9-Benzyl-6-(dimethylamino)-9*H*-purines with Antirhinovirus Activity

James L. Kelley,*,† James A. Linn,† Mark P. Krochmal,† and J. W. T. Selway‡

Organic Chemistry Department, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709, and and Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS, U.K. *Received January 8, 1988*

A series of 9-benzyl-6-(dimethylamino)-9*H*-purines and 9-benzyl-2-chloro-6-(dimethylamino)-9*H*-purines were synthesized and tested in cell culture for activity against rhinovirus type 1B. The 9-benzylpurines that were unsubstituted in the 2-position had weak activity. However, introduction of a 2-chloro substituent resulted in a substantial increase in antiviral activity. One of the most active compounds, 2-chloro-6-(dimethylamino)-9-(4-methylbenzyl)-9*H*-purine (**29**), had an IC_{50} value of 0.08 μM against serotype 1B. Four compounds were tested against 18 other rhinovirus serotypes, but the majority tested were less sensitive than type 1B. The range of serotype sensitivity for **29** varied from 0.08 to 14 μM. These 9-benzyl-2-chloro-9*H*-purines represent a new class of antiviral agents with in vitro activity against rhinoviruses.

RNA viruses are the major causative factors of acute respiratory diseases.[1] The family Picornaviridae includes the rhinoviruses, which are the most important causative agents of the common cold.[2] There are over 100 serotypes of rhinovirus; such numbers have precluded the development of an adequate vaccine.[3] A number of different chemical agents have in vitro antirhinovirus activity.[4] A few have been tested in humans, but none has shown significant clinical efficacy.[5] Thus, the clinician's armamentarium of drugs remains devoid of an agent for prevention of the common cold.

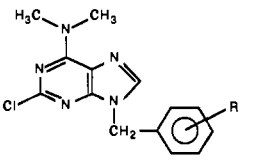
As an outgrowth of a program directed to the discovery and development of antiviral agents,[6-10] we identified a series of 9-benzylpurines with good activity in cell culture against rhinoviruses. The antirhinovirus activity of the (aminoacylamido)benzyl purine 1 (Table III) against rhinovirus 1B was recently reported.[11] Because of its interesting, albeit weak in vitro activity, we initiated a research program to determine the structure–activity relationship (SAR) between analogues of 1 and antiviral activity. The synthesis and SAR of these 9-benzylpurines are reported herein.

Chemistry

The 2-chloro purines **27–45** were prepared in two or three steps from 2,6-dichloropurine (I) (Scheme I). Alkylation of I with the appropriate benzyl halide gave a mixture of the 9-benzylpurine II and the 7-benzylpurine V.[12] The 9-isomers were easily separated from V by flash chromatography[13] and were usually used without further purification. Compounds **46–51**, which were thoroughly characterized, were prepared in 27–59% yields (Table II). The 6-chloro group in II was selectively displaced with 40% aqueous dimethylamine in ethanol to give **27–35** and **37–44** in 67–91% yields (Table I).

During the preparation of **27**, the 7-benzyl isomer of **46** was also isolated from the chromatography column and then converted to **52** (VI) with dimethylamine (Scheme I). The UV spectra provided a convenient means for distinguishing the 9- (III) and 7-isomers (VI). The λ_{max} for III was typically near 278 nm at pH 7, whereas the λ_{max} for VI (**52**) was at 296.5 nm. To further substantiate the assigned structures as III, in several cases (**27, 28, 29, 33**) the 2-chloro group of III was removed by catalytic hydrogenolysis—as illustrated for **27** in method D—to give the 9-benzylpurines IV, which had been previously prepared by an alternate method.[14,15]

