denoted by CMA and BAW, respectively. Unless otherwise stated, all reagents and solvents were reagent grade and used without subsequent purification.

Reaction of (+)- and (−)-Naltrexone Hydrochloride with *N*-Aminosuccinimide. To a stirred solution of (+)-naltrexone hydrochloride (110 mg, 0.29 mmol) and (−)-naltrexone hydrochloride (110 mg, 0.29 mmol) in DMF (2.5 mL) was added *N*-aminosuccinimide hydrochloride[5] (200 mg, 1.33 mmol). The mixture was stirred at 100 °C for 18 h, and the solvent was removed in vacuo. Methanol, saturated sodium bicarbonate solution, and chloroform were added to the residue. The mixture was filtered (Celite), and the filtrate was extracted with chloroform (three times). The combined organic phases were washed with brine, dried, and concentrated to give a crude product that was purified on a Sephadex column (LH-20, MeOH) to afford pure meso isomer **2** (50 mg, 26%) and (±)-**1** (90 mg, 46.9%). Data for **2**: R_f, 0.25 (CMA 18:2:0.1); IR (KBr, cm^{-1}) 3400, 3000, 2830, 1640, 750; ^1H NMR ($CDCl_3$) δ 0.12 (4 H, m), 0.52 (4 H, m), 0.82 (2 H, m), 1.63 (2 H, d, J = 8.2 Hz), 2.00–2.50 (12 H, m), 2.65 (4 H, m), 3.06 (2 H, d, J = 18.4 Hz), 3.20 (2 H, d, J = 5.8 Hz), 5.56 (2 H, S), 6.45 (2 H, d, J = 7.8 Hz), 6.60 (2 H, d, J = 7.8 Hz); FABMS 662.2 ($M^+ + 1$), 660.1 ($M^+ - 1$). Data for **2**·2HCl: mp >265 °C dec; R_f, 0.37 (BAW, 2:1:1); $[\alpha]^{25}_D$ −2.1° (*c* 0.1, MeOH). Anal. ($C_{40}H_{43}O_6N_3$·2HCl·4H_2O) C, H, N, Cl. Data for (±)-**1**: R_f, 0.36 (CMA, 18:2:0.1); IR (KBr, cm^{-1}) 3400, 2920, 2830, 1630, 1500, 1458; ^1H NMR ($CDCl_3$) δ 0.13 (4 H, m), 0.52 (4 H, m), 0.84 (2 H, m), 1.67 (2 H, d, J = 9.5 Hz), 2.15–2.50 (12 H, m), 2.65 (4 H, m), 3.05 (2 H, d, J = 18.4 Hz), 3.16 (2 H, d, J = 6.0 Hz), 5.50 (2 H, S), 6.46 (2 H, d, J = 8.0 Hz), 6.63 (2 H, d, J = 8.0 Hz); FABMS 662.2 ($M^+ + 1$), 660.1 ($M^+ - 1$). Data for (±)1·2HCl: mp >265 °C dec; $[\alpha]^{25}_D$ −5.2° (*c* 0.1, MeOH); R_f, 0.46 (BAW, 2:1:1). Anal. ($C_{40}H_{43}O_6N_3$·2HCl·4H_2O) C, H, N, Cl.

(5*S*,5′*S*,9*S*,9′*S*,13*R*,13′*R*,14*R*,14′*R*)-17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetrahydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol, (+)-1. The procedure was identical with that employed for the preparation[2] of (−)-**1** except that (+)-naltrexone hydrochloride (50 mg, 0.13 mmol) was employed in place of (−)-naltrexone hydrochloride. Column chromatography (Sephadex L-20, MeOH) afforded pure (+)-**1** (20 mg, 40%): R_f, 0.36 for free base (CMA, 18:2:0.1) and 0.46 for hydrochloride (BAW, 2:1:1); IR of (+)-**1** was identical with that of nor-BNI, (−)-**1**.

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Registry No. (−)-**1**, 105618-26-6; (+)-**1**, 114375-46-1; (±)-**1**, 114375-45-0; **2**, 114375-44-9; (+)-naltrexone·HCl, 114274-32-7; (−)-naltrexone·HCl, 16676-29-2; *N*-aminosuccinimide, 19283-13-7.

