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PURINES—I

ALKYLATION OF ADENINE 1-OXIDE AND 1-ALKOXYADENINES: THE SYNTHESIS OF 1-ALKOXY-, 1-ALKOXY-9-ALKYL-, AND 9-ALKYLADENINES[1]

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Abstract—The reaction of adenine 1-oxide (II) with alkyl halides in N,N-dimethylacetamide resulted in O-alkylation. These 1-alkoxyadenine salts (III) were readily converted into the corresponding free bases (IV). The alkylation of IV in a similar manner gave 1-alkoxy-9-alkyladenine salts (V) in 52–71% yield. This method was applied to the synthesis of 9-alkyladenines (VII), by transformation of the free bases (VI) of 1-alkoxy-9-alkyladenines into VII by catalytic hydrogenolysis over Raney nickel.

THE early work of Fischer and Helferich and the subsequent studies on alkylation of the heavy metal salts[2,3] of adenine derivatives have led to the successful synthesis of numbers of nucleosides, and in particular the synthesis of 9-substituted adenines.[4–6] In addition, the recent isolation from natural sources of 1-, 3-, N^6-, and 7-substituted adenine derivatives has prompted the development of synthetic methods for each N-alkyl isomer.[6,7] The N-oxide function as a blocking and directing group was investigated in the reaction of adenine 1-oxide (II)[8,9] with alkyl halides and a detailed account of our preliminary communication[10] is given in this paper.

When II was treated with an excess of methyl iodide in N,N-dimethylacetamide, 1-methoxyadenine hydriodide (IIIa: X = I) was obtained in a good yield. Although the reaction of II with methyl *p*-toluenesulfonate required a reaction temperature of 110°, it also produced 1-methoxyadenine as the *p*-toluenesulfonate salt (IIIa: X = *p*-TsO). Similarly, treatment of II with ethyl iodide or ethyl *p*-toluenesulfonate furnished the corresponding 1-ethoxyadenine salts (IIIb); and with benzyl bromide, 1-benzyloxyadenine hydrobromide (IIIc: X = Br) was produced. Other useful dipolar aprotic solvents were N,N-dimethylformamide and dimethyl sulfoxide. The N-oxide (II) used in this investigation was either in the form of anhydrous filamentous crystals[8] or heavy prisms of a monohydrate, which we obtained in the course of recrystallization. Later it was found that the anhydrous filaments were converted into the monohydrate by contact with water in the presence of a few crystals of the monohydrate. Although there is no difference in reactivity between the filaments and the prisms, the latter are more readily dissolved. The results of the alkylation are summarized in Table 1.

Although the salts (IIIa, b, c) obtained were slightly unstable, the corresponding free bases (IVa, b, c) were easily obtained (Experimental) without structural breakdown as evidenced by conversion of the free bases (IV) into the corresponding picrates, which were identical with authentic specimens prepared directly from the

