Chem. Pharm. Bull. 19(8)1611—1617(1971)

UDC 547.857.7.04 : 542.951

Purines. IV.[1] O→$N_{(9)}$ Alkyl Migration in the Alkylation of 1-Alkoxyadenines[2]

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(Received January 7, 1971)

Treatment of 1-alkoxyadenine (I) with reactive alkyl halides (R^2X) in N,N-dimethylacetamide yielded the 9-alkylated salts (II) in good yields. However, an alkyl halide (R^2X) less reactive than that (R^1X) whose alkyl group was the same as in I reacted with I to give a mixture of at most four possible 1-alkoxy-9-alkyladenine salts (II, IV, V, and VII), two 9-alkyladenine 1-oxides (III and VI), and, possibly, a more reactive alkyl halide (R^1X). The intricate pattern of formation of products was due to O→$N_{(9)}$ alkyl migration during the reaction, and a plausible mechanism is presented. A clear O→$N_{(9)}$ benzyl migration was demonstrated by the reaction of 1-benzyloxyadenine (I:R^1=$C_6H_5CH_2$) with 0.1 equivalent of benzyl bromide to give 0.58 equivalent of 9-benzyladenine 1-oxide (VI:R^1=$C_6H_5CH_2$).

In earlier publications[4,5] we have illustrated two methods for the synthesis of 1-alkoxy-9-alkyladenine salts (type V or VII); one is alkylation of 1-alkoxyadenines (I) with alkyl halides in N,N-dimethylacetamide (DMAC),[4] and the other, alkylation of 9-alkyladenine 1-oxides (type III or VI) in a similar way.[5] It has also been noted that the latter method is capable of affording the salts (type V or VII) possessing any combinations of two kinds of alkyl groups in the molecules in excellent yields, whereas cross alkylation of I by the former method leading to 9-alkylated salts (type II) in which R^1 and R^2 are different gives a complicated pattern of product formation in certain cases depending on the nature of the alkyl groups. In the present paper a detailed account is given of such a cross alkylation of I in terms of an oxygen to nitrogen alkyl migration during the reaction.

On treatment with methyl iodide in DMAC at room temperature, 1-ethoxyadenine (I: R^1=C_2H_5)[4] underwent methylation almost exclusively at the 9-position to give 1-ethoxy-9-methyladenine hydriodide (II: R^1=C_2H_5; R^2=CH_3; X=I)[5] in a good yield. The assignment of the 9-methylated structure was based on identity of the hydriodide with an authentic specimen[5] and catalytic hydrogenolysis of the corresponding free base over Raney nickel to yield 9-methyladenine. Likewise, benzylation with benzyl bromide produced 1-ethoxy-9-benzyladenine hydrobromide (II: R^1=C_2H_5; R^2=$C_6H_5CH_2$; X=Br) as a dihydrate, which was characterized by conversion into the corresponding picrate.[5] A similar benzylation of 1-methoxyadenine (I: R^1=CH_3)[4] furnished, after treatment with sodium iodide, 1-methoxy-9-benzyladenine hydriodide (II: R^1=CH_3; R^2=$C_6H_5CH_2$; X=I)[5] in 64% yield. It may be seen from these results that the cross alkylation of I with reactive alkyl halides (R^2X) proceeds quite normally, being consistent with the previously reported homogeneous alkylation[4] to afford the 9-alkylated derivatives (type V) in which the two alkyl groups are the same.

1) Paper III: T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).
2) A preliminary communication on this subject appeared in *Chem. Pharm. Bull.* (Tokyo), **14**, 1452 (1966).
3) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
4) *a*) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 1017 (1965); *b*) T. Fujii and T. Itaya, *Tetrahedron*, **27**, 351 (1971).
5) *a*) T. Fujii, C.C. Wu, T. Itaya, and S. Yamada, *Chem. Ind.* (London), **1966**, 1598; *b*) T. Fujii, C.C. Wu, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1368 (1971).

