(+)-11, 114884-15-0; (−)-11, 125353-66-4; 11a, 125353-65-3; 11a epimer, 125353-67-5; 12, 125353-59-5; 12 triacetyl derivative, 125249-79-8; (−)-13, 125353-60-8; 14, 125353-61-9; 15, 125249-63-0; 16, 125353-62-0; 17, 125353-63-1; 18, 114489-63-3; (+)-19, 116183-74-5; 20, 125249-64-1; 20 R=H, 125249-73-2; 20a, 125249-74-3; 21, 125353-64-2; (+)-22, 125408-90-4; (+)-22 acetyl derivative, 125249-75-4; 23, 121236-40-6; 24, 121236-48-4; 25, 125249-65-2; 26, 125249-66-3; 26 diacetyl derivative, 125249-76-5; (+)-27, 125249-67-4; (+)-27 ring-opened derivative, 125280-78-6; 28, 125249-68-5; 29, 125249-69-6; (+)-30, 125249-70-9; (+)-30 triacetyl derivative, 125249-77-6; (+)-31, 125249-71-0; (+)-31 ring-opened derivative, 125249-78-7; 32, 121236-42-8; 33, 125249-72-1; (−)-34, 32233-40-2; (−)-35, 117957-63-8; (+)-36, 57345-51-4; 3-methoxy-2-methylacryloyl chloride, 52410-41-0.

Antirhinovirus Activity of 6-Anilino-9-benzyl-2-chloro-9*H*-purines

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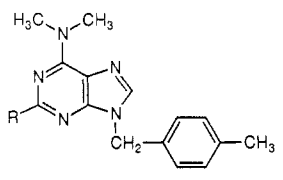
A series of 6-anilino-9-benzyl-2-chloropurines was synthesized and tested for antirhinovirus activity. Most of the compounds were prepared by reaction of the appropriate aniline with 9-benzyl-2,6-dichloro-9*H*-purine. Structure–activity relationship studies revealed that compounds with small, lipophilic para substituents were good inhibitors of serotype 1B. Several compounds had good activity against four representative serotypes.

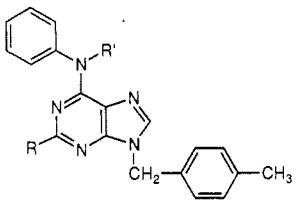
A variety of structural types have in vitro activity against rhinoviruses,[1,2] which are recognized as the most important causative agents of the common cold.[3] Several 2-substituted 9-benzylpurines have potent in vitro activity against rhinovirus serotype 1B, but most other serotypes are less sensitive.[4,5] Two of the most active compounds are the 2-trifluoromethyl (1) and 2-chloro (2) benzylpurines, which have IC_{50} values of 0.03 and 0.08 μM, respectively.

Structure–activity studies show that optimum activity is associated with 9-benzylpurines that contain a lipophilic, electron-withdrawing 2-substituent,[5] a small lipophilic substituent on the phenyl ring,[6] and a dimethylamino group at the 6-position.[7] Although many of these compounds have potent activity against serotype 1B, none have a uniform profile of potent antirhinovirus serotype activity. The 6-anilinopurine 3 has moderate activity against serotype 1B (IC_{50} = 1.9 μM), and it is also active against many other serotypes with IC_{50}s ranging over 5-fold.[8] To develop a more active agent with a broad spectrum of rhinovirus serotype activity, we prepared a series of 6-anilino-2-chloro-9-benzylpurines related to 4. The synthesis and antirhinovirus structure–activity relationships of these new compounds are reported herein.



1; R = CF_3

2; R = Cl

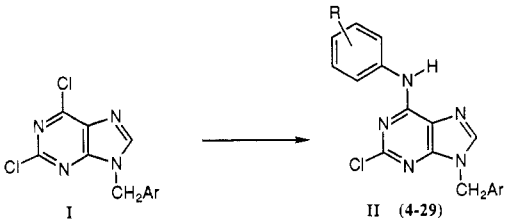


3; R = CF_3, R' = CH_3

4; R = Cl, R' = H

Chemistry

Most of the compounds in Table I were prepared from 9-benzyl-2,6-dichloro-9*H*-purine (I) and the appropriate aniline. Reaction of the aniline and I was a facile process if the aniline was unsubstituted or contained an electron-donating substituent. Excess aniline or triethylamine served as the acid acceptor, and the reaction proceeded in high yield at solvent reflux or at ambient temperature for the amino and dimethylamino analogues. However,



