sulting clear solution evaporated under reduced pressure. Crude **8** was obtained in about 90% yield by trituration of the residue with Et_2O.

Part b.—The appropiate dihalogeno- or dimethanesulfonyloxy-dimethanesulfonamidobutanes (**5**, **9a**, **9b**, or **10**) (0.1 mol) was dissolved in 10% NaOH (about 450 ml). After a few moments the biaziridine started to separate. Washing with H_2O, EtOH, and Et_2O gave 75–90% of crude **8**.

1,1′-Di(*p*-toluenesulfonyl)-2,2′-biaziridines (17). Method J.—(Table II) Method I, Part b was followed using **16** as starting material. The yield of crude **17** was 60–70%.

1,4-Dihalogeno-2,3-dimethanesulfonamidobutanes (9a,b) by Opening of the Biaziridines 8 with Halo Acids. Method K (Table III).—The biaziridine **8** was dissolved in a large excess of the appropiate haloacid (5 *N* HCl or 3 *N* HBr). After a few moments the reaction product started to separate. Washing with H_2O, EtOH, and Et_2O gave 70–75% of crude **9a** or 90–95% of crude **9b**, respectively. The physical properties were identical with those of the compounds prepared as in method H.

1,4-Dihalogeno-2,3-di(*p*-toluenesulfonamido)butanes (18a and 18b). Method L (Table III).—To a solution of the biaziridine **17** (7.85 g) in MeCN (20 ml), the appropiate concentrated haloacid (20 ml) was rapidly added while stirring. After a few moments the reaction product started to separate. The mixture was diluted with H_2O (20 ml) and kept in a refrigerator for about 20 hr. Washing with H_2O, EtOH, and Et_2O gave 70–75% of crude **18a** or **18b**, respectively.

1,4-Dimethanesulfonyloxy-2,3-dimethanesulfonamidobutanes (10) by Opening of the Biaziridines 8 with $MeSO_3H$. Method M (Table III).—To a solution of the biaziridine **8** (4.8 g) in MeCN (50 ml), a mixture of $MeSO_3H$ (6.0 g) and H_2O (1.0 ml) was rapidly added while stirring. After additional stirring for about 2 hr the solvent was removed under reduced pressure. The residue was washed with Et_2O and triturated with MeCN (10 ml) to give about 2.6 g of crude **10**. The physical properties were identical with those of the compounds prepared as in Method E.

Attempts to open the biaziridine (*S*,*S*)-**17** with $MeSO_3H$ using method M resulted in **(2*S*,3*S*)-1-acetamido-4-methanesulfonyloxy-2,3-di-(*p*-toluenesulfonamido)butane**, mp 193.5–195° (MeCN), $[\alpha]^{20}D$ +66.0° (*c* 2, DMF). *Anal.* ($C_{23}H_{29}N_3O_8S_3$) H, N, S; Calcd C: 46.06; found: 45.48.

3,4-Disubstituted-2,5-dimethanesulfonyl-1,2,5-thiadiazolidine-1-oxides (13a,b, and c). Method N, Part a (Table IV).—A mixture of **9a**, **9b**, or **10** (0.01 mol), $SOCl_2$ (50 ml), pyridine[10] (3.0 ml), and $CHCl_3$ (20 ml) was refluxed for 4 hr. The resulting solution was evaporated under reduced pressure and the residue washed with H_2O, EtOH, and Et_2O to give 85–95% of crude **13a,b**, or **c**, respectively.

Part b.—Compound 11 was treated with $SOCl_2$ as in Part a except that no $CHCl_3$ and only a catalytical amount of pyridine was added. The yield of crude **13a** was about 45%.

(3*S*,4*S*)-3,4-Diaminotetrahydrofuran Dihydrobromide [(*S*,*S*)-12·2HBr].—A solution of **18b** (2.8 g) in 48% HBr (30 ml) and AcOH (30 ml) was refluxed for about 48 hr, evaporated under reduced pressure, and the residue triturated with Me_2CO to give 0.7 g of crude (*S*,*S*)-**12**·2HBr. After recrystallization from H_2O–48% HBr the material started to decomposes at about 270°, $[\alpha]^{20}D$ −20.9° (*c*, H_2O). *Anal.* ($C_4H_{10}N_2O$, 2 HBr) C, H, Br, N.