On the other hand, an alkyl halide (R^2X) less reactive than that (R^1X) whose alkyl group was the same as in I reacted with I to give a mixture of at most four possible 1-alkoxy-9-alkyladenine salts (II, IV, V, and VII), two 9-alkyladenine 1-oxides (III and VI), and a more reactive alkyl halide (R^1X) derived from the 1-alkoxy group. For example, treatment of 1-benzyloxyadenine (I: $R^1=C_6H_5CH_2$) with an excess of ethyl iodide in DMAC at room temperature gave an intractable reaction mixture, in which the presence of seven products, namely, 1-benzyloxy-9-ethyladenine hydriodide (II: $R^1=C_6H_5CH_2$; $R^2=C_2H_5$; X=I),

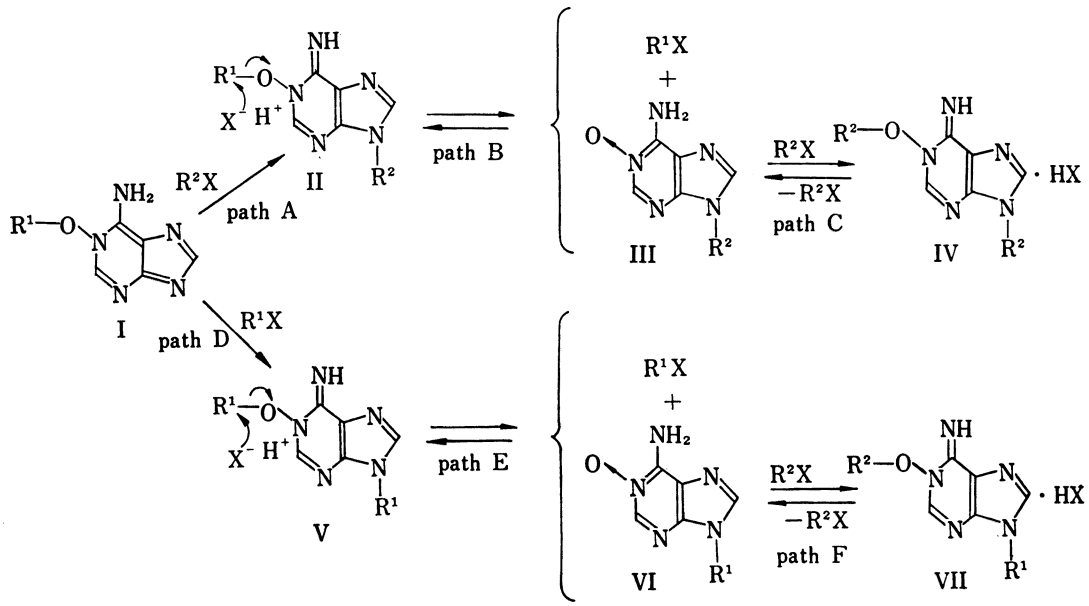

Chart 1

9-ethyladenine 1-oxide (III: $R^2=C_2H_5$), 1-ethoxy-9-ethyladenine hydriodide (IV: $R^2=C_2H_5$; X=I), 1-benzyloxy-9-benzyladenine hydriodide (V: $R^1=C_6H_5CH_2$; X=I), 9-benzyladenine 1-oxide (VI: $R^1=C_6H_5CH_2$), 1-ethoxy-9-benzyladenine hydriodide (VII: $R^1=C_6H_5CH_2$; $R^2=C_2H_5$; X=I), and, possibly, benzyl iodide, was suggested by paper chromatographical comparison with known samples.[4,5] Among the reaction products, 1-ethoxy-9-ethyladenine hydriodide (IV: $R^2=C_2H_5$; X=I)[4] was isolated from the mixture in 16% yield. Conversion of the reaction mixture into the form of free base and catalytic hydrogenation over Raney nickel yielded 9-benzyladenine and 9-ethyladenine. These observations indicate the displacement of the benzyl group from the oxygen atom of I ($R^1=C_6H_5CH_2$) and migration to the $N_{(9)}$ atom during the ethylation. Ethylation of 1-methoxyadenine (I: $R^1=CH_3$) under similar reaction conditions was also found to involve $O\rightarrow N_{(9)}$ methyl migration since 1-methoxy-9-methyladenine hydriodide (V: $R^1=CH_3$; X=I) was detectable in the reaction mixture.