I II (4-29)

in cases where the anilino substituent was an electron-withdrawing group, triethylamine was a better nucleophile and reacted with I to give a 6-(diethylamino)purine. This side reaction was circumvented by using collidine as a base or by using excess aniline. The excess aniline was removed with a hydrochloric acid wash; the 2-chloro-6-anilinopurines II are weak bases and are not soluble in acid. The 4-(methylsulfonyl)aniline was too deactivated to react under these conditions. Consequently, 4-(methylthio)aniline was reacted with I to give 11, and the sulfide was oxidized to give sulfone 19.

Biological Results and Discussion

Although 6-(dimethylamino)purines like 1 and 2 have potent activity against serotype 1B,[4-6] the 6-anilino-2-(trifluoromethyl)purine 3 had a more uniform profile of antirhinoviral activity.[8] Since the 2-chloro analogue of 3, compound 4 (Table II), had a comparable profile of activity, analogues of 4 were prepared to examine the effect of aryl substituents on antiviral activity. Compounds that contained aryl substituents with a wide range of physicochemical properties were selected for synthesis so that meaningful structure–activity relationships (SAR) might be derived.[9,10]

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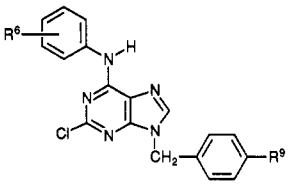
Table I. Physical Properties of 6-Anilinopurines



no.	R^6	R^9	method	yield, %	mp, °C	formula[a]
4	H	CH_3	A	57[b]	140–142	$C_{19}H_{16}ClN_5$
5	H	H	F	32[c]	225–230	$C_{18}H_{14}ClN_5 \cdot HCl$
6	4-C_4H_9	H	B	59[d]	118–123	$C_{22}H_{22}ClN_5$
7	4-OC_4H_9	H	B	70[e]	137–138	$C_{22}H_{22}ClN_5O$
8	4-CF_3	H	C	29[f]	180–182	$C_{19}H_{13}ClF_3N_5$
9	4-Br	H	B	11[f]	156–157	$C_{18}H_{13}BrClN_5$
10	4-$OCH(CH_3)_2$	H	E	26[g]	148–153	$C_{21}H_{20}ClN_5O$
11	4-SCH_3	H	C	17[f]	130–131	$C_{19}H_{16}ClN_5S$
12	4-CH_3	H	F	33[f]	131–132	$C_{19}H_{16}ClN_5$
13	4-$CO_2C_2H_5$	H	F	53[f]	164–165	$C_{21}H_{18}ClN_5O_2$
14	4-$N(CH_3)_2$	H	B[h]	48[i]	233–240 (dec)	$C_{20}H_{19}ClN_6 \cdot HCl \cdot 2H_2O$
15	4-F	H	B	54[j]	190–192	$C_{18}H_{13}ClFN_5 \cdot HCl$
16	4-CN	H	C	44[e]	203–204	$C_{19}H_{13}ClN_6$
17	4-$NHCOCH_3$	H	B	52[e]	221–223	$C_{20}H_{17}ClN_6O$
18	4-NH_2	H	B[h]	60[e]	160–162	$C_{18}H_{15}ClN_6$
19	4-SO_2CH_3	H	D	78[i]	210–211	$C_{19}H_{16}ClN_5O_2S$
20	3-OC_4H_9	H	E	71[e]	120–122	$C_{22}H_{22}ClN_5O$
21	3-Br	H	F	23[f]	186–187	$C_{18}H_{13}BrClN_5$
22	3-$OCH(CH_3)_2$	H	E	43[k]	107–108	$C_{21}H_{20}ClN_5O$
23	3-$CO_2C_2H_5$	H	F	68[f]	138–140	$C_{21}H_{18}ClN_5O_2$
24	3-$N(CH_3)_2$	H	B[h]	46[f]	155–156	$C_{20}H_{19}ClN_6$
25	3-F	H	F	68[f]	131–132	$C_{18}H_{13}ClFN_5$
26	3-NO_2	H	F	45[f]	217–218	$C_{18}H_{13}ClN_6O_2$
27	3-$NHCOCH_3$	H	F	53[e]	142–144	$C_{20}H_{17}ClN_6O \cdot {}^1/_2H_2O$
28	3-NH_2	H	F[h]	56[e]	185–186	$C_{18}H_{15}ClN_6$
29	3-SO_2CH_3	H	F	62[l]	186–188	$C_{19}H_{16}ClN_5O_2S$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from cyclohexane–ethyl acetate. [c] Recrystallized from ethanol–ethyl acetate. [d] Recrystallized from hexane–ether. [e] Recrystallized from ethanol–water. [f] Recrystallized from hexane–ethyl acetate. [g] Recrystallized from hexane–ether–ethyl acetate. [h] The reaction was done at ambient temperature instead of at reflux. [i] Recrystallized from ethanol. [j] Recrystallized from ethanol–ether. [k] Recrystallized from pentane–ethyl acetate. [l] Recrystallized from ether.