7-Aminoquinolines. A Novel Class of Agents Active against Herpesviruses

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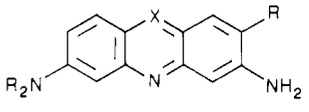
A series of 7-aminoquinoline derivatives was synthesized and evaluated for their capacity to produce cytotoxicity in KB cells and to inhibit the replication of herpes simplex virus (HSV) type 1. All compounds tested inhibited the replication of HSV-1 with 50% inhibitory concentrations in the range of 2–50 μg/mL. The antiviral activity of many compounds, however, was separated from cytotoxicity to replicating uninfected cells by only two- to fivefold higher than those required for antiviral activity. Nonetheless, six compounds (**10**, **28**, **29**, **32**, **34**, and **36**) were identified in which the separation was greater than fivefold. All compounds examined were more potent inhibitors of viral DNA synthesis than the cellular DNA synthesis.

In recent years considerable research efforts have been conducted in order to find drugs useful for the treatment of herpes virus infections.[1–5] Also, herpes viruses have been implicated as the cause of a number of carcinomas.[6–9] Heterocyclic dyes, such as neutral red (**1a**) and proflavine (**1b**), are among the wide variety of compounds that exhibit



1a: R = Me; X = N
b: R = H; X = CH

activity against herpesviruses.[1,10,11] These drugs act by intercalation and photodynamic disruption of DNA. Although these dyes are not appropriate for human therapy,[11] another group of planar heterocyclic compounds—the 4-aminoquinolines such as chloroquine—act through intercalation[12] and have extensive therapeutic usefulness.[13] Because 7-aminoquinolines may be considered analogues of proflavine and because they are relatives of chloroquine, we have prepared and tested a series of such compounds. This article describes the synthesis and evaluation of novel

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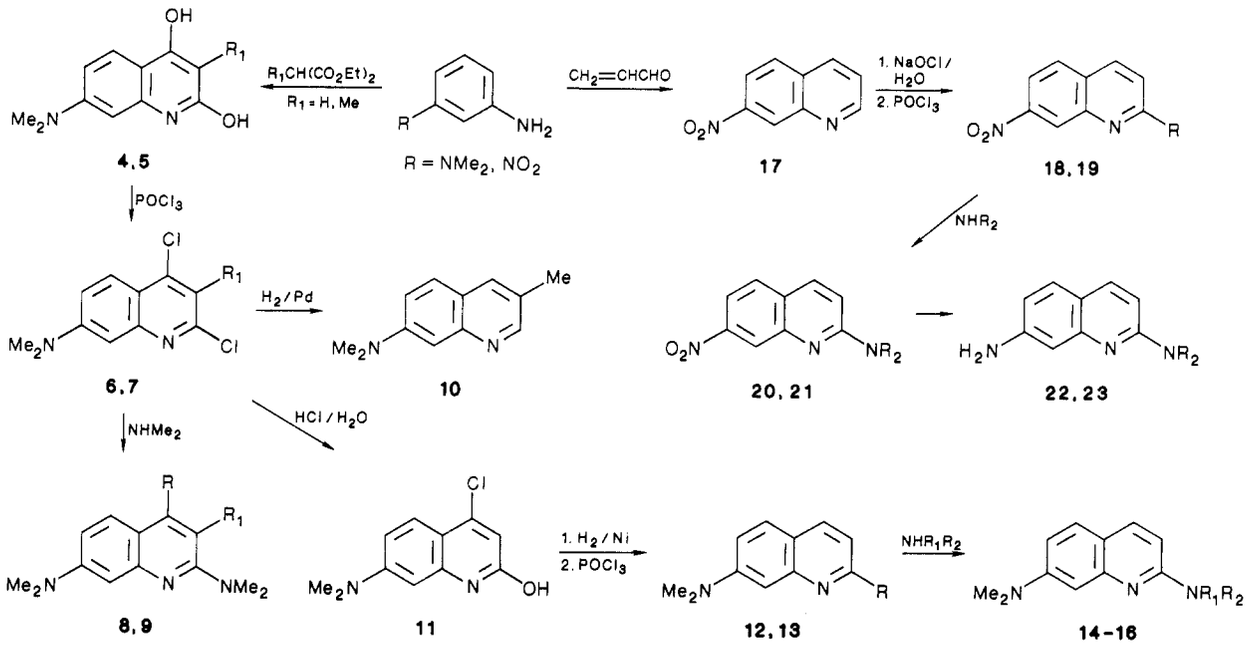
Scheme I

