Method B——To a chilled solution of *o*-aminophenyl 1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside[9] (0.01 mole) in pyridine (30 ml) was added dropwise mesyl chloride (0.02 mole), and the mixture, protected from moisture, was stirred for 1 hr, and kept overnight at room temperature, then poured into ice-water (300 ml). The product was extracted with $CHCl_3$ (50 ml × 3), and the $CHCl_3$ layer was washed with diluted H_2SO_3, aq. $NaHCO_3$, and water, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to give a slight yellow sirup which crystallized from a small amount of EtOH. Recrystallization from EtOH gave pure material.

Method C——To a solution of cinnamyl 1-thio-2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (0.01 mole) in THF (50 ml) was added 10% Pd/C (500 mg). The mixture was agitated for 5 hr at 20° under hydrogen at a pressure of 30—35 atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to give a sirup which crystallized. Recrystallization from EtOH gave a pure material.

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9) G. Wagner and C. Lenk, *Arch. Pharmaz.*, **295**, 415 (1962).

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Purines. VIII.[1] An Improved Procedure for the Synthesis of 9-Alkyladenines

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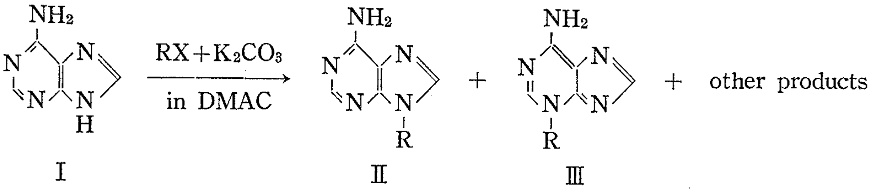
During the course of an investigation of the synthesis of 1-alkoxy-9-alkyladenine salts,[3,4] the need for a convenient method of preparing 9-alkyladenines (type II) became evident in our laboratory. Among the several methods reported for the alkylation of adenine (I) at the 9-position,[5–8] alkylation of the sodium salt of I in N,N-dimethylformamide[7] or that



a: $R=CH_3$ b: $R=C_2H_5$ c: $R=C_6H_5CH_2$
d: $R=C_6H_5CH_2CH_2$

Chart 1

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[1] Paper VII in this series, T. Fujii, T. Itaya, and S. Moro, *Chem. Pharm. Bull.* (Tokyo), **20**, 958 (1972).
[2] Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
[3] *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).
[4] *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).
[5] For reviews, see *a*) S. Yamada and T. Fujii, *Kagaku* (Kyoto), 21, 442 (1966); *b*) R.K. Robins, "Heterocyclic Compounds," Vol. 8, ed. by R.C. Elderfield, John Wiley & Sons, Inc., New York, 1967, pp. 372—379.
[6] *a*) T.C. Myers and L. Zeleznick, *J. Org. Chem.*, **28**, 2087 (1963), and references cited therein; *b*) E.P. Lira and C.W. Huffman, *ibid.*, **31**, 2188 (1966).
[7] K.L. Carraway, P.C. Huang, and T.G. Scott, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, ed. by W.W. Zorbach and R.S. Tipson, Interscience Publishers, Inc., New York, 1968, p. 3—5.
[8] K. Shimo, Japan. Patent 7102028 (1971) [*Chem. Abstr.*, **74**, 125733*a* (1971)].

of I in N,N-dimethylacetamide (DMAC) in the presence of potassium carbonate⁹⁾ seems most simple and advantageous. However, yields (18—40%) of 9-alkyladenines obtained by this method are usually not too encouraging. This paper describes a modification of the latter procedure⁹⁾ to give more satisfactory results.

Montgomery and Thomas have reported that the reaction of I with benzyl chloride in DMAC in the presence of potassium carbonate at 110° for 16 hr furnished 9-benzyladenine (IIc) in 27% yield. We followed the progress of this benzylation by means of thin-layer chromatography (TLC) and column chromatography. It may be seen from Table I that prolonged heating probably causes both IIc, a major primary product, and 3-benzyladenine (IIIc), a minor primary product, to react further with benzyl chloride, giving dibenzyladenines and other unidentified products. In a run in which heating was continued for 9 hr, it was possible to isolate 9,N-dibenzyladenine¹⁰⁾ in 15% yield. The formation of this product may be ascribed to the benzylation of IIc at the 1-position¹¹⁾ followed by the Dimroth rearrangement. Thus, it appears that an optimum reaction time is 1—2 hr.