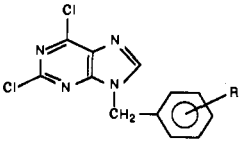
Table I. Physical Properties of 9-Benzyl-2-chloro-9*H*-purines



no.	R	method	yield, %	mp, °C	formula[a]
27	H	B	72[b]	118–120	$C_{14}H_{14}ClN_5$
28	4-Cl	B	85[c]	136–137	$C_{14}H_{13}Cl_2N_5$
29	4-CH_3	B	74[b]	117–118	$C_{15}H_{16}ClN_5$
30	4-CH_2CH_3	B	81[d]	120–122	$C_{16}H_{18}ClN_5$
31	4-$CH(CH_3)_2$	B	77[d]	124–125	$C_{17}H_{20}ClN_5$
32	4-$C(CH_3)_3$	B	71[d]	139–140	$C_{18}H_{22}ClN_5$
33	4-OCH_3	B	82[e]	164–166	$C_{15}H_{16}ClN_5O$
34	4-NO_2	B	87[e]	173–175	$C_{14}H_{13}ClN_6O_2$
35	4-CN	B	91[f]	235–236	$C_{15}H_{13}ClN_6$
36	4-NH_2	C	20[e]	200–201	$C_{14}H_{15}ClN_6$
37	3-I	B	77[d]	184–186	$C_{14}H_{13}ClIN_5$
38	3-Cl	B	67[g]	166–168	$C_{14}H_{13}Cl_2N_5$
39	3,4-Cl_2	B	10[d]	88–90	$C_{14}H_{12}Cl_3N_5$
40	3-CH_3	B	76[e]	167–169	$C_{15}H_{16}ClN_5$
41	3,4-benzo	B	70[d]	132–134	$C_{18}H_{16}ClN_5$
42	3-OCH_3	B	90[h]	106–108	$C_{15}H_{16}ClN_5O$
43	3-NO_2	B	88[f]	212–214	$C_{14}H_{13}ClN_6O_2$
44	3-$OCH_2C_6H_5$	B	64[d]	116–117	$C_{21}H_{20}ClN_5O$
45	3-NH_2	C	55[g]	157–160	$C_{14}H_{15}ClN_6$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from toluene–hexane. [c] Recrystallized from heptane. [d] Recrystallized from ethanol–water. [e] Recrystallized from methanol. [f] Recrystallized from toluene. [g] Recrystallized from ethanol. [h] Recrystallized from toluene–petroleum ether (30–60 °C).

Table II. Physical Properties of 9-Benzyl-2,6-dichloro-9*H*-purines



no.	R	method	yield, %	mp, °C	formula[a]
46	H	A	35	147–149[b,c]	$C_{12}H_8Cl_2N_4$
47	4-Cl	A	35	158–160[d]	$C_{12}H_7Cl_3N_4$
48	4-CH_3	A	44[d]	147–148	$C_{13}H_{10}Cl_2N_4$
49	4-OCH_3	A	59	132–134[d]	$C_{13}H_{10}Cl_2N_4O$
50	4-NO_2	A	27	169–171[e]	$C_{12}H_7Cl_2N_5O_2$
51	4-CN	A	36[e]	201–203	$C_{13}H_7Cl_2N_5$

[a] All compounds were analyzed for C, H, N. [b] Recrystallized from toluene. [c] Mp 148 °C reported for this compound by ref 12. [d] Recrystallized from methanol. [e] Recrystallized from ethanol.

The 9-(aminobenzyl)purines **36** and **45** were prepared from **34** and **43** by catalytic hydrogenation in acetic acid.

