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A General and Convenient Synthesis of 7-Alkyladenines from Adenine by Regioselective Alkylation Utilizing Blocking/Deblocking at the 3-Position

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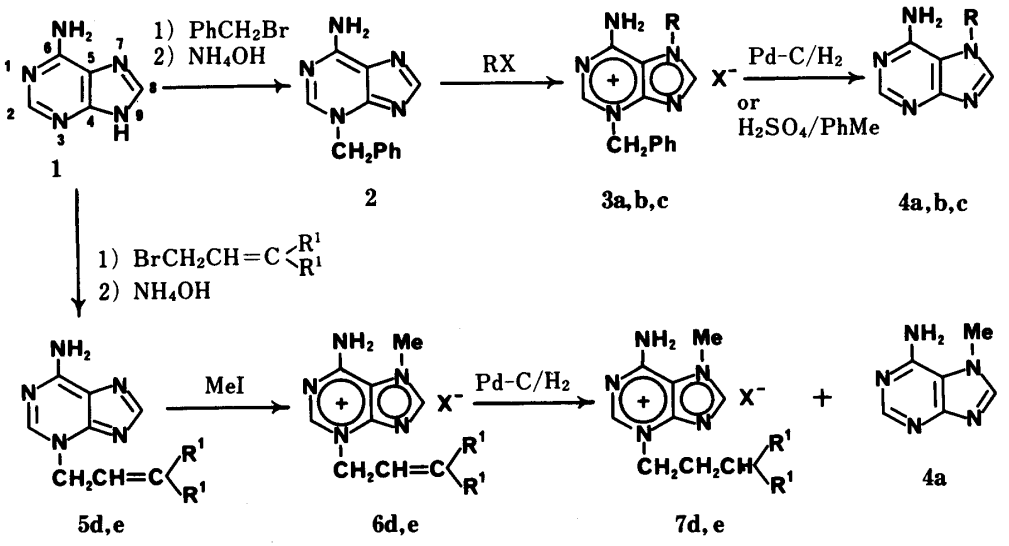
A detailed account is given of the final step of the general 7-alkylation procedure for adenine (**1**), which consists of the preferential benzylation at the 3-position of **1**, regioselective alkylation of the resulting 3-benzyladenine (**2**) to give 7-alkyl-3-benzyladenine salts (**3a**—**c**), and debenzylation of **3a**—**c** leading to 7-alkyladenines (**4a**—**c**). Debenzylation of **3a**—**c** (X=Cl or ClO_4) has been achieved by hydrogenolysis using hydrogen and Pd–C catalyst at atmospheric pressure, producing 7-alkyladenines (**4a**—**c**) in 38—74% yields. The use of the allyl or γ,γ-dimethylallyl group at the 3-position instead of the benzyl group for the synthesis of 7-methyladenine (**4a**) by this procedure has no practical value. Alternatively, the salts **3a**—**c** (X=Br, ClO_4, or I) have been debenzylated efficiently by treatment with conc. H_2SO_4 in the presence of toluene at room temperature for 3—6 h or at 60 °C for 0.5—2 h, giving **4a**—**c** in 73—93% yields.

Keywords——7-alkyl-3-benzyladenine; 7-alkyladenine synthesis; 3-allyladenine derivative; selective debenzylation; catalytic hydrogenolysis; debenzylation; deallylation; allyl group saturation; sulfuric acid debenzylation

The direct alkylation of adenine (**1**) at the 3-position in the absence of base presents the most convenient method of securing 3-alkyl-, 3-allyl-, and 3-benzyladenines (type **2**),[1] and the second stage of alkylation of the 3-substituted adenines (type **2**) provides a ready and convenient access to 3,7-disubstituted adenines (type **3**).[1,2] If such a two-step reaction sequence would be coupled with removal of the 3-substituent, it should constitute a general synthesis of 7-alkyladenines (**4**), which have previously been prepared[3] by inconvenient methods. This has now been realized by the use of the benzyl group at the 3-position. Brief accounts of some of the results recorded here have been published in preliminary form,[1,2a] but we are responding to many requests for detailed directions.

