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Synthesis and Bronchodilating Activity of 2,9-Disubstituted Adenine Derivatives: BB-1502 (9-Cyclohexyl-2-*n*-propoxy-9*H*-adenine) and Its Analogs

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A series of 2,9-disubstituted adenine derivatives was prepared and evaluated for bronchodilating activity. 9-(2-Cyclohexenyl), 9-tetrahydropyranyl and 9-benzyl derivatives of 2,6-dichloropurine were converted to the 2-chloroadenines. Subsequent nucleophilic substitution of the 2-chloro group with alkoxides, mercaptides and amines afforded the desired compounds. 9-Cyclohexyl derivatives were prepared by hydrogenation of the corresponding 9-cyclohexenyl compounds. Bronchodilating activities of the new adenine derivatives were evaluated in a number of biological systems. 9-(2-Cyclohexenyl)- and 9-cyclohexyladenines having an ethoxy, *n*-propoxy, *n*-butoxy or *n*-propylthio group at the 2-position showed potent bronchodilating activity. Reduced activity was observed with lower or higher alkoxy homologs and branched alkoxy congeners. 9-Cyclohexyl-2-*n*-propoxy-9*H*-adenine (designated as BB-1502) was selected for further studies in view of its high intrinsic activity and favorable pharmacological profile.

Keywords——synthesis; bronchodilating activity; 2,9-disubstituted adenines; 9-cyclohexyl-2-*n*-propoxy-9*H*-adenine; BB-1502; 2-alkoxyadenines; 9-cycloalkyladenines

In the course of our pharmacological screening program of natural products, a crude extract of marine sponge collected in the coastal waters of the Bahamas showed a significant hypotensive activity. The active principle of the extract was isolated in a crystalline form and its structure determined as 2-methoxyadenosine, a compound that had been discovered and designated as spongosine by Bergmann and Burke.[1] 2-Substituted adenosine derivatives including 2-alkoxyadenosines are known to have various pharmacological activities, such as coronary dilation, cardiac stimulation and systemic hypotension.[2–4] Subsequent studies in our laboratories to improve the pharmacological profile of 2-alkoxyadenosines resulted in the finding that replacement of the 9-ribofuranosyl group with a non-sugar moiety produced a unique bronchodilating activity. A series of 2,9-disubstituted adenine derivatives was, therefore, synthesized in a search for potent bronchodilators; among them, 9-cyclohexyl-2-*n*-propoxy-9*H*-adenine (BB-1502) appeared promising in view of its high intrinsic activity and minimal side effects.

The present paper describes the preparation and bronchodilating activity of a number of substituted purine and adenine derivatives. Their structure–activity relationships are also discussed.

Chemistry

2, 6-Dichloropurine (**1**), a key intermediate for the synthesis of various 2,9-disubstituted adenines, was prepared by chlorination of xanthine with pyrophosphoryl chloride.[5] A series of 2,9-disubstituted adenines was prepared from **1** as described below and shown in Chart 1: (A) substitution at the 9-position of **1** with 2-cyclohexenyl, tetrahydropyranyl or benzyl group, (B) formation of adenine derivatives by displacement of the 6-chlorine atom with ammonia and (C) nucleophilic substitution of the 2-chlorine atom with alkoxides, mercaptides or amines. The 9-cyclohexyl derivatives were prepared by reduction of cyclohexenyl deriva-

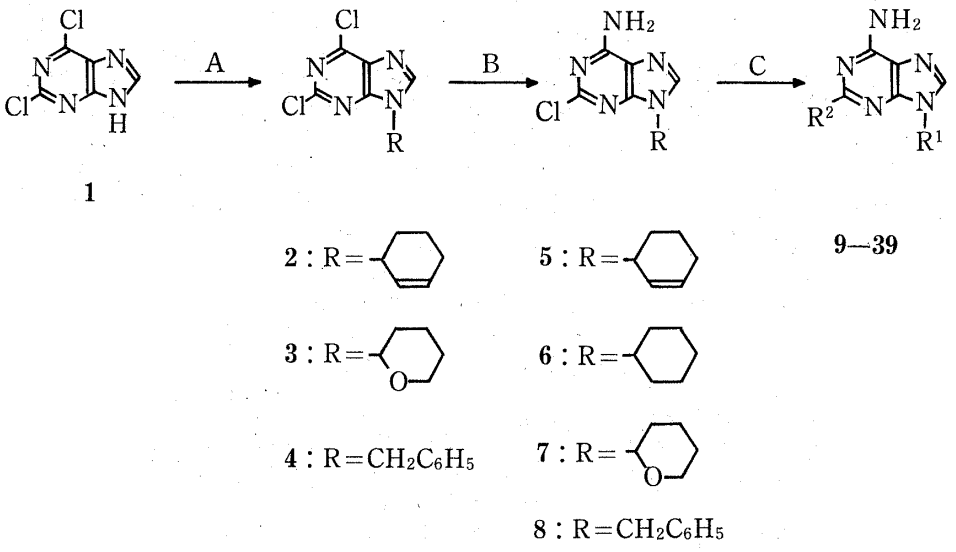
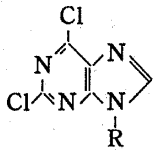


