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Purines. VII.[1] 1-Alkoxy-9-alkyladenine Salts as Possible Alkylating Reagents[2]

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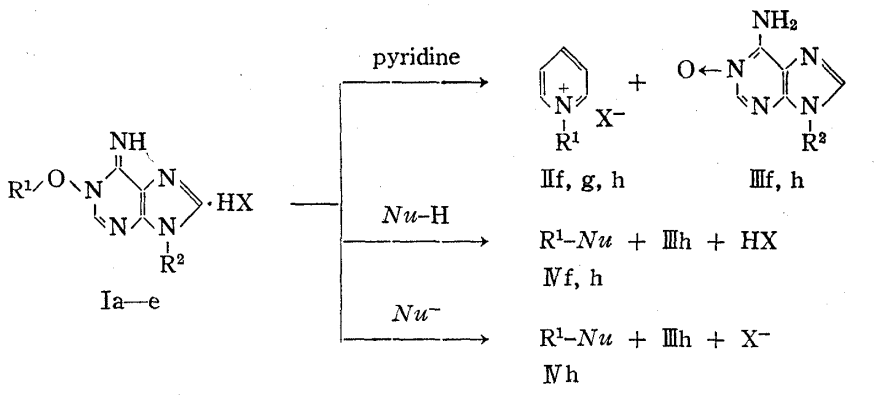
Treatment of 1-methoxy-9-methyladenine hydriodide (Ia) with hot pyridine has been found to produce 1-methylpyridinium salt (IIf) and 9-methyladenine 1-oxide (IIIf). Similarly, pyridine was ethylated with 1-ethoxy-9-benzyladenine hydriodide (Ic) to give 1-ethylpyridinium iodide (IIg: X=I) and 9-benzyladenine 1-oxide (IIIh). Benzyl alcohol was possible to be methylated with 1-methoxy-9-benzyladenine hydriodide (Ib), although yield of benzyl methyl ether was poor.

Reactions of 1-benzyloxy-9-benzyladenine hydrobromide (Id) with various nucleophiles such as pyridine, aniline, $C_2H_5S^-$, $CH_3CO_2^-$, ethanol, and water also proceeded smoothly and yielded the corresponding benzylated products and IIIh in good yields. Benzylation of adenine with Id in N,N-dimethylacetamide at 35° furnished 3-benzyladenine as the major product and 9-benzyladenine and 1-benzyladenine as the minor products. The reactivities of Id toward pyridine and ethanol have been compared with those of 1-benzyloxy-9-benzyladenine perchlorate (Ie), and possible mechanisms of the alkylation with 1-alkoxyadenine derivatives (type I) are discussed.

The facile synthesis of 1-alkoxy-9-alkyladenine salts (type I)[4,5] from adenine 1-oxide or 9-alkyladenine 1-oxides (type III) has fostered a continuing study of the chemistry of such a new class of adenine derivatives, and some reactions involving cleavage of the N—O bond,[4] dissociation of the salts (type I) into 1-oxides (type III) and alkyl halides,[6] and ring-opening in the pyrimidine moiety followed by reclosure to the isomeric N^6-alkoxy derivatives[1,7] have been previously reported. The $O \rightarrow N_{(9)}$ alkyl migration observed in the alkylation of 1-alkoxyadenines under certain conditions[6] has been suggestive of the use of the salts (type I) as possible alkylating reagents. In the present paper the behavior of I toward various nucleophilic reagents is described.

The nucleophile examined first was pyridine. When 1-methoxy-9-methyladenine hydriodide (Ia)[4,5] was treated with an excess of hot pyridine, formation of 1-methylpyridinium iodide (IIf: X=I) was evidenced by the isolation of the salt as the picrate (56% yield) and by the simultaneous formation of 9-methyladenine 1-oxide (IIIf)[5] (95% yield). A similar treatment of 1-ethoxy-9-benzyladenine hydriodide (Ic)[5,6b] with pyridine gave 1-ethylpyridinium iodide (IIg: X=I) in 54% yield and 9-benzyladenine 1-oxide (IIIh)[4,5] in 82% yield. Likewise, 1-benzyloxy-9-benzyladenine hydrobromide (Id)[4,5] furnished 1-benzylpyridinium salt (IIh) in 89% yield and IIIh in 96% yield. Following these reactions at room tempera-