Adenine (**1**) was converted into 3-benzyl-7-methyladenine hydriodide [**3a** (X=I)] or perchlorate [**3a** (X=ClO_4)] in 58% or 50% overall yield through 3-benzyladenine (**2**) according to the previously reported procedure.[1,2a,e] For removal of the benzyl group at the 3-position, the hydrochloride salt **3a** (X=Cl), prepared in 99% yield from the hydriodide **3a** (X=I) by treatment with AgCl, was then subjected to hydrogenolysis using hydrogen and 10% Pd–C catalyst in aqueous MeOH at atmospheric pressure and 25—55 °C, giving 7-methyladenine (**4a**) in 72% yield along with toluene. The perchlorate **3a** (X=ClO_4) also produced the desired compound **4a** efficiently on similar hydrogenolysis.

The synthesis of 7-methyladenine (**4a**) by benzyl blocking at the 3-position of adenine (**1**), methylation at the 7-position, and hydrogenolysis is only one representative of a general 7-alkylation procedure. The analogous hydrogenolytic debenzylation of 3-benzyl-7-ethyladenine perchlorate [**3b** (X=ClO_4)], obtained from **1** through **2** according to the literature procedure,[2e] afforded 7-ethyladenine (**4b**) in 74% yield. Similar blocking/deblocking has



a : R=Me b : R=Et c : R=PhCH$_2$
d : R^1=H e : R^1=Me

Chart 1

been utilized for the synthesis of the anomeric 7-D-ribofuranosyladenines[3h,i] and of 7-(3-hydroxypropyl)adenine.[2d] Selective hydrogenolysis was also possible, as illustrated with 3,7-dibenzyladenine hydrochloride [**3c** (X=Cl)] or perchlorate [**3c** (X=ClO$_4$)], which was obtained from the hydrobromide **3c** (X=Br)[1,2a,e] available by the reaction of benzyl bromide with **2**. The hydrogenolyzed product obtained in 41% or 38% yield was 7-benzyladenine (**4c**), indicating that the *N*-benzyl group on the pyrimidine ring is hydrogenolyzed more easily than that on the imidazole ring. This was also recognized when a mixture of 3-benzyladenine and 9-benzyladenine was treated with hydrogen and 5% Pd–C catalyst, resulting in selective cleavage of 3-benzyladenine to adenine (**1**) and toluene, leaving most of the 9-benzyladenine unchanged. Resistance to catalytic hydrogenolysis by the 7- and 9-benzyl groups on purines was also observed earlier by Montgomery *et al.*[3e,4] The mediocre yield of 7-benzyladenine (**4c**) in the above selective debenzylation of **3c** (X=Cl or ClO$_4$) is probably due to overhydrogenolysis leading to the formation of adenine (**1**). In the attempt to retard such overhydrogenolysis, the hydrobromide salt **3c** (X=Br) was directly subjected to similar catalytic hydrogenolysis. However, the reaction was too slow to be completed.

As had seemed probable, deblocking of an allylic group at the 3-position was much less effective than that of the benzyl group. In the cases of catalytic hydrogenolyses of 3-allyl-7-methyladenine salts [**6d** (X=I or ClO$_4$)] and of 3-(3-methyl-2-butenyl)-7-methyladenine perchlorate [**6e** (X=ClO$_4$)] [prepared[1,2a] from **1** through a reaction sequence (Chart 1) paralleling that of the 3-benzyl series], the major products were the hydrogenated salts **7d** and **7e**, while the hydrogenolyzed product **4a** was only detected by paper chromatography.

In order to improve the yield of 7-benzyladenine (**4c**) in the selective debenzylation of **3c**, we next tried to remove the benzyl group at the 3-position by application of the method of Weinstock *et al.*,[5] who recently reported a specific debenzylation of 3-benzyladenine (**2**) and 3-(substituted benzyl)adenines that proceeds in a mixture of conc. H$_2$SO$_4$ and toluene through benzyl carbenium ion formation and trapping of the cation by transbenzylation with toluene. Treatment of **3c** (X=Br) with *ca.* 4 molar eq of conc. H$_2$SO$_4$ at room temperature for 6 h in the presence of toluene was found to furnish 7-benzyladenine (**4c**) in 82% yield, indicating much higher selectivity in debenzylation than that observed for the catalytic hydrogenolysis. Similar debenzylations of **3a** (X=I), **3b** (X=ClO$_4$), and **3c** (X=ClO$_4$) for 3 h afforded the

TABLE I. Debenzylation of 7-Alkyl-3-benzyladenine Salts (**3a—c**) with H_2SO_4/Toluene

