Experimental

Apparatus——Absorbance at various wavelengths was recorded with a Hitachi 323 recording spectrophotometer. Absorbance measurements at fixed wavelengths were made with a Shimadzu 150 double beam spectrophotometer. Matched glass cells of 10 mm path length were used. A Toa HM-5A pH meter with a saturated calomel-glass electrode system was used for all pH measurements. An Iwaki KM shaker was used to shake the separatory funnels.

Reagents——DABTB: The reagent was prepared by the condensation of 2-thiobarbituric acid with *p*-dimethylaminobenzaldehyde in EtOH, and the crude product thus obtained was recrystallized from MeOH.[4] DABTB was dissolved in DMSO to give a 1.5×10^{-3} M solution for method A. The solution should be used within 3 days. DABTB-DMSO solution (10 ml) was diluted with benzene to 1 l and used as the reagent for method B.

Standard Silver(I) Solution: Standard silver solution (1 mg/ml, $f=1.00$, Wako) was diluted when necessary.

Buffer Solution: McIlvaine buffer was used.[15]

pH 6: 73.7 ml of 0.1 M citric acid solution and 126.3 ml of sodium phosphate solution were mixed and checked with the pH meter.

pH 5: 97.0 ml of 0.1 M citric acid solution and 103 ml of 0.1 M sodium phosphate solution were mixed and checked with the pH meter.

All the other reagents used were of reagent grade.

Recommended Procedures——Method A: The solution containing 1—50 μg of silver(I) is pipetted into a 25 ml volumetric flask, 5 ml of buffer (pH 6) and 5 ml of EtOH are added, and the whole is diluted to about 24 ml with water. After adding 0.5 ml of DABTB–DMSO solution (1.5×10^{-3} M) to this, it is diluted to 25 ml with water and mixed. Absorbance measurements are made at 400 nm with matched 10 mm glass cells against the reagent blank similarly prepared but free from silver(I).

Method B: The solution containing 1—35 μg of silver(I) and 5 ml of buffer (pH 5) are pipetted into a 100 ml separatory funnel and diluted to about 50 ml with water. After adding 25 ml of DABTB–benzene solution, the mixture is shaken for 2 minutes using a shaker. The separated organic phase is filtered and the absorbance is measured with matched 10 mm glass cells against benzene.

Analyses of Commercial Preparations——Sample Solution: Silver nitrate eye lotion; One-half ml of silver nitrate eye lotion in an ampoule (1 w/v%) was diluted to 250 ml with water. Silver protein;[16] Three hundredth grams of silver protein powder (7.5—8.5 w/w%) was dissolved in 1 ml of conc.HNO_3 and it was heated until the solution became clear in the presence of 0.6 ml of conc.H_2SO_4. The mixture was allowed to cool to room temperature and was then diluted to 250 ml with water.

The absorbances of all sample solutions were measured by the recommended procedures and the contents of silver were estimated from the calibration curves obtained with standard silver solutions.

15) Editorial committee of tables of chemical constants (ed.), "Tables of Chemical Constants for Laboratory Use," 6th ed., Hirokawa, Tokyo, 1971, p. 403.
16) E. Saitō, *Eisei Shikensho Hokoku*, **81**, 44 (1963).

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Synthesis of N,N,3,9-Tetraalkyladeninium Halides by Alkylations of N,N,3- and N,N,9-Trialkyladenines[1]

