_2$ (30 ml) was stirred at room temperature for 140 hr. The reaction mixture was worked up as described above for **7**, furnishing crude **11** (2.10 g, 60%), mp 184—188° (dec.). Recrystallization from EtOH gave an analytical sample as colorless needles, mp 185—188° (dec.); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 259 nm (ε 12700); $\lambda_{max}^{H_2O}$ (pH 1) 260 (12500); $\lambda_{max}^{H_2O}$ (pH 7) 260 (12700); $\lambda_{max}^{H_2O}$ (pH 13)[10] 258 (13800), 265 (sh) (12300); NMR (Me_2SO-d_6) δ: 0.87 (3H, t, J=7 Hz, $CH_2CH_2\underline{Me}$), 1.43 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.85 (2H, m, $CH_2C\underline{H}_2Me$), 4.23 (2H, t, J=7 Hz, $C\underline{H}_2CH_2Me$), 4.42 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 8.59 and 9.11 (1H each, s, purine protons), 9.53 and 10.25 (1H each, b, $=NH_2^+$ or $2\times NH$). *Anal.* Calcd for $C_{10}H_{16}IN_5O$: C, 34.40; H, 4.62; N, 20.06. Found: C, 34.36; H, 4.69; N, 20.16.

9-Propyladenine (10)——i) From **4**: A stirred mixture of **4** (2.70 g, 20 mmol) and anhyd. K_2CO_3 (2.76 g, 20 mmol) in $AcNMe_2$ (80 ml) was heated at 110° for 3 hr. The mixture was cooled to 85°, and a solution of PrI (6.80 g, 40 mmol) in $AcNMe_2$ (20 ml) was added. The resulting mixture was then stirred at 85° for 50 min. The excess of PrI and the solvent were removed by vacuum distillation, and the residue was extracted with three 100-ml portions of hot benzene. Removal of the benzene from the combined extracts by evaporation and recrystallization of the resulting solid from EtOH (15 ml) furnished **10** (1.16 g, 33%), mp 169.5—173.5°. Further recrystallization from 2-propanol gave an analytical sample as colorless needles, mp 173.5—175° (lit.[11] mp 168°); UV $\lambda_{max}^{95\%\ aq.\ EtOH}$ 262 nm (ε 14600); $\lambda_{max}^{H_2O}$ (pH 1) 261 (14400); $\lambda_{max}^{H_2O}$ (pH 7) 263 (14600); $\lambda_{max}^{H_2O}$ (pH 13) 263 (14600); NMR (Me_2SO-d_6) δ: 0.84 (3H, t, J=7 Hz, $CH_2\underline{Me}$), 1.82 (2H, m, $C\underline{H}_2Me$), 4.11 (2H, t, J=7 Hz, $NC\underline{H}_2CH_2$), 7.20 (2H, b, NH_2), 8.14 (2H, s, purine protons). *Anal.* Calcd for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.21; H, 6.47; N, 39.28.

ii) From **3**: A solution of **3** (172 mg, 0.9 mmol) in H_2O (20 ml) was hydrogenated over Raney Ni catalyst (1 ml) at atmospheric pressure and 27° for 1.5 hr. The catalyst was removed by filtration and washed with H_2O. The combined filtrate and washings were evaporated to dryness *in vacuo* to leave a solid (122 mg, 77%), mp 171—174.5°. Recrystallization from 2-propanol afforded **10** as colorless needles, mp 172.5—175°, identical [by thin-layer chromatography (TLC), infrared (IR) spectroscopy, and mixed melting-point test] with a sample prepared by method (i) or (iii).

iii) From **11**: A solution of **11** (244 mg, 0.7 mmol) in H_2O (17 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (1.5 ml). Elution with H_2O (30 ml) and concentration of the eluate *in vacuo* left a pale yellow solid, which was dissolved in EtOH (6 ml). The ethanolic solution was hydrogenated over Raney Ni catalyst (1 ml) at 1 atm and 50° for 2 hr. The reaction mixture was then worked up as described above under item (ii), producing **10** (92 mg, 74%), mp 171—173.5°. This specimen was identical [by TLC, IR and UV spectroscopy, and mixed melting-point test] with a sample synthesized by method (i).

Acknowledgment We are grateful to Mr. M. Naruse, Kyowa Hakko Kogyo Co., for a generous gift of adenine. Financial assistance of this work by a Grant-in-Aid for Cancer Research (to Professor D. Mizuno) from the Ministry of Education, Science and Culture, Japan, is also gratefully acknowledged.

11) T. C. Myers and L. Zeleznick, *J. Org. Chem.*, **28**, 2087 (1963).