Compound			Reaction conditions		Product	
No.	R	X	Temp. (°C)	Time (h)	No.	Yield (%)
3a	Me	I	30	3	**4a**	85
3a	Me	ClO_4	60	0.5	**4a**	93
3b	Et	ClO_4	30	3	**4b**	91
3b	Et	ClO_4	60	0.5	**4b**	75
3c	$PhCH_2$	ClO_4	30	3	**4c**	73
3c	$PhCH_2$	ClO_4	60	2	**4c**	78
3c	$PhCH_2$	Br	26	6	**4c**	82

desired 7-alkyladenines (**4a—c**) in 73—91% yields. It was possible to reduce the reaction time to 0.5—2 h by raising the reaction temperature to 60 °C. The results are summarized in Table I.

In conclusion, the above results have established that the benzyl group at the 3-position of 7-alkyl-3-benzyladenine salts (type **3**) is easily removed by catalytic hydrogenolysis or, more conveniently, by treatment with conc. H_2SO_4/toluene, giving 7-alkyladenines (**4**) in good yields. Thus, the three-step sequence **1**→**2**→**3**→**4** (Chart 1) provides a general and convenient synthetic route to 7-alkyladenines from adenine by regioselective alkylation utilizing blocking/deblocking at the 3-position.

Experimental

General Notes——All melting points are corrected. Paper chromatographies (PPC) were developed on Whatman No. 1 filter paper by the ascending method with solvent system A [1-butanol–H_2O–AcOH (75 : 20 : 5, v/v)] or solvent system B [2-propanol–H_2O–conc. aqueous NH_3 (7 : 3 : 0.5, v/v)]. Spots were detected by means of the Dragendorff spray and/or ultraviolet (UV) absorbance. The UV spectra were recorded on a Cary Model 15 spectrophotometer. The infrared (IR) spectra were measured with a Perkin–Elmer Model 21 or a JASCO A-202 spectrophotometer. The nuclear magnetic resonance (NMR) spectra were determined with a Varian Associates A-60 spectrometer using Me_4Si as an internal standard. The following conventions and abbreviations are used: br = broad, D = signal disappears on exchange with D_2O, m = multiplet, s = singlet, sh = shoulder, t = triplet.

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3-Benzyl-7-methyladenine Hydrochloride [3a (X = Cl)]——A stirred mixture of AgCl, prepared freshly from $AgNO_3$ (37.4 g, 220 mmol) and 3 N aqueous HCl in the usual manner, and a hot solution of **3a** (X = I)[1,2a,e] (32.3 g, 88 mmol) in 70% (v/v) aqueous EtOH (670 ml) was heated under reflux for 4 h. The insoluble mixture of silver halides was filtered and washed successively with two 200-ml portions of hot 50% (v/v) aqueous EtOH and hot H_2O (100 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo*. The residual solid was recrystallized from 70% (v/v) aqueous EtOH to yield **3a** (X = Cl) (23.9 g, 99%) as colorless silky needles, mp 264—266 °C (dec.); UV, virtually identical with that reported[2e] for the corresponding perchlorate **3a** ($X = ClO_4$); NMR (Me_2SO) δ: 4.20 (3H, s, NMe), 5.72 (2H, s, NCH_2Ph), 7.46 (5H, m, $NCH_2\underline{Ph}$), 8.78 and 9.28 (1H each, s, purine H's), 9.28 (2H, D, NH's). This sample was used directly in the next hydrogenolysis step without further purification.

3,7-Dibenzyladenine Perchlorate [3c ($X = ClO_4$)]——A solution of $NaClO_4$ (367 mg, 3 mmol) in H_2O (1 ml) was added to a solution of the hydrobromide **3c** (X = Br)[1,2a,e] (793 mg, 2 mmol) in hot H_2O (10 ml). The mixture immediately formed an insoluble colorless oil, which solidified on standing at room temperature. The solid was filtered, washed with H_2O, and dried over P_2O_5 at 2 mmHg at 70 °C for 2 h and then at 100 °C for 3 h to afford the perchlorate **3c** ($X = ClO_4$) (816 mg, 98%), mp 181—183 °C. Recrystallization from MeOH gave an analytical sample as colorless prisms, mp 183—185 °C. *Anal.* Calcd for $C_{19}H_{18}ClN_5O_4$: C, 54.88; H, 4.36; N, 16.84. Found; C, 55.14; H, 4.37; N, 16.47.