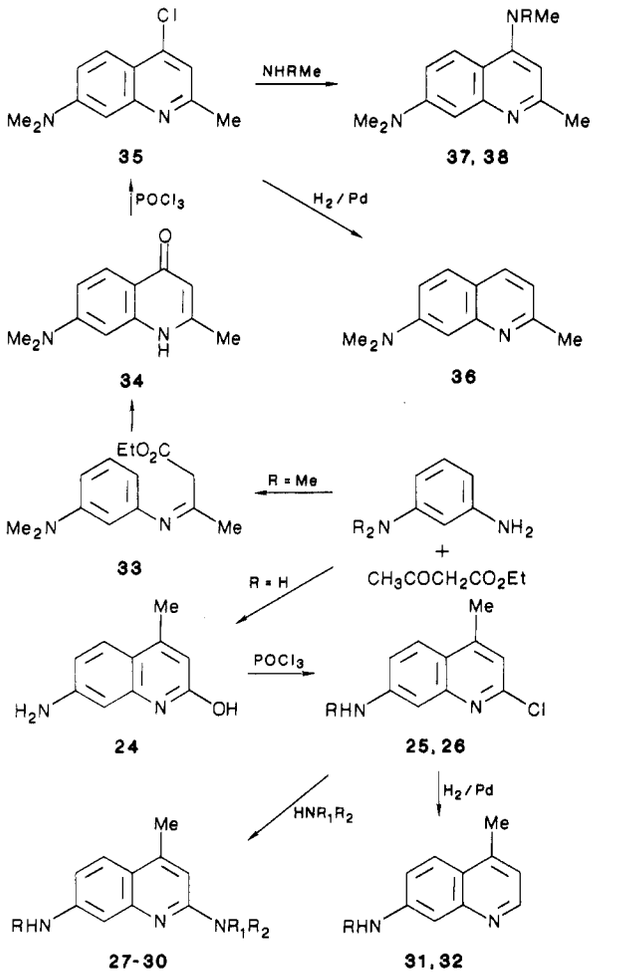


2,7- and 4,7-quinolinediamine and 7-quinolinamine derivatives as potential antiherpes agents.

Chemistry. Methods for the synthesis of the aminoquinolines are depicted in Schemes I and II. In scheme I, 2,4-dihydroxy-7-(dimethylamino)quinoline (**4**)[14] and the 3-methyl derivative **5** were prepared, respectively, through condensation of *N,N*-dimethyl-*m*-phenylenediamine with diethyl malonate and diethyl methylmalonate. Reaction of **4** and **5** with $POCl_3$ gave the corresponding 2,4-dichloro derivatives **6** and **7**. Condensation of these 2,4-dichloro derivatives **6** and **7** with dimethylamine gave the corresponding substituted amines **8** and **9**. Although condensation of **6** with dimethylamine gave the 2,4-disubstituted amine **8**, only the 2-amino substituent **9** was obtained through the condensation of **7** with dimethylamine. This can be explained because the chlorine at position 2 of quinoline is more reactive to nucleophilic substitution than at position 4.[15] Catalytic hydrogenolysis of **7** gave 3-methyl-7-(dimethylamino)quinoline (**10**). Hydrolysis of 2,4-dichloroquinoline (**6**) gave the corresponding 4-chlorocarbostyril **11**. Catalytic hydrogenolysis of 4-chloro-7-(dimethylamino)carbostyril (**11**) gave 7-(dimethylamino)carbostyril (**12**), which upon treatment with $POCl_3$ gave the 2-chloro derivative **13**. Condensation of **13** with ammonia, methylamine, and dimethylamine afforded the corresponding 2,7-quinolinediamines **14–16**.