Chart 1. Preparation of 2,9-Disubstituted Adenines

TABLE I. 2,6-Dichloro-9-substituted Purines



Compd.	R	mp (°C)	UV: λ_{max}^{EtOH}nm (ε)	Formula	Analyses[a]
2		133—135	276(9500)[b]	$C_{11}H_{10}Cl_2N_4$	C, H, Cl, N
		119—121	273(9900)	$C_{10}H_{10}Cl_2N_4O$	[c]
4	$C_6H_5CH_2$	146—147	275(9400)	$C_{12}H_8Cl_2N_4$	C, H, Cl, N

a) Satisfactory analyses were obtained for the elements indicated.
b) Recorded in CH_3OH.
c) Known compound. See ref. 7.

tives obtained in step B or C. The derivatives prepared in the present study are listed in Tables I, II and III.

9-Substituted 2,6-Dichloropurines (2—4) (Table I)

9-(2-Cyclohexenyl)-2,6-dichloro-9*H*-purine (**2**) was prepared in 70% yield by conversion of **1** into its chloromercuri salt, followed by condensation with 3-bromocyclohexene under reaction conditions similar to those reported for the synthesis of the 6-monochloro analog of **2**.[6] Attempted direct introduction of a cyclohexyl group at the 9 position of **1** was unsuccessful.

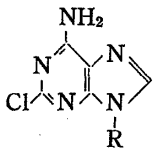
2,6-Dichloro-9-(2-tetrahydropyranyl)-9*H*-purine (**3**) was obtained in 90% yield from **1** and 3,4-dihydro-2*H*-pyran in ethyl acetate in the presence of *p*-toluenesulfonic acid according to a published method.[7]

Alkylation of **1** with benzyl bromide in the presence of sodium hydride in dimethyl formamide (DMF) afforded 9-benzyl-2,6-dichloro-9*H*-purine (**4**) in 21% yield along with 9-benzyl-6-benzyloxy-2-chloro-9*H*-purine (**40**) in 11% yield. It was supposed that the latter compound was obtained by displacement of the 6-chloro group with benzyl alcohol which might have been

formed by moisture contained in the reaction mixture.

The ultraviolet (UV) spectra of the alkylated products **2**, **3** and **4** were very similar to that of 2,6-dichloro-9-ribofuranosyl-9*H*-purine[8] (λ_{max} 275 nm, ε 9300), indicating that the alkylation had taken place at the 9 position of **1**.

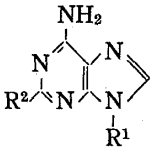
TABLE II. 9-Substituted 2-Chloroadenines

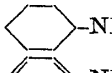
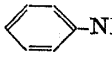


Compd.	R	mp (°C)	UV: λ_{max}^{EtOH} nm (ε)	Formula	Analyses[a]
5		195—197	266(14600)[b]	$C_{11}H_{12}ClN_5$	C, H, Cl, N
6		206—209	267(14200)	$C_{11}H_{14}ClN_5$	C, H, Cl, N
7		204—210 (dec.)	263(14300)[b]	$C_{10}H_{12}ClN_5O$	C, H, Cl, N
8	$C_6H_5CH_2$	228—229	266(15000)	$C_{12}H_{10}ClN_5$	C, H, Cl, N

a) Satisfactory analyses were obtained for the elements indicated.
b) Recorded in CH_3OH.