The compounds in Table II were tested initially in a plaque inhibition assay using monolayers of M-HeLa cells.[11] The 50% inhibitory concentration was measured with the plaque reduction assay if the IC_{50} was 10 μM or less. For several compounds the IC_{50} is reported as greater than a concentration; more specific values could not be quantitated due to limited solubility.

The parent 6-anilino-2-chloropurine **4** was active against rhinovirus 1B with an IC_{50} = 1.0 μM. Removal of the *p*-methyl group on the benzyl moiety to give **5** resulted in little change in activity against serotype 1B. Fourteen para and 10 meta substitutions were made on the anilino moiety of **5**. Compounds with para substituents that were lipophilic and relatively small (MR = 13 or less) (MR, the molar refractivity, is a measure of the "bulk" of substituents.[5]) were as active (*p*-F (**15**)) or up to 10-fold more active (*p*-SCH_3 (**11**)) than the parent **5**. Compounds with large, lipophilic para substituents (**6**, **7**, **10**, **13**; MR = 16 and greater) were weak inhibitors. The potency of the SCH_3 analogue **11** (IC_{50} = 0.14 μM) was greater than expected on the basis of these generalizations, since its MR of 13 falls between the extremes of the small lipophilic substituents (**8**, **9**, **12**, **15**; MR = −0.4 to 7.6) and the large lipophilic substituents (**6**, **7**, **10**, **13**; MR = 16–20.7). The enhancement in activity by the SCH_3 substituent may be due to its angular shape. The CF_3, Br, CH_3, and F substituents are largely symmetrical groups that project in the plane of the phenyl ring. The CH_3 moiety of SCH_3 can project out of the plane of the ring, which may introduce an additional binding interaction not available to the small, linear substituents.

The compounds with polar para substituents (**14**, **16**, **17**, **18**, **19**) were less active than the parent **5**. The polar but small CN substituent in **16** gave a compound with a 5-fold loss in activity relative to **5**. However, **16** was 30-fold less active than the *p*-Br compound **9**. Since the electronic and size (MR) parameters of CN and Br are very similar, but the lipophilic properties are quite different (π Br = 1.19 and π CN = −0.33) (π is the hydrophobic parameter.[5]), the correlation of lipophilicity with activity is supported further. However, the polar *p*-SO_2CH_3 substituent imparts activity to **19** (IC_{50} = 2 μM) that appears to be inconsistent with the SAR found for **5**–**18**. However, the SO_2CH_3 group has a shape similar to the SCH_3 group; it is angular, which may project the CH_3 moiety out of the plane of the ring resulting in a favorable binding interaction.

The meta-substituted compounds have activity over a wide range of IC_{50}s. Although no compound is more active than the parent **5**, both polar and lipophilic substituents are tolerated in the meta position. For example, the small lipophilic Br (**21**) and F (**25**) as well as the large lipophilic $OCH(CH_3)_2$ (**22**) substituents gave compounds with activity comparable to the parent **5**. But compounds with large polar substituents like $N(CH_3)_2$ (**24**) and $NHC(O)CH_3$ (**27**) were also active, with IC_{50}s comparable to **5**. However, various other substituents, whether small or large, lipophilic or polar, are less active (IC_{50} > 10 μM) (i.e., OC_4H_9 (**20**), NH_2 (**28**), SO_2CH_3 (**29**)). The tolerance for both

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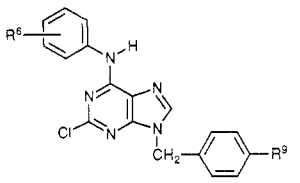
(10) Craig, P. N. *J. Med. Chem.* **1971**, *14*, 680.
(11) Kelley, J. L.; Miller, C. A.; Selway, J. W. T.; Schaeffer, H. J. *Eur. J. Med. Chem.* **1988**, *23*, 319.