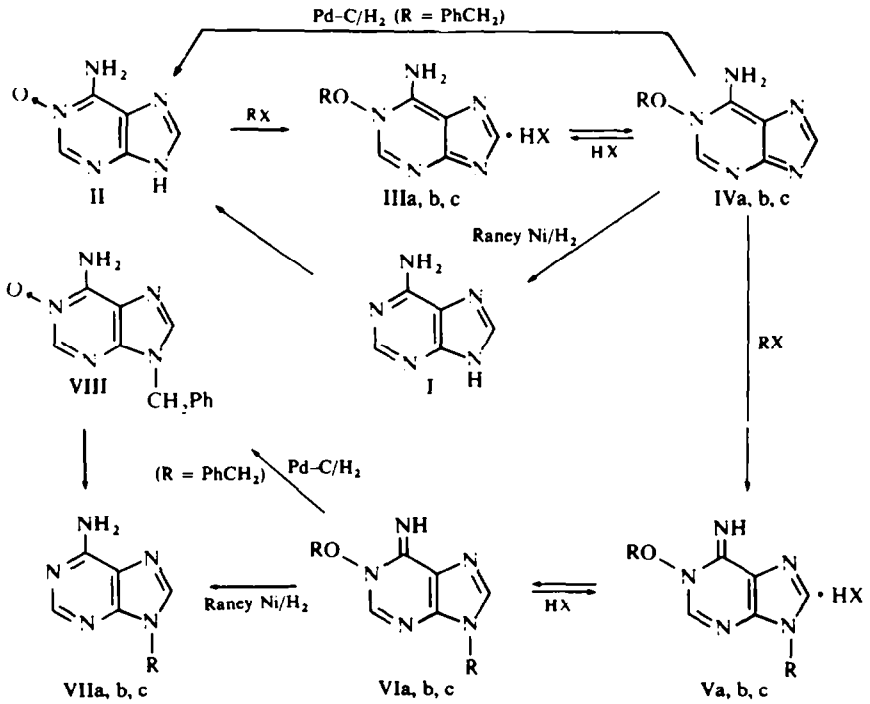

CHART 1

salts (III). Table 2 records the physical properties of the picrates and perchlorates of 1-alkoxyadenines (IVa, b, c).

The location of the alkyl groups in compounds III and IV was established by catalytic hydrogenolysis of the free bases (IVa, b, c) to adenine (I) (84–90% yield), with uptake of one equivalent mole of hydrogen. Additional evidence was provided by the facile debenzylation of 1-benzyloxyadenine (IVc)to II.

As shown in Table 3, the 1-alkoxyadenines (IV) have similar UV spectra and acid dissociation constants to 1-alkyladenines.[11–13] Next it was shown that compound IVa undergoes methylation mainly at the 9-position producing 1-methoxy-9-methyladenine hydriodide (Va: X = I) in 71% yield. Likewise, ethylation of IVb gave 1-ethoxy-9-ethyladenine hydriodide (Vb: X = I), and benzylation of IVc furnished 1-benzyloxy-9-benzyladenine hydrobromide (Vc: X = Br). These salts (V) had UV spectra and p*Ka* values (Table 3) similar to those[11,13–15] of 1,9-dialkyladenine salts. As these salts (Va, b, c) are unstable, prolonged heating in recrystallization solvents of a nucleophilic nature had to be avoided.[16] However, they were readily converted into the corresponding free bases (VIa, b, c) which were unstable especially in aqueous solutions[17] and failed to give analytically pure samples because of their hygroscopic nature. They were nevertheless converted to the picrates which were identical with those derived directly from the salts (V) (Table 2).

TABLE 1. ALKYLATION OF ADENINE 1-OXIDE (II)

Product	Alkylating reagent	Reaction condition			Appearance and recrystn. solvent[b]	M.p.[c] (°C)	Formula	Analysis (%)		
		Temp[a] (°C)	Time (hr)	Yield (%)				C	H	N
1-Methoxyadenine hydriodide (IIIa: X = I)	MeI	r.t.	19	93	Prisms (A)	222	$C_6H_8ON_5I$	Calcd.: 24·59 Found: 24·86	2·75 2·87	23·90 24·15
1-Methoxyadenine *p*-toluenesulfonate (IIIa: X = *p*-TsO)	*p*-TsOMe	110	0·7	36	Prisms (B)	233–235	$C_{13}H_{15}O_4N_5S$	Calcd.: 46·29 Found: 46·25	4·48 4·49	20·76 20·59
1-Ethoxyadenine hydriodide (IIIb: X = I)	EtI	80	3	85	Prisms (A)	208	$C_7H_{10}ON_5I$	Calcd.: 27·38 Found: 27·67	3·28 3·50	22·81 22·48
1-Ethoxyadenine *p*-toluenesulfonate (IIIb: X = *p*-TsO)	*p*-TsOEt	110	3	78	Leaflets (B)	218–219	$C_{14}H_{17}O_4N_5S$	Calcd.: 47·85 Found: 47·54	4·88 5·04	19·93 20·25
1-Benzyloxyadenine hydrobromide (IIIc: X = Br)[d]	$PhCH_2Br$	r.t.	24	96	Prisms (C)	215	$C_{12}H_{12}ON_5Br \cdot H_2O$[e]	Calcd.: 42·36 Found: 42·35	4·15 4·16	20·59 20·57

[a] r.t., room temperature.
[b] The letter in parentheses refers to the recrystallization solvent with A, 70% EtOH aq; B, 90% EtOH aq; C, MeOH.
[c] With decomposition.
[d] As a monohydrate.