TABLE III. 2,9-Disubstituted Adenines



Compd.	R^1	R^2	mp (°C)	UV: λ_{max}^{EtOH} nm (ε)	Formula	Analyses[a]
9		CH_3O	233—236	sh 253(9000) 269(13200)	$C_{12}H_{15}N_5O$	C, H, N
10		C_2H_5O	138—139	sh 253(8500) 270(12900)	$C_{13}H_{17}N_5O$	C, H, N
11		*n*-C_3H_7O	157—159	sh 253(7500) 269)11500)	$C_{14}H_{19}N_5O$	C, H, N
12		*n*-C_4H_9O	114—115	sh 253(8300) 270(11500)	$C_{15}H_{21}N_5O$	C, H, N
13		iso-C_4H_9O	132—135	sh 253(8300) 269(13000)	$C_{15}H_{21}N_5O$	C, H, N
14		*sec*-C_4H_9O	56—63	sh 254(8300) 271(12300)	$C_{15}H_{21}N_5O\cdot 1/4H_2O\cdot 1/10C_6H_6$	C, H, N
15		*n*-$C_5H_{11}O$	[e]	sh 252(8400) 269(12500)	$C_{16}H_{23}N_5O$	C, H, N
16		*n*-$C_6H_{13}O$	[e]	sh 252(6900) 268(10200)	$C_{17}H_{25}N_5O$	C, H, N
17		*n*-C_3H_7S	108—113	237(23300) 278(13800)	$C_{14}H_{19}N_5S$	C, H, N, S
18		*n*-C_3H_7NH	73—80	259(5700) 290(5300)	$C_{14}H_{20}N_6\cdot 1/2H_2O$	C, H, N
19			108—111	224(26500) 259(11100)	$C_{17}H_{24}N_6$	C, H, N
20			184—185	248(18900) 276(20600) 288(20700)	$C_{17}H_{18}N_6\cdot H_2O$	C, H, N
21		H	196—201	262(13300)	$C_{11}H_{15}N_5$	[d]

Compd.	R^1	R^2	mp (°C)	UV: λ_{max}^{EtOH} nm (ε)	Formula	Analyses[a]
22		CH_3O	233—236	sh 253(9900) 269(13200)[b]	$C_{12}H_{17}N_5O$	C, H, N
23		C_2H_5O	156—159	sh 253(6800) 269(10200)	$C_{13}H_{19}N_5O$	C, H, N
24		*n*-C_3H_7O	148—150	sh 252(8400) 269(13200)	$C_{14}H_{21}N_5O$	C, H, N
25		*n*-C_4H_9O	140—141	sh 253(8300) 269(12800)	$C_{15}H_{23}N_5O \cdot 1/4H_2O$	C, H, N
26		iso-C_4H_9O	123—134	sh 253(7000) 269(11000)	$C_{15}H_{23}N_5O \cdot 1/5H_2O$	C, H, N
27		*sec*-C_4H_9O	56—63	sh 254(8400) 270(12800)	$C_{15}H_{23}N_5O$	C, H, N
28		*n*-$C_5H_{11}O$	64—68	sh 253(10900) 269(16800)	$C_{16}H_{25}N_5O$	C, H, N[f]
29		*n*-$C_6H_{13}O$	57—60	sh 253(7200) 270(10900)	$C_{17}H_{27}N_5O$	C, H, N
30		*n*-C_3H_7S	149—150	247(23900) 288(13800)	$C_{14}H_{21}N_5S$	C, H, N, S
31		*n*-C_3H_7NH	155—156	223(24100) 258.5(8800) 289.5(8400)	$C_{14}H_{22}N_6 \cdot 1/2H_2O$	C, H, N
32			109—117	224(25600) 259(10000)	$C_{17}H_{26}N_6 \cdot 1/2C_2H_5OH$	C, H, N
33			272—285	248(17000) 275(19000)	$C_{17}H_{20}N_6 \cdot 2H_2O$	C, H, N
34		H	187—189	260(14600)	$C_{10}H_{13}N_5O$	[c]
35		CH_3O	199—233 (dec.)	267(12100)[b]	$C_{11}H_{15}N_5O_2$	C, H, N
36		*n*-C_3H_7O	138—140	268(12600)[b]	$C_{13}H_{19}N_5O_2$	C, H, N
37	$C_6H_5CH_2$	*n*-C_3H_7O	178—180	sh 254(8800) 269.5(12800)	$C_{15}H_{17}N_5O$	C, H, N
38	$C_6H_5CH_2$	*n*-C_4H_9O	174—175	sh 254(9300) 269(13600)	$C_{16}H_{19}N_5O$	C, H, N
39	$C_6H_5CH_2$	*n*-C_3H_7S	158—160	237.5(23200) 278(14400)	$C_{15}H_{17}N_5S$	C, H, N, S

a) Satisfactory analyses were obtained for the elements indicated.
b) Recorded in CH_3OH.
c) Known compound. See ref 11.
d) Known compound. See ref 9.
e) Obtained as a viscous oil.
f) N: Calcd, 23.08; Found, 21.98.