Table II. Activity of 6-Anilino-2-chloropurines against Rhinovirus Types 1B, 2, 4, and 5



no.	R^6	R^9	IC_{50},[a] μM 1B	2	4	5
3[b]	H	CH_3	1.9	2.7	5.1	>8
4	H	CH_3	1.0	3.9	6.4	>8
5	H	H	1.65	8.3	14.2	16.3
6	4-C_4H_9	H	>10			
7	4-OC_4H_9	H	>40			
8	4-CF_3	H	0.3	16.6	85	200
9	4-Br	H	0.3	2.2	7.8	9.5
10	4-$OCH(CH_3)_2$	H	>40			
11	4-SCH_3	H	0.14	11	8.7	
12	4-CH_3	H	0.3	1.2		
13	4-$CO_2C_2H_5$	H	>10			
14	4-$N(CH_3)_2$	H	>40			
15	4-F	H	1.28	6.2	6.8	10
16	4-CN	H	9.4			
17	4-$NHCOCH_3$	H	>20			
18	4-NH_2	H	>20			
19	4-SO_2CH_3	H	2	10.5	4.5	
20	3-OC_4H_9	H	22			
21	3-Br	H	2.9	2.8	5.7	7.6
22	3-$OCH(CH_3)_2$	H	2	3.6	8.3	
23	3-$CO_2C_2H_5$	H	>10			
24	3-$N(CH_3)_2$	H	2.4	3.1	8.4	8.5
25	3-F	H	1.2	5.6	5.5	5.6
26	3-NO_2	H	>10			
27	3-$NHCOCH_3$	H	1.3		2.8	3.6
28	3-NH_2	H	>10			
29	3-SO_2CH_3	H	>40			
4',6-dichloroflavan (BW683C)			0.007	0.04	>10	>100

[a] The 50% inhibitory concentration (IC_{50}) was measured as described in ref 11. [b] This compound is a 2-(trifluoromethyl)-6-(*N*-methylanilino)purine.

lipophilic and polar substituents may be explained by the presence of two different binding sites adjacent to the 3- and 5-positions of the anilino moiety. One site may tolerate lipophilic meta substituents, whereas the second may tolerate polar meta substituents. In neither case is activity enhanced over parent compound **5**.

More detailed analysis of virus–inhibitor interactions might emerge from QSAR analysis of the data. However, this analysis was hampered by the absence of quantitative inhibition data for all compounds.

Several compounds with good activity against serotype 1B were also tested against serotypes 2, 4, and 5. We felt that these four serotypes could give an indication of breadth of serotype activity, without actually testing each agent against 19 or more serotypes as was done earlier.[4-6] Five compounds were active against all four serotypes with IC_{50}s = 10 μM or less (**9**, **15**, **21**, **24**, **25**). The compound with the most uniform profile of antirhinovirus activity was the *m*-F analogue **25**, which had IC_{50}s against types 1B, 2, 4, and 5 of 1.2, 5.6, 5.5, and 5.6 μM, respectively.

An animal model of rhinovirus infection, which is amenable to evaluation of in vitro antiviral agents, has not been reported. To obtain information on the in vivo behavior of these compounds, preliminary pharmocokinetic studies were performed in dogs. Compound **25** and **27** had elimination half-lives of 17.5 and 76 min, respectively, following intravenous dosing. However, concentrations of **25** and **27** in plasma after oral dosing in gelatin capsules were very low, which indicated poor oral bioavailability for these compounds.

Conclusion

The synthesis and antirhinovirus evaluation of this set of 6-anilino-9-benzyl-2-chloropurines has led to an improved understanding of SAR against rhinovirus serotype 1B. We identified several compounds with good activity against four serotypes, but secondary evaluation revealed in vivo properties incompatible with further development of these compounds. However, the 6-anilino-9-benzyl-2-chloropurines represent a new class of antiviral agent, which may serve as a useful lead for further research on antirhinovirus agents.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. NMR spectra were recorded on a Varian XL-100-15-FT or Varian FT-80A spectrometer using Me_4Si as an internal standard. UV absorption spectra were measured on a Cary 118 UV–vis spectrophotometer. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLCs were developed on Whatman 200 micron MK6F plates of silica gel (SG) with fluorescent indicator. Preparative flash chromatography[12] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385). The analytical samples gave combustion values for C, H, and N within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. 6-Anilino-2-chloro-9-(4-methylbenzyl)-9*H*-purine (4). A mixture of 2,6-dichloro-9-(4-methylbenzyl)-9*H*-purine[4] (0.500 g, 1.71 mmol), aniline (0.50 g, 5.37 mmol), ethanol