Acknowledgment.—The authors are indebted to the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md., for the screening of the compounds and for making the results available.

(10) When **9b** or **10** was reacted, pyridine was replaced by pyridine hydrobromide (4.5 g) or pyridine methanesulfonic acid salt (5.0 g), respectively.

Structure–Activity Relationships in Adenosine Deaminase Inhibitors[1]

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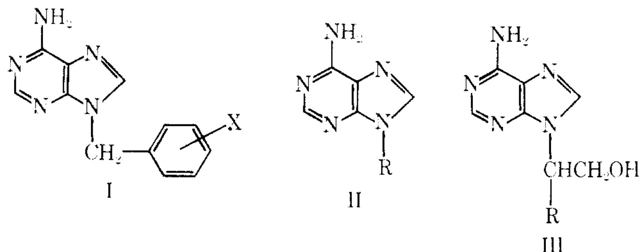
Received October 20, 1969

Structure–activity correlations for a series of 9-*n*-alkyladenines (II) and 9-(1-hydroxy-2-alkyl)adenines (III) as inhibitors of adenosine deaminase have shown a high dependence of inhibitory activity on the hydrophobic character (π) of the 9 substituent. The slope of the equation derived from compounds related to III is greater than the slope derived from compounds related to II. This increase in slope for III may reflect a conformational change in the enzyme. A comparison of some *meta* and *para* isomers of 9-benzyladenines (I) reveals that the *meta* isomers are correlated by an equation containing both a π and σ term. However, no correlation could be found for the *para*-substituted isomers. This variation in the binding regions of adenosine deaminase for the *meta* and *para* isomers of I is also reflected in the dramatic difference in the ability of the *para* and *meta* isomers of 9-(bromoacetamidobenzyl)adenines to cause irreversible inhibition of the enzyme.

In continuing our study[2,3] of the structure–activity relationships in adenosine deaminase inhibitors we consider in this report derivatives of 9-benzyladenines (I).



In the present study a variety of substituents (X) have been placed in the 3 and 4 position of the benzyl moiety of I in order to assess their hydrophobic, electronic, and steric effects on inhibitory action.

In previous studies of the effect of substituents attached to adenine, as in II and III, a strong dependence of inhibitory action on hydrophobic binding has been established. The structure–activity relationship for the derivatives[4] in Table I is defined in eq 1 and that for the congeners[3] of Table II is contained in eq 2 and 3. The quality of the fit obtained with eq 1 and 2 as

Inhibitors Table I	*n*	*r*	*s*	
$-\log (I/S)_{0.5} =$ $0.452(\pm 0.06)\pi - 1.194(\pm 0.15)$	8	0.992	0.078	(1)

(1) This work was supported by Grant CA 11110 from the National Institutes of Health, by Grant T-337C from the American Cancer Society, and by a Public Health Service Training Grant 5-T1-GM 00 555 from the Division of Medical Sciences, Bethesda, Md.

(2) H. J. Schaeffer, and R. Vince, *J. Med. Chem.*, **10**, 689 (1967).

(3) H. J. Schaeffer, and C. F. Schwender, *J. Pharm. Sci.*, **57**, 1070 (1968).

(4) H. J. Schaeffer, and D. Vogel, *J. Med. Chem.*, **8**, 507 (1965).

Inhibitors Table II, R = CH_3 to R = C_6H_{13}

$-\log (I/S)_{0.5} = 0.932(\pm 0.21)\pi - 0.483(\pm 0.41)$ 6   0.987   0.157   (2)

Inhibitors Table II, R = C_7H_{15} to R = C_9H_{19}

$-\log (I/S)_{0.5} = 0.19\pi + 1.66$ 3   0.996   0.012   (3)

judged either by r or s is good to excellent so that we can make comparisons of the two equations with some confidence. Because of the different stereoelectronic character of the two parent molecules we cannot compare intercepts, but we can compare the dependence of inhibitory activity on hydrophobic character (π). The difference of slope for the two equations is quite striking and highlights the point previously made[2] that the positioning of hydrophobic groups on this part of the inhibitor molecule is quite critical. The slope of essentially 1 of eq 2 indicates that the part of the enzyme into which these alkyl groups are fitting resembles the octanol–water reference system which defines[5] π. This dependence of biochemical activity on π is similar to the highest found (~1.2) in investigation of many systems.[6] The apolar region in which binding characterized by eq 2 occurs must be one of considerable fluidity. The slope of approximately 0.5 for eq 1 is close to that found for nonspecific binding by a wide variety of small molecules to various macromolecules.[6,7] The difference in slope of these two equations must result from the different character of the area in which the R groups find themselves.