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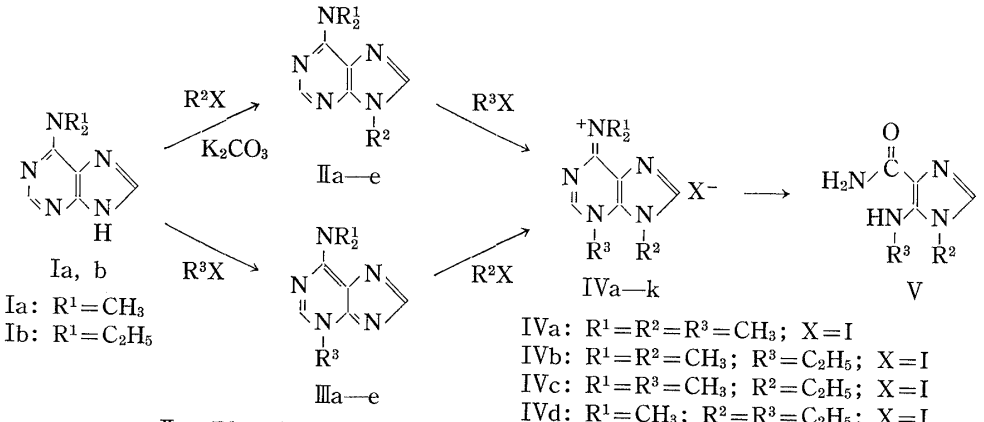
The reactions of N,N,9-trialkyladenines (II) with alkyl halides in N,N-dimethylacetamide gave N,N,3,9-tetraalkyladeninium halides (IV) in good yields. N,N,3-Trialkyl-

1) A part of this work was reported in preliminary form.[3a]
2) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*

adenines (III) underwent the alkylation more smoothly to provide an alternative synthesis of IV.

Keywords——N,N,3,9-tetraalkyladeninium salts; regiospecific N-alkylation; N,N,3-trialkyladenines; N,N,9-trialkyladenines; UV; NMR

N,N,3,9-Tetraalkyladeninium salts (IV) have been shown to be good synthetic intermediates for various 3,9-dialkylpurine derivatives.[3] Marsico and Goldman first synthesized N,N-diethyl-3,9-dimethyladeninium iodide (IVg) in 41% yield by the reaction of N,N-diethyl-9-methyladenine (IIc) with methyl iodide in boiling ethanol for 24 hr.[4] Montgomery *et al.* obtained 3,9-dibenzyl-N,N-dimethyladeninium bromide (IVf) in 51% yield by treating 9-benzyl-N,N-dimethyladenine (type II) with benzyl bromide in boiling acetonitrile for 3 days.[5] An alternative route was recorded for the synthesis of N,N,3,9-tetramethyladeninium iodide (IVa); the 9-methyl group was introduced into N,N,3-trimethyladenine (IIIa).[6] We describe here a general synthesis of IV by the alkylation of N,N,9- (II) or N,N,3-trialkyladenines (III).



Ia: $R^1=CH_3$
Ib: $R^1=C_2H_5$

IIa: $R^1=R^2=CH_3$
IIb: $R^1=CH_3$; $R^2=C_2H_5$
IIc: $R^1=C_2H_5$; $R^2=CH_3$
IId: $R^1=R^2=C_2H_5$
IIe: $R^1=C_2H_5$; $R^2=C_6H_5CH_2$

IIIa: $R^1=R^3=CH_3$
IIIb: $R^1=CH_3$; $R^3=C_2H_5$
IIIc: $R^1=CH_3$; $R^3=C_6H_5CH_2$
IIId: $R^1=C_2H_5$; $R^3=CH_3$
IIIe: $R^1=R^3=C_2H_5$

IVa: $R^1=R^2=R^3=CH_3$; X=I
IVb: $R^1=R^2=CH_3$; $R^3=C_2H_5$; X=I
IVc: $R^1=R^3=CH_3$; $R^2=C_2H_5$; X=I
IVd: $R^1=CH_3$; $R^2=R^3=C_2H_5$; X=I
IVe: $R^1=R^3=CH_3$; $R^2=C_6H_5CH_2$; X=Br
IVf: $R^1=CH_3$; $R^2=R^3=C_6H_5CH_2$; X=Br
IVg: $R^1=C_2H_5$; $R^2=R^3=CH_3$; X=I
IVh: $R^1=R^3=C_2H_5$; $R^2=CH_3$; X=I
IVi: $R^1=C_2H_5$; $R^2=CH_3$; $R^3=C_6H_5CH_2$; X=Br
IVj: $R^1=R^2=C_2H_5$; $R^3=CH_3$; X=I
IVk: $R^1=C_2H_5$; $R^2=R^3=C_6H_5CH_2$; X=Br