With 7-nitroquinoline (**17**) as the starting material, prepared by the Skraup reaction with *m*-nitroaniline,[16] the required 2,7-quinolinediamine (**22**) and N^2,N^2-dimethyl-2,7-quinolinediamine (**23**) were synthesized as described in Scheme I. Treatment of **17** with sodium hypochlorite and water gave 7-nitrocarbostyril (**18**),[17] which was treated with $POCl_3$, and the resultant 2-chloro derivative **19** was condensed with ammonia in a bomb under pressure to give **20**, which upon catalytic hydrogenation gave **22**. By the same method **19** was condensed with dimethylamine and the resultant **21** was reduced with $SnCl_2$/HCl to **23**.

Scheme II



The synthesis of 4-methyl-2,7-quinolinediamines **27–30** (Table I) is described in Scheme II. The condensation of *m*-phenylenediamine with ethyl acetoacetate gave 7-amino-4-methylcarbostyril (**24**).[18,19] Chlorination of **24**

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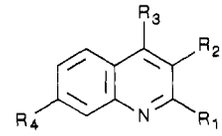
Table I. Physical Properties and Antiviral Activity of 7-Aminoquinolines



compd no.	R_1	R_2	R_3	R_4	recrystn solvent	mp, °C	method	yield, %	formula	IC_{50}, μg/mL[a] cytotoxicity	IC_{50}, μg/mL[a] HSV-1 replication	in vitro therapeutic index[b]
5	OH	Me	OH	NMe_2	ethanol	352–355	A	75	$C_{12}H_{14}N_2O_2$	80	29	3
6	Cl	H	Cl	NMe_2	hexane	108–110	B	72	$C_{11}H_{10}Cl_2N_2$	*c*		
7	Cl	Me	Cl	NMe_2	hexane	117–119	B	77	$C_{12}H_{12}Cl_2N_2$	>32[d]	13	2
8	NMe_2	H	NMe_2	NMe_2	hexane	118–120	C	99	$C_{15}H_{22}N_4$	19	5	4
9	NMe_2	Me	Cl	NMe_2	ethyl acetate	135–137	C	89	$C_{14}H_{18}ClN_3$	>32[d]	49	
10	H	Me	H	NMe_2	petr ether	54–56	D	48	$C_{12}H_{14}N_2$	70	7.6[e]	9
11	OH	H	Cl	NMe_2	ethanol	279–283	E	99	$C_{11}H_{11}ClN_2O$			
12	OH	H	H	NMe_2	ethanol	240–242	D	90	$C_{11}H_{12}N_2O$	139	30	5
13	Cl	H	H	NMe_2	hexane	105–107	B	94	$C_{11}H_{11}ClN_2$	*c*		
14	NH_2	H	H	NMe_2	hexane	140–142	F	30	$C_{11}H_{13}N_3$	10	2[e]	5
15	NHMe	H	H	NMe_2	hexane	115–117	C	71	$C_{12}H_{15}N_3$	24	11	2
16	NMe_2	H	H	NMe_2	H_2O/methanol	106–108	C	86	$C_{13}H_{17}N_3$	17	6[e]	3
19	Cl	H	H	NO_2	ethanol	137–139	B	95	$C_9H_5ClN_2O_2$			
20	NH_2	H	H	NO_2	acetone	247–249	C	90	$C_9H_7N_3O_2$			
21	NMe_2	H	H	NO_2	methanol	168–170	C	79	$C_{11}H_{11}N_3O_2$	*c*		
22	NH_2	H	H	NH_2	ether	147–149	D	96	$C_9H_9N_3$	40	10	4
23	NMe_2	H	H	NH_2	ether	105–106	*f*	50	$C_{11}H_{13}N_3$	130	51	3
25	Cl	H	Me	NH_2	H_2O/methanol	126–128	B	78	$C_{10}H_9ClN_2$	133	53	3
26	Cl	H	Me	NHAc	acetone	205–207	*f*	99	$C_{12}H_{11}ClN_2O$	86[e]	21[e]	4
27	NH_2	H	Me	NHAc	cloroform	237–239	F	25	$C_{12}H_{13}N_3O$	34	10[e]	3
28	NMe_2	H	Me	NHAc	acetone	229–231	C	74	$C_{14}H_{17}N_3O$	>100[d]	18	6
29	NH_2	H	Me	NH_2	ethanol	325–327	*f*	82	$C_{10}H_{11}N_3$·HCl	27	4[e]	7
30	NMe_2	H	Me	NH_2	methanol/H_2O	147–149	C	70	$C_{12}H_{15}N_3$	11[e]	6[e]	2
31	H	H	Me	NH_2	hexane	79–81	D	25	$C_{10}H_{10}N_2$	63	40[d,e]	2
32	H	H	Me	NHAc	benzene	201–202	D	75	$C_{12}H_{12}N_2O$	215[e]	31[e]	7
34	Me	H	OH	NMe_2	ethanol	325–328	*f*	30	$C_{12}H_{14}N_2O$	447[e]	23[e]	19
35	Me	H	Cl	NMe_2	hexane	90–92	B	76	$C_{12}H_{13}ClN_2$	22	7	3
36	Me	H	H	NMe_2	hexane	59–62	E	84	$C_{12}H_{14}N_2$	40	4.5[e]	9
37	Me	H	NMe_2	NMe_2	ethyl acetate	78–80	C	60	$C_{14}H_{19}N_3$	15	9	2
38	Me	H	NHMe	NMe_2	ethanol	266–270	C	25	$C_{13}H_{17}N_3$	14	6	2