1) Paper VI in this series, T. Itaya, F. Tanaka, and T. Fujii, *Tetrahedron*, **28**, 535 (1972).
2) Presented in part at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970. A portion of this work was reported earlier in a preliminary form.[6a]
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).
6) *a*) T. Fujii, T. Itaya, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **14**, 1452 (1966); *b*) T. Fujii and T. Itaya, *ibid.*, **19**, 1611 (1971).
7) *a*) T. Fujii, T. Itaya, C.C. Wu, and S. Yamada, *Chem. Ind.* (London), **1966**, 1967; *b*) T. Fujii, T. Itaya, C.C. Wu, and F. Tanaka, *Tetrahedron*, **27**, 2415 (1971).



a : $R^1=R^2=CH_3$; X=I
b : $R^1=CH_3$; $R^2=C_6H_5CH_2$; X=I
c : $R^1=C_2H_5$; $R^2=C_6H_5CH_2$; X=I
d : $R^1=R^2=C_6H_5CH_2$; X=Br
e : $R^1=R^2=C_6H_5CH_2$; $X=ClO_4$
f : R^1 or $R^2=CH_3$
g : R^1 or $R^2=C_2H_5$
h : R^1 or $R^2=C_6H_5CH_2$

Chart 1[a)]

a) The symbol *Nu* represents a nucleophile; *Nu*-H, a neutral molecule with active hydrogens; Nu^-, an anion.

ture by means of thin-layer and paper chromatographies revealed that the reaction of Id was the fastest and was complete within 9 hr, and that the reactivity of the 1-alkoxy derivatives decreased in the order Id>Ia>Ic. The alkylating capability of the 1-alkoxy group was also demonstrated by the reaction of Ib[5,6)] with benzyl alcohol, although yield of benzyl methyl ether, the alkylated product, was poor even after prolonged heating.

Next the 1-benzyloxy derivative (Id), selected out of the 1-alkoxy-9-alkyladenine salts for alkylation study, was allowed to react with a variety of nucleophiles such as aniline, $C_2H_5S^-$, $CH_3CO_2^-$, ethanol, and water with or without solvent. Most of the reactions were found to proceed smoothly and gave the corresponding benzylated products and the 1-oxide (IIIh) in good yields. The results are summarized in Table I. In the reaction of Id with water, the mediocre yields of benzyl alcohol and IIIh may be partly ascribed to occurrence of the Dimroth rearrangement[1,7)] of Id leading to N-benzyloxy-9-benzyladenine.

Table I. Reactions of 1-Benzyloxy-9-benzyladenine Hydrobromide (Id) and Perchlorate (Ie) with Nucleophilic Reagents

Salt	Nucleophile	Solvent[a)]	Reaction conditions		Benzylated product (IVh)	Yield (%)	
			Temp. (°C)	Time (hr)		IVh	1-Oxide (IIIh)
Id	pyridine	—	80—85	1.5	1-benzylpyridinium picrate[b)]	89	96
Ie	pyridine	—	80—85	5	1-benzylpyridinium picrate[b)]	96	90
Id	aniline	—	86—88	2.5	N-benzylaniline	73	42
Id	C_2H_5SNa	DMAC	70—77	5	benzyl ethyl sulfide	66	81
Id	CH_3CO_2Na	DMAC	80—85	23	benzyl acetate	53	95
Id	C_2H_5OH	—	reflux	7	benzyl ethyl ether	62	86
Ie	C_2H_5OH	—	reflux	7	benzyl ethyl ether	3	trace
Id	H_2O	—	reflux	8	benzyl acohol[c)]	50	50

a) The abbreviation DMAC stands for N, N-dimethylacetamide.
b) Since the corresponding bromide that formed was hygroscopic, it was converted into the picrate in order to facilitate the isolation of the benzylated product.
c) isolated as benzyl N-phenylcarbamate.

For mechanisms of these alkylations two modes of reactions, as shown in Chart 2, may warrant consideration: (a) nucleophilic attack by a nucleophile (*Nu*:) on the α-carbon of the alkoxyl group to give the 1-oxide (III), alkylated product (R^1-*Nu*), and X^- (course A); (b)

a similar attack by the anion (X^-) of the salt (I) to yield an equilibrated mixture of I, III, and R^1X,[6] followed by the reaction of the generated R^1X with a nucleophile (course B). The mechanism of course A may be the most likely mode of reaction, particularly in view of an analogous mechanism[8] suggested for the dealkylation of 1-alkoxypyridinium cations with nucleophiles. However, the course B mechanism may also be operative especially in the case that the anion (X^-) of I is more nucleophilic than the attacking nucleophile. Evidence for such a mode of indirect alkylation was the observation that treatment of the hydrobromide (Id) with hot acetic acid for 9 hr led to formation of a major amount of benzyl bromide and a minor amount of benzyl acetate.