To explain the intricate pattern of product formation and the oxygen to nitrogen alkyl migration described above, an equilibrium among 1-alkoxy-9-alkyladenine salt (type II), 9-alkyladenine 1-oxide (type III), and alkyl halide has been postulated. As shown in Chart 1, the normally alkylated salt (II) produced by slow reaction of I with a less reactive alkyl halide (R^2X)(path A) would undergo nucleophilic attack of the halide ion on the α-carbon

of the alkoxyl group, analogous to the case of 1-alkoxypyridinium salts,[6] to give an equilibrated mixture of II, III, and R^1X (path B). The 1-oxide (III) thus formed should react further with an excess of R^2X to provide IV (path C),[5] and the more reactive alkyl halide (R^1X) generated in path B should alkylate, competitively with R^2X, the unaltered I to give V (path D). Compound (V) could then be converted further into VI and VII through paths E and F which correspond to paths B and C.

In the reaction of 1-benzyloxyadenine (I: $R^1=C_6H_5CH_2$) with methyl iodide, $O\rightarrow N_{(9)}$ benzyl migration was found not to occur since the reaction products detected were only four, namely, 1-benzyloxy-9-methyladenine hydriodide (II: $R^1=C_6H_5CH_2$; $R^2=CH_3$; X=I),[5] 9-methyladenine 1-oxide (III: $R^2=CH_3$),[5] 1-methoxy-9-methyladenine hydriodide (IV: $R^2=CH_3$; X=I), and, possibly, benzyl iodide. The absence of the 9-benzylated products was further evidenced by hydrogenolysis of the reaction mixture, after converted into the free bases, which gave 9-methyladenine as a sole product. This is probably due to the rapid 9-methylation in path A (Chart 1), which would be fast enough to have consumed I ($R^1=C_6H_5CH_2$) before II ($R^1=C_6H_5CH_2$; $R^2=CH_3$; X=I) equilibrates with III ($R^2=CH_3$) and benzyl iodide, rendering path D virtually impracticable.

In order to demonstrate $O\rightarrow N_{(9)}$ alkyl migration more clearly, reactions of 1-benzyloxy derivatives (type I) were examined next. When 1-benzyloxyadenine (I: $R^1=C_6H_5CH_2$) was treated with 0.1 mole equivalent of benzyl bromide in DMAC at 60—70° for 58 hr, 0.58 mole equivalent of 9-benzyladenine 1-oxide (VI: $R^1=C_6H_5CH_2$) was obtained, whereas the free base (I: $R^1=C_6H_5CH_2$) alone was stable under the identical reaction conditions. It is assumed that 0.1 equivalent of 1-benzyloxy-9-benzyladenine hydrobromide (V: $R^1=C_6H_5CH_2$; X=Br) is formed first (path D in Chart 1) and then dissociates into VI ($R^1=C_6H_5CH_2$) and benzyl bromide (path E). The benzyl bromide generated should react with the unchanged I ($R^1=C_6H_5CH_2$) to give an additional amount of V ($R^1=C_6H_5CH_2$; X=Br). Recycle of benzyl bromide in such a way finally would be able to transform I into a mixture of a large amount of VI ($R^1=C_6H_5CH_2$) and a small amount of V ($R^1=C_6H_5CH_2$; X=Br), and, if there is any, a trace of benzyl bromide. The use of a catalytic amount of methyl