To obtain evidence that the change in the slope of the two equations was not caused by some unexpected intramolecular bonding in the inhibitors which could cause a change in the partition coefficient of the compounds, the 1-octanol–water partition coefficients were measured for three sets of compounds (Table I and II). Calculation of the contribution of the CH_2 group to log P within either series of compounds gave results which agreed well with the expected π value of 0.50. Comparison of series III with series II revealed a difference in log P values near −0.66, the calculated value for CH_2OH. Because no unusual effects are observed in the partition coefficients in this series of compounds, we suggest that the difference in the slopes of eq 1 and 2 must be a result of the difference in the interaction with the enzyme of compounds of set II compared with compounds of set III.

Since the dimension of the hydrophobic region is the same for compounds of sets II and III, it is probable that there is a single, large hydrophobic area on the enzyme and that both sets of compounds form complexes with this site. Previously we have compared,[3,4] for a series of compounds generalized by structures II and III, the changes in free energy resulting from the addition of a single methylene group to the alkyl chain, and it was found that in III when R is lengthened from ethyl to propyl, the $\Delta F/CH_2$ was −1.14 kcal. The magnitude of this change in free energy is clearly beyond simple hydrophobic transfer forces and probably reflects a conformational change in the enzyme. We suggest that the change in the slope of eq 1 and 2 from 0.45 to 0.93 supports the concept that compounds of general structure II, where R = propyl through hexyl, induce a conformation change in the enzyme which makes the hydrophobic area more accessible to the alkyl residue. Beginning with the heptyl group in set III, a dramatic break in the activity occurs. Comparison of eq 2 and 3 shows the great drop in activity compared with π which starts with the heptyl group. The critical positioning role of the OH can be seen from another viewpoint by comparing inhibitors IV, V, and VI. Comparing IV and V, we find greater activity in V, presumably because of better positioning of the methyl group. This same anchoring by Me and OH yields the highly active VI. The slope of the line determined by V and VI is $(4.7 - 2.0)/(3 - 0) = 0.90$, in good agreement with that of eq 2. Thus it appears that Me and OH attached to the 2 position of the adenine side chain cooperate to position the inhibitor and enzyme so that an alkyl moiety attached to the 1 position of the side chain (VI) finds a more favorable binding pocket. Exactly how the OH, the Me, and the alkyl group attached to the 1 position of the side chain combine to permit the favorable binding is not clear. It may be through positioning

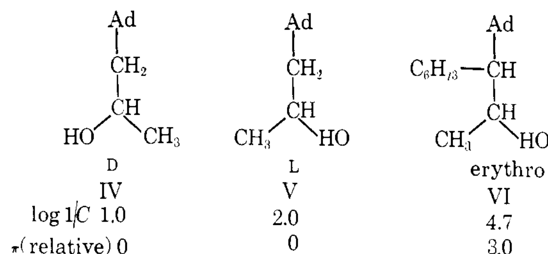


Table I
Inhibition of Adenosine Deaminase by Some 9-Alkyladenines

$-\log (I/S)_{0.5}$[a]	π	Alkyl group	log P[b]
−0.86	0.50	Me	
−0.79	1.00	Et	
−0.52	1.50	Pr	0.74
−0.36	2.00	Bu	1.25
−0.15	2.50	Pent	1.79
0.15	3.00	Hex	
0.49	3.50	Hept	
0.62	4.00	Oct	

[a] From ref 4. [b] Log P values determined by Dennis Azaro and H. J. Schaeffer using uv analysis in 1-OctOH-H_2O system.