TABLE I. Benzylation of Adenine (1 mmole) with Benzyl Chloride (2 mmoles) in DMAC (10 ml) in the Presence of Potassium Carbonate (1 mmole) at 110°

Run	Reaction time (hr)	Yield (%)		
		IIc	IIIc	Recovery of I
1	0.25	72	18	10
2	0.5	72	20	—
3	1	72	15	—
4	2	71	12	—
5	9	62	4	—
6[a]	16	50	4	—

[a] The reaction conditions were identical to those reported in the literature.⁹⁾

TABLE II. Influence of Volume of the Solvent DMAC on the Reaction of Adenine (1 mmole) with Benzyl Chloride (2 mmoles) in the Presence of Potassium Carbonate (1 mmole) at 110° for 1 hr

Run	DMAC Volume (ml)	Yield (%)		
		IIc	IIIc	Recovery of I
7	20	73	16	—
8[a]	10	72	15	—
9	5	72	15	—
10	1	67	11	—
11	0.5	62	12	26

[a] Except for the reaction time, the conditions were identical with those employed by Montgomery and Thomas.⁹⁾

Next the same benzylation was carried out for 1 hr in a variable amount of DMAC in order to investigate the effect of amount of the solvent on yield of IIc. The results shown in Table II reveal that the volume of DMAC can be reduced to 1/10 of that used in the original procedure⁹⁾ without causing appreciable decrease in the yield of IIc.

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9) J.A. Montgomery and H.J. Thomas, *J. Heterocyclic Chem.*, **1**, 115 (1964).

10) N.J. Leonard, K.L. Carraway, and J.P. Helgeson, *J. Heterocyclic Chem.*, **2**, 291 (1965).

11) *a*) J.W. Jones and R.K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); *b*) N.J. Leonard and T. Fujii, *Proc. Natl. Acad. Sci. U.S.*, **51**, 73 (1964).

On the basis of the findings described, a preparative run for IIc was accomplished, and purification of the desired product without recourse to column chromatography was effected by treating the crude product with a mixture of conc. hydrochloric acid and ethanol and recrystallizing the resulting hydrochloride from ethanol. The yield of IIc obtained in this way was 61%. The direct recrystallization of the crude free base from ethanol proved to be less efficient since it had to be repeated several times for removal of the 3-isomer (IIIc) contained in the mixture.

Similarly, the reactions of I with methyl iodide, ethyl iodide, and phenethyl bromide were separately examined, and 9-methyladenine (IIa), 9-ethyladenine (IIb), and 9-phenethyladenine (IId) were prepared in 38—55% yields. The present procedure increases yields of 9-alkyladenines (type II) as compared with earlier methods,[7,9] and may be useful for synthesizing II on a preparative scale.

Experimental[12]

Benzylation Study——A stirred mixture of I (135 mg, 1 mmole), anhyd. K_2CO_3 (138 mg, 1 mmole), benzyl chloride (253 mg, 2 mmoles), and an appropriate amount of N,N-dimethylacetamide (DMAC) was ketp at 110° for an adequate period of time. After cooling, the reaction mixture was filtered to remove an insoluble solid. The filtrate was evaporated *in vacuo* to dryness, and the residue was chromatographed on a column packed with silica gel (25 g). The column was eluted with benzene–ethanol (6:1, v/v), and fractions containing IIc, IIIc, and I were collected. The results are summarized in Table I and Table II.

In Run 5 of Table I, the chromatographic separation as described gave a fraction which was eluted faster than IIc. Re-chromatography [silica gel, benzene–ethanol (9:1, v/v)] of this component yielded 9,N-dibenzyladenine (48 mg, 15%) as a colorless solid, mp 169—171°. Recrystallization from benzene produced colorless needles, mp 172—173° (lit.[10] mp 174.5—175.5°), undepressed on admixture with an authentic sample.[10] The infrared (IR) spectra of both samples were also identical.

9-Benzyladenine (IIc)——To a warm, stirred mixture of I (2.70 g, 20 mmoles), anhyd. K_2CO_3 (2.76 g, 20 mmoles), and DMAC (15 ml) was added dropwise a solution of benzyl chloride (5.06 g, 40 mmoles) in DMAC (5 ml). The resulting mixture was stirred at 110° for 1 hr. The precipitates that resulted were filtered off and washed with hot 99% aq. ethanol. The combined filtrate and washings were evaporated under diminished pressure. The residue was dissolved in 99% aq. ethanol (170 ml) by heating, and conc. hydrochloric acid (4 g) was added. The mixture was kept in a refrigerator overnight. The colorless needles that formed were collected by filtration and recrystallized from 90% aq. ethanol (75 ml) to give a pure sample of the hydrochloride of IIc. The total amount of the salt was dissolved in hot H_2O (80 ml). The solution was made basic with conc. aq. NH_4OH and cooled, and the precipitates were filtered off, washed with H_2O, and dried to give colorless prisms (2.74 g, 61%), mp 232—234°, shown to be homogeneous by a single spot on a TLC plate. Recrystallization from 99% aq. ethanol produced colorless prisms, mp 233—235° (lit.[3] mp 233—236°). The IR spectra of both the crude and purified samples were identical to that of authentic IIc.