7-Methyladenine (4a)——i) By Hydrogenolysis of the Hydrochloride **3a** (X = Cl): A solution of **3a** (X = Cl) (*vide supra*) (25.2 g, 91 mmol) in 70% (v/v) aqueous MeOH (1100 ml) was hydrogenated over 10% Pd–C (7.5 g) at atmospheric pressure and 25 °C for 2 h and then at 50—55 °C for 3 h. Uptake of H_2 ceased after *ca.* 96% of the theoretical amount of H_2 had been absorbed. The catalyst was filtered and washed with three 100-ml portions of H_2O.

The filtrate (the odor of toluene was readily detected) and washings were combined and evaporated to dryness *in vacuo*. The residual solid was dissolved in hot H_2O (200 ml), and the resulting solution was kept in a refrigerator after its pH had been brought to 10—11 with conc. aqueous NH_3. The crystals that deposited were filtered, washed with two 20-ml portions of H_2O, and dried to give **4a** (11.0 g, 81%), mp 345—348 °C (dec.). Recrystallization from H_2O (330 ml) produced a pure sample (9.84 g, 72%) as colorless minute crystals, mp 349—350 °C (dec.) [lit. mp 351 °C[3a]; 344—346 °C (dec.)[3b]; 345 °C (dec.)[3c]]. The identity of this sample with authentic **4a**[6] was confirmed by mixture melting point test and comparison of the PPC behavior and UV and IR spectra.

ii) By Hydrogenolysis of the Perchlorate **3a** (X=ClO_4): A solution of **3a** (X=ClO_4)[1,2a,e] (1.25 g, 3.68 mmol) in 80% (v/v) aqueous MeOH (250 ml) was hydrogenated over 10% Pd–C (1.0 g) at atmospheric pressure at 27 °C. After *ca.* 40% of the theoretical amount of H_2 was taken up, the reaction became slow. The hydrogenation flask was then warmed to 50—55 °C and the reaction was continued at that temperature for 7.5 h. After cooling the mixture, the catalyst was filtered and washed successively with H_2O (60 ml) and MeOH (60 ml). The filtrate and washings were combined and distilled under ordinary pressure to collect a few ml of forerun. On dilution with H_2O, the distillate became turbid and the smell of toluene was markedly positive. The UV spectrum of the distillate showed maxima at 255, 261, and 267.5 nm and shoulders at 243 and 249 nm, characteristic of toluene. The residual main solution was then evaporated to dryness *in vacuo* to leave a colorless solid. Recrystallization of the solid from 90% (v/v) aqueous EtOH gave 7-methyladenine perchlorate (**4a**·$HClO_4$) (700 mg, 76%) as colorless prisms, mp 281—283 °C (dec.). Two more recrystallizations from 50% (v/v) aqueous EtOH yielded an analytical sample, mp 285—287 °C (dec.); NMR (Me_2SO) δ: 4.21 (3H, s, NMe), 8.67 and 8.77 (1H each, s, purine H's), 8.91 (2H, D, NH_2), 9.78 (1H, D, NH). *Anal.* Calcd for $C_6H_8ClN_5O_4$: C, 28.87; H, 3.23; N, 28.06. Found: C, 29.05; H, 3.28; N, 27.90.

The melting point of this sample did not depress on admixture with the perchlorate prepared from an authentic free base[6] **4a** and 70% aqueous $HClO_4$ in EtOH. The IR spectra and PPC mobilities of both samples of the perchlorate were also identical.

For further identification, a hot solution of the perchlorate (450 mg, 1.80 mmol), derived from the above hydrogenolysis, in H_2O (5 ml) was made alkaline (pH 10—11) with 1 N aqueous NaOH. The crystals that deposited were filtered, washed with H_2O, and dried to yield the free base **4a** (220 mg, 82%), mp 349—350 °C (dec.). Two recrystallizations from H_2O gave a pure sample (170 mg, 63%) of **4a** as colorless minute crystals, mp 350—351 °C (dec.); UV λ_{max}^{EtOH} nm (ε) 269 (11600), 283 (sh) (6900); $\lambda_{max}^{H_2O}$ 269 (11900), 280 (sh) (7300); $\lambda_{max}^{0.1Naq.HCl}$ 272 (15400); $\lambda_{max}^{0.1Naq.NaOH}$ 270 (11100), 280 (sh) (6800). *Anal.* Calcd for $C_6H_7N_5$: C, 48.32; H, 4.73; N, 46.95. Found: C, 48.13; H, 4.74; N, 46.99. This sample was identical (by comparison of UV and IR spectra and PPC behavior) with authentic **4a**.[6]