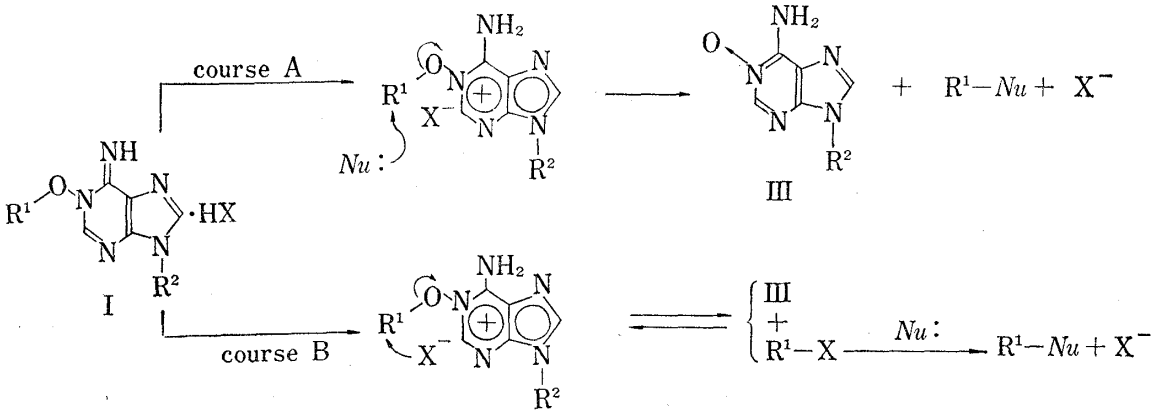


Chart 2[a]

a) The symbol *Nu*: is used in a broad sense to depict a nucleophile.

In order to investigate the effect of the anion in the alkylating salt (I) on the reactivity, it was necessary to obtain a salt of a I-type carrying the perchlorate ion which was regarded as almost powerless in nucleophilicity.[9] Thus, 1-benzyloxy-9-benzyladenine perchlorate (Ie) was prepared from the corresponding hydrobromide (Id) by treating it with ammonium perchlorate, and reactions of Ie with pyridine and ethanol were separately examined. It may be seen from Table I that the alteration in the anion of 1-benzyloxy-9-benzyladenine salt from the bromide ion to the perchlorate ion resulted in a marked decrease in the reactivity of the salt toward such a weak nucleophile as ethanol, whereas in the reaction with pyridine, a more powerful nucleophile, Ie gave a result almost comparable to that recorded for the hydrobromide (Id).

For further comparison, both salts were separately treated with the nucleophiles under identical conditions, and the yield of the 1-oxide (IIIh) at an early stage in each reaction was adopted as a quick guide to the reaction rate. As shown in Table II, it is evident that the hydrobromide (Id) is more reactive to both pyridine and ethanol than the perchlorate (Ie), and that difference in reactivity between both salts is much more great toward ethanol than toward pyridine.

On the basis of the results described, it is assumed that in the reaction of 1-alkoxy-9-alkyladenine salt (I) with a reagent more powerful in nucleophilicity than the anion of I, course A (Chart 2) is dominant and it is superseded in importance by course B when a reagent is less nucleophilic. Thus, in the reaction of the perchlorate salt (Ie), course A only seems

8) For reviews, see *a*) T. Okamoto, *Yuki Gosei Kagaku Kyokai Shi*, **19**, 790 (1961); *b*) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N.Y., 1971, pp. 448—450, pp. 550—552.

9) *a*) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt & Co., New York, N.Y., 1959, p. 259; *b*) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Co., New York, N.Y., 1968, p. 288.

operative since the perchlorate ion itself is a very poor nucleophile,[9] while in the case of the hydrobromide (Id) the simultaneous reactions, courses A and B, could be competitively operative.

Table II. Comparison of the Reactivities of the Salts (Id and Ie) of 1-Benzyloxy-9-benzyladenine toward Nucleophiles

Salt	Nucleophile	Reaction conditions[a]		Debenzylated product (IIIh) Yield (%)
		Temp (°C)	Time (hr)	
Hydrobromide Id	C_2H_5OH	reflux	1.5	44
Perchlorate Ie	C_2H_5OH	reflux	1.5	4
Perchlorate Ie[b]	C_2H_5OH	reflux	15	22
Hydrobromide Id	pyridine	20	2	38
Perchlorate Ie	pyridine	20	2	15

a) The salts were separately dissolved in the nucleophiles at 1.66×10^{-3}M concentration.
b) Dissolved in ethanol at 1.70×10^{-3}M concentration.