Table II
Inhibition of Adenosine Deaminase by Some 9-(1-Hydroxy-2-alkyl)adenines

$-\log (I/S)_{0.5}$[a]	π	Alkyl group[b,c]	log P[d]
−0.08	0.50	Me	
0.31	1.00	Et	0.14
1.15	1.50	Pr	0.66
1.48	2.00	Bu	1.16
1.82	2.50	Pent	
2.21	3.00	Hex	
2.33	3.50	Hept	
2.41	4.00	Oct	
2.52	4.50	Non	

[a] From ref 3. [b] A break in activity occurred starting with the heptyl group. For this reason the heptyl, octyl, and nonyl functions are not included in the derivation of eq 2. [c] Alkyl group is R in structure III. [d] See Table I, footnote b.

(5) C. Hansch, and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

(6) C. Hansch in "Drug Design," Vol. I, E. J. Ariëns, Ed., Academic Press, New York, N. Y. (in press).

(7) F. Helmer, K. Kiehs, and C. Hansch, *Biochemistry*, **7**, 2858 (1968).

and/or the production of a favorable conformational change in the enzyme.

Because of the quite different behavior of the 3 and 4 derivatives of I we have treated the two sets of isomers independently. Using the data in Table III, the *meta* isomers are correlated in eq 4 and 5. Equation 4 shows that the *meta* isomers are only poorly correlated with

TABLE III
INHIBITION OF ADENOSINE DEAMINASE BY SOME 9-(X-BENZYL)ADENINES

X	π[a]	σ[b]	$-\log (I/S)_{0.5}$ obsd	$-\log (I/S)_{0.5}$ calcd
3-COOEt	0.49	0.37	0.69	0.51
3-NO_2	−0.28	0.71	0.52[c]	0.66
3-CN	−0.57	0.56	0.48	0.41
3-$COOCH_3$[d]	−0.01	0.37	0.44	0.36
3-CH_2Br	0.79	0.16[e]	0.32	0.37
3-NHAc	−0.97	0.21	−0.16[c]	−0.10
H	0.00	0.00	−0.20[f]	−0.26
3-CH_2OH	−1.03	0.08[g]	−0.27	−0.04
3-NH_2	−1.23	−0.16	−0.48[c]	−0.58
3-Ac	−0.55	0.38	0.61	0.23
4-NHAc	−0.97	0.00	0.32[f]	
4-$COOCH_3$	−0.01	0.45	0.08	
4-CH_2Br	0.79	0.12[e]	−0.15	
4-NH_2	−1.23	−0.66	−0.33[f]	
4-CN	−0.57	0.66	−0.55	
4-NO_2	−0.28	0.78	−0.56[f]	
4-CH_2OH	−1.03	0.08[g]	−0.59	

[a] From the benzene system, T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964). [b] Except where indicated, these values are from H. D. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [c] Data from H. J. Schaeffer, and R. N. Johnson, *J. Pharm. Sci.*, **55**, 929 (1966). [d] Prepared by the method of B. R. Baker, and H. S. Sachdev, *ibid.*, **52**, 933 (1963). [e] From M. Charton, *J. Org. Chem.*, **30**, 552 (1965). [f] H. J. Schaeffer, and E. Odin, *J. Med. Chem.*, **9**, 576 (1966). [g] From G. B. Barlin, and D. Perrin, *Quart. Rev.*, **20**, 75 (1966).

$$-\log (I/S)_{0.5} = 0.421(\pm 0.39)\pi + 0.278(\pm 0.29) \quad n = 9 \quad r = 0.687 \quad s = 0.334 \quad (4)$$

$$-\log (I/S)_{0.5} = 0.296(\pm 0.17)\pi + 1.096(\pm 0.43)\sigma - 0.039(\pm 0.17) \quad n = 9 \quad r = 0.963 \quad s = 0.132 \quad (5)$$

the single parameter π. Equation 5, employing both π and σ, gives a good correlation for nine *meta* derivatives. The 3-$COCH_3$ derivative is not included (see Table III). Some special intermolecular activity of this function causes unusually high activity when compared to the other 3 isomers. The coefficient with π in eq 5 is closer to that in eq 1 than that in eq 2, indicating that substituents in the *meta* position of the benzyl moiety do not induce the more favorable binding site characterized by eq 2.