iii) By Debenzylation of **3a** with H_2SO_4/Toluene: To a stirred suspension of the hydriodide **3a** (X=I)[1,2a,e] (367 mg, 1 mmol) in toluene (1.5 ml) was added dropwise conc. H_2SO_4 (0.22 ml, *ca.* 4 mmol). The mixture was stirred vigorously at 30 °C for 3 h, during which time a dark, reddish purple color was produced. The reaction mixture was then poured onto crushed ice (5 g). After all the ice had melted, the aqueous layer was separated from the toluene layer, washed with three 3-ml portions of toluene, and passed through a column of Amberlite IRA-402 (HCO_3^-) (15 ml). The column was eluted with H_2O, and the eluate (*ca.* 250 ml) was concentrated to dryness *in vacuo* to leave **4a** (127 mg, 85%), mp >300 °C. Recrystallization from H_2O furnished colorless prisms, mp>300 °C, identical [by comparison of IR spectrum and thin-layer chromatographic (TLC) behavior] with a sample of **4a** prepared by method (i).

The perchlorate **3a** (X=ClO_4) was similarly debenzylated at 60 °C for 30 min, giving **4a** in 93% yield.

7-Ethyladenine (4b)——i) By Hydrogenolysis of the Perchlorate **3b** (X=ClO_4): A solution of **3b** (X=ClO_4)[2e] (500 mg, 1.41 mmol) in 50% (v/v) aqueous AcOH (40 ml) was hydrogenated over 10% Pd–C (500 mg) at atmospheric pressure and 45—50 °C for 6 h. The catalyst was removed by filtration and washed with MeOH (40 ml). The filtrate and washings were combined and concentrated to dryness *in vacuo* to leave a solid (337 mg), which was dissolved in H_2O (10 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (3 ml), and the column was eluted with H_2O. Evaporation of the eluate (*ca.* 70 ml) under reduced pressure left **4b** (170 mg, 74%) as a colorless solid, mp 254—258 °C (dec.). Recrystallization from 1-butanol gave colorless prisms, mp 257—259 °C (dec.) [lit. mp 258—259 °C (dec.)[3o]; 263—264 °C[3n]], identical (by comparison of IR spectrum and TLC mobility) with authentic **4b**.[3o]

ii) By Debenzylation of **3b** (X=ClO_4) with H_2SO_4/Toluene: Conc. H_2SO_4 (0.22 ml, *ca.* 4 mmol) was added dropwise to a stirred suspension of **3b** (X=ClO_4)[2e] (354 mg, 1 mmol) in toluene (1.5 ml). The mixture was stirred vigorously at 30 °C for 3 h. The pink-colored reaction mixture was poured onto crushed ice (5 g), forming a precipitate. The resulting mixture was warmed to dissolve the precipitate, and the aqueous layer was worked up as described above for **4a** under method (iii), yielding **4b** (148 mg, 91%), mp 246—250 °C (dec.). Recrystallization from 1-butanol provided colorless prisms, mp 258—259 °C (dec.), identical (by comparison of IR spectrum and TLC behavior) with authentic **4b**.[3o]

When the above debenzylation was carried out at 60 °C for 30 min, **4b** was obtained in 75% yield.

7-Benzyladenine (4c)——i) By Hydrogenolysis of the Hydrochloride **3c** (X=Cl) or the Perchlorate **3c** (X=ClO_4): A stirred mixture of AgCl, which was freshly prepared from $AgNO_3$ (2.12 g, 12.5 mmol) and 3 N aqueous HCl in the