Chart 1

Treatment of IIc with methyl iodide in N,N-dimethylacetamide (DMAc) at 40° for 87 hr resulted in a remarkable improvement in the yield of IVg (see Table I). Similarly, 9-ethyl-N,N-dimethyladenine (IIb) and N,N,9-triethyladenine (IId) gave 9-ethyl-N,N,3-trimethyl- (IVc) and N,N,9-triethyl-3-methyladenium iodide (IVj), respectively, in satisfactory yields. On treatment with ethyl iodide at 100°, IIc gave N,N,3-triethyl-9-methyladeninium iodide (IVh) in good yield. The reaction of IIc with benzyl bromide at 40° took place smoothly and 3-benzyl-N,N-diethyl-9-methyladeninium bromide (IVi) was obtained. However, the reaction of 9-benzyl-N,N-diethyladenine (IIe) with benzyl bromide proceeded sluggishly even at 80° probably owing to steric hindrance caused by the 9-benzyl group and 1-benzyl-5-

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TABLE I. Alkylations of N,N,9- (II) and N,N,3-Trialkyladenines (III)

Product	Starting material	Reagent[a]	Volume of DMAc[b]	Reaction temp. (°C)	Reaction time (hr)	Yield (%)	Appearance[c]	mp (°C) (dec.)	Formula	Analysis (%) Calcd (Found) C	H	N
IVa	IIa[d]	CH_3I (3.0)	1.2	40	50	95[e]	Colorless needles (M)	>300	$C_9H_{14}IN_5$	33.87 (33.88	4.42 4.48	21.95 21.92)
IVb	IIIb	CH_3I (3.0)	2.7	40	72	78	Colorless plates (E)	260	$C_{10}H_{16}IN_5$	36.05 (36.02	4.84 4.88	21.02 20.73)
IVc	IIb	CH_3I (3.1)	1.1	40	210	82	Colorless plates (E)	261	$C_{10}H_{16}IN_5$	36.05 (36.20	4.84 4.89	21.02 21.31)
IVd	IIIb	C_2H_5I (3.0)	2.6	40	168	58	Colorless needles (E)	202—204	$C_{11}H_{18}IN_5$	38.05 (38.11	5.23 5.34	20.17 20.17)
IVe	IIIa	$C_6H_5CH_2Br$ (2.0)	2.0	40	48	93	Colorless plates (P)	213—214	$C_{15}H_{18}BrN_5$	51.73 (51.73	5.21 5.32	20.11 20.20)
IVf[f]	IIIc	$C_6H_5CH_2Br$ (3.0)	1.0	40	72	35[g]	—	—	—	—	—	—
IVg	IIc	CH_3I (*ca.* 4)	*ca.* 2	40	87	71[e]	Colorless pillars (E)	231—232	$C_{11}H_{18}IN_5$	38.05 (38.20	5.23 5.28	20.17 20.16)
IVg	IIc[h]	CH_3I (3.1)	1.4	40	50	79[e]						
IVg	IIId	CH_3I (2.0)	1.4	40	24	90						
IVh	IIc	C_2H_5I (*ca.* 3.5)	*ca.* 1.5	100	48	57[e]	Colorless prisms (E)	228—230	$C_{12}H_{20}IN_5$	39.90 (39.82	5.58 5.82	19.39 19.32)
IVh	IIIe	CH_3I (1.9)	1.1	40	37	80						
IVi	IIc	$C_6H_5CH_2Br$ (*ca.* 2.5)	*ca.* 2	40	168	59[e]	Colorless prisms (P)	207—208	$C_{17}H_{22}BrN_5$	54.26 (54.24	5.89 5.96	18.61 18.51)
IVj	IId	CH_3I (*ca.* 4)	*ca.* 2	40	192	75[e]	Colorless prisms (E)	213—214	$C_{12}H_{20}IN_5$	39.90 (39.84	5.58 5.52	19.39 19.28)
IVj	IIId	C_2H_5I (3.0)	1.4	50	168	62						
IVk[f]	IIe	$C_6H_5CH_2Br$ (2.0)	1.3	80	48	28[g]	—	—	—	—	—	—