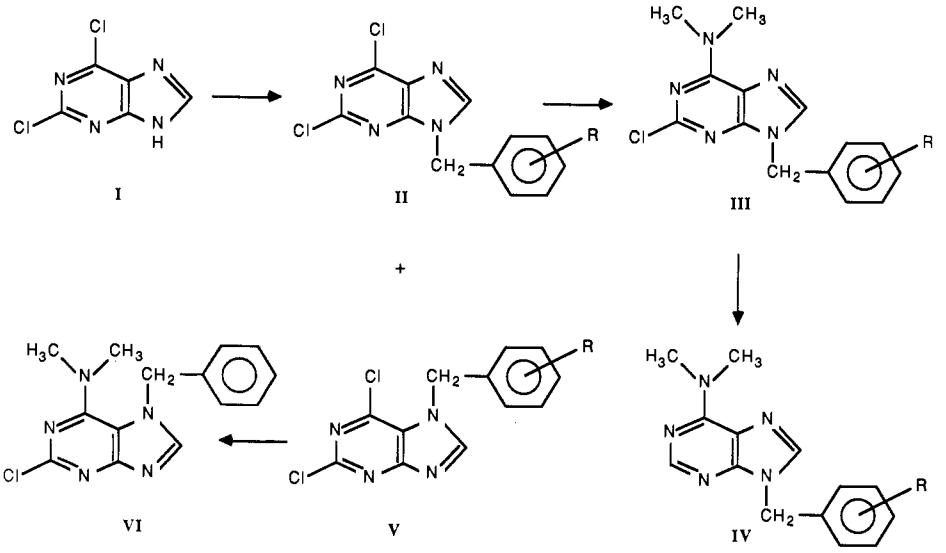
† Burroughs Wellcome Co.

‡ Wellcome Research Laboratories.

(1) Anderson, L. J.; Patriarca, P. A.; Hierholzer, J. C.; Noble, G. R. *Medical Clin. North Am.* **1983**, *67*, 1009.

0022-2623/88/1831-2001$01.50/0

Scheme I



Reduction of the nitro group was fast and resulted in negligible dechlorination.

Biological Results and Discussion

As part of a broad program on substituted purines, we reported the anticonvulsant activity[14] of **3** and its analogues and the antiviral activity[11] of 1 and its analogues. To study the SAR of analogues of 1 and possible antirhinovirus activity, compounds from the anticonvulsant program were tested for antiviral activity. The antirhinovirus 1B activity of a variety of compounds from the anticonvulsant program are tabulated in Table III.

Compounds were tested initially in a plaque inhibition assay using monolayers of M-HeLa cells. If the compound was active or slightly active at 50 μg/disk, the 50% inhibitory concentration was measured with the plaque reduction assay.[11]

The phenylalanyl benzylpurine 1 was active against rhinovirus 1B with an IC_{50} value of 17 μM.[11] Removal of the phenylalanyl moiety of 1 to give the 3-amino derivative **2** or the unsubstituted analogue **3** resulted in a 2–3-fold loss in activity. Substitution on **3** with 10 different para substituents gave compounds less active than 1, except for the 4-methyl derivative **5**, which was twice as active against rhinovirus type 1B with an IC_{50} value of 8.6 μM. Eleven meta-substituted derivatives of **3** were also tested, but only the 3-iodo analogue **15** was as active as **5** with an IC_{50} value of 6.7 μM. Two dichloro compounds, **18** and **19**, were quite active with IC_{50} values of 4.6 and 2.5 μM, respectively.

When a chloro group was substituted in the purine 2-position of **3** to give **27**, a substantial increase in potency resulted. Compound **27**, which had an IC_{50} value of 0.82 μM, was 40-fold more active than **3** against rhinovirus type 1B. Nine para-substituted analogues of 2-chloropurine **27** were prepared, and several were found to have increased activity. The most active derivatives were **29** (4-CH_3), **30** (4-CH_2CH_3), and **31** (4-$CH(CH_3)_2$) with IC_{50} values of 0.08 and 0.07 μM. Compound **29** was 100-fold more active than its 2-deschloro analogue **5**. Several meta-substituted analogues were also prepared, but none were as active as **29**, **30**, or **31**.

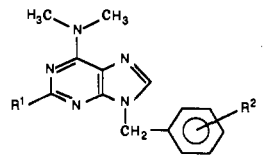
The 2-chloro substituent imparted a substantial increase in antirhinovirus type 1B activity in many of the 9-(substituted benzyl)purines **2–26**. These 2-chloro purines represent a new class of potent, in vitro antirhinovirus agents that, at least against serotype 1B, have activity only 2–10-fold less than enviroxime[16] (**54**) or 4′,6-dichloroflavan[9] (**53**) (Table III).