usual manner, and a solution of the hydrobromide **3c** (X=Br)[1,2a,e] (1.98 g, 5 mmol) in 70% (v/v) aqueous EtOH (40 ml) was heated under reflux for 4 h. The AgBr that formed and the excess of AgCl were filtered and washed with four 40-ml portions of hot 70% (v/v) aqueous EtOH. The filtrate and washings were combined and evaporated to dryness *in vacuo*, leaving the hydrochloride **3c** (X=Cl) as a hygroscopic colorless solid. The solid was dissolved in 70% (v/v) aqueous EtOH (70 ml), and the solution was hydrogenated over 5% Pd–C (1.5 g) at atmospheric pressure and 29—32 °C. After having taken up *ca.* 0.5 molar eq of H_2 during 3.5 h, the hydrogenation became slow. Then, an additional amount (1.5 g) of the catalyst was added, and the reaction was continued further under the same conditions as above until 1 molar eq of H_2 had been taken up (totally 10.5 h). The catalyst was removed by filtration and washed with hot H_2O. The filtrate and washings were combined and distilled at ordinary pressure, and a few drops of forerun were collected. The forerun smelled of toluene and its UV spectrum in EtOH showed maxima at 255, 260, 261.5, 264.5, and 268 nm and shoulders at 243 and 249 nm, characteristic of toluene. The residual main solution was then evaporated to dryness *in vacuo* to leave a colorless solid, which was dissolved in H_2O (30 ml). The aqueous solution was made alkaline (pH 10) with conc. aqueous NH_3 and kept in a refrigerator. The crystals that deposited were filtered, washed with H_2O, and dried to yield **4c** (460 mg, 41%), mp 232—236 °C (dec.). Two recrystallizations from H_2O gave an analytical sample as colorless prisms, mp 236—238 °C (dec.) [lit. mp 234 °C[3f,7]; 238—239 °C (dec.)[3e]]; UV λ_{max}^{EtOH} nm (ε) 272 (11100), 283 (sh) (7200); $\lambda_{max}^{H_2O}$ 271 (11500), 280 (sh) (7900); $\lambda_{max}^{0.1\,Naq.\,HCl}$ 273.5 (15100); $\lambda_{max}^{0.1\,Naq.\,NaOH}$ 270 (11700), 280 (sh) (8100); NMR (Me_2SO) δ: 5.80 (2H, s, $NC\underline{H}_2Ph$), 6.93 (2H, s, D, NH_2), 7.33 (5H, $NCH_2\underline{Ph}$), 8.35 and 8.55 (1H each, s, purine H's). *Anal.* Calcd for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 64.27; H, 4.95; N, 31.26. The UV spectra of this sample agreed with those reported[3f,7] for **4c**.

Direct hydrogenolysis of the hydrobromide **3c** (X=Br)[1,2a,e] under similar conditions was too slow to complete the reaction even at 50—60 °C.

When the perchlorate **3c** ($X=ClO_4$) (*vide supra*) was subjected to hydrogenolysis in 50% (v/v) aqueous AcOH over 10% Pd–C at atmospheric pressure and 35 °C for 11 h, **4c** was obtained in 38% yield.

ii) By Debenzylation of **3c** with H_2SO_4/Toluene: Conc. H_2SO_4 (1.10 ml, *ca.* 20 mmol) was added dropwise to a stirred suspension of the hydrobromide **3c** (X=Br)[1,2a,e] (1.98 g, 5 mmol) in toluene (7.5 ml), and the mixture was stirred vigorously at 26 °C for 6 h. The brownish-yellow reaction mixture was poured onto crushed ice (25 g), forming a precipitate. The resulting mixture was warmed to dissolve the precipitate. The aqueous layer was separated from the toluene layer, washed with three 15-ml portions of toluene, and made alkaline (pH 10) with conc. aqueous NH_3. The crystals that resulted were filtered, washed with H_2O, and dried to give **4c** (925 mg, 82%), mp 224—228 °C (dec.). Recrystallization from H_2O furnished colorless prisms, mp 234—236 °C (dec.), identical with a sample of **4c** obtained by method (i).

A similar debenzylation of the perchlorate **3c** ($X=ClO_4$) (*vide supra*) at 30 °C for 3 h or at 60 °C for 2 h produced **4c** in 73% or 78% yield.