a) The figures in parentheses denote the molar equivalents.
b) Milliliters per millimole of II or III.
c) The letters in parentheses refer to the recrystallization solvents: E, ethanol; M, methanol; P, isopropanol.
d) A mixture with IIIa.
e) Overall yield based on I.
f) Not isolated.
g) Yield of 1-benzyl-5-(benzylamino)imidazole-4-carboxamide.[7]
h) A mixture with IIId.

(benzylamino)imidazole-4-carboxamide (type V) was isolated in only 28% overall yield after alkaline hydrolysis[7] of the resulting 3,9-dibenzyl-N,N-diethyladeninium bromide (IVk).

N,N-Diethyl-3-methyladenine (IIId) underwent the methylation more rapidly than the corresponding 9-methyl isomer (IIc) to provide IVg in 90% yield. The identity of this product with that derived from IIc established the location of the second methyl group. Although IVh could be obtained by the ethylation of IIc at 100°, the same compound was prepared more conveniently by the reaction of N,N,3-triethyladenine (IIIe) with methyl iodide at 40°. In a similar manner, 3-ethyl-N,N,9-trimethyladeninium iodide (IVb) was synthesized from 3-ethyl-N,N-dimethyladenine (IIIb). Synthesis of 3,9-diethyl-N,N-dimethyladeninium iodide (IVd) was achieved in 58% yield by the reaction of IIIb with ethyl iodide at 40°, whereas treatment of IIb under the same reaction conditions resulted in recovery of IIb in 76% yield. The reaction of IIIa with benzyl bromide took place smoothyl at 40° to give 9-benzyl-N,N,3-trimethyladeninium bromide (IVe) in excellent yield. 1-Benzyl-5-(benzylamino)imidazole-4-carboxamide (type V) was obtained in 35% yield by a similar benzylation of 3-benzyl-N,N-dimethyladenine (IIIc) followed by alkaline hydrolysis.[7]

Since the alkylation of N,N-dialkyladenines (I) gives a mixture of the 3- and 9-alkylated isomers,[8] the reciprocal orientation in alkylation of the 3- and 9-substituents on I is particularly advantageous for the synthesis of IV with the same substituents at the 3- and 9-positions. Thus, IVa was prepared in 95% overall yield by treating N,N-dimethyladenine (Ia) with methyl iodide in the presence of potassium carbonate,[8] followed by a second methylation of the resulting mixture of IIa and IIIa. Similar treatment of N,N-diethyladenine (Ib) also gave IVg in 79% yield.

The N,N,3,9-tetraalkyaldeninium structures were assigned to IVb—e, h—j on the basis of ultraviolet (UV) spectral similarity to IVa and IVg and comparison of the proton magnetic resonance (PMR) spectra (Tables II and III). The structures were further confirmed by

Table II. Ultraviolet Spectra of N,N,3,9-Tetraalkyladeninium Halides (IV)

Compound	UV spectra[a]					
	95% aqueous ethanol		H_2O (pH 1)[b]		H_2O (pH 7)[c]	
	λ_{max} (nm)	$\varepsilon \times 10^{-4}$	λ_{max} (nm)	$\varepsilon \times 10^{-4}$	λ_{max} (nm)	$\varepsilon \times 10^{-4}$
IVa	290	1.81	223	2.40	223	2.42
			288	1.81	288	1.82
IVb	290	1.73	223	2.30	223	2.28
			288	1.71	288	1.71
IVc	290	1.79	224	2.28	224	2.28
			288	1.77	288	1.78
IVd	291	1.79	223	2.47	223	2.46
			289	1.78	289	1.78
IVe	289	2.08	288	1.86	288	1.86
IVg	292	1.92	223	2.43	223	2.33
			290	1.90	291	1.90
IVh	293	1.89	223	2.38	223	2.38
			292	1.87	292	1.87
IVi	294	2.07	292	1.98	292	1.98
IVj	291	1.92	223	2.30	223	2.28
			290	1.89	290	1.88

a) The spectra in 0.1 N aqueous sodium hydroxide (pH 13) changed rapidly.
b) 0.1 N hydrochloric acid.
c) 0.005 M phosphate buffer.