The most active compounds in the series (**28–31**) were tested against 18 other rhinovirus serotypes (Table IV). No other serotypes were as sensitive as type 1B. For example, the range of serotype sensitivity for **29** varied from 0.08 to 14 μM. Only three serotypes had IC_{50} values ≤ 1 μM. Nine serotypes had IC_{50} values ≥ 5 μM. A comparable profile of sensitivity was found for **28** and **31**. The *p*-ethyl analogue **30** had the best profile of antirhinovirus serotype activity. Five serotypes were sensitive at 1 μM or less and only five serotypes had IC_{50} values ≥ 5 μM.

The 9-benzyl-2-chloro-9*H*-purines represent a new class of antirhinovirus agents. Although these compounds have potent in vitro activity against rhinovirus serotype 1B, the majority of other serotypes tested were less sensitive. Introduction of a 2-chloro substituent had a big effect on

(2) Douglas, R. G., Jr. In *Antiviral Agents and Viral Diseases of Man*; Galasso, G. J., Merigan, T. C., Buchanan, R. A., Eds.; Raven: New York, 1984; pp 313–367.
(3) Lennette, E. H. *Bull. W.H.O.* **1981**, *59*, 305.
(4) Kelley, J. L. *Annu. Rep. Med. Chem.* **1984**, *19*, 117.
(5) Ahmad, A. L. M.; Tyrrell, D. A. J. *Antiviral Res.* **1986**, *6*, 241.
(6) Schaeffer, H. J.; Beauchamp, L.; de Miranda, P.; Elion, G. B.; Bauer, D. J.; Collins, P. *Nature (London)* **1978**, *272*, 583.
(7) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.
(8) Schaeffer, H. J. *Nucleosides, Nucleotides and Their Biological Applications*; Rideout, J. L., Henry, D. W., Beacham, L. M., III, Eds.; Academic: New York, 1983; p 1.
(9) Bauer, D. J.; Selway, J. W. T.; Batchelor, J. F.; Tisdale, M.; Caldwell, I. C.; Young, D. A. B. *Nature (London)* **1981**, *292*, 369.
(10) Mitsuya, H.; Weinhold, K. J.; Furman, P. A.; St. Clair, M. H.; Nusinoff-Lehrman, S.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.
(11) Kelley, J. L.; Miller, C. A.; Selway, J. W. T.; Schaeffer, H. J. *Eur. J. Med. Chem.*, in press.
(12) Montgomery, J. A.; Hewson, K.; Temple, C., Jr. *J. Pharm. Med. Chem.* **1962**, *5*, 15.
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(14) Kelley, J. L.; Linn, J. A.; Krochmal, M. P.; McLean, E. W.; Soroko, F. *J. Med. Chem.* **1988**, *31*, 606.
(15) Montgomery, J. A.; Temple, C., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 630.
(16) Wikel, J. H.; Paget, C. J.; DeLong, D. C.; Nelson, J. D.; Wu, C. Y. E.; Paschal, J. W.; Dinner, A.; Templeton, R. J.; Chaney, M. O.; Jones, N. D.; Chamberlin, J. W. *J. Med. Chem.* **1980**, *23*, 368.