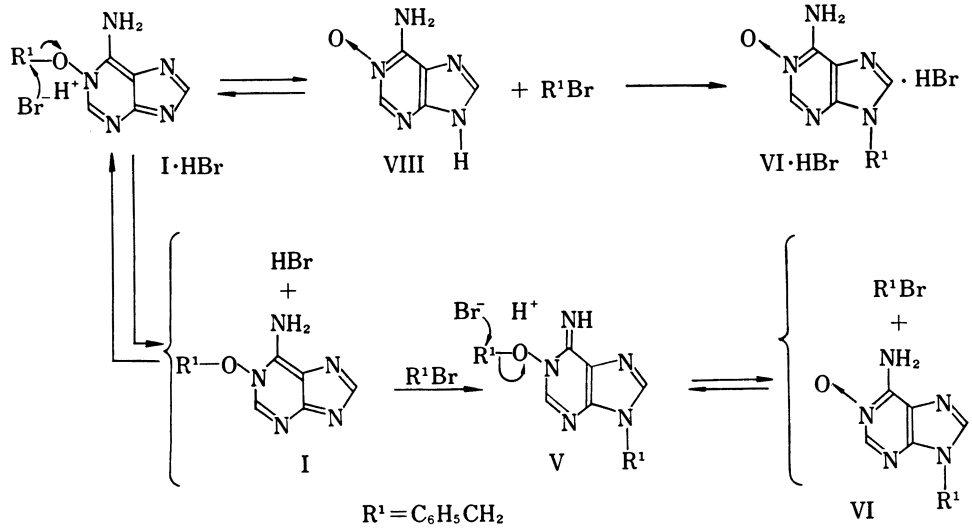

Chart 2

6) For reviews, see *a*) T. Okamoto, *Yuki Gosei Kagaku Kyokai Shi*, **19**, 790 (1961); *b*) R. Eisenthal and A.R. Katritzky, *Tetrahedron*, **21**, 2205 (1965); *c*) S. Takahashi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **14**, 375 (1966).

iodide in a similar manner for the synthesis of 1-methyl-4-pyridone from 4-methoxypyridine has been reported.[7] On the other hand, treatment of 1-benzyloxyadenine hydrobromide (I·HBr: $R^1=C_6H_5CH_2$) in DMAC at 90—100° was found to give 9-benzyladenine 1-oxide (VI: $R^1=C_6H_5CH_2$) (22% yield) and adenine 1-oxide (VIII) (35% yield). The formation of VIII would be a result of nucleophilic attack of the bromide ion on the benzylic carbon of I·HBr ($R^1=C_6H_5CH_2$) as depicted in Chart 2, and the benzyl bromide that resulted presumably reacts with the free base (I: $R^1=C_6H_5CH_2$) dissociated from I·HBr ($R^1=C_6H_5CH_2$), in a way similar to that of path D (Chart 1), to produce V ($R^1=C_6H_5CH_2$). The 9-benzylated salt (V: $R^1=C_6H_5CH_2$) could then be converted into thermodynamically stable VI ($R^1=C_6H_5CH_2$) in the same manner as explained already. However, the possibility that VIII is directly benzylated at the 9-position by the dissociated benzyl bromide under the reaction conditions used should not be excluded. Such dissociation-recombination mechanisms of the benzyl group would be closely related to the recently reported benzyl (or allyl or glycosyl) migrations of 1,3-dibenzylhypoxanthine bromide to both 7- and 9-positions[8] and of N-acyl-3-benzyl (or allyl or 3-methyl-2-butenyl or glycosyl) adenine hydrobromides to the 9-position.[9]

The utility of $O\rightarrow N_{(9)}$ benzyl migration in the thermal degradation of I·HBr ($R^1=C_6H_5CH_2$) described above was exemplified by the one-step synthesis of VI·HBr ($R^1=C_6H_5CH_2$) (57% yield) from adenine 1-oxide (VIII), in which VIII and two equivalents of benzyl bromide were heated in DMAC at 120°. In this reaction application of higher temperatures seemed undesirable, because it was found that heating VI·HBr ($R^1=C_6H_5CH_2$) in DMAC at reflux for 1 hr resulted in deoxygenation[4a] to give 9-benzyladenine.

It is interesting to note that the $O\rightarrow N_{(9)}$ alkyl migration discussed above is suggestive of the use of 1-alkoxyadenine derivatives as possible alkylating reagents. The behavior of 1-alkoxy-9-alkyladenine salts (type V) toward nucleophiles will be the subject of our forthcoming paper.[2]

Experimental[10]

Methylation of 1-Ethoxyadenine (I: $R^1=C_2H_5$)——A mixture of I ($R^1=C_2H_5$)[4] (5.38 g, 0.03 mole), methyl iodide (12.8 g, 0.09 mole), and DMAC (40 ml) was stirred at room temperature for 19 hr. The precipitates that resulted were collected by filtration, washed with ethanol (30 ml), and dried to give a sample (7.77 g, 81%) of 1-ethoxy-9-methyladenine hydriodide (II: $R^1=C_2H_5$; $R^2=CH_3$; X=I), shown to be pure by paper chromatography. Recrystallization from 50% aq. ethanol produced an analytical sample as colorless prisms, mp 203—204° (decomp.). *Anal.* Calcd. for $C_8H_{12}ON_5I$: C, 29.92; H, 3.77; N, 21.81. Found: C, 30.03; H, 3.78; N, 21.58. Identity of this sample with authentic 1-ethoxy-9-methyladenine hydriodide[5b] was established by paper chromatography and comparison of the infrared (IR) spectra.