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(10 mL), and water (10 mL) was heated on a steam bath for 1.5 h. The reaction was cooled, and the volatiles were spin evaporated in vacuo. The residual solid was triturated with water and collected to give 0.50 g of **4**. Recrystallization from cyclohexane–ethyl acetate gave 0.34 g (57%) of analytically pure material: mp 140–142 °C; TLC-SG, ethyl acetate–cyclohexane (1:2); UV (pH 7 buffer–95% EtOH 1:1) λ_{max} 301 nm (ϵ 32000); NMR (DMSO-d_6) δ 10.28 (br s, 1 H, NH), 8.37 (s, 1 H, purine H), 7.57 (q, 4 H, ArH), 7.19 (s, 5 H, ArH), 5.35 (s, 2 H, CH_2), 2.26 (s, 3 H, CH_3). Anal. ($C_{19}H_{16}ClN_5$) C, H, N.

Method B. 9-Benzyl-6-(4-butoxyanilino)-2-chloro-9*H*-purine (7). A mixture of 9-benzyl-2,6-dichloro-9*H*-purine[4] (1.00 g, 3.58 mmol), 4-butoxyaniline (0.887 g, 5.37 mmol), triethylamine (1.09 g, 10.7 mmol), and ethanol (20 mL) was refluxed with stirring for 18 h. The mixture was spin evaporated in vacuo, and the residual paste was extracted with ether (2 × 100 mL). The combined ether extract was washed with 0.1 N hydrochloric acid (3 × 125 mL) and dried (sodium sulfate). The organic phase was concentrated under reduced pressure to give 1.40 g of **7** as a foam. Recrystallization from ethanol–water gave 1.02 g (70%) of analytically pure product: mp 137–138 °C; TLC-SG, ethyl acetate–cyclohexane (1:1). Anal. ($C_{22}H_{22}ClN_5O$) C, H, N.

Method C. 9-Benzyl-2-chloro-6-[4-(methylthio)anilino]-9*H*-purine (11). A mixture of 9-benzyl-2,6-dichloro-9*H*-purine[4] (1.00 g, 3.58 mmol), 4-(methylthio)aniline hydrochloride (0.819 g, 4.66 mmol), 2,4,6-collidine (0.997 g, 8.23 mmol), ethanol (20 mL), and water (10 mL) was refluxed with stirring for 5 h. The reaction was cooled to ambient temperature, the solids were diluted with ethanol (20 mL) and 1 N hydrochloric acid (150 mL), and the mixture was stirred for 0.5 h. The solids were collected and dissolved in boiling ethanol (100 mL), and then silica gel 60 (10 g) was added to the solution. The mixture was spin evaporated in vacuo, and the residual solid was introduced on a column (5 cm × 18 cm) of silica gel 60 wetted with ethyl acetate–hexane (1:2). The column was eluted initially with ethyl acetate–hexane (1:2) and then with ethyl acetate–hexane (1:1) by using the flash chromatography technique. The fractions containing the highest R_f, major component were combined, and the volume was reduced to 100 mL by spin evaporation in vacuo. The dark mother liquor was decanted from the white solid. The mother liquor was concentrated to dryness to give 0.81 g of a brown solid, which was used to prepare **19**. Recrystallization of the white solid from hexane–ethyl acetate gave 0.243 g (17%) of analytically pure **11**: mp 130–131 °C; TLC-SG, ethyl acetate–cyclohexane (1:1); NMR (DMSO-d_6) δ 10.30 (br s, 1 H, NH), 8.41 (s, 1 H, purine H), 7.54 (q, 4 H, ArH), 7.33 (s, 5 H, ArH), 5.40 (s, 2 H, CH_2), 2.46 (s, 3 H, SCH_3). Anal. ($C_{19}H_{16}ClN_5S$) C, H, N.