Table III. Activity of 9-Benzylpurines against Rhinovirus Type 1B in Vitro



no.	R^1	R^2	IC_{50},[a,b] μM
1[c]	H	3-NHCOCH(NH_2)$CH_2C_6H_5$	17
2[c]	H	3-NH_2	50
3[d]	H	H	33
4[d]	H	4-Cl	>25
5[d]	H	4-CH_3	8.6
6[d]	H	4-F	–
7[d]	H	4-OCH_3	38
8[d]	H	4-NO_2	–
9[d]	H	4-CN	–
10[d]	H	4-OH	34
11[d]	H	4-$OCH_2C_6H_5$	–
12[e]	H	4-$NHCOCH_3$	–
13[d]	H	4-NH_2	–
14[d]	H	3-CF_3	19.6
15[d]	H	3-I	6.7
16[d]	H	3-Br	14.4
17[d]	H	3-Cl	30.5
18[d]	H	3,5-Cl_2	4.6
19[d]	H	3,4-Cl_2	2.5
20[d]	H	3-CH_3	32
21[d]	H	3-F	23
22[d]	H	3-OCH_3	50
23[d]	H	3-NO_2	–
24[d]	H	3-CN	–
25[d]	H	3-OH	–
26[d]	H	3-$OCH_2C_6H_5$	13
27	Cl	H	0.82
28	Cl	4-Cl	0.12
29	Cl	4-CH_3	0.08
30	Cl	4-CH_2CH_3	0.08
31	Cl	4-$CH(CH_3)_2$	0.07
32	Cl	4-$C(CH_3)_3$	0.44
33	Cl	4-OCH_3	0.7
34	Cl	4-NO_2	0.51
35	Cl	4-CN	–
36	Cl	4-NH_2	0.3
37	Cl	3-I	0.36
38	Cl	3-Cl	0.59
39	Cl	3,4-Cl_2	0.32
40	Cl	3-CH_3	0.6
41	Cl	3,4-benzo	1.1
42	Cl	3-OCH_3	2.0
43	Cl	3-NO_2	–
44	Cl	3-$OCH_2C_6H_5$	– T
45	Cl	3-NH_2	13
53		4′,6-dichloroflavan (BW683C)	0.007
54		enviroxime	0.04

[a] The plaque inhibition assay was performed as described in ref 11. T = toxic; – = inactive at 50 μg/disk. [b] The 50% inhibitory concentration was measured as described in ref 11. [c] For synthesis, see ref 11. [d] For synthesis, see ref 14. [e] For synthesis, see: Kelley, J. L.; McLean, E. W.; Ferris, R. M.; Howard, J. L., submitted for publication.

the activity of the parent 9-benzyl purines. Further studies on the effect of various purine 2-substituents may lead to an understanding of the SAR of this series.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and were uncorrected. UV spectra were measured on a Unicam SP 800 or Cary 118 UV–vis spectrophotometer. NMR data were recorded on a Varian XL-100-15-FT, a Varian FT-80A, a Varian T-60, or a Hitachi Perkin-Elmer R-24 spectrometer with Me_4Si as an internal standard. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLC's were developed on Whatman 200 μ MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[13] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385). All compounds were analyzed for C, H, N and gave combustion values within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. 2,6-Dichloro-9-(4-methylbenzyl)-9*H*-purine (48). A mixture of 2,6-dichloropurine (13.11 g, 69.38 mmol), dimethyl sulfoxide (150 mL), anhydrous potassium carbonate (9.59 g, 69.38 mmol), and 4-methylbenzyl bromide (12.84 g, 69.38 mmol) was stirred at ambient temperature for 22 h. The reaction mixture was poured into ice water and extracted with methylene chloride (4 × 30 mL). The combined extracts were washed with 0.1 M sodium hydroxide (2 × 30 mL) and water (4 × 30 mL). The solution was filtered through glass wool and spin evaporated in vacuo. The residual solid was dissolved in methylene chloride (200 mL) and added to silica gel 60 (20 g). This mixture was spin evaporated in vacuo, and the residual solids were introduced on a column (8 cm × 15 cm) of silica gel 60 wetted with ethyl acetate–cyclohexane (1:3). The column was eluted with ethyl acetate–cyclohexane (1:3) by using the flash chromatography technique. The fractions containing the higher R_f, major component were combined and spin evaporated in vacuo to give 9.11 g (44%) of 48, mp 147–148 °C. Recrystallization from methanol gave analytically pure 48: mp 148–150 °C; UV (0.1 N HCl + 20% EtOH) λ_{max} 276.5 nm (ε 9900); UV (pH 7 buffer + 20% EtOH) λ_{max} 276.5 nm (ε 9700); UV (0.1 N NaOH + 20% EtOH) λ_{max} 261 nm (ε 12 000); NMR (Me_2SO-d_6) δ 8.76 (s, 1 H, purine H), 7.14 (m, 4 H, Ar), 5.39 (s, 2 H, CH_2), 2.21 (s, 3 H, CH_3); MS, *m/e* 292 (M^+), 105 ($C_8H_9^+$).