Hydrogenolysis of 1-Ethoxy-9-methyladenine——A solution of the hydriodide (II: $R^1=C_2H_5$; $R^2=CH_3$; X=I) (640 mg, 2 mmole) in H_2O (50 ml) was passed through a column of Amberlite IRA-402 (HCO_3^-) (10 ml), and the column was further eluted with H_2O. The eluate (300 ml) was evaporated *in vacuo* to give 1-ethoxy-9-methyladenine as a partially crystallized, yellowish oil. The total amount of the free base was dissolved in 2-methoxyethanol (50 ml), and the resulting solution was hydrogenated over Raney Ni W-2 catalyst (*ca.* 0.6 g) at 55° and atmospheric pressure for 7 hr. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to dryness to leave almost colorless crystals (260 mg, 87% based on the hydriodide). Recrystallization from H_2O furnished 9-methyladenine as colorless prisms, mp 305—307° (lit.[11] mp 310°), undepressed upon mixture with an authentic sample.[12] The paper chromatographical behavior and IR spectra of both samples were also identical.

7) *a*) P. Beak and J. Bonham, *Tetrahedron Letters*, **1964**, 3083; *b*) *Idem*, *J. Am. Chem. Soc.*, **87**, 3365 (1965).
8) *a*) J.A. Montgomery, H.J. Thomas, and K. Hewson, *Chem. Ind.* (London), **1965**, 1596; *b*) J.A. Montgomery, K. Hewson, S.J. Clayton, and H.J. Thomas, *J. Org. Chem.*, **31**, 2202 (1966).
9) *a*) B. Shimizu and M. Miyaki, *Tetrahedron Letters*, **1965**, 2059; *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **18**, 570 (1970); *c*) *Idem*, *ibid.*, **18**, 732 (1970).
10) All melting points are corrected. Paper chromatographies were developed as described previously.[4b] See also ref. 4*b* for details of instrumentation and measurement.
11) R.K. Robins and H.H. Lin, *J. Am. Chem. Soc.*, **79**, 490 (1957).
12) N.J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.*, **51**, 73 (1964).

Benzylation of 1-Ethoxyadenine (I: $R^1=C_2H_5$)——A mixture of I($R^1=C_2H_5$)[4] (1.79 g, 0.01 mole), benzyl bromide (4.50 g, 0.026 mole), and DMAC (10 ml) was stirred at room temperature for 18 hr. The resulting clear solution was evaporated *in vacuo* to leave a yellowish oil, which was triturated successively with ether (70 ml) and ethanol–ether (1:1) (40 ml) to effect crystallization. The crystals (1.42 g), shown to be contaminated with 1-ethoxyadenine by paper chromatography, were repeatedly recrystallized from H_2O until a pure sample (730 mg, 19%) was obtained. For analysis it was dried over P_2O_5 at 50° and 3 mmHg for 20 hr to give 1-ethoxy-9-benzyladenine hydrobromide (II: $R^1=C_2H_5$; $R^2=C_6H_5CH_2$; X=Br) as a dihydrate, colorless prisms of mp 221—225° (decomp.) (sintered at *ca.* 130°); UV $\lambda_{max}^{95\%\,EtOH}$: 259 mμ (ε 13400); $\lambda_{max}^{0.1N\,HCl}$ 260 (13000); $\lambda_{max}^{H_2O}$ (pH 7),[13] 259 (13000); $\lambda_{max}^{0.1N\,NaOH}$ 258 (13000). *Anal.* Calcd. for $C_{14}H_{16}ON_5Br\cdot 2H_2O$: C, 43.53; H, 5.22; N, 18.13. Found: C, 43.53; H, 5.25; N, 18.36. When the crude hydrobromide was purified, after treatment with NaI, in a manner similar to that described below for the benzylation of 1-methoxyadenine, the corresponding hydriodide, mp 167—168° (decomp.), which was identical with an authentic sample,[5b] was obtained in 35% yield.