It is of interest to compare the unsubstituted benzyladenine with the derivatives in set II. This can be done by adding 2.13 (π for C_6H_6) to 0.5 (π for the NCH_3 derivative) and substituting the value of 2.63 into eq 1. This yields a calculated value of 0.01. The experimental value is 0.20. This indicates that the aromatic ring of the benzyl moiety finds itself in the same enzymic environment as the alkyl groups of set II. The slightly higher-than-calculated value is probably due to the greater polarizability of the benzene ring. This importance of electron density on the aromatic ring is evident from a comparison of eq 4 and 5. Electron withdrawal by substituents (indicated by the positive coefficient with σ) increases activity.

Part of the weight of the σ term may be associated with π since the π constants used in this analysis are from the benzene system.[8] However, this would seem to be a very small portion in view of previous experience.[9]

The substituent in the *para* position of the benzyl group finds itself in a different enzymic milieu. All attempts to obtain good correlations with 4 isomers of Table III were unsuccessful. Not only were π and σ constants explored in the regression studies, but the steric parameters E_s and molar volume, as well as polarizability were all tested alone and in all reasonable combinations. The best correlation with an equation using less than three variables was the linear relation with the molar volume of the substituent; however, r for this case was only 0.716. Extremely complex intermolecular reactions between inhibitor and enzyme must occur in the area where the 4 substituent is positioned. This great difference in binding areas between areas as close as those found by a *meta* or *para* isomer have been previously noted.[3]

Experimental Section[10]

Method A. 9- and 7-(*m*-Cyanobenzyl)-6-chloropurine.—A mixture of 6.72 g (34.2 mmol) of *m*-cyanobenzyl bromide, 4.92 g (31.9 mmol) of 6-chloropurine, and 4.72 g (34.2 mmol) of K_2CO_3 in 50 ml of DMF was stirred for 23 hr at room temperature. To the cooled mixture was added 500 ml of H_2O and the mixture was kept at 0° for 1 hr. The solvent was decanted, and the residue dissolved in 250 ml of $CHCl_3$, dried with $MgSO_4$, and filtered. Evaporation of the filtrate *in vacuo* gave 6.68 g (78.1%), mp 105–125°. Addition of 500 ml of H_2O to the DMF–H_2O decantate produced an additional 1.18 g of crude material; total yield, 7.86 g (91.8%). A $CHCl_3$ solution of the crude material was chromatographed on a column of neutral alumina (210 g); 9-(*m*-cyanobenzyl)-6-chloropurine was eluted with $CHCl_3$ (900 ml); yield, 4.60 g (53.7%); mp 153–154°. One recrystallization (PhMe) gave 4.22 g (48.6%) of pure material, mp 153–154°. *Anal.* ($C_{13}H_8ClN_5$) C, H, Cl, N.

7-(*m*-Cyanobenzyl)-6-chloropurine was eluted with an additional 1.2 l. of $CHCl_3$; yield, 1.04 g (13.1%); mp 167–170°. Two recrystallizations of the crude material (PhMe) gave 590 mg (6.88%) of the analytical material, mp 176–177°. *Anal.* ($C_{13}H_8ClN_5$) C, H, Cl, H.

Method B. 9-(*m*-Cyanobenzyl)adenine.—A mixture of 307 mg (1.14 mmol) of 9-(*m*-cyanobenzyl)-6-chloropurine in *ca.* 15 ml of liquid NH_3 was heated in a steel bomb at 45° for 21 hr. The volatile materials were evaporated at room temperature. Two recrystallizations from MeOH gave 201 mg (72.6%) of the analytical sample, mp 234–235°. *Anal.* ($C_{13}H_{10}N_6$) C, H, N.

9-(*m*-Carboxybenzyl)adenine Hydrochloride.—A solution of 250 mg (1.00 mmol) of 9-(*m*-cyanobenzyl)adenine in 5 ml of concentrated HCl was heated under reflux for 21 hr. The precipitate was collected by filtration and dried at 100° to give 202 mg (66.2%) of the analytical sample, mp 299–300°. *Anal.* ($C_{13}H_{12}ClN_5O_2$) C, H, Cl, N.

Method C. 9-(*m*-Methoxycarbonylbenzyl)adenine.—A mixture of 268 mg (0.875 mmol) of 9-(*m*-carboxybenzyl)adenine hydrochloride in 15 ml of MeOH saturated with HCl was heated

(8) T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964).