Method B. 2-Chloro-6-(dimethylamino)-9-(4-ethylbenzyl)-9*H*-purine (30). A solution of 2,6-dichloro-9-(4-ethylbenzyl)-9*H*-purine (1.28 g, 4.17 mmol) and ethanolic dimethylamine (50 mL, 2.2 M) was stirred at ambient temperature for 18 h. The volatiles were removed by spin evaporation in vacuo, and water (50 mL) was added to the residue. The mixture was reduced in volume by half by spin evaporation and additional water (75 mL) was added to the mixture. The solids were collected by suction filtration to give 1.25 g (95%) of crude product. Recrystallization of the solids from ethanol–water afforded 1.07 g (81%) of analytically pure **30**: mp 120.5–122 °C; UV (pH 7 buffer + 10% EtOH) λ_{max} 278.5 nm (ε 20 400); NMR (Me_2SO-d_6) δ 8.22 (s, 1 H, purine H), 7.18 (m, 4 H, Ar), 5.30 (s, 2 H, NCH_2), 3.43 (br s, 6 H, NMe_2), 2.57 (q, 2 H, CH_2C), 1.12 (t, 3 H, CCH_3); MS, *m/e* 315 (M^+), 286 (M^+ – 29), 196 (M^+ – C_9H_{11}), 119 ($C_9H_{11}^+$).

Method C. 9-(3-Aminobenzyl)-2-chloro-6-(dimethylamino)-9*H*-purine (45). A mixture of **43** (1.22 g, 3.67 mmol), acetic acid (100 mL), and 10% Pd/C (0.15 g) was shaken in the presence of hydrogen at 2–3 atm for 0.5 h. The reaction mixture was filtered through Celite (Preiser Scientific, Inc.) and concentrated under reduced pressure. The residue was recrystallized from ethanol to give 0.96 g (86%) of **45**, mp 156–158 °C, which contained a lower R_f impurity on TLC. The product was dissolved in dichloromethane (100 mL) and applied to a column (5 cm × 15 cm) of silica gel 60. The column was eluted with dichloromethane–ethyl acetate (1:1) by flash chromatography.[13] The

Table IV. Activity of 28–31 against 19 Rhinovirus Serotypes[a]

no.	1A	1B	2	3	4	5	8	9	12	13	14	15	16	18	19	21	29	30	31
28	3.	0.12	2.5	3.1	>2.5	5.2	4.5	2.1	5.4	(12%)[b]	(32%)[c]	(40%)[c]	NT	(35%)[b]	>5.	>5.	(31%)[c]	>2.5	(42%)[c]
29	0.12	0.08	11.	7.2	4.6	6.2	13.	2.	5.4	2.3	7.	3.5	1.	4.	14.	5.6	>5.	NT	1.6
30	0.5	0.08	2.8	4.	4.	5.6	(30%)[d]	0.4	7.	4.9	3.3	3.9	0.2	(42%)[d]	4.6	8.	0.3	4.	3.5
31	<1.	0.07	1.2	7.	6.1	8.	6.	<1.	3.4	5.8	5.9	4.5	0.2	4.3	7.	NT	0.5	8.	4.

[a] The numbers are the 50% inhibitory concentration (IC_{50}) measured as described in ref 11. In several cases the exact IC_{50} was not determined and is denoted as greater than (>) or less than (<) the concentration. NT = not tested. [b] Percent inhibition of plaque formation at 5 μM. [c] Percent inhibition of plaque formation at 2.5 μM. [d] Percent inhibition of plaque formation at 4 μM.

appropriate fractions were combined and spin evaporated in vacuo. The residue was recrystallized from ethanol to give 0.61 g (55%) of **45**: mp 157–160 °C; UV (pH 7 buffer + 9.5% EtOH) λ_{max} 279 (ϵ 21 300); NMR (Me_2SO-d_6) δ 8.18 (s, 1 H, purine H), 6.29–7.16 (complex m, 4 H, Ar), 5.19 (s, 2 H, CH_2), 5.08 (br s, 2 H, NH_2), 3.45 (br s, 6 H, NMe_2); MS, *m/e* 302 (M^+), 273 ($M^+ - 29$), 196 ($M^+ - C_7H_8N$), 106 ($C_7H_8N^+$).