[a] 50% inhibitory concentration, see text for methods. [b] Ratio of cytotoxicity to inhibition of viral replication, rounded to nearest whole numbers. [c] Compound insufficiently soluble to be tested in vitro. [d] Low drug solubility, IC_{50} not reached at maximum solubility. [e] Average of replicate analyses performed at two or three separate times. [f] Method described in the Experimental Section. All compounds had elemental analysis for C, H, N.

with $POCl_3$ gave the 2-chloro derivative **25**. Acetylation of **25** gave the 7-acetamido derivative **26**, which was aminated to **27** and **28**. Hydrolysis of **27** gave 4-methyl-2,7-quinolinediamine (**29**). Compound **25** was directly condensed with dimethylamine to give **30**. A similar condensation failed with ammonia or methylamine. Catalytic hydrogenation of **25** and **26** gave 7-amino- and 7-acetamido-4-methylquinolines (**31** and **32**).

The synthesis of 2-methyl-4,7-quinolinediamines **37** and **38** is also described in Scheme II. The condensation of *N,N*-dimethyl-*m*-phenylenediamine with ethyl acetoacetate in refluxing benzene gave the intermediate β-*m*-(dimethylamino)anilino crotonic ester (**33**). Heating **33** at 260 °C in phenyl ether gave 7-(dimethylamino)-2-methyl-4(1*H*)-quinolone (**34**). Chlorination of **34** gave the 4-chloro derivative **35**, which upon condensation with dimethylamine and methylamine, gave the 4-amino derivatives **37** and **38**. Catalytic hydrogenolysis of **35** gave 7-(dimethylamino)-2-methylquinoline (**36**).

Antiviral Activity. The quinolines were evaluated for antiviral activity by comparing effects on titers of herpes simplex virus type 1 (HSV-1) in infected cells to effects on four biochemical parameters in uninfected cells. The latter effects on protein and DNA synthesis were taken as measures of cytotoxicity. The ratio between cytotoxicity and inhibition of virus replication was called the "in vitro therapeutic index". Table I summarizes results with compounds for which adequate amounts were available and which were sufficiently soluble in cell culture medium to be evaluated. All 24 compounds tested inhibited the replication of HSV-1; 50% inhibitory (I_{50}) concentrations ranged from 2 to 50 μg/mL. All compounds also inhibited cellular protein and DNA synthesis but at generally higher concentrations (I_{50} = 10–447 μg/mL). Thus, as a group,

Table II. Antiviral Activity of Known Drugs[a]

compd	IC_{50}, μg/mL cytotoxicity	IC_{50}, μg/mL HSV-1 replication	in vitro therapeutic index
acyclovir[b]	>100	2.6	>38[d]
ara-A	39	5.6	7
ara-T	>500[c]	0.6	833
phosphonoformate	1490	189	8
arildone	75	11	7
chloroquine	85	27	3

[a] All terms and units defined in legend to Table I. [b] Averages of replicate experiments. [c] I_{50} concentrations not reached at highest level tested (500 μg/mL). [d] Plaque reduction assay with HSV-1 strain 148.