Method D. 9-Benzyl-2-chloro-6-[4-(methylsulfonyl)anilino]-9*H*-purine (19). A mixture of **11** (0.810 g, 2.12 mmol), acetic anhydride (4.18 g, 40.9 mmol), and acetic acid (20 mL) was heated to 50 °C with stirring. Hydrogen peroxide (12.6 M) (3.25 mL, 40.9 mmol) was added, and the reaction was refluxed with stirring for 1 h. The reaction was cooled, and the solids were collected and washed with water (50 mL). Recrystallization from ethanol gave 0.689 g (78%) of analytically pure product: mp 210–211 °C. Anal. ($C_{19}H_{16}ClN_5O_2S$) C, H, N.

Method E. 9-Benzyl-6-(3-butoxyanilino)-2-chloro-9*H*-purine (20). A mixture of 3-nitrophenol (5.00 g, 35.9 mmol), sodium hydride (60.2% dispersion in mineral oil) (2.15 g, 53.8 mmol), and dimethylformamide (30 mL) was stirred at ambient temperature for 0.5 h. Butyl bromide (5.90 g, 43.1 mmol) was added, and the reaction was heated at 120–140 °C for 2 h. The reaction mixture was poured into ice water (200 mL), and the aqueous phase was extracted with ether (2 × 150 mL). The combined ether extract was washed with 0.1 N sodium hydroxide (2 × 125 mL), and the ethereal solution was dried (magnesium sulfate). The organic phase was concentrated under reduced pressure to give 7.62 g of 3-butoxynitrobenzene as a brown liquid: NMR (DMSO-d_6) δ 7.1–7.8 (m, 4 H, ArH), 3.94 (t, 2 H, OCH_2), 1.9–0.6 (m, 7 H, $CH_2CH_2CH_3$).

A mixture of 3-butoxynitrobenzene (6.62 g, 33.9 mmol), 5% Pd/C (0.66 g), and methanol (50 mL) was shaken in the presence of hydrogen at 2–3 atm for 1 h. The reaction mixture was filtered through a pad of Celite and washed with methanol (20 mL). The filtrate was spin evaporated in vacuo to give 4.94 g (88%) of 3-butoxyaniline as a brown liquid: NMR (DMSO-d_6) δ 6.0–7.0 (m, 3 H, ArH), 4.86 (br s, 2 H, NH_2), 3.82 (t, 2 H, OCH_2), 2.0–0.7 (m, 7 H, $CH_2CH_2CH_3$).

A mixture of 9-benzyl-2,6-dichloro-9*H*-purine[4] (1.00 g, 3.58 mmol), 3-butoxyaniline (2.96 g, 17.9 mmol), ethanol (20 mL), and water (10 mL) was refluxed with stirring for 4 h. The volatiles were removed by spin evaporation in vacuo, and the residue was extracted with ether (100 mL). The organic phase was washed with 1 N hydrochloric acid (2 × 100 mL) and dried (sodium sulfate). The organic phase was concentrated with reduced pressure to give 1.52 g of an oil. The oil was dissolved in ethyl acetate (100 mL) and silica gel 60 (10 g) was added to the solution. This mixture was spin evaporated in vacuo, and the residual solid was introduced on a column (5 cm × 18 cm) of silica gel 60 wetted with ethyl acetate–hexane (2:3). The column was eluted with ethyl acetate–hexane (2:3) by using the flash chromatography technique. The fractions containing the lowest R_f, major component were combined and spin evaporated in vacuo to give 1.26 g of **20** as a white solid. Recrystallization from ethanol–water gave 1.04 g (71%) of analytically pure **20**: mp 120–122 °C; TLC-SG, ethyl acetate–cyclohexane (1:1). Anal. ($C_{22}H_{22}ClN_5O$) C, H, N.

Method F. 9-Benzyl-2-chloro-6-[3-(methylsulfonyl)anilino]-9*H*-purine (29). A mixture of 3-(methylsulfonyl)nitrobenzene[13] (10.0 g, 49.7 mmol) and methanol (200 mL) was warmed on a steam bath to effect dissolution. To the solution was added 5% Pd/C (1.0 g), and the mixture was shaken in the presence of hydrogen at 2–3 atm for 1.5 h. The reaction mixture was filtered through a pad of Celite and washed with methanol. The filtrate was spin evaporated in vacuo to give 7.89 g (93%) of 3-(methylsulfonyl)aniline as an oil: NMR (DMSO-d_6) δ 6.6–7.3 (m, 4 H, ArH), 5.52 (br s, 2 H, NH_2), 2.98 (s, 3 H, SO_2CH_3).