(9) C. Hansch, E. W. Deutsch, and R. N. Smith, *ibid.*, **87**, 2738 (1965).

(10) The melting points, unless noted otherwise, were taken in open capillary tubes on a Mel-Temp block and are uncorrected. All analytical samples had ir spectra compatible with their assigned structures and moved as a single spot on tlc on Brinkman silica gel. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. The analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

under reflux for 22 hr. The white precipitate was collected by filtration; yield, 280 mg (100%), mp 243–244.5° dec. The crude product was dissolved in 25 ml of H_2O and filtered to remove insoluble material. To the cold filtrate was added 10 ml of 5% aqueous $NaHCO_3$ and the white precipitate was collected by filtration: yield, 169 mg (68.6%); mp 198–199°. Two recrystallizations from MeOH gave the analytical sample, mp 200–201°. *Anal.* ($C_{14}H_{13}N_5O_2$) C, H, N.

9-(*m*-Ethoxycarbonylbenzyl)adenine.—This compound was prepared by method C except EtOH saturated with HCl was used, and the product was isolated as the HCl salt, mp 246–247° (EtOH). *Anal.* ($C_{15}H_{16}ClN_5O_2$) C, H, Cl, N.

Method D. 4-Chloro-5-amino-6-(*m*-hydroxymethylbenzylamino)pyrimidine.—A solution of 7.45 g (54.4 mmol) of *m*-(hydroxymethyl)benzylamine, 9.85 g (60.0 mmol) of 4,6-dichloro-5-aminopyrimidine, and 6.06 g (60.0 mmol) of $(Et)_3N$ in 150 ml of *n*-PrOH was heated under reflux for 23 hr. After the volatile materials were removed *in vacuo*, the residue was triturated with H_2O to give 13.7 g (95.2%) of crude product, mp 145–149°. Recrystallization from EtOAc gave 8.69 g (60.3%) of pure material, mp 152–154°. *Anal.* ($C_{12}H_{13}ClN_4O$) C, H, Cl, N.

Method E. 9-(*m*-Hydroxymethylbenzyl)-6-chloropurine.—A solution of 2.65 g (10.0 mmol) of 4-chloro-5-amino-6-(*m*-hydroxymethylbenzylamino)pyrimidine in 27 ml of triethyl orthoformate containing 22 mg (0.20 mmol) of $EtSO_3H$ was stirred at room temperature for 112 hr. After evaporation of the volatile materials *in vacuo*, the residual oil was stirred at room temperature with 30 ml of MeOH–C_6H_{14} (1:12) for 2 hr and the solid collected by filtration; yield, 2.57 g (93.8%); mp 110–118°. Recrystallization of the crude material from MeOH gave 1.82 g (66.2%) of material, mp 124–125°. *Anal.* ($C_{13}H_{11}ClN_4O$) C, H, Cl, N.

9-(*m*-Hydroxymethylbenzyl)adenine.—Prepared by method B from 9-(*m*-hydroxymethylbenzyl)-6-chloropurine: yield, 71%; mp 219–220° (MeOH). *Anal.* ($C_{13}H_{13}N_5O$) C, H, N.

Method F. 9-(*m*-Bromomethylbenzyl)adenine.—Dry HBr was bubbled into a cold suspension of 511 mg (2.00 mmol) of 9-(*m*-hydroxymethylbenzyl)adenine in 25 ml of anhydrous MeOH over a period of 30 min. Evaporation of the clear solution *in vacuo* gave a thick oil. Addition of 5 ml of H_2O to the oil, followed by addition of 25 ml of 5% $NaHCO_3$ gave 601 mg (94.4%) of crude material. Recrystallization from MeOH gave 357 mg (55.8% of pure material which softens with decomposition at *ca.* 250°. *Anal.* ($C_{13}H_{12}BrN_5$) C, H, Br, N.