It may be seen from their p*K*a values (*e.g.*, 8.55 for 1-methoxy-9-methyladenine perchlorate)[1,4b] that 1-alkoxy-9-alkyladenine salts should exist for the most part in the protonated form under conditions of physiological pH. This may be suggestive of potential but unrealized usefulness of such salts as water-soluble cytotoxic alkylating reagents. In addition, it would not be too unreasonable to imagine that the neutral species of 1-alkoxy-9-alkyladenines could be bound to certain bases of nucleic acids by interaction similar to complementary hydrogen bonding and they could alkylate other bases or the hydroxyl groups in the sugar moieties in the immediate vicinity. As preliminary to an attempt at such a specific alkylation of nucleic acids, benzylation of adenine with the hydrobromide (Id) was carried out in N,N-dimethylacetamide (DMAC) at 35° for 100 hr, and a major amount (55% yield) of 3-benzyladenine and minor amounts of 9-benzyladenine and 1-benzyladenine were obtained. The facile and preferential 3-benzylation on adenine observed is similar to the result[10] of the direct benzylation of adenine with benzyl bromide. The previously reported formation[11] of N-benzyloxy-9-benzyladenine from 1-benzyloxyadenine in boiling aqueous DMAC may be another example of the benzylation of the adenine nucleus with the 1-benzyloxy group.

In contrast to the nucleophiles described above, strong bases such as the ethoxide ion and the hydroxide ion were found to cause 1-benzyloxy-9-benzyladenine salt to undergo the Dimroth rearrangement and related reactions,[1,7] which were accompanied by formation of benzaldehyde. Details of the deoxygenation will be reported elsewhere in the near future. The reaction of Id with potassium cyanide in DMAC seems to proceed in a complicated manner, and separation and characterization of the products are currently under way.

In conclusion, it may be noted that the utility of 1-alkoxy-9-alkyladenine salts as alkylating reagents may be increased by the easy and efficient recovery of 9-alkyladenine 1-oxide together with its facile and well-established O-alkylation[5] to regenerate the alkylating salts. Moreover, since the direct $N_{(1)}$-oxidation of 9-alkyladenines usually proceeds slowly[5] and yields of the resulting 1-oxides (type III) are not too high,[5] the dealkylation of I described, coupled with the 9-alkylation[4] of 1-alkoxyadenines, should constitute an alternative route for the synthesis of III.

10) *a*) N.J. Leonard and T. Fujii, *J. Am. Chem. Soc.*, **85**, 3719 (1963); *b*) T. Fujii and N.J. Leonard, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, ed. by W.W. Zorbach and R.S. Tipson, Interscience Publishers, Inc., New York, N.Y., 1968, pp. 13—14.
11) T. Fujii, T. Sato, and T. Itaya, *Chem. Pharm. Bull.* (Tokyo), **19**, 1731 (1971).

Experimental[12]

1-Benzyloxy-9-benzyladenine Perchlorate (Ie)——To a warm solution of 1-benzyloxy-9-benzyladenine hydrobromide monohydrate (Id·H_2O)[4,5] (1.00 g, 2.32 mmoles) in H_2O (30 ml) was added 15% aq. NH_4ClO_4 (2 ml). The mixture was chilled to deposit colorless needles (878 mg, 88%), mp 190—193° (decomp.), which were collected by filtration. Recrystallization from 30% aq. ethanol produced an analytical sample of Ie, mp 191—193° (decomp.); UV $\lambda_{max}^{95\%aq.EtOH}$ 259 mμ (ε 12700); $\lambda_{max}^{0.1N\ HCl}$ 261 (12600); $\lambda_{max}^{H_2O}$ (pH 7)[13] 261 (12600); $\lambda_{max}^{0.1N\ NaOH}$ 258 (13300). *Anal.* Calcd. for $C_{19}H_{18}O_5N_5Cl$: C, 52.84; H, 4.20; N, 16.22. Found: C, 53.05; H, 4.24; N, 16.05.