Catalytic Reduction of 3-Allyl-7-methyladenine Salt (6d)——i) Reduction of the Perchlorate **6d** ($X=ClO_4$): A solution of **6d** ($X=ClO_4$)[1,2a] (1.10 g, 3.80 mmol) in 80% (v/v) aqueous MeOH (150 ml) was hydrogenated over 10% Pd–C (1.0 g) at atmospheric pressure and 30 °C. One molar eq of H_2 was taken up within 40 min, and absorption of H_2 ceased. The catalyst was filtered and washed successively with H_2O (60 ml) and MeOH (60 ml). The filtrate and washings were combined and evaporated to dryness *in vacuo* to leave a colorless solid. Recrystallization of the solid from 90% (v/v) aqueous EtOH (25 ml) yielded colorless leaflets (740 mg). On PPC analysis, this sample was found to consist of two components [of *Rf* values 0.35 (major) and 0.25 (minor) in solvent system A], one of which had the identical *Rf* value with that (0.25 in solvent system A) of 7-methyladenine perchlorate (**4a**·$HClO_4$) (*vide supra*). The mother liquor, from which the above crude crystals were isolated, also gave a similar chromatogram. The above crude crystals were recrystallized from 90% (v/v) aqueous EtOH to afford the major product (560 mg, 51%), mp 245—248 °C (dec.). Two more recrystallizations in the same way furnished an analytical sample of 7-methyl-3-propyladenine perchlorate [**7d** ($X=ClO_4$)] as colorless pillars, mp 250—252 °C (dec.); NMR (Me_2SO) δ: 0.92 (t, $J=ca.$ 8 Hz, $NCH_2CH_2\underline{Me}$), 4.20 (s, NMe), 4.46 (t, $J=ca.$ 8 Hz, $NC\underline{H}_2CH_2Me$), 8.82 and 8.95 (1H each, s, purine H's), *ca.* 9.0 (2H, D, NH's). *Anal.* Calcd for $C_9H_{14}ClN_5O_4$: C, 37.06; H, 4.84; N, 24.01. Found: C, 37.06; H, 4.99; N, 23.94.

Replacement of the catalyst in the above reduction by 5% Pd–$SrCO_3$ catalyst poisoned with quinoline[8] or by 5% Pd–C catalyst poisoned with quinoline[8] gave results similar to those described above.

ii) Reduction of the Hydriodide **6d** (X=I): A solution of **6d** (X=I)[1,2a] (2.00 g, 6.31 mmol) in 80% (v/v) aqueous MeOH (125 ml) was hydrogenated over 10% Pd–C (1.0 g) at atmospheric pressure and 27—28 °C. After having taken up 1 molar eq of H_2 during 135 min, the reaction ceased. The catalyst was filtered and washed with hot 50% (v/v) aqueous MeOH (80 ml). The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residual solid was recrystallized from 70% (v/v) aqueous EtOH (10 ml) to yield crude **7d** (X=I) (1.37 g, 68%) as colorless leaflets. A portion of the crude **7d** (X=I) was recrystallized twice from 70% (v/v) aqueous EtOH to give an analytical sample of 7-methyl-3-propyladenine hydriodide [**7d** (X=I)] as colorless leaflets, mp 257—259 °C (dec.); NMR (Me_2SO) δ: 0.95 (t, $J=8$ Hz, $NCH_2CH_2\underline{Me}$), 4.17 (s, NMe), 4.40 (t, $J=8$ Hz, $NC\underline{H}_2CH_2Me$), 8.73 and 8.97 (1H each, s, purine H's), 8.87 (2H, D, NH's). *Anal.* Calcd for $C_9H_{14}IN_5$: C, 33.87; H, 4.42; N, 21.94. Found: C, 33.76; H, 4.51; N, 21.74. The rest of the crude **7d** (X=I) was converted into the perchlorate **7d** ($X=ClO_4$) by treatment with $AgClO_4$

in H_2O. The perchlorate [mp 250—252 °C (dec.)] thus obtained was identical (by mixture melting point test and comparison of IR spectrum and PPC behavior) with the sample obtained by method (i).

The presence of 7-methyladenine (**4a**) in the reaction mixture was shown in the following manner. To the mother liquor, which was obtained when the above crude **7d** (X=I) was isolated, was added a slight excess of a 20% aqueous solution of $AgClO_4$, and the AgI that precipitated was filtered. The filtrate was shown to contain two components (of *Rf* values 0.29 and 0.21 in solvent system A or 0.60 and 0.48 in solvent system B) by PPC analysis. The spot with the lower *Rf* value was identical with that of 7-methyladenine perchlorate (**4a**·$HClO_4$) (*vide supra*). A portion of this filtrate was applied along a base line on Whatman No. 1 filter paper and the chromatogram was developed using solvent system B. The zone corresponding to *Rf* 0.48, located under UV light, was excised and extracted with 0.1 N aqueous HCl. The UV spectrum of the extracts showed $\lambda_{max}^{0.1\,N\,aq.\,HCl}$ 272 nm, λ_{min} 239 nm; $\lambda_{max}^{0.1\,N\,aq.\,NaOH}$ 270 nm, λ_{min} 232 nm. This UV spectral feature was virtually identical with that of 7-methyladenine (**4a**).