Table 2. 1-Alkoxyadenine salts (III) and 1-alkoxy-9-alkyladenine salts (V)

Compound	Appearance and recrystn. solvent[a]	M.p.[b] (°C)	Formula		Analysis (%) C	H	N
1-Methoxyadenine picrate	Yellow needles (A)	210–211	$C_{12}H_{10}O_8N_8$	Calcd. :	36·56	2·56	28·43
				Found :	36·51	2·77	28·10
1-Methoxyadenine perchlorate	Colorless pillars (C)	235–236	$C_6H_8O_5N_5Cl$	Calcd. :	27·13	3·04	26·37
				Found :	27·09	3·00	26·26
1-Ethoxyadenine picrate	Yellow needles (A)	219–220	$C_{13}H_{12}O_8N_8$	Calcd. :	38·24	2·96	27·45
				Found :	38·09	3·27	27·13
1-Ethoxyadenine perchlorate	Colorless pillars (C)	260–261	$C_7H_{10}O_5N_5Cl$	Calcd. :	30·06	3·60	25·04
				Found :	30·08	3·73	25·33
1-Benzyloxyadenine picrate	Yellow needles (B)	195–196	$C_{18}H_{14}O_8N_8$	Calcd. :	45·96	3·00	23·83
				Found :	46·14	3·15	23·91
1-Methoxy-9-methyladenine picrate	Yellow prisms (B)	212–213	$C_{13}H_{12}O_8N_8$	Calcd. :	38·24	2·96	27·45
				Found :	38·49	3·14	27·33
1-Methoxy-9-methyladenine perchlorate	Colorless plates (A)	257–258	$C_7H_{10}O_5N_5Cl$	Calcd. :	30·06	3·60	25·04
				Found :	30·21	3·56	24·88
1-Ethoxy-9-ethyladenine picrate	Yellow pillars (B)	223–225	$C_{15}H_{16}O_8N_8$	Calcd. :	41·29	3·70	25·68
				Found :	41·07	3·80	25·88
1-Ethoxy-9-ethyladenine perchlorate	Colorless plates (A)	272–273	$C_9H_{14}O_5N_5Cl$	Calcd. :	35·13	4·59	22·76
				Found :	35·26	4·68	22·52
1-Benzyloxy-9-benzyladenine picrate	Yellow prisms (D)	211–212	$C_{25}H_{20}O_8N_8$	Calcd. :	53·57	3·60	19·99
				Found :	53·46	3·72	19·98

[a] The letter in parentheses designates the recrystallization solvent: A, H_2O; B, 50% EtOH aq; C, 70% EtOH aq; D, abs EtOH.
[b] With decomposition.

TABLE 3. UV SPECTRA AND ACID DISSOCIATION CONSTANTS OF 1-ALKOXYADENINES AND 1-ALKOXY-9- ALKYLADENINES

Compound	pKa[a]	UV Spectra							
		Solvent E[b]		Solvent A[c]		Solvent N[d]		Solvent B[e]	
		λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$	λ_{max} (mμ)	$\varepsilon \times 10^{-3}$
1-Methoxyadenine	6·66 ± 0·02 11·45 ± 0·03	272	11·6	258	11·6	267	10·7	269	14·3
1-Ethoxyadenine	6·68 ± 0·03 11·50 ± 0·04	272	10·7	258	11·3	267	10·6	269	13·5
1-Benzyloxyadenine	—	272	11·4	258	11·9	268	10·7	269	13·0
1-Methoxy-9-methyladenine perchlorate	8·55 ± 0·04	259	12·3	260	11·9	260	11·9	258	13·0
1-Ethoxy-9-ethyladenine perchlorate	8·62 ± 0·05	259	12·0	260	12·3	260	12·2	258	13·0
1-Benzyloxy-9-benzyladenine hydrobromide[f]	- -	259	12·7	260	12·5	260	12·2	258	12·6