9-Substituted 2-Chloroadenines (5—8) (Table II)

Ammonolysis of **2**, **3** and **4** was effected by heating with methanolic ammonia in a sealed tube to afford 2-chloroadenines, **5**, **7** and **8**, in 96, 84 and 94% yields, respectively. 9-Benzyl-6-benzyloxy-2-chloro-9*H*-purine (**40**), a by-product obtained in the synthesis of **4**, also gave **8** in 67% yield by the above treatment. The cyclohexyl derivative, **6**, was prepared by catalytic reduction of **5** with Pd on charcoal in 55% yield together with 9-cyclohexyl-9*H*-adenine (**21**)[9] in 14% yield; the latter appeared to be formed by a simultaneous reductive cleavage of the 2-chlorine atom. The UV spectra of 9-*N*-substituted 2-chloroadenines (**5**—**8**, λ_{max} 263—267 nm) are similar to that of 2-chloroadenosine[10] (λ_{max} 264 nm).

2,9-Disubstituted Adenines (9—39) (Table III)

Nucleophilic substitution of **5** with sodium *n*-propoxide under reflux in *n*-propanol gave 9-(2-cyclohexenyl)-2-*n*-propoxy-9*H*-adenine (**11**) in 90% yield. A series of 2-alkoxy analogs, **9**, **10** and **12**—**16**, were prepared in a similar manner by refluxing **5** with an appropriate alkoxide.

The 2-*n*-propylthio derivative, **17**, was obtained by treatment with sodium *n*-propyl mercaptide in DMF. The 2-*n*-propylamino derivative, **18**, was prepared by heating with *n*-propylamine in methyl cellosolve. The cyclohexylamino (**19**) and anilino (**20**) derivatives were prepared by a similar procedure.

9-Cyclohexyl-2-*n*-propoxy-9*H*-adenine, **24** (designated as BB-1502), was obtained in 76% yield by hydrogenation of the corresponding cyclohexenyl derivative, **11**, in ethanol in the presence of 10% Pd on charcoal. A series of 2-substituted 9-cyclohexyladenine derivatives, **22**, **23**, **25**—**29** and **31**—**33**, was similarly prepared by catalytic reduction of the corresponding 9-cyclohexenyl adenines. The 2-*n*-propylthio derivative, **30**, was obtained by the reaction of **6** with sodium *n*-propyl mercaptide. Similarly **24** was prepared from **6** by nucleophilic substitution with *n*-propoxide.

2-Substituted 9-(2-tetrahydropyranyl)adenines (**35** and **36**) and 9-benzyl derivatives (**37**—**39**) were similarly synthesized from **7** and **8**, respectively. The UV spectra of 9-*N*-substituted 2-alkoxyadenines (**9**—**16**, **22**—**29** and **35**—**38**, λ_{max} 267—271 nm) are similar to those of 2-alkoxyadenosines[4] (λ_{max} 266—269 nm).

Pharmacological Activity

The series of 2,9-disubstituted adenine derivatives prepared in the present study was examined for *in vitro* and *in vivo* bronchodilator activity and *in vivo* hypotensive potential. The latter test was performed to assess the separation of cardiovascular side effect from bronchodilator activity. For *in vivo* evaluation, test compounds were administered to guinea pigs by the intravenous (*i.v.*) route in the primary screening, and selected compounds were further tested by the intraduodenal (*i.d.*) route and also by inhalation.

The *in vitro* bronchodilator activity of the test compounds was evaluated by measuring the relaxation of bronchial smooth muscle using isolated guinea pig tracheal tissues. Tracheal chains of guinea pigs were prepared by the method described by Castillo and de Beer.[12] The response of the tracheal muscle to each test compound was recorded by the Magnus method and compared to the maximum response obtained with 0.1 μg/ml of isoproterenol prior to each experiment. The *in vitro* bronchodilator activity of test compounds was expressed as an EC_{50} (μg/ml) value, *i.e.*, the concentration producing a tracheal muscle relaxation equivalent to 50% of the response induced by 0.1 μg/ml of isoproterenol.