Reaction of 1-Methoxy-9-methyladenine Hydriodide (Ia) with Pyridine——A strirred mixture of Ia[4,5] (12.28 g, 40 mmoles) and pyridine (100 ml) was heated at reflux for 30 min. Evaporation of the pyridine under vacuum left a solid. The residue was triturated with H_2O (30 ml), and insoluble crystals were filtered off, washed successively with H_2O (10 ml) and ethanol (30 ml), and dried over P_2O_5 at 110° and 2 mm Hg for 5.5 hr to afford a first crop (6.03 g) of 9-methyladenine 1-oxide (IIIf). The filtrate and washings were combined and evaporated *in vacuo*, and the residue was dissolved in H_2O. The aq. solution was passed through a column of Amberlite IR-120 (Na^+) and the column was eluted with H_2O. Evaporation of the eluate and drying the residue, after washed with a small amount of H_2O, gave a second crop (0.28 g: total yield, 6.31 g or 95%) of IIIf. Recrystallization of the crude IIIf from H_2O yielded colorless prisms, mp 292—294° (decomp.), identical with authentic IIIf[5] by comparison of the IR spectra.

Next the column was eluted with 0.1N HCl in order to remove Na^+. Further elution of the column with 1N HCl and evaporation of the eluate gave a crystalline residue, which was dissolved in ethanol (5 ml) and a hot solution of picric acid (10 g) in ethanol (60 ml) was added to produce yellow precipitates (7.28 g, 56%). Recrystallization from ethanol furnished 1-methylpyridinium picrate (IIf) as yellow plates, mp 116—117° (lit.[14] mp 114—115°), identified with an authentic specimen by mixed melting-point test and infrared IR spectrum.

Reaction of 1-Ethoxy-9-benzyladenine Hydriodide (Ic) with Pyridine——A mixture of Ic[5,6b] (2.30 g, 5.79 mmoles) and pyridine (50 ml) was stirred at 80—85° for 46 hr. The precipitates that resulted were collected by filtration, washed with pyridine (10 ml), then with a small amount of ethanol, and dried to give 9-benzyladenine 1-oxide (IIIh) as a colorless solid (1.15 g, 82%), which was identical (by paper chromatography and IR spectrum) with an authentic sample.[4,5] The filtrate and washings were combined and evaporated *in vacuo* to dryness, and the crystalline residue was dissolved in ethanol (10 ml). To the resulting ethanolic solution was added ether (15 ml) and the mixture was kept in a refrigerator for a day. The precipitates that formed were filtered off, washed with ether, and dried to give 1-ethylpyridinium iodide (IIg: X=I) as almost colorless scales (733 mg, 54%), mp 88—90° (lit.[15] mp 90.5°), undepressed upon mixture with an authentic sample. The IR spectra of both samples were also identical.

Reaction of 1-Benzyloxy-9-benzyladenine Hydrobromide (Id) with Pyridine——A mixture of the monohydrate[4,5] (2.00 g, 4.65 mmoles) of Id and pyridine (50 ml) was stirred at 80—85° for 1.5 hr. The precipitates that formed were filtered off, washed successively with ethanol and ether, and dried to give a crude sample (1.08 g, 96%) of IIIh, mp 264—268° (decomp.). Recrystallization of this sample from 30% aq. ethanol yielded colorless needles, mp 280—281° (decomp.), identical with authentic IIIh[4,5] by mixed melting-point test and comparison of the IR spectra. The filtrate of the reaction mixture and the washings of the crude IIIh were combined and evaporated *in vacuo* to leave a brown oil. The oil was dissolved in H_2O (10 ml), and a saturated solution (90 ml) of picric acid in H_2O was added. Yield of the resulting picrate, mp 106—116°, was 1.64 g (89%). When recrystallized from H_2O, the picrate gave yellow plates, mp 118—119° (lit.[16] mp 118°). *Anal.* Calcd. for $C_{18}H_{14}O_7N_4$: C, 54.27; H, 3.54; N, 14.07. Found: C, 54.02; H, 3.62; N, 14.16. This sample was identified with an authentic specimen of 1-benzylpyridinium picrate (IIh) by means of thin-layer chromatography (TLC), mixed melting-point test, and IR spectrum.

Reaction of 1-Benzyloxy-9-benzyladenine Perchlorate (Ie) with Pyridine——A mixture of Ie (2.00 g, 4.63 mmoles) and pyridine (50 ml) was stirred at 80—85° for 5 hr, and the reaction mixture was worked up in the same way as described for Id. The result is shown in Table I.

12) All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Paper chromatographies were developed as described previously.[5b] For gas liquid chromatography (GLC) a Shimadzu GC-3AH gas chromatograph, equipped with a 3 m×3 mm column containing 1.5% SE-30 (methyl silicone) on Chromosorb W, was used. Spectra reported herein were measured with a Hitachi EPS-2U UV spectrometer, a JASCO-DS-402G IR spectrometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard.

13) Determined in 0.005M phosphate buffer.