[a] Measured on aqueous solutions of the corresponding perchlorates spectrophotometrically[21] at 20°.
[b] 95% EtOHaq.
[c] 0·1 N hydrochloric acid (pH 1).
[d] 0·005 M phosphate buffer (pH 7).
[e] 0·1 N NaOHaq (pH 13).
[f] As a monohydrate.

The 9-substituted structure of V and VI was established by catalytic hydrogenolysis of the free bases (VIa, b, c) and formation (67–74%) of 9-alkyladenines (VIIa, b, c) with uptake of one equivalent mole of hydrogen, and by the facile selective debenzylation of VIc leading to 9-benzyladenine 1-oxide (VIII). Characterization of VIII as the 1-N-oxide was achieved by determination of its UV spectra at various pH's, which are similar to those[8,9] of adenosine 1-oxide; and by deoxygenation to VIIc. Final identification as VIII was established on its identity with a sample[18] obtained by the N-oxidation of VIIc. The catalytic hydrogenolysis of 1-methoxy-9-methyladenine perchlorate (Va: X = ClO_4) over palladium-on-carbon was rather slow, but yielded 9-methyladenine (VIIa).

The directive alkylation described is analogous to that reported[13] and the reaction sequence II → III → V → VII (Chart 1) constitutes a new route for the synthesis of 9-alkyladenines starting from adenine. It is interesting that in the rice plant, *Oryza sativa* L., callus induction on the synthetic medium including 2,4-dichlorophenoxyacetic acid and Vb has been observed by Yamada *et al.*[19,*]

In the catalytic hydrogenation of IVc and VIc over Raney nickel a small amount of benzaldehyde was formed. This was probably caused by a trace of sodium aluminate and alkali included in the catalyst and explained by a mechanism analogous to that proposed for the aldehyde formation of 1-alkoxypyridinium salts[20] by base.

EXPERIMENTAL

All m.ps are corrected. Paper chromatography was developed on Toyo Roshi No. 51 filter paper by the ascending method with solvent system A [n-BuOH: H_2O: AcOH (75:20:5, v/v)], solvent system B [n-BuOH: 28% NH_4OH aq: H_2O (4:1:1, v/v)], solvent system C [iso-PrOH: 1% $(NH_4)_2SO_4$ aq (2:1, v/v)], or solvent system D [iso-AmOH: 0·05 M phosphate buffer (pH 7) (10:1, v/v)]. Spots were located under UV rays or by means of the Dragendorff spray. UV spectra were recorded on a Cary Model 11 spectrophotometer. IR spectra were measured on a JASCO-DS-301 or -402G spectrophotometer in the solid state using a KBr disk. Acid dissociation constants were determined by UV spectrophotometry[21] using a Hitachi EPU-2A spectrophotometer; pH's were measured on a Hitachi–Horiba F-5 pH meter.

Adenine 1-oxide monohydrate (II·H_2O)

In following the procedure[8] for recrystallization of II, the monohydrate was obtained as colorless, heavy prisms. For analysis they were dried over P_2O_5 at 30°/2 mm Hg until they reached to constant weight (within 33 hr), m.p. above 300°. (Found: C, 35·63; H, 4·27; N, 41·26; H_2O, 10·61. $C_5H_5ON_5 \cdot H_2O$ requires: C, 35·50; H, 4·17; N, 41·41; H_2O, 10·65%). Identity of the UV spectra [$\lambda_{max}^{H_2O}$ (pH 1) 259 mμ (ε 12,400); $\lambda_{max}^{H_2O}$ (pH 7) 232 (42,300), 263 (8000); $\lambda_{max}^{H_2O}$ (pH 13) 234 (49,200), 274 (7200)] and paper chromatographical behavior of this sample with those of the anhydrous filamentous crystals[8] of II was verified by direct comparison. The IR spectra of both samples in the solid state were different. When dried over P_2O_5 at 90°/2 mm Hg for 11 hr, the monohydrate turned anhydrous with loss of one equiv mole of H_2O. Reversely, the anhyd filaments were easily changed into prisms of the monohydrate when a suspension of the former in H_2O was allowed to stand at room temp for a certain period of time (several hr—a few days) in the presence of a few crystals of the latter previously obtained.