The *in vivo* brochodilator activity observed following *i.v.* administration of test compounds was evaluated by measuring the decrease in the intratracheal pressure (ITP) of guinea pigs according to the method described by James.[13] The tracheas of anesthetized guinea pigs were cannulated and the ITP recorded on a polygraph (Sanei Instrument, type 142-8) under artificial ventilation. Arterial blood pressure (ABP) was measured through the cannulated carotid artery during the experiment. The ITP of control guinea pigs decreased to an approximately 50% level after an *i.v.* administration of 0.03 μg/kg of salbutamol. The *in vivo* bronchodilator activity of test compounds was compared with that of salbutamol and expressed as an ED_{50} value (mg/kg), which was defined as the dose of a test compound producing a decrease of ITP equivalent to that induced by 0.03 μg/kg of salbutamol. The hypotensive effect of test compounds was expressed as an ED_{20} value (mg/kg) which was the dose reducing ABP by 20% compared to the predrug control measurement. Aminophylline was used as a reference compound in the pharmacological evaluation of test compounds in the present study.

The results of the primary *in vitro* and *in vivo* screening tests described above are summarized in Table IV. The right column of Table IV shows the ratio of the hypotensive effect (ABP, ED_{20}) to the bronchodilator activity (ITP, ED_{50}) of a given compound determined by *i.v.* administration. Those compounds exhibiting a large ABP–ITP ratio are considered to have a wide separation of cardiovascular side effect from bronchodilator activity.

The 2,6-dichloro-9-substituted purine derivatives (**2**—**4**) were devoid of bronchodilating

Table IV. *In Vitro* and *in Vivo* Activities of Substituted Purine and Adenine Derivatives

Compd.	Bronchodilation		Hypotension	Ratio
	In vitro EC_{50} (μg/ml)	ITP ED_{50} (mg/kg, *i.v.*)	ABP ED_{20} (mg/kg, *i.v.*)	ABP ED_{20} / ITP ED_{50}
2	>1	>1	>1	—
3	3	—	—	—
4	>3	>3	>3	—
5	0.12	0.15	2.5	17
6	0.15	0.74	>3	>4.1
7	0.45	0.23	>1	>4.4
8	1.8	1.3	1.7	1.3
9	0.32	>3	>3	—
10	0.088	0.33	4.0	12
11	0.027	0.34	2.0	5.9
12	0.045	0.65	>3	>4.8
13	0.41	>3	2.4	—
14	0.11	>3	2.6	—
15	0.59	>3	1.9	—
16	>3	>3	2.7	—
17	0.02	0.31	>3	>9.7
18	0.47	1.4	>3	>2.1
19	0.24	>3	2.4	—
20	0.34	>3	>3	—
21	0.91	2.4	>3	>1.2
22	0.18	>3	>3	—
23	0.18	0.37	2.9	7.8
24	0.024	0.37	4.4	12
25	0.025	<0.10	4.4	>44
26	0.31	>3	>3	—
27	0.21	>3	2.2	—
28	1.8	>3	>3	—
29	1.4	>3	>3	—
30	0.19	1.1	>3	>2.7
31	0.75	0.49	2.8	5.7
32	0.21	1.5	>3	>2.0
33	>3	>3	>3	—
34	>1	>1	>1	—
35	>1	>1	>1	—
36	0.17	0.26	1.9	7.3
37	0.34	0.83	1.7	2.0
38	>3	>3	>3	—
39	2.5	>3	2.0	—
Aminophylline	17	0.58	1.4	2.4

Table V. Bronchodilating and Anti-asthma Activities of Selected Compounds

Compd.	Bronchodilation ITP ED_{50} (mg/kg, *i.d.*)	Hypotension ABP ED_{20} (mg/kg, *i.d.*)	Ratio ABP ED_{20} / ITP ED_{50}	Anti-asthma Inhalation EC_{50}[a] (μg/ml)
10	0.62	12	19	10
11	1.2	2.4	2.0	>10
17	1.9	13	6.8	5.2
24	1.2	18	15	0.97
25	1.4	8.3	5.9	2.9
36	1.4	14	10	4.2
Aminophylline	5.9	9.5	1.6	>10000

a) The EC_{50} value is defined as the concentration of a test compound required to protect 50% of test animals from antigen-induced dyspnea (10 min inhalation at 0.4 ml/min).

activity, while the 2-chloro-9-substituted adenines (**5**—**8**) were active. All the 9-(2-cyclohexenyl)-2-substituted adenine derivatives (**9**—**20**) except **16** showed *in vitro* bronchodilator activity. Those compounds having an ethoxy, *n*-propoxy, *n*-butoxy or *n*-propylthio group at the 2-position (**10**, **11**, **12** and **17**) were the most potent among the series in the *in vitro* and *in vivo* bronchodilating activity tests. The methoxy analog (**9**), higher or branched alkoxy homologs (**13**, **14**, **15** and **16**) and two substituted amino derivatives (**19** and **20**) did not show *in vivo* bronchodilator activity at 3 mg/kg, the highest dose tested. The 2-*n*-propylamino derivative (**18**) was moderately active in the *in vivo* bronchodilator test.