14) Beilstein's, "Handbuch der Organischen Chemie," 20, E II 131.

15) Beilstein's, "Handbuch der Organischen Chemie," 20, 214, E I 71.

16) Beilstein's, "Handbuch der Organischen Chemie," 20, E II 135.

Reaction of Hydrobromide Id with Aniline——A mixture of Id·H_2O[4,5] (3.00 g, 6.97 mmoles) and aniline (61.5 g) was stirred at 86—88° for 2.5 hr. To the resulting solution was added benzene until the precipitation of the hydrobromide of IIIh appeared to be complete. The precipitates were collected by filtration, washed with benzene, and dried to give crude IIIh·HBr (2.00 g). The salt was dissolved in H_2O (100 ml) by warming and the solution was brought to pH 9—10 by addition of 10% aq. NaOH solution. The precipitates that resulted were filtered off, washed with H_2O, and dried to afford grayish minute crystals (710 mg, 42%), mp 264—268° (decomp.), identical (by TLC and IR spectrum) with authentic IIIh.[4,5]

The benzene solution, which was obtained by removing the crude IIIh·HBr described above, was evaporated *in vacuo* to leave a brown oil. The oil was then distilled at 55—60° and 4—5 mm Hg in order to remove the unaltered aniline, and the dark brown residue (*ca.* 3 g) was obtained. The residue was chromatographed on a column packed with alumina (300 g). Elution with hexane yielded N-benzylaniline[17] as slightly yellowish crystals (932 mg, 73%). Identity was confirmed by TLC and IR spectrum.

When this benzylation was carried out at room temperature, completion of the reaction within 4 hr was evidenced by disappearance of Id on a TLC plate.

Reaction of Hydrobromide Id with Sodium Ethyl Mercaptide——A mixture of Id·H_2O[4,5] (4.00 g, 9.3 mmoles), sodium (708 mg, 0.031 g.-atom) which had been dissolved in ethanethiol (25 ml), and N,N-dimethylacetamide (DMAC) (50 ml) was stirred at 70—77° for 5 hr. The precipitates that formed were collected by filtration, washed with ether, then with H_2O, and dried to give a first crop (1.06 g) of IIIh. The filtrate and the ethereal washings were combined, and ether (120 ml) was added. Collection of the resulting precipitates by filtration yielded a second crop (755 mg), total yield 81%. The ethereal filtrate was evaporated *in vacuo* in a stream of nitrogen to remove the ether and most of the DMAC. The resulting dark brown residue (*ca.* 6 g) was chromatographed on silica gel (250 g). Elution with hexane yielded benzyl ethyl sulfide as a pale yellow oil (938 mg, 66%). This sample was identified with an authentic specimen[18] by means of TLC, GLC, nuclear magnetic resonance (NMR) spectrum, and IR and mass spectra. Identification was further established by converting the sample into benzyl ethyl sulfone, mp 82—85° (lit.[18] mp 84°), according to the reported procedure.[18]

Reaction of Hydrobromide Id with Sodium Acetate——A mixture of Id·H_2O[4,5] (4.00 g, 9.3 mmoles), anhyd. sodium acetate (1.15 g, 14 mmoles), and DMAC (40 ml) was stirred at 80—85° for 23 hr. The precipitates of IIIh that resulted were filtered off, washed with benzene, and dried, yield 2.12 g (95%). The filtrate and washings were combined, and benzene (100 ml) was added. The mixture was then filtered, and the filtrate was evaporated *in vacuo* to remove the benzene and most of the DMAC. The resulting residual oil (*ca.* 3 g) was chromatographed on silica gel (300 g). Elution with benzene gave benzyl acetate as a pale yellowish oil (746 mg, 53%). This sample was identified (by TLC, GLC, and IR spectrum) with an authentic sample.[19]

Reaction of 1-Methoxy-9-benzyladenine Hydriodide (Ib) with Benyl Alcohol——A mixture of Ib[5,6] (7.66 g, 20 mmoles) and benzyl alcohol (60 ml) was stirred at 80—82° for 50 hr. The reaction mixture was distilled under vacuum to give a fraction containing benzyl alcohol and benzyl methyl ether. The distillate was re-distilled under ordinary pressure, and a fore-run (5.2 g) boiling up to 195° was collected. The oil thus obtained was then chromatographed on silica gel (200 g). Elution with benzene–hexane (1:2, v/v) yielded a yellowish oil, which was distilled under ordinary pressure to give benzyl methyl ether as a colorless oil (160 mg, 7%). The IR and NMR spectra of this sample were virtually superimposable with those of an authentic specimen.[20]