7) T. Itaya, K. Ogawa, H. Matsumoto, and T. Watanabe, *Chem. Pharm. Bull.*, in press.
8) T. Itaya, H. Matsumoto, and K. Ogawa, *Chem. Pharm. Bull.*, **28**, 1920 (1980).

Table III. PMR Spectra of N,N,3,9-Tetraalkyladeninium Halides (IV) in Deuterated Dimethyl Sulfoxide

Compound	Chemical shift (δ)[a]									
	Methyl protons						Methylene protons		Phenyl protons	Purinyl protons
	N–Me	N–Et	3-Me	3-Et	9-Me	9-Et	N–Et	3- or 9-Et	$C_6H_5CH_2$	
IVa[b]	3.39(s) 3.86(s)		4.14(s) or 4.22(s)		4.22(s) or 4.14(s)					8.32(s) 8.60(s)
IVb	3.41(s) 3.87(s)			1.51(t)	4.15(s)			4.64(q)		8.42(s) 8.79(s)
IVc	3.42(s) 3.88(s)		4.24(s)			1.52(t)		4.58(q)		8.49(s) 8.68(s)
IVd[c]	3.41(s) 3.88(s)			1.49(t) or 1.50(t)		1.50(t) or 1.49(t)		4.48(q) 4.55(q)		8.49(s) 8.75(s)
IVe	3.41(s) 3.90(s)		4.02(s)						5.95(s)	7.37(m) 8.63(s) 8.70(s)
IVg		1.26(t) 1.31(t)	4.20(s) or 4.29(s)		4.29(s) or 4.20(s)		3.88(q) 4.34(q)			8.44(s) 8.71(s)
IVh		1.28(t) 1.32(t)		1.54(t)	4.18(s)		3.90(q) 4.35(q)	4.67(q)		8.50(s) 8.84(s)
IVi		1.29(t) 1.33(t)			3.83(s)		3.91(q) 4.34(q)		5.98(s)	7.38(m) 8.37(s) 8.92(s)
IVj		1.25(t) 1.31(t)	4.24(s)			1.52(t)	3.88(q) 4.33(q)	4.60(q)		8.52(s) 8.70(s)

a) At a concentration of 0.25 M unless otherwise stated. The letters in parentheses designate the multiplicity of the signal: m=multiplet, q=quartet with J=7 Hz, s=singlet, t=triplet with J=7 Hz.
b) Measured with a saturated solution.
c) Measured with a 0.13 M solution.

transformation of IV into 1-alkyl-5-(alkylamino)imidazole-4-carboxamides (V).[7]

We reported previously that the regioselectivity of alkylation in the synthesis of III from I is higher than that in the synthesis of II from I.[8] It is now clear that III undergoes alkylation faster than II does. Accordingly, we conclude that the route (I→III→IV) is superior to the alternative one (I→II→IV) especially when the reaction is carried out with a relatively inactive reagent and/or is subject to steric hindrance.

Experimental[9]

The procedures for the syntheses of IVa, IVe, and IVg will be described in detail as typical examples. The other compounds were synthesized similarly, except IVd (see below). For the reaction conditions and the physical properties of IV, see Tables I, II, and III.

N,N,3,9-Tetramethyladeninium Iodide (IVa)——A mixture of IIa and IIIa, which had been obtained from Ia (20.0 g, 0.123 mol) by methylation in the presence of K_2CO_3,[8] was dissolved in DMAc (150 ml). Methyl iodide (23 ml, 0.37 mol) was added to the solution and the mixture was kept at 40° for 50 hr. The resulting precipitate was filtered off, washed with ethanol (2×10 ml), then dried to give colorless needles (36.25 g, 93%). The filtrate and the washings were combined and evaporated to dryness *in vacuo*. The residue was then washed with a little ethanol to afford an additional crop (0.82 g, 2%). Recrystallization from methanol gave an analytically pure sample, mp>300° (lit.[6] mp 335—345°).