A similar structure–activity relationship was observed for the series of 9-cyclohexyladenine derivatives (**21**—**33**). The 2-ethoxy, 2-*n*-propoxy and 2-*n*-butoxy derivatives (**23**, **24** and **25**) were the most active among the series both *in vitro* and *in vivo*, and showed a good separation of hypotensive effect from bronchodilator activity. 2-*n*-Propylthio and 2-*n*-propylamino derivatives (**30** and **31**) were fairly active *in vivo*, as was the case with the 9-(2-cyclohexenyl) series of compounds.

Among three 9-(2-tetrahydropyranyl) and three 9-benzyl derivatives (**34**—**36** and **37**—**39**, respectively), compounds with a 2-*n*-propoxy substitution (**36** and **37**) showed *in vitro* and *in vivo* bronchodilator activity.

Based on the results obtained in the primary pharmacological screening tests, compounds **10**, **11**, **17**, **24**, **25** and **36** were selected for secondary evaluation. The bronchodilator activity and hypotensive effect of each selected compound were further tested in guinea pigs by the same procedure as that used in primary screening except that test compounds were administered by the *i.d.* route. The anti-asthmatic activity of test compounds was tested by aerosol administration in the egg albumin-induced anaphylaxis of guinea pigs by the method described in a separate paper.[14] The results of the secondary evaluations are shown in Table V.

On *i.d.* administration, compound **10** was the most active in the bronchodilation test followed by **11**, **24**, **25** and **36**, which were approximately one-half as active as **10** but 4—5 times more potent than aminophylline in terms of ITP ED_{50}. Compound **24** had the least significant hypotensive effect, followed by **36**, **17** and **10**. The hypotensive activity of **24** was about one-half that of aminophylline. In the evaluation of anti-asthmatic activity of test compounds when administered by inhalation, **24** was the most potent in protecting animals from antigen-induced dyspnea. Aminophylline was inactive by inhalation in this model.

In view of the *in vitro* tracheal muscle relaxation at low concentration, the potent bronchlodilating activity demonstrated after *i.v.*, *i.d.*, and aerosol administrations and the wide margin for potential hypotensive side effect, compound **24** (designated as BB-1502) has been chosen for detailed pharmacological studies.[14,15]

Experimental

2,6-Dichloro-9-(2-cyclohexenyl)-9*H*-purine (2)——To a stirred solution of 41.7 g (0.153 mol) of $HgCl_2$ in 564 ml of 50% (v/v) aqueous EtOH were added 29 g (0.153 mol) of 2,6-dichloropurine (**1**)[5] and then 60 ml of 10% NaOH. The mixture was stirred overnight. The precipitates were filtered off, washed successively with water, ethanol and ether and dried to give 44 g (74%) of the chloromercuri salt of **1**. To an azeotropically dried mixture of 52.3 g (0.153 mol) of the chloromercuri salt and 50 g of Celite in 800 ml of benzene was added 24.6 g (0.153 mol) of 3-bromocyclohexene with stirring. The mixture was heated at reflux for 2.5 h with stirring and then filtered. The filter cake was washed with a small amount of benzene. The filtrate and wash were concentrated *in vacuo*. The residue was dissolved in 150 ml of benzene. The solution was shaken with 20% KI solution (120 ml×3) and with NaCl solution (100 ml×2), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from ethanol to yield 23.5 g (65%) of **2**. A second crop (10.9 g; 30%) was obtained from the filtrate by chromatographic separation on silica gel. Total yield 34.4 g (95% from the chloromercuri salt of **1**; 70% overall yield from **1**).