Method D. 9-Benzyl-6-(dimethylamino)-9*H*-purine (3). A mixture of **27** (0.900 g, 3.13 mmol), sodium acetate (0.41 g, 5.0 mmol), absolute ethanol (200 mL), and 5% Pd/C (0.090 g) was shaken in the presence of hydrogen at 2–3 atm for 6.5 h. The reaction mixture was left idle for 18 h, then filtered through Celite (Preiser Scientific, Inc.), and concentrated under reduced pressure. The residue was recrystallized from heptane to give 0.53 g (67%) of **3**, mp 126–127 °C, which was identical with a sample prepared from 6-chloropurine by mixture melting point, TLC, UV, and NMR.[14,15]

7-Benzyl-2-chloro-6-(dimethylamino)-7*H*-purine (52). A mixture of 7-benzyl-2,6-dichloro-7*H*-purine[12] (1.00 g, 3.58 mmol) and ethanolic dimethylamine (2.2 M, 100 mL) was warmed to dissolve the solids and then stirred at ambient temperature for 18 h. The resultant mixture was concentrated under reduced pressure to near dryness, and the solids were dispersed in ethyl acetate. The dimethylamine hydrochloride salt was removed by filtration, and the filtrate was concentrated to an oil. The oil was dissolved in toluene and filtered, and the filtrate was diluted with petroleum ether (bp 30–60 °C). Cooling on ice caused a solid to form, mp 122–126 °C. The solids were redissolved in toluene and washed with water, and the organic phase was dried over calcium chloride. The mixture was filtered, and the filtrate was concentrated to a solid residue. The solid was recrystallized from toluene–petroleum ether (bp 30–60 °C) to give 0.70 g (68%) of **52**, mp 128–130 °C. To remove a fluorescent impurity, the solids were dissolved in dichloromethane, and the solution was passed through Super Filtrol No. 19. The filtrate was reduced to dryness, and the solid residue was recrystallized from toluene–petroleum ether (bp 30–60 °C) to give an analytically pure material: mp 130–31 °C; UV (pH 7 buffer + 9.5% EtOH) λ_{max} 296.5 (ϵ 13 100); NMR (Me_2SO-d_6) δ 8.20 (s, 1 H, purine H), 6.97–7.47 (complex m, 5 H, Ar), 5.61 (s, 2 H, CH_2), 3.03 (s, 6 H, NMe_2); MS, *m/e* 287 (M^+), 258 ($M^+ - 29$), 196 ($M^+ - C_7H_7$), 91 ($C_7H_7^+$). Anal. ($C_{14}H_{14}ClN_5$) C, H, N.

Acknowledgment. We thank A. Emmerson and C. J. Bradley for skilled technical assistance in determining the antiviral activities and Dr. B. S. Hurlbert and his staff for some of the NMR spectra. We acknowledge the assistance of T. Cozart, J. Appleton, and D. Alston in preparation of the manuscript and thank Allen Jones for proofreading the manuscript.