Catalytic Reduction of 7-Methyl-3-(3-methyl-2-butenyl)adenine Perchlorate [6e (X=ClO_4)]——A solution of **6e** (X=ClO_4)[1,2a] (500 mg, 1.57 mmol) in 80% (v/v) aqueous MeOH (100 ml) was hydrogenated over 10% Pd–C (150 mg) at atmospheric pressure and 30 °C for 10 h. The catalyst was filtered and washed with H_2O (50 ml). The filtrate and washings were combined and evaporated to dryness *in vacuo*, leaving a colorless solid. The solid was recrystallized from H_2O to yield 3-isopentyl-7-methyladenine perchlorate [**7e** (X=ClO_4)] (310 mg, 62%) as colorless needles, mp 261—264 °C (dec.), identical (by mixture melting point test and comparison of IR spectrum and PPC behavior) with an authentic sample.[1]

The presence of 7-methyladenine (**4a**) in the mother liquor of the above recrystallization was confirmed in a manner similar to that described above for the catalytic reduction of **6d** under item (ii).

The use of 5% Pd–$SrCO_3$ catalyst, which had been poisoned with quinoline,[8] in this reduction gave similar results.

Selective Hydrogenolysis of a Mixture of 3- and 9-Benzyladenines——An 11:10 mixture (2.03 g) of 3-benzyladenine and 9-benzyladenine was dissolved in a mixture of 1 N aqueous HCl (100 ml) and AcOH (25 ml). The resulting solution was hydrogenated over 5% Pd–C (2.0 g) at atmospheric pressure and 27—29 °C. When *ca.* 60% of the theoretical amount of H_2 (based on both the 3- and 9-benzyladenines used) had been taken up within 4.5 h, the reaction was interrupted. The catalyst was removed by filtration, and the colorless filtrate smelling of toluene was concentrated *in vacuo* to remove the AcOH and toluene. The residual aqueous solution was basified (pH 9.5) with conc. aqueous NH_3. The colorless crystals that deposited were filtered, washed with H_2O, and dried to give 550 mg (57% based on the 9-benzyladenine present in the starting mixture) of practically pure 9-benzyladenine, mp 230—232 °C; PPC *Rf* 0.79 (solvent system A). Recrystallization from EtOH provided an analytical sample as colorless pillars, mp 233—235 °C [lit. mp 235 °C[3e]; 224—225 °C (dec.)[9]]; pK_a *ca.* 3.2 (50% aqueous $HCONMe_2$); UV λ_{max}^{EtOH} 261 nm (ε 15100); $\lambda_{max}^{H_2O}$ 261 (14700); $\lambda_{max}^{0.1\,N\,aq.\,HCl}$ 260 (14400); $\lambda_{max}^{0.1\,N\,aq.\,NaOH}$ 261 (14800); NMR (Me_2SO) δ: 5.50 (2H, s, NCH_2Ph), 7.46 (5H, NCH_2Ph), 7.46 (2H, D, NH_2), 8.37 and 8.43 (1H each, s, purine H's). *Anal.* Calcd for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.69; H, 4.66; N, 31.10.

For further characterization, the above free base, 9-benzyladenine was converted into the hydrochloride in the following manner. To a solution of the free base (500 mg, 2.22 mmol) in EtOH (50 ml) were added successively 8.6% (w/w) ethanolic HCl (3.0 g) and dry ether (250 ml). The precipitate that resulted was filtered and dried to give crude hydrochloride (570 mg, 98%). Two recrystallizations from 90% (v/v) aqueous EtOH afforded an analytical sample of 9-benzyladenine hydrochloride as colorless needles, mp 273—274 °C (dec.) (with previous shrinking at *ca.* 240 °C); NMR (Me_2SO) δ: 5.60 (2H, s, NCH_2Ph), 7.44 (NCH_2Ph), 8.70 and 8.84 (1H each, s, purine H's). *Anal.* Calcd for $C_{12}H_{12}ClN_5$: C, 55.07; H, 4.62; N, 26.76. Found: C, 55.02; H, 4.48; N, 26.59.

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