1-*Alkoxyadenine salts* (III)

All alkylations were carried out by the procedure employed for the reaction of II with MeI using the reaction conditions specified in Table 1.

1-*Methoxyadenine hydriodide* (IIIa: X = I). A mixture of II·H_2O (10·1 g, 0·06 mole), MeI (21·3 g, 0·15 mole), and $AcNMe_2$ (80 ml) was stirred at room temp for 19 hr. The resultant ppts were filtered off, washed with a small amount of EtOH, and dried to give an almost colorless solid (14·2 g), which was pure

* In view of the recently reported instability[17] of 1-alkoxy-9-alkyladenines, the possibility that Vb in the medium could have been converted into N'-ethoxy-1-ethyl-5-formamidoimidazole-4-carboxamidine[17] and/or 6-ethoxyamino-9-ethylpurine[17] should not be excluded.

by paper chromatography. The filtrate and washings were combined and evaporated *in vacuo*. The residue was washed with a small amount of EtOH and recrystallized from 70% EtOHaq to give colorless prisms (2·1 g) as a second crop, total yield 16·3 g (93%). For analysis the hydriodide (IIIa: X = I) thus obtained was further recrystallized from 70% EtOHaq (Table 1).

1-*Methoxyadenine perchlorate* (IIIa: X = ClO_4). A soln of the hydriodide (IIIa: X = I) (8·79 g, 0·03 mole) tosylate (IIIa: X = *p*-TsO) by dissolving it in H_2O and adding a sat soln of picric acid in H_2O. Recrystallization from H_2O gave yellow needles (Table 2).

1-*Methoxyadenine perchlorate* (IIIa: X = ClO_4). A soln of the hydriodide (IIIa: X = I) (8·79 g, 0·03 mole) in H_2O (350 ml) was passed through a column of Amberlite IRA-402 (ClO_4^-) (120 ml, 0·15 mole equiv), and the column was further eluted with H_2O. The eluate (*ca* 1·5 l.) was evaporated *in vacuo*, and the residual solid was recrystallized from 70% EtOHaq to produce colorless pillars (Table 2).

1-*Alkoxyadenines* (IV)

1-*Methoxyadenine* (IVa). The hydriodide (IIIa: X = I) (14·2 g, 0·049 mole) was dissolved in H_2O (400 ml), and the soln was passed through a column of Amberlite IRA-402 (HCO_3^-) (120 ml). Elution with H_2O and evaporation of the eluate (1 l.) *in vacuo* left a colorless solid (6·88 g, 86%), which was recrystallized from H_2O to give colorless prisms, m.p. 255–257° (dec); UV (Table 3). (Found: C, 43·39; H, 4·43; N, 42·18. $C_6H_7ON_5$ requires: C, 43·63; H, 4·27; N, 42·41%). In this reaction, Amberlite IR-45 was also utilizable as an anion exchanger.

The preparation of IVa from the *p*-toluenesulfonate (IIIa: X = *p*-TsO) followed the procedure described.

1-*Ethoxyadenine* (IVb). Prepared from IIIb (X = I or *p*-TsO) in 98% yield in the manner described for IVa. Recrystallization from H_2O afforded colorless prisms, m.p. 219° (dec); UV (Table 3). (Found: C, 47·28; H, 5·15; N, 38·69. $C_7H_9ON_5$ requires: C, 46·92; H, 5·06; N, 39·09%).