9-Ethyladenine (IIb)——A mixture of I (1.35 g, 10 mmoles), anhyd. K_2CO_3 (1.38 g, 10 mmoles), and DMAC (40 ml) was stirred at 110° for 2 hr. The mixture was cooled to 65°, and a solution of ethyl iodide (1.6 ml. 20 mmoles) in DMAC (10 ml) was added. The resulting mixture was further stirred at 65° for 30 min. The excess of ethyl iodide and the DMAC were removed by vacuum distillation, and the residue was extracted with eight 50-ml portions of hot benzene. Evaporation of the solvent from the combined benzene extracts and recrystallization of the resulting residue from 99% aq. ethanol (6 ml) afforded IIb (897 mg, 55%) as colorless needles, mp 194—195° (lit.[3] mp 193—195°), identical (by mixed melting-point test and IR spectrum) with an authentic specimen.

9-Methyladenine (IIa)——A stirred mixture of I (1.35 g, 10 mmoles), anhyd. K_2CO_3 (1.38 g, 10 mmoles), and DMAC (40 ml) was kept at 110° for 2 hr. The mixture was cooled to 35°, and a solution of methyl iodide (1.25 ml, 20 mmoles) in DMAC (10 ml) was added. After having been stirred at 35° for 1.5 hr, the reaction mixture was evaporated *in vacuo* to leave a residue, which was washed with ether (50 ml) and dissolved in H_2O (170 ml). The aq. solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (48 ml), and the column was eluted with H_2O. The eluate was evaporated *in vacuo* to dryness, and the residue was washed with ether and recrystallized from boiling H_2O (20 ml) to give a first crop of IIa, mp 302—303°. Recrystallization of this sample from H_2O (10 ml) produced colorless prisms (477 mg), mp 303—304° (lit.[3b] mp 303—304°), identical with authentic IIa. Evaporation of the mother liquor of the first recrystallization and recrystallizations of the residue from H_2O gave a second crop (88 mg); total yield 565 mg (38%).

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[12] All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected.

In a run on 1/10 scale, IIa was isolated in 42% yield by means of column chromatography on alumina (60 g) [benzene–ethanol (20:1, v/v)].

9-Phenethyladenine (IId)——To a warm, stirred mixture of I (2.70 g, 20 mmoles), anhyd. K_2CO_3 (2.76 g, 20 mmoles), and DMAC (15 ml) was added dropwise a solution of phenethyl bromide (7.40 g, 40 mmoles) in DMAC (5 ml). The resulting mixture was stirred at 110° for 1 hr and was treated in the same way as described above for IIc. The crude IId thus obtained was dissolved in hot 99% aq. ethanol (60 ml), and conc. hydrochloric acid (4.5 g) and ether (100 ml) were successively added. The colorless needles that formed were filtered off and recrystallized from 99% aq. ethanol to give a pure sample of the hydrochloride of IId. The total amount of the purified salt was then dissolved in hot H_2O (20 ml), and the aq. solution was rendered alkaline with conc. aq. NH_4OH and cooled to produce colorless minute crystals (2.48 g, 52%), mp 178—179° (lit.[13] mp 179—180°), homogeneous by TLC on silica gel. This material was found to be identical to an authentic sample of IId.

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UDC 547.269.3.09 : 615.277.3.076.9

Antitumor Effects of Pentamethylene Bismethanethiosulfonate Hydrolysates and Difunctional Bunte Salt

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Hayashi, *et al.*[2,3] synthesized a series of polymethylene bisalkanethiosulfonate which is a isoster of Myleran (I) and showed that trimethylene bismethanethiosulfonate, tetramethylene bismethanethiosulfonate and pentamethylene bismethanethiosulfonate (II) had antitumor effect on the solid form, but not on the ascites form, of Ehrlich carcinoma. From the relationship between the antitumor effect and the toxicity of these compounds, II was found to be the most effective of the three.[3]

$$\underset{\text{I}}{CH_3SO_2O(CH_2)_4OSO_2CH_3} \qquad \underset{\text{II}}{CH_3SO_2S(CH_2)_5SSO_2CH_3} \qquad \underset{\text{III}}{NaO_3SS(CH_2)_nSSO_3Na}$$

Owing to the structural similarlity, difunctional polymethylene bisthiosulfate (Bunte salt) (III) may be expected to show chemical behaviors and antitumor effects analogous to that of II. Thus, III and the related compounds were prepared by heating the corresponding dihalide with sodium thiosulfate heptahydrate in 50% ethanol under reflux according to the following schema.

It is known that the nucleophilic attack of OH anion to thiosulfonate is achieved on the sulfenyl S atom but not on the sulfinyl S atom to give the corresponding sulfinic acid and

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[1] Location: *Oe-motomachi, Kumamoto.*

[2] S. Hayashi, H. Ueki, S. Harano, J. Komiya, S. Iyama, K. Harano, K. Miyata, K. Niigata and Y. Yonemura, *Chem. Pharm. Bull.* (Tokyo), **12**, 1271 (1964).

[3] S. Hayashi, H. Ueki and J. Komiya, *Gann*, **55**, 289 (1964).