Treatment of the dihydrate of the hydrobromide with a saturated solution of picric acid in H_2O produced the corresponding picrate as yellow needles, mp 212° (decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_8N_8$: C, 48.20; H, 3.64; N, 22.48. Found: C, 48.19; H, 3.59; N, 22.39. This sample was identical (by mixed melting point test and IR spectrum) with authentic 1-ethoxy-9-benzyladenine picrate.[5b]

Benzylation of 1-Methoxyadenine (I: $R^1=CH_3$)——A suspension of I ($R^1=CH_3$)[4] (4.95 g, 0.03 mole) in a mixture of benzyl bromide (15.4 g, 0.09 mole) and DMAC (20 ml) was stirred at room temperature for 50 hr. The resulting solution was evaporated *in vacuo* to dryness. The residue was dissolved in H_2O (80 ml) and a solution of NaI (10.3 g) in H_2O (10 ml) was added. The precipitates that resulted were filtered, washed with a small amount of H_2O, and dried to give a crude sample (6.96 g) of 1-methoxy-9-benzyladenine hydriodide (II: $R^1=CH_3$; $R^2=C_6H_5CH_2$; X=I), mp 204—207° (decomp.), shown to be homogeneous by paper chromatography. The filtrate and washings were combined and concentrated to a small volume (*ca.* 10 ml), and the resulting precipitates were recrystallized twice from H_2O to afford a second crop (0.45 g) of the hydriodide. Total yield was 7.41 g or 64%. Recrystallization from 90% aq. ethanol furnished colorless prisms, mp 213—215° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}ON_5I$: C, 40.74; H, 3.68; N, 18.28. Found: C, 40.59; H, 3.63; N, 18.65. This sample was identified with an authentic specimen[5b] by mixed melting point test and comparison of the IR spectra. The picrate, mp 212—213° (decomp.), prepared from the hydriodide was also identical with authentic 1-methoxy-9-benzyladenine picrate.[5b]

Ethylation of 1-Benzyloxyadenine (I: $R^1=C_6H_5CH_2$)——A mixture of 1-benzyloxyadenine monohydrate[4b] (4.41 g, 0.017 mole), ethyl iodide (8.4 g, 0.054 mole), and DMAC (18 ml) was stirred at room temperature for 20 hr. The resulting clear solution was evaporated *in vacuo* to leave a partially crystallized oil, which had a smell resembling that of benzyl iodide and was assumed, from paper chromatograms using four different solvent systems,[10] to contain 1-benzyloxy-9-ethyladenine hydriodide (II: $R^1=C_6H_5CH_2$; $R^2=C_2H_5$; X=I),[5] 9-ethyladenine 1-oxide (III: $R^2=C_2H_5$),[5] 1-ethoxy-9-ethyladenine hydriodide (IV: $R^2=C_2H_5$; X=I),[4] 1-benzyloxy-9-benzyladenine hydriodide (V: $R^1=C_6H_5CH_2$; X=I), 9-benzyladenine 1-oxide (VI: $R^1=C_6H_5CH_2$),[5] and 1-ethoxy-9-benzyladenine hydriodide (VII: $R^1=C_6H_5CH_2$; $R^2=C_2H_5$; X=I).[5] The residue was recrystallized from 90% aq. ethanol to give 1-ethoxy-9-ethyladenine hydriodide (IV: $R^2=C_2H_5$; X=I) (860 mg) as yellowish minute crystals of mp 181—183° (decomp.). Evaporation of the mother liquor and recrystallization of the resulting residue from methanol afforded a second crop (70 mg) of the hydriodide; total yield, 930 mg (16%). The combined first and second crop of crystals were further recyrstallized to yield colorless prisms, mp 186° (decomp.), shown to be identical (by mixed melting-point test and IR spectrum) with an authentic sample[4] of IV ($R^2=C_2H_5$; X=I).

On the other hand, the mother liquor, which was obtained on the filtration of the second crop of the hydriodide described above, was evaporated *in vacuo*, and the residual oil was poured into H_2O (300 ml). The mixture was extracted with benzene to leave a colorless aq. solution. The aq. solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (50 ml), and the column was further eluted with H_2O. Evaporation of the eluate (600 ml) *in vacuo* left a yellowish oil, which was hydrogenated in 2-methoxyethanol (200 ml) over Raney Ni W-2 catalyst at 55° and atmospheric pressure for 17 hr. The catalyst was filtered, and the filtrate was evaporated *in vacuo* to give a partially crystallized oil. The oil was triturated with ethanol, and the insoluble crystals (270 mg) that resulted were filtered and recrystallized from ethanol to produce colorless needles (180 mg), mp 233—236°, which were shown to be identical with authentic 9-benzyladenine[14] by mixed melting-point test and comparison of the ultraviolet (UV) and IR spectra. The ethanolic filtrate, which was obtained by isolation of the crude 9-benzyladenine from the triturated mixture, was evaporated *in vacuo* to dryness. The crystalline residue was extracted with hot benzene (50 ml), and the benzene solution was concentrated to a small volume to furnish colorless leaflets (290 mg), mp 193—195°, undepressed on admixture with authentic 9-ethyladenine. The IR spectra of both samples were also superimposable.