1-*Benzyloxyadenine* (IVc). 1-Benzyloxyadenine hydrobromide monohydrate (IIIc: X = Br) was dissolved in H_2O and the pH of the soln was adjusted to 7·5 with sat $NaHCO_3$aq. The ppts that formed were filtered off, washed with H_2O, and dried over P_2O_5 at 25°/15 mm Hg for 40 hr to furnish a monohydrate of IVc in 99% yield. Recrystallization of the monohydrate from EtOH gave an anhydrous sample as colorless prisms, which were dried over P_2O_5 at 70°/3 mm Hg for 26 hr, m.p. 170° (dec); UV (Table 3). (Found: C, 59·56; H, 4·71; N, 29·06. $C_{12}H_{11}ON_5$ requires: C, 59·74; H, 4·60; N, 29·03%).

Picrates from IV. Each of the free bases (IVa, b, c) was dissolved in H_2O (EtOH for IVc), and a soln of picric acid in H_2O (EtOH for IVc) was added. The resulting ppts were filtered off and recrystallized to give yellow needles, which were identical with those prepared directly from the corresponding salts (III) (Table 2).

Hydrogenolysis of 1-*alkoxyadenines* (IV)

The hydrogenolysis of 1-ethoxyadenine (IVb) is described in detail as a typical example.

A soln of IVb (1·79 g, 0·01 mole) in 2-methoxyethanol (270 ml) was hydrogenated over Raney Ni W-2 catalyst (1·5 g) at 55° and atm press; one equiv mole of H_2 was taken up within 10 hr. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness to leave a solid, which was washed with a small amount of EtOH and dried to give the crude I (1·22 g, 90%) shown to be homogeneous by paper chromatography. For analysis the solid was recrystallized from H_2O and dried over P_2O_5 at 130°/3 mm Hg, m.p. above 340°. (Found: C, 44·41; H, 3·88; N, 51·50. $C_5H_5N_5$ requires: C, 44·44; H, 3·73; N, 51·83%). The IR spectrum of this sample was superimposable with that of authentic adenine (I). The picrate prepared from I melted at 294–295° (dec) (lit.[12] m.p. 291°) and was identified with authentic adenine picrate by mixed m.p. and comparison of IR spectra.

In a similar hydrogenolysis, IVa also gave I in 85% yield; 1-benzyloxyadenine (IVc), in 84% yield. In the case of IVc, formation of a small amount of benzaldehyde was confirmed by the following procedure: the distillate, which was obtained by evaporating the reaction mixture [started from IVc (550 mg, 2·1 mmoles)] after filtration of the catalyst, was concentrated to a small volume (*ca* 10 ml). To this soln was added a soln[22] of 2,4-dinitrophenylhydrazine—H_3PO_4 in EtOH. The yellow ppts (50 mg) that formed were filtered off, washed with EtOH, and recrystallized from EtOH to yield orange needles, m.p. 240–241°, undepressed in m.p. on admixture with authentic benzaldehyde 2,4-dinitrophenylhydrazone. The IR spectra of both samples were also identical.

Debenzylation of 1-*benzyloxyadenine* (IVc)

1-Benzyloxyadenine monohydrate (IVc·H_2O; 520 mg, 2 mmoles) in 2-methoxyethanol (300 ml) was

hydrogenated over 10% Pd–C (500 mg) at 25° and atm press; one equiv mole of H_2 was absorbed within a few min. The catalyst was filtered off, a small amount of H_2O was added to the filtrate, and the soln was distilled under ordinary atm press to yield a small amount of fore-run. The UV spectrum of the fore-run indicated the presence of toluene. The residual main soln was then evaporated *in vacuo* to dryness to give a colorless solid, which was triturated with a small amount of EtOH, filtered, and dried to give II (260 mg, 87%). Paper chromatography revealed that this sample was contaminated with a trace of adenine. Recrystallization from H_2O gave colorless needles, which were identified with an authentic sample[6] of anhydrous adenine 1-oxide (II) by comparison of IR spectra and paper chromatography.