9-Benzyl-2,6-dichloro-9*H*-purine (4)——To a stirred solution of 2.8 g (15 mmol) of 2,6-dichloropurine (**1**) in 50 ml of dry DMF were added 1.44 g (30 mmol) of 50% sodium hydride and 5.5 ml of benzyl bromide at ambient temperature, and the mixture was stirred for 1 h at room temperature. After treatment with water, insoluble materials were filtered off. The filtrate was neutralized with NaOH solution and concentrated

in vacuo. The residue was extracted with $CHCl_3$. The $CHCl_3$ extracts were concentrated *in vacuo* to give an oil, which was chromatographed on a silica gel column using $CHCl_3$–MeOH as the eluant to give 856 mg (21%) of the desired product **4** and 590 mg (11%) of 9-benzyl-6-benzyloxy-9*H*-purine (**40**). mp 127—129°C, IR ν_{max}^{KBr} cm^{-1}: 1600, 1575, 1355, 1320, 1230. UV λ_{max}^{EtOH} nm (ε): 260.5 (14300), sh 268.5 (10400). NMR ($CDCl_3$) δ: 5.24 (2H, s, N–C$\underline{H}_2$C$_6$H$_5$), 5.54 (2H, s, OC$\underline{H}_2$C$_6$H$_5$), 7.1—7.5 (10H, m), 7.77 (1H, s, H-8). *Anal.* Calcd for $C_{19}H_{15}ClN_4O$: C, 65.05; H, 4.31; Cl, 10.11; N, 15.97. Found: C, 65.17; H, 4.23; Cl, 10.53; N, 15.84.

2-Chloro-9-(2-cyclohexenyl)-9*H*-adenine (**5**)——An ammonia-saturated mixture of 2.8 g (10.3 mmol) of **2** in 50 ml of MeOH was heated at 100°C for 4 h in a sealed tube, then cooled. The mixture was concentrated to deposit crystals, which were filtered off to give 2.5 g (96%) of **5**.

2-Chloro-9-cyclohexyl-9*H*-adenine (**6**) **and 9-Cyclohexyl-9*H*-adenine** (**21**)——A mixture of 252 mg (1 mmol) of **5** in 15 ml of EtOH was hydrogenated for 2 d with 93 mg of 10% Pd on charcoal. The reaction mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was subjected to silica gel chromatography with $CHCl_3$–MeOH to give 134 mg (55%) of **6** and 33 mg (14%) of **21**.[9]

2-Chloro-9-(2-tetrahydropyranyl)-9*H*-adenine (**7**)——A suspension of 2.0 g (7.3 mmol) of 2,6-dichloro-9-(2-tetrahydropyranyl)-9*H*-purine (**3**)[7] in 50 ml of MeOH was saturated with ammonia at 0°C, during which time a solution formed. The solution was heated at 100°C for 4 h in a sealed tube and cooled. Concentration of the cooled reaction mixture afforded 1.55 g (84%) of **7**.

9-Benzyl-2-chloro-9*H*-adenine (**8**)——a) From 9-Benzyl-2,6-dichloro-9*H*-purine (**4**): A mixture of 500 mg (1.8 mmol) of **4** and 5 ml of saturated methanolic ammonia was heated at 100°C for 6 h in a sealed tube. The reaction mixture was concentrated to give 437 mg (95%) of **8**, thin layer chromatography (TLC) (Merck Silica Gel 60F-254): *Rf* 0.29; AcOEt–EtOH (20: 1).

b) From 9-Benzyl-6-benzyloxy-2-chloro-9*H*-purine (**40**): A 300 mg (0.86 mmol) sample of **40** was aminated in a similar way, giving 149 mg (67%) of **8**.

9-(2-Cyclohexenyl)-2-*n*-propoxy-9*H*-adenine (**11**)——A solution of 2.4 g (9.2 mmol) of **5** in 60 ml of 1 N sodium *n*-propoxide in *n*-propanol was heated at reflux for 3 h under a nitrogen atmosphere. The mixture was neutralized with 6 N HCl and concentrated *in vacuo*. The residue was taken up in $CHCl_3$ and shaken with water. The $CHCl_3$ layer was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column and crystallized from cyclohexane–hexane to give 2.53 g (90%) of **11**.

2-Alkoxy-9-(2-cyclohexenyl)-9*H*-adenines (**9**, **10**, **12**—**16**) were prepared in a similar manner from 2-chloro-9-(2-cyclohexenyl)-9*H*-adenine (**5**) by the action of appropriate alkoxides.

9-(2-Cyclohexenyl)-2-*n*-propylthio-9*H*-adenine (**17**)——A mixture of 159 mg (0.64 mmol) of **5**, 223 mg (4.7 mmol) of 50% sodium hydride in mineral oil and 2 ml of *n*-propanethiol in 10 ml of DMF was refluxed for 5 h under nitrogen. The reaction mixture was then poured into ice water and neutralized with 1 N HCl. Excess mercaptan was evaporated off and the residual solution was extracted with $CHCl_3$. The organic layer was washed with water, dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified on a silica gel column to give **17**.