3,9-Diethyl-N,N-dimethyladeninium Iodide (IVd)——A solution of IIIb (800 mg, 4.18 mmol) and ethyl iodide (1.0 ml, 12.5 mmol) in DMAc (11 ml) was kept at 40° for 168 hr. The mixture was evaporated to dryness *in vacuo* and the solid residue was dissolved in chloroform–ethanol (10: 1, v/v). After adding Merck silica gel 60 (5 g), the mixture was evaporated to dryness and then the solid was placed on top of a 20-g silica gel column. The column was eluted with chloroform–ethanol (10: 1, v/v; *ca.* 160 ml) then with ethanol. The ethanolic eluate was evaporated to dryness to give a solid (840 mg, 58%). Recrystallization from ethanol gave colorless needles, mp 202—204° (dec.).

9) Melting points are corrected. UV spectra were measured on a Hitachi 323 spectrometer. PMR spectra were measured on a JEOL JNM-PS-100 or a JEOL JNM-FX 100 spectrometer at 23—25° using tetramethylsilane as an internal standard.

9-Benzyl-N,N,3-trimethyladeninium Bromide (IVe)——A solution of IIIa (3.544 g, 20 mmol) and benzyl bromide (6.8 g, 40 mmol) in DMAc (40 ml) was kept at 40° for 48 hr. The resulting precipitate was filtered off, washed with ethanol (20 ml), and dried to give 5.91 g (85%) of a colorless solid. The combined filtrate and washing were evaporated to dryness *in vacuo* and the residue was dissolved in a little ethanol. An additional crop (0.57 g, 8%) was obtained by adding ether (100 ml) to this solution. Recrystallization from isopropanol gave colorless plates, mp 213—214° (dec.).

N,N-Diethyl-3,9-dimethyladeninium Iodide (IVg)——A mixture of IIId (1.44 g, 7.02 mmol), methyl iodide (0.87 ml, 14 mmol), and DMAc (10 ml) was kept at 40° for 24 hr. The resulting mixture was treated in a manner similar to that described for IVa, giving 2.19 g (90%) of IVg. Recrystallization from ethanol gave colorless pillars, mp 231—232° (dec.) [lit.[4] 231.5—232.5° (dec.)].

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A Convenient Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo-[2,3-*a*]quinolizine

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A convenient synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1**) is described. The condensation of tryptamine (**2**) with diethyl (2-formylethyl)malonate (**3a**), followed by treatment with alkali, gave the lactam ester (**5a**). Decarbethoxylation of **5a** with LiCl–H_2O–Me_2SO afforded the lactam (**8a**), which was reduced with $LiAlH_4$ to give the indoloquinolizine (**1**). The lactam (**8b**) which has an ethyl group at C_3 was prepared from tryptamine (**2**) and diethyl ethyl(2-formylethyl)malonate (**3b**) instead of **3a**.

Keywords——indole alkaloid; synthesis; octahydroindolo[2,3-*a*]quinolizine; Pictet-Spengler reaction; lactamization

Several syntheses of the indoloquinolizine (**1**), even before its isolation[2] from natural source, have been reported.[3] In the present paper, a convenient synthesis of **1** is described. This forms a part of our work on the synthesis of *Corynanthé* type alkaloids.

The indoloquinolizine (**1**) is considered to be composed of a tryptamine moiety and the residual C-5 unit. In our synthetic plan, the aldehyde (**3a**),[4] prepared from acrolein and diethyl malonate, was chosen as the C-5 unit equivalent, since an ester group can easily be removed in a later step.

The Pictet–Spengler reaction of tryptamine (**2**) with the aldehyde (**3a**) was carried out in 80% acetic acid (AcOH) at room temperature to afford in quantitative yield of a mixture

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