1-*Alkoxy*-9-*alkyladenine salts* (V)

1-*Methoxy*-9-*methyladenine hydriodide* (Va: X = I). A mixture of IVa (1·65 g, 0·01 mole), MeI (3·55 g, 0·025 mole), and $AcNMe_2$ (30 ml) was stirred at room temp for 93 hr. The ppts that formed were collected by filtration, washed with a small amount of EtOH, and dried to give Va (X = I; 2·18 g, 71%) as a colorless solid, which was paper chromatographically homogeneous. For analysis this sample was recrystallized from 50% EtOHaq to yield colorless pillars, m.p. 214–215° (dec); UV (Table 3). (Found: C, 27·26; H, 3·48; N, 22·80. $C_7H_{10}ON_5I$ requires: C, 27·38; H, 3·28; N, 22·81%). The *picrate* of IVa was prepared in the same way as described for 1-methoxyadenine picrate (Table 2).

1-*Methoxy*-9-*methyladenine perchlorate* (Va: X = ClO_4) was obtained from Va (X = I; 3·99 g, 0·013 mole) by dissolving it in warm H_2O (*ca* 40°) and adding 15% NH_4ClO_4aq (15 ml). The resulting ppts were filtered off, washed with a small amount of H_2O, and dried, yield, 3·18 g or 84%. Recrystallization from H_2O produced colorless plates (Table 2).

1-*Ethoxy*-9-*ethyladenine hydriodide* (Vb: X = I). By treating IVb with EtI as described above for 140 hr, Vb (X = I) was obtained in 71% yield. Recrystallization from H_2O gave colorless prisms, m.p. 186° (dec); UV (Table 3). (Found: C, 32·33; H, 4·12; N, 20·90. $C_9H_{14}ON_5I$ requires: C, 32·25; H, 4·21; N, 20·90%). The corresponding *picrate* and *perchlorate* were prepared as described for Va (Table 2).

1-*Benzyloxy*-9-*benzyladenine hydrobromide* (Vc: X = Br). This was obtained in 52% yield from the monohydrate of IVc by treating it with benzyl bromide for 60 hr as described for Va (X = I). Recrystallization from EtOH yielded a monohydrate of Vc as colorless pillars, m.p. 218° (dec) (dried over P_2O_5 at 25°/3 mm Hg for 21 hr); UV (Table 3). (Found: C, 53·46; H, 4·92; N, 16·16. $C_{19}H_{18}ON_5Br \cdot H_2O$ requires: C, 53·04; H, 4·68; N, 16·27%). The corresponding *picrate* was prepared in the same manner as described for the picrate of IVc (Table 2).

1-*Alkoxy*-9-*alkyladenines* (VI)

1-*Methoxy*-9-*methyladenine* (VIa). A soln of Va (X = I; 1·54 g, 5 mmoles) in H_2O (150 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (25 ml), and the column was eluted with H_2O. The eluate (300 ml) was evaporated *in vacuo* to dryness to leave a colorless solid, which was dried over conc H_2SO_4 at 25°/15 mm Hg overnight. The solid (900 mg) was recrystallized from isopropyl ether to yield colorless needles. Since this sample was very hygroscopic, it was characterized as the picrate, which was prepared as described for the picrate of IVa and found to be identical with the one derived directly from Va (X = I) (Table 2).

1-*Ethoxy*-9-*ethyladenine* (VIb). Prepared from Vb (X = I) in the manner described.

1-*Benzyloxy*-9-*benzyladenine* (VIc). Compound Vc (X = Br; 2·06 g, 4·8 mmoles) was dissolved in H_2O (150 ml), and the pH of the soln was adjusted to 8 with sat $NaHCO_3$aq. The almost colorless needles were filtered off, washed with H_2O, and dried to give VIc (1·36 g). The picrate was prepared from a soln of VIc in EtOH as described for the picrate of IVc, and found to be identical with the sample obtained directly from Vc (X = Br) (Table 2).