***m*-(α-Ethylenedioxoethyl)toluene.**—A mixture of 23.8 g (17.8 mmol) of *m*-methylacetophenone in 200 ml of C_6H_6, 20 ml of ethylene glycol, and 133 mg (0.638 mmol) of *p*-toluenesulfonic acid was heated under reflux for 19 hr, and the H_2O formed collected in a Dean–Stark trap. The cooled C_6H_6 solution was washed with 5% aqueous Na_2CO_3 (2 × 50 ml), then with H_2O (2 × 50 ml). The organic phase was dried ($MgSO_4$), filtered, and the filtrate evaporated *in vacuo* to give 30.5 g (96.5%) of crude product. Fractional distillation of the product gave 17.4 g (70.6%) of analytically pure material, bp 98–98.5° (7.5 mm). *Anal.* ($C_{11}H_{14}O_2$) C, H.

9-(*m*-α-Ethylenedioxoethylbenzyl)-6-chloropurine.—To a mixture of 21.8 g (123 mmol) of *N*-bromosuccimide and 528 mg (2.18 mmol) of benzoyl peroxide in 25 ml of CCl_4 was added dropwise 17.8 g (100 mmol) of *m*-(α-ethylenedioxoethyl)toluene in 200 ml of CCl_4. Upon heating, a vigorous exothermic reaction took place. After the reaction had subsided, the reaction mixture was heated under reflux for 0.5 hr. The mixture was filtered and the filtrate evaporated *in vacuo* to give 34.4 g of crude *m*-(α-ethylenedioxoethyl)benzyl bromide which was used with 6-chloropurine in a modification of method A: yield, 63%; mp 138–140° (toluene–hexane). *Anal.* ($C_{16}H_{15}ClN_4O_2$) C, H, Cl, N.

9-(*m*-Acetylbenzyl)adenine Hydrochloride.—9-(*m*-α-Ethylenedioxoethylbenzyl)-6-chloropurine was used in a modification of method B. The crude adenine derivative was heated with 1 *N* HCl for 1 hr, cooled, and the product was collected by filtration. One recrystallization from H_2O gave the analytical product, mp 245–247°. *Anal.* ($C_{14}H_{14}ClN_5O$) C, H, Cl, N.

6-Chloro-9- and 7-(*p*-cyanobenzyl)purines.—These compounds were prepared from 6-chloropurine and *p*-cyanobenzyl bromide by a modification of method A: yield of the 9 isomer, 50%, mp 200–201° (MeOH). *Anal.* ($C_{13}H_8ClN_5$) C, H, Cl, N. Yield of the 7 isomer, 13%, mp 197–199° (MeOH). *Anal.* ($Cl_{13}H_8ClN_5$) C, H, Cl, N.

9-(*p*-Cyanobenzyl)adenine was prepared from 6-chloro-9-(*p*-cyanobenzylpurine by method B: yield, 67%; mp 255–257° (*i*-PrOH). *Anal.* ($C_{13}H_{10}O_6$) C, H, N.

4-Chloro-5-amino-6-(*p*-hydroxymethylbenzylamino)pyrimidine was prepared from 5-amino-4,6-dichloropyrimidine and *p*-hydroxymethylbenzylamine·HCl[11] by a modification of method D: yield, 79%; mp 211–212° dec (H_2O). *Anal.* ($C_{12}H_{13}ClN_4O$) C, H, Cl, N.

6-Chloro-9-(*p*-hydroxymethylbenzyl)purine was prepared by method E: yield, 59%; mp 142–143° (H_2O). *Anal.* ($C_{13}H_{11}ClN_4O$) C, H, Cl, N.

9-(*p*-Hydroxymethylbenzyl)adenine was prepared by method B from 6-chloro-9-(*p*-hydroxymethylbenzyl)purine: yield, 66%; mp 248–250° dec (H_2O). *Anal.* ($C_{13}H_{13}N_5O$) C, H, N.

9-(*p*-Bromomethylbenzyl)adenine hydrobromide was prepared by a modification of method F from 9-(*p*-hydroxymethylbenzyl)-adenine: yield, 37%; mp 247–249° dec (MeOH). *Anal.* ($C_{13}H_{13}Br_2N_5$) C, H, Br, N.

Reagents and Assay Procedures.—Adenosine deaminase (Type I, calf intestinal mucosa) was purchased from the Sigma Chemical Co. The assay procedure for the study of reversible inhibitors has previously been described[8] and is a modification of the procedure of Kaplan[12] based on the work of Kalckar.[13]

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