13) Determined in 0.005 M phosphate buffer (pH 7).

14) *a*) J.W. Daly and B.E. Christensen, *J. Org. Chem.*, **21**, 177 (1956); *b*) J.A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961); *c*) N.J. Leonard and T. Fujii, *ibid.*, **85**, 3719 (1963).

Ethylation of 1-Methoxyadenine (I: $=R^1CH_3$)——A stirred mixture of I ($R^1=CH_3$)[4] (3.30 g, 0.02 mole), ethyl iodide (9.36 g, 0.06 mole), and DMAC (10 ml) was heated at 70—75° for 4 hr. After having been cooled, the precipitates that resulted were filtered, washed with ethanol, and dried to give a crude product (4.36 g). The presence of 1-methoxy-9-methyladenine hydriodide (V: $R^1=CH_3$; X=I), 1-methoxy-9-ethyladenine hydriodide (II:$R^1=CH_3$;$R^2=C_2H_5$; X=I), and 1-ethoxy-9-ethyladenine hydriodide (IV:$R^2=C_2H_5$; X=I) was suggested by paper chromatographical comparison with known samples.[4,5] Attempts to separate any one of the hydriodides by recrystallization were unsuccessful.

Methylation of 1-Benzyloxyadenine (I: $R^1=C_6H_5CH_2$)——A mixture of 1-benzyloxyadenine monohydrate[4b] (780 mg, 3 mmole), methyl iodide (1.28 g, 9 mmole), and DMAC (8 ml) was stirred at room temperature for 1.5 hr. To the resulting clear solution, which was somewhat lachrymatory, was added H_2O (50 ml), and the mixture was extracted with benzene. The aq. solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (5 ml), and the column was eluted with H_2O. The eluate (150 ml) was evaporated *in vacuo* to leave a yellowish oil, which was hydrogenated in 2-methoxyethanol (80 ml) over Raney Ni W-2 catalyst (*ca.* 1 g) at 50° and atmospheric pressure for 3 hr. Filtration of the catalyst and evaporation of the filtrate left a solid, which was shown to be homogeneous by paper chromatography. Recrystallization of the solid from H_2O afforded colorless prisms (160 mg), mp 305—307°, identified with authentic 9-methyladenine[12] by mixed melting point test and IR spectrum.

Reaction of 1-Benzyloxyadenine (I: $R^1=C_6H_5CH_2$) with 0.1 Equivalent of Benzyl Bromide——A stirred mixture of 1-benzyloxyadenine monohydrate[4b] (1.30 g, 5 mmole), benzyl bromide (90 mg, 0.5 mmole), and DMAC (20 ml) was kept at 60—70° for 58 hr. The precipitates that resulted were filtered, washed with a small amount of ethanol, and dried. The solid (800 mg) was triturated with 7% aq. ammonia (20 ml), and insoluble crystals were filtered, washed successively with dilute aq. ammonia (10 ml), H_2O (4 ml), and ethanol (4 ml), and dried to give a sample (700 mg, 58%) of 9-benzyladenine 1-oxide (VI:$R^1=C_6H_5CH_2$), shown to be identical (by paper chromatography and IR spectrum) with an authentic sample.[5] On the other hand, the ammoniacal mother liquor obtained on filtration of VI ($R^1=C_6H_5CH_2$) was evaporated *in vacuo* to dryness to leave a solid. Recrystallization of the solid from 30% aq. ethanol gave adenine 1-oxide monohydrate (100 mg) as colorless prisms. This sample was identified with an authentic specimen[4b] by paper chromatography and IR spectrum.