Hydrogenolysis of 1-*alkoxy*-9-*alkyladenines* (VI)

The experiment with VIa is described in detail. A soln of VIa (500 mg) in 100 ml 2-methoxyethanol or $AcNMe_2$ was hydrogenated at 50° and atm press in the presence of Raney Ni W-2 catalyst (0·7 g); approximately one equiv mole of H_2 was absorbed during 7 hr. Removal of the catalyst and evaporation of the filtrate furnished almost colorless crystals [(280 mg, 67% based on Va (X = I)], m.p. 296–297°. Recrystallization from H_2O gave VIIa as colorless prisms, m.p. 305–307° (lit.[23] m.p. 310°), undepressed upon mixture with an authentic sample.[13] Identity of both samples was also established by paper chromatography and UV and IR spectra.

The hydrogenolysis of the perchlorate of VIa was carried out as follows: A warm soln of Va (X = ClO_4; 1·07 g, 3·8 mmoles) in H_2O (200 ml) was hydrogenated over 10% Pd–C (300 mg) at 55° and atm press for 14 hr, taking up one equiv mole of H_2. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness to leave a solid, which was dissolved in a small volume of H_2O. The aq soln was rendered basic (pH 9) with conc NH_4OHaq, and the ppts were filtered off, washed with H_2O, and dried to afford VIIa (420 mg, 73%). Recrystallization from H_2O gave colorless prisms, m.p. 303–304°, identified with an authentic sample of VIIa as described.

In a similar manner, VIb was converted into VIIb (72%), m.p. 193–195° (recrystallized from benzene) (lit.[24] m.p. 194–195°). *9-Ethyladenine picrate* was prepared from a portion of the free base by dissolving it in EtOH and adding a sat soln of picric acid in EtOH. After recrystallization from H_2O, yellow needles were obtained, m.p. 269–271° (dec). (Found: C, 39·98; H, 3·21; N, 28·69. $C_{13}H_{12}O_7N_8$ requires: C, 39·80; H, 3·08; N, 28·57%).

Hydrogenolysis of VIc was also accomplished as described, and VIIc,[25–27] m.p. 233–236° [picrate, m.p. 259–261° (dec)], was obtained in 74% yield. In this reaction, the formation of a trace of benzaldehyde was confirmed by the same procedure described for the isolation of benzaldehyde 2,4-dinitrophenylhydrazone from the hydrogenolysis mixture of IVc.

9-Benzyladenine 1-oxide (VIII)

A mixture of a soln of VIc obtained from Vc (X = Br; 860 mg, 2 mmoles) in 2-methoxyethanol (100 ml) and 10% Pd–C (300 mg) was hydrogenated at room temp and atm press; the reaction was complete within a few min, absorbing one equiv mole of H_2. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness to leave a solid, which was dried. The solid (410 mg, 85%) was recrystallized from 90% EtOHaq to give VIII as colorless needles, m.p. 280–281° (dec); UV $\lambda_{max}^{H_2O}$ (pH 1) 259 mμ (ε 12,600); $\lambda_{max}^{H_2O}$ (pH 7) 232 (44,600), 262 (8100), 291 (2000); $\lambda_{max}^{H_2O}$ (pH 13) 231 (27,500), 268 (8600), 305 (4000). (Found: C, 59·74; H, 4·43; N, 28·85. $C_{12}H_{11}ON_5$ requires: C, 59·74; H, 4·60; N, 29·03%). This sample was identical (by mixed m.p., paper chromatography, and UV and IR spectra) with the one[18] prepared by the N-oxidation of VIIc.

Deoxygenation of 9-benzyladenine 1-oxide (VIII)

A soln of VIII (970 mg, 4·02 mmoles) in 2-methoxyethanol (200 ml) was hydrogenated over Raney Ni W-2 catalyst (0·9 g) at room temp and atm press for 3·5 hr, taking up one equiv mole of H_2. The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to dryness. The residue (850 mg, 95%), shown to be homogeneous by paper chromatography, was recrystallized from EtOH to give VIIc as colorless needles, m.p. 233–236°, which were shown to be identical with authentic 9-benzyladenine[25–27] by mixed m.p. and comparison of UV and IR spectra.

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