A mixture of 9-benzyl-2,6-dichloro-9*H*-purine[4] (1.00 g, 3.58 mmol), 3-(methylsulfonyl)aniline (3.06 g, 17.9 mmol), ethanol (30 mL), and water (10 mL) was refluxed with stirring for 18 h. The reaction mixture was concentrated to 15 mL under reduced pressure and then extracted with ether (2 × 175 mL). The combined ether extract was washed with 1 N hydrochloric acid (3 × 125 mL) and dried (sodium sulfate). The organic phase was concentrated under reduced pressure to give 1.30 g of **29** as a white foam. Recrystallization from ether gave 0.921 g (62%) of analytically pure **29**: mp 186–188 °C; TLC-SG, ethyl acetate. Anal. ($C_{19}H_{16}ClN_5O_2S$) C, H, N.

Acknowledgment. The authors thank Mr. C. J. Bradley and Mr. A. Emmerson for skilled technical assistance in determining the antiviral activities. We are indebted to Dr. J. P. Hubbell, Ms. B. F. Whitehead, and Mr. M. E. Grace for the in vivo experiments with **25** and **27**. Dr. B. S. Hurlbert and his staff provided some of the NMR spectra. The authors also thank Ms. T. Cozart, S. Paris, J. Appleton, and D. Tabon for assistance in preparation of the manuscript.

Registry No. **4**, 125802-42-8; **5**·HCl, 125802-43-9; **6**, 125802-44-0; **7**, 125827-87-4; **8**, 125802-45-1; **9**, 125802-46-2; **10**, 125802-47-3; **11**, 125802-48-4; **12**, 125802-49-5; **13**, 125802-50-8; **14**, 125802-51-9; **15**·HCl, 125802-52-0; **16**, 125802-53-1; **17**, 125802-54-2; **18**, 125802-55-3; **19**, 125802-56-4; **20**, 125802-57-5; **21**, 125802-58-6; **22**, 125802-59-7; **23**, 125802-60-0; **24**, 125802-61-1; **25**, 125802-62-2; **26**, 125802-63-3; **27**, 125827-88-5; **28**, 125802-64-4; **29**, 125802-65-5; I (Ar = 4-MeC_6H_4), 115204-73-4; I (Ar = Ph), 79064-26-9; $PhNH_2$, 62-53-3; 4-$C_4H_9C_6H_4NH_2$, 104-13-2; 4-$C_4H_9OC_6H_4NH_2$, 4344-55-2; 4-$CF_3C_6H_4NH_2$·HCl, 90774-69-9; 4-$BrC_6H_4NH_2$, 106-40-1; 4-$OCH(CH_3)_2C_6H_4NH_2$, 7664-66-6; 4-$SCH_3C_6H_4NH_2$·HCl, 39870-00-3; 4-$CH_3C_6H_4NH_2$, 106-49-0; 4-$CO_2C_2H_5C_6H_4NH_2$, 94-09-7; 4-$N(CH_3)_2C_6H_4NH_2$, 99-98-9; 4-$FC_6H_4NH_2$, 371-40-4; 4-$CNC_6H_4NH_2$·HCl, 2570-98-1; 4-$NHCOCH_3C_6H_4NH_2$, 122-80-5; 4-$NH_2C_6H_4NH_2$, 106-50-3; 3-$OC_4H_9C_6H_4NH_2$, 23079-68-7; 3-$BrC_6H_4NH_2$, 591-19-5; 3-$OCH(CH_3)_2C_6H_4NH_2$, 41406-00-2; 3-$CO_2C_2H_5C_6H_4NH_2$, 582-33-2; 3-$N(CH_3)_2C_6H_4NH_2$, 2836-04-6; 3-$FC_6H_4NH_2$, 372-19-0; 3-$NO_2C_6H_4NH_2$, 99-09-2; 3-$NHCOCH_3C_6H_4NH_2$, 102-28-3; 3-$NH_2C_6H_4NH_2$, 108-45-2; 3-$CH_3SO_2C_6H_4NH_2$, 35216-39-8; 3-$NO_2C_6H_4OH$, 554-84-7; 3-$BuOC_6H_4NO_2$, 122329-01-5; 3-$MeSO_2C_6H_4NO_2$, 2976-32-1.

(13) Twist, R. F.; Smiles, S. *J. Chem. Soc.* **1925**, *127*, 1248.