9-Benzyl-2-*n*-propylthio-9*H*-adenine (**39**) was prepared from the corresponding 2-chloroadenine (**8**) by the action of sodium *n*-propyl mercaptide in a similar manner.

9-(2-Cyclohexenyl)-2-*n*-propylamino-9*H*-adenine (**18**)——A solution of 300 mg (1.2 mmol) of 2-chloro-9-(2-cyclohexenyl)-9*H*-adenine (**5**) and 0.3 ml (3.6 mmol) of *n*-propylamine in 3 ml of dry methyl cellosolve was heated at 110°C for 15 h in a sealed tube. The reaction mixture was concentrated *in vacuo* to leave an oil, which was chromatographed on a silica gel column using $CHCl_3$–MeOH (50: 1) to give 282 mg (87%) of **18**.

2-Cyclohexylamino-9-(2-cyclohexenyl)-9*H*-adenine (**19**) and 2-anilino-9-(2-cyclohexenyl)-9*H*-adenine (**20**) were prepared from 2-chloro-9-(2-cyclohexenyl)-9*H*-adenine (**5**) by the action of appropriate amines in a similar manner.

9-Cyclohexyl-2-*n*-propoxy-9*H*-adenine (**24**)——Preparation from **11**: A solution of 2.21 g (7.8 mmol) of **11** in 30 ml of EtOH was hydrogenated overnight with 250 mg of 10% Pd on charcoal. The reaction mixture was filtered and the filtrate was concentrated, giving a residue, which was crystallized from AcOEt–hexane to afford 1.85 g (86%) of **24**.

2-Alkoxy-9-cyclohexyl-9*H*-adenines (**22**, **23**, **25**—**29**) and the 2-substituted amino derivatives (**31**—**33**) were prepared in the same way from the corresponding cyclohexenyladenines by catalytic hydrogenation.

Preparation from **6**: To a solution of 258 mg (5.38 mmol) of 50% sodium hydride in 5 ml of propanol was added 32 mg (0.18 mmol) of **6**. The mixture was refluxed for 1 h under a nitrogen atmosphere. The cooled solution was poured into ice water and taken up in $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. The resulting oil was chromatographed on a column of silica gel, eluted with MeOH–$CHCl_3$ (3: 97) and crystallized from isopropyl ether to give 19 mg (53%) of **24**.

9-Cyclohexyl-2-*n*-propylthio-9*H*-adenine (**30**)——A mixture of 136 mg (0.54 mmol) of the 2-chloro derivative (**6**), 2.3 ml of *n*-propanethiol and 220 mg (4.5 mmol) of sodium hydride in 12 ml of DMF was gently refluxed for 2.5 h, then cooled. The mixture was neutralized with 1 N HCl and excess propanethiol was removed by evaporation. The residual mixture was shaken with $CHCl_3$ and water. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to leave an oil. The oily residue was chromatographed on silica gel using MeOH–$CHCl_3$ (1: 99) to afford a crude product, which was crystallized from cyclohexane to afford 112 mg (70%) of colorless prisms, **30**.

2-*n*-Propoxy-9-(2-tetrahydropyranyl)-9*H*-adenine (36)——A solution of 253 mg (1 mmol) of the 2-chloro derivative (**7**) in 10 ml of 1 N sodium *n*-propoxide in *n*-propanol was refluxed under nitrogen for 1 h. The mixture was neutralized with acetic acid and concentrated *in vacuo*. The residue was triturated with water, giving 213 mg of crude **35**, which was crystallized from AcOEt–hexane to afford 147 mg (57%) of needles, **36**.

2-Methoxy-9-(2-tetrahydropyranyl)-9*H*-adenine (**35**) was prepared in a similar way from **7** by reaction with sodium methoxide.

9-Benzyl-2-*n*-propoxy-9*H*-adenine (37)——A mixture of 130 mg (0.5 mmol) of **8** and 1.5 ml of 1 N sodium *n*-propoxide in 13 ml of *n*-propanol was refluxed overnight, neutralized with HCl and concentrated *in vacuo*. The residue was triturated with water to give 118 mg of crude **37**, which was crystallized from EtOH–H_2O, giving 90 mg (64%) of **37**.

9-Benzyl-2-*n*-butoxyadenine (**38**) was prepared in the same way from **8** by the action of sodium *n*-butoxide.

References and Notes

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