Registry No. 1, 115204-49-4; 2, 115204-50-7; 3, 6332-42-9; 4, 112089-03-9; 5, 112089-04-0; 6, 112089-05-1; 7, 112089-06-2; 8, 13233-85-7; 9, 112089-07-3; 10, 112089-08-4; 11, 112089-09-5; 12, 115204-51-8; 13, 112089-10-8; 14, 112089-11-9; 15, 112089-12-0; 16, 112089-13-1; 17, 112089-14-2; 18, 112089-15-3; 19, 112089-16-4; 20, 112089-17-5; 21, 112089-18-6; 22, 112089-19-7; 23, 7008-56-2; 24, 112089-20-0; 25, 115204-52-9; 26, 112089-22-2; 27, 115204-53-0; 28, 115204-54-1; 29, 115204-55-2; 30, 115204-56-3; 31, 115204-57-4; 32, 115204-58-5; 33, 115204-59-6; 34, 115204-60-9; 35, 115204-61-0; 36, 115204-62-1; 37, 115204-63-2; 38, 115204-64-3; 39, 115204-65-4; 40, 115204-66-5; 41, 115204-67-6; 42, 115204-68-7; 43, 115204-69-8; 44, 115204-70-1; 45, 115204-71-2; 46, 79064-26-9; 47, 115204-72-3; 48, 115204-73-4; 49, 115204-74-5; 50, 115204-75-6; 51, 115204-76-7; 52, 115204-77-8; I, 5451-40-1; II (R = 4-Et), 115204-78-9; II (R = 4-Pr-*i*), 115204-79-0; II (R = 4-*t*-Bu), 115204-80-3; II (R = O-I), 115204-81-4; II (R = 3-Cl), 115204-82-5; II (R = 3,4-Cl_2), 115204-83-6; II (R = 3-Me), 115204-84-7; II (R = 3-OMe), 115204-85-8; II (R = 3-NO_2), 115204-86-9; II (R = 3-OCH_2Ph), 115204-87-0; V (R = H), 56025-87-7; *p*-$ClC_6H_4CH_2Br$, 622-95-7; *p*-$MeC_6H_4CH_2Br$, 104-81-4; *p*-$MeOC_6H_4CH_2Br$, 2746-25-0; *p*-$O_2NC_6H_4CH_2Br$, 100-11-8; *p*-$NCC_6H_4CH_2Br$, 17201-43-3; benzyl bromide, 100-39-0; 9-(2-naphthylmethyl)-2,6-dichloro-9*H*-purine, 115204-88-1.

New "Ofloxacin" Type Antibacterial Agents. Incorporation of the Spiro Cyclopropyl Group at N-1

John S. Kiely,* Mel C. Schroeder, and Josephine C. Sesnie

Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105.
Received February 24, 1988

The first example incorporating a spiro cyclopropyl group into an "ofloxacin" type of quinolone antibacterial agent has been prepared by potassium fluoride mediated ring closure of the hydroxymethyl cyclopropyl intermediate to give 9′-fluoro-7′-oxo-10′-(1-piperazinyl)spiro[cyclopropane-1,3′(2′*H*)-[7*H*]pyrido[1,2,3-*de*][1,4]benzoxazine]-6′-carboxylic acid. Analogues were made by substitution at C-7 by various complex amines. Evaluation of these compounds for antibacterial activity was carried out. All examples prepared and examined showed in vitro minimum inhibitory values and in vivo mouse protection results to be diminished as compared to the parent, ofloxacin.

Within the "quinolone" class of antiinfective agents, there exists a series of potent tricyclic compounds containing a three-atom bridge connecting the quinolone N-1 and C-8 positions. This series is typified by ofloxacin[1-4] (**1a**), flumequine, and methylflumequine[5] (**1b,c**) (Figure 1).

Various modifications of this class of compounds have been reported. The information available suggests that the benzoxazine quinolone structural framework (**1**), formally 7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, is optimal relative to the carbon[5] or sulfur[6]

(1) Imamura, I.; Shibamura, S.; Hayakawa, I.; Osada, Y. *Antimicrob. Agents Chemother.* **1987**, *31*, 325.
(2) Daiichi, S. *Drugs Future* **1983**, *8*, 395.
(3) Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907.
(4) Tanaka, Y.; Suzuki, N.; Hayakawa, I. *Chem. Pharm. Bull.* **1984**, *32*, 4923.
(5) Gerster, J. F.; Rohlfing, S. R.; Pecore, S. E.; Winandy, R. M.; Stern, R. M.; Lundmesser, J. E.; Olsen, R. A.; Gleason, W. B. *J. Med. Chem.* **1987**, *30*, 839.

0022-2623/88/1831-2004$01.50/0