Reaction of Hydrobromide Id with Ethanol——A suspension of Id·H_2O[4,5] (4.30 g, 10 mmoles) in abs. ethanol (100 ml) was heated at reflux with stirring for 7 hr. After cooling, the mixture was filtered to collect the coloress precipitates (3.11 g) that had resulted. The filtrate was evaporated under ordinary pressure, leaving a partially crystallized oil. The residue was triturated with ether (10 ml) and an insoluble solid (770 mg) was collected by filtration. The first and second crop of crystals (IIIh·HBr) were combined and dissolved in H_2O (60 ml) by heating. The resulting solution was made basic (pH 8) with conc. aq. NH_4OH and cooled, and the crystalline solid (2.06 g, 86%) was collected by filtration. This sample was identified with authentic IIIh[4,5] by means of TLC and IR spectrum.

The ethereal filtrate, derived from the removal of the second crop of IIIh·HBr, was washed with H_2O, dried over anhyd. $CaCl_2$, filtered and evaporated *in vacuo* to dryness to leave a yellowish oil (850 mg, 62%), bp 189° [lit.[21] bp 68—69° (13 mm Hg)], identical (by TLC, GLC, and IR and NMR spectra) with authentic benzyl ethyl ether.[21]

Reaction of Perchlorate Ie with Ethanol——A suspension of Ie (4.02 g, 9.3 mmoles) in a mixture of H_2O (168 mg, 9.3 mmoles) and abs. ethanol (100 ml) was heated at reflux with stirring for 7 hr. Filtration of

17) Beilstein's, "Handbuch der Organischen Chemie," 12, 1023, E I 449, E II 548.
18) J. Büchi, M. Prost, H. Eichenberger, and R. Lieberherr, *Helv. Chim. Acta*, **35**, 1527 (1952).
19) R.L. Merker and M.J. Scott, *J. Org. Chem.*, **26**, 5180 (1961).
20) Beilstein's, "Handbuch der Organischen Chemie," 6, E III 1453.
21) R.L. Letsinger and D.F. Pollart, *J. Am. Chem. Soc.*, **78**, 6079 (1956).

the colorless precipitates that resulted gave the unchanged perchlorate (Ie: 3.59 g, 89%), mp 190—193° (decomp.). The filtrate was evaporated under ordinary pressure to remove most of the ethanol. The residue was triturated with ether (18 ml), and the mixture was filtered. The ethereal filtrate was washed with H_2O, dried, and concentrated. The residual oil was then chromatographed on silica gel. Elution with ether yielded a small amount (42 mg, 3%) of a slightly brownish oil, which was identified with authentic benzyl ethyl ether[21] by means of TLC, GLC, and IR spectrum.

Comparison of the Reactivities of Hydrobromide Id and Perchlorate Ie toward Pyridine and Ethanol——The salts, Id·H_2O[4,5] and Ie, were separately dissolved in pyridine or in abs. ethanol at 1.66×10^{-3}M concentration. Each of the solutions was allowed to react under the conditions as specified in Table II. After cooling, 0.5 ml of the reaction mixture was applied along a 10 cm line on Toyo Roshi No. 51 filter paper. The chromatogram was developed by the ascending method in a solvent system of 1-butanol: conc. aq. NH_4OH: H_2O (4:1:1, v/v). A zone whose *Rf* value was corresponding to that of authentic 9-benzyladenine 1-oxide (IIIh) was located under UV rays and was excised and extracted with 0.1N HCl (10 ml). The optical density of the resulting solution at 260 mμ was then determined, and concentration of the 1-oxide (IIIh) was estimated from a calibration curve which had been constructed on an analytical sample of IIIh. The results are summarized in Table II.

Reaction of Hydrobromide Id with H_2O——A stirred mixture of Id·H_2O[4,5] (4.00 g, 9.3 mmoles) and H_2O (100 ml) was heated at reflux for 8 hr. After cooling, the mixture was filtered to collect the precipitates (1.65 g) of IIIh·HBr. The filtrate was extracted with seven successive 40 ml portions of benzene. The combined benzene extracts were dried over anhyd. Na_2SO_4, filtered and evaporated to leave an oily residue. The oil was then allowed to react with phenyl isocyanate (960 mg, 8.07 mmoles) in the usual manner, giving benzyl N-phenylcarbamate as colorless needles (1.05 g, 50%), mp 76—77° (lit.[22] mp 78°), identical (by TLC, mixed melting-point test, and IR spectrum) with an authentic specimen.[22]