Thermal Degradation of 1-Benzyloxyadenine Hydrobromide (I·HBr: $R^1=C_6H_5CH_2$)——A suspension of 1-benzyloxyadenine hydrobromide monohydrate[4b] (1.70 g, 5 mmole) in DMAC (20 ml) was heated at 90—100° with stirring for 22 hr. The resulting precipitates were collected by filtration and washed with ethanol. The filtrate and washings were combined and evaporated *in vacuo* to leave a partially crystallized oil. Trituration of the oil with ethanol–ether (1:1) (10 ml) and filtration of insoluble crystals gave a second crop of the crude product. The first and second crop of crystals were combined and triturated with hot H_2O (20 ml), and insoluble crystals were filtered while hot and washed successively with H_2O and ethanol to furnish a paper chromatographically homogeneous sample (100 mg, 8%) of 9-benzyladenine 1-oxide (VI:$R^1=C_6H_5CH_2$), shown to be identical with an authentic sample[5] by comparison of the IR spectra. The hot aq. filtrate described above was combined with 28% aq. ammonia (20 ml), and the almost colorless needles formed were filtered, washed successively with H_2O and ethanol, and dried to give an additional crop (170 mg, 14%) of VI ($R^1=C_6H_5CH_2$). Evaporation of the ammoniacal filtrate left almost colorless prisms (300 mg, 35%) of adenine 1-oxide monohydrate.[4b] Identity of this sample with an authentic specimen[4b] was established by paper chromatography and IR spectrum.

Direct Synthesis of 9-Benzyladenine 1-Oxide (VI: $R^1=C_6H_5CH_2$) from Adenine 1-Oxide (VIII)——A mixture of anhydrous adenine 1-oxide[15] (VIII:6.04 g, 0.04 mole), benzyl bromide (15.1 g, 0.088 mole), and DMAC (60 ml) was heated at 120° with stirring for 3 hr. The resulting precipitates were filtered, washed successively with ethanol and ether, and dried to give 9-benzyladenine 1-oxide hydrobromide (4.59 g) as colorless minute crystals, mp 240—243° (decomp.), which were identical (by paper chromatography and IR spectrum) with an authentic sample.[16] The filtrate and washings were combined and evaporated *in vacuo* to dryness, and the residue was triturated successively with ether and ethanol. Filtration of insoluble crystals afforded a second crop (2.7 g) of the hydrobromide. Total yield was 7.29 g (57%). The free base of 9-benzyladenine 1-oxide was prepared in 85% yield from the hydrobromide by dissolving it in hot H_2O and adjusting the pH of the aq. solution to 7.5. Recrystallization from ethanol gave an analytical sample, mp 280° (decomp.), identical with an authentic specimen.[5]

Deoxygenation of 9-Benzyladenine 1-Oxide Hydrobromide (VI·HBr: $R^1=C_6H_5CH_2$)——A mixture of 9-benzyladenine 1-oxide hydrobromide (322 mg, 1 mmole) and DMAC (10 ml) was gently refluxed for 1 hr. The resulting solution was evaporated *in vacuo* to leave a partially crystallized oil, which was triturated with hot 5% aq. HCl (50 ml). The mixture was filtered, and filtrate was treated with charcoal and rendered alkaline (pH 9) with 28% aq. ammonia. The precipitates that resulted were filtered, washed successively with

15) M.A. Stevens, D.I. Magrath, H.W. Smith, and G.B. Brown, *J. Am. Chem. Soc.*, **80**, 2755 (1958).
16) The hydrobromide, mp 242—244° (decomp.), has been prepared from the corresponding free base (VI: $R^1=C_6H_5CH_2$) and 10% aq. HBr by Mr. S. Moro of Kanazawa University.

H_2O (20 ml) and ethanol (2 ml), and dried to give 9-benzyladenine (131 mg, 58%), mp 230—233°. Recrystallization from ethanol furnished colorless pillars, mp 233—236°, shown to be identical (by mixed melting point test and IR spectrum) with authentic 9-benzyladenine.[14]

Acknowledgement We are pleased to acknowledge the support of our research by a grant from the Matsunaga Science Foundation. We also wish to thank Professor S. Yamada of University of Tokyo for his interest and encouragement and Dr. E. Kimura and his associates at University of Tokyo and Mr. Y. Itatani and his associate at Kanazawa University for microanalyses and UV and IR spectral data.