The crude IIIh·HBr described above was dissolved in H_2O (100 ml) by warming. The resulting solution was rendered basic (pH 8) with conc. aq. NH_4OH, and the precipitates that formed were collected by filtration. The solid was recrystallized from 30% aq. ethanol to yield colorless needles (1.12 g, 50%), mp 274—275° (decomp.), identical (by TLC and IR spectrum) with authentic IIIh.[4,5]

Reaction of Hydrobromide Id with Acetic Acid——A mixture of Id·H_2O[4,5] (4.00 g, 9.3 mmoles) and glacial acetic acid (50 ml) was stirred at 80—85° for 9 hr. Evaporation of the acetic acid at 35 mm Hg left a yellowish oil, which was then triturated with benzene. The resulting mixture was filtered in order to remove insoluble solid, and the filtrate was washed successively with H_2O, a saturated solution of $NaHCO_3$ in H_2O, and H_2O, and dried (fraction A). On the other hand, the distillate from the reaction mixture was diluted with H_2O (600 ml), and the resulting solution was extracted with three successive 100 ml poritons of benzene. The combined benzene extracts were washed and dried (fraction B) in the same way as described above for fraction A. Both fractions A and B were combined and evaporated *in vacuo* to leave a dark red oil (546 mg). GLC and TLC analyses suggested that the oil consisted of two components, benzyl bromide (major product) and benzyl acetate (minor product).

Reaction of Hydrobromide Id with Adenine——A mixture of adenine (680 mg, 5 mmoles), Id·H_2O[4,5] (3.44 g, 8 mmoles), and DMAC (20 ml) was stirred at 35° for 100 hr. The precipitates that resulted were filtered off, washed successively with ethanol and ether to give a first crop (1.11 g) of IIIh. The combined filtrate and washings were evaporated *in vacuo* to leave an oil, which was then washed with ether. The residue was dissolved in ethanol (10 ml), and the mixture was kept at room temperature. Filtration of the resulting mixture gave colorless precipitates (1.22 g) and filtrate (fraction A). Two recrystallizations of the solid from H_2O yielded a second crop (100 mg) of IIIh. The mother liquors of the recrystallizations were evaporated *in vacuo* to dryness, and the residue was recrystallized from 90% aq. ethanol to produce colorless pillars (670 mg), mp 246—248°, identical (by TLC and IR spectrum) with authentic 3-benzyladenine hydrobromide prepared according to the reported method.[10]

Next fraction A was evaporated *in vacuo*, and the residue was chromatographed on a column packed with silica gel (205 g). Elution with chloroform–ethanol (8:1, v/v) produced 9-benzyladenine as colorless needles (20 mg, 2%), mp 233—236°, identical (by mixed melting-point test and IR spectrum) with an authentic sample.[10a] Further elution of the column with the same solvent system gave a second crop of 3-benzyladenine, which was converted into the corresponding hydrochloride[23] (110 mg), mp 270—272° (decomp.). Total yield of the two salts of 3-benzyladenine was 55%.

Continuation of elution of the column as described above yielded a third crop (110 mg) of IIIh. Next the column was eluted with ethanol (*ca.* 900 ml), and the eluate was evaporated *in vacuo*. The residue was triturated with dilute aq. NH_4OH (*ca.* 10 ml). Filtration of the insoluble solid followed by washing with H_2O gave a colorless solid (5 mg), mp 226—228° (decomp.). The IR spectrum of this sample was virtually superimposable with that of authentic 1-benzyladenine.[24] Further elution of the column with ethanol

22) Beilstein's, "Handbuch der Organischen Chemie," 12, 328.
23) J.A. Montgomery and H.J. Thomas, *J. Heterocyclic Chem.*, **1**, 115 (1964).
24) N.J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.*, **51**, 73 (1964).

(*ca.* 1 liter) and evaporation of the eluate *in vacuo* gave a crystalline solid (*ca.* 30 mg). The solid was dissolved in ethanol (5 ml), and a saturated solution (0.5 ml) of picric acid in ethanol was added. The yellow precipitates (20 mg, 1%) that formed were filtered off and recrystallized from 50% aq. ethanol to give 1-benzyladenine picrate as yellow needles, mp 238—241° (decomp.). *Anal.* Calcd. for $C_{18}H_{14}O_7N_8$: C, 47.58; H, 3.10; N, 24.66. Found: C, 47.54; H, 3.20; N, 24.70. The IR spectrum of this sample was virtually identical with that of the picrate prepared from authentic 1-benzyladenine.[24]

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