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the compounds possessed a positive in vitro therapeutic index. Most compounds, however, had in vitro therapeutic indexes of only 2–4.

Several known antiherpes drugs that act by various mechanisms were evaluated for comparative purposes (Table II). Acyclovir is highly specific because it is phosphorylated by herpes virus thymidine kinase but not by cellular kinases and therefore has a high therapeutic index. Vidarabine (9-β-D-arabinofuranosyladenine, *ara*-A) and phosphonoformate—two clinically useful antivirals that act by selective inhibition of herpes DNA polymerase—differed markedly in their potency but had essentially the same in vitro therapeutic indexes. Arildone (4-[6-(2-chloro-4-methoxyphenoxy)hexyl]-3,5-heptanedione), an experimental antiviral drug, also had a similar in vitro therapeutic index. *ara*-T (1-β-D-arabinofuranosylthymine) was more potent and much more selective than the other compounds owing to its known preferential activation in herpes-infected cells by HSV-induced pyrimidine deoxynucleoside kinase.[4] Chloroquine [7-chloro-4-[[4′-(diethylamino)-1′-methylbutyl]amino]-quinoline], which is known to possess activity against herpesviruses in vitro[21,22] but not in vivo,[22] was more potent than phosphonoformate but was not as selective as the known antiviral drugs against HSV-1 replication. These observations, plus the known selectivity of other antivirals,[1-5] led us to conclude that unless in vitro antiviral activity is separated from cytotoxicity by at least seven- to eightfold, compounds probably do not merit additional consideration. On this basis, compounds, **10**, **29**, **32**, **34**, and **36** were considered to be active antivirals and merit additional investigation.

Experimental Section

Melting points were determined in a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer spectrophotometer Model 337, in KBr disks on Nujol mulls. NMR spectra were run on a Varian A-60 spectrometer. The IR and NMR spectra were consistent with the assigned structures. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, IN. Where analyses are indicated only by the symbols of elements, they are within ±0.4% of the theoretical values. Hydrogenations were carried out in a Parr hydrogenator. The general procedures listed in Table I and the preparation of the requisite starting materials are described by the following examples.

Method A. 7-(Dimethylamino)-4-hydroxy-3-methylcarbostyril (5). A mixture of 13.6 g (0.1 mol) of *N,N*-dimethyl-*m*-phenylenediamine and 17.4 g (0.1 mol) of diethyl methylmalonate was heated in an oil bath at 180–200 °C for 1.5 h with an alcohol separator. Only 4.5 g of ethanol was separated. The reaction mixture was then heated on a heating mantle at 260–270 °C. A yellow precipitate was obtained, and an additional 4.5 g ethanol was separated after 20 min of heating. The resulting yellow solid was cooled and washed with acetone, giving 15 g (75%) of **5**. Recrystallization from ethanol gave 15 g (75%) of **5**: ^{1}H NMR (Me_2SO-d_6) δ 2.47 (s, 3 H, Me), 2.95 (s, 6 H, NMe_2), 6.47 (s, H-8), 6.72 (d, J = 9 Hz, H-6), 7.57 (d, H-5). Anal. ($C_{12}H_{14}N_2O_2$) C, H, N.

Method B. Chlorination of the 2- or 4-hydroxyquinolines was accomplished by the following general method. A mixture of 0.1 mol of the hydroxyquinoline and excess phosphorus oxychloride (0.2 mol) was heated gently until complete solution was achieved. The reaction mixture was refluxed for 1 h and then kept in ice to cool. It was diluted with water while being cooled. After dilution it was neutralized with NH_4OH, and the resulting precipitate was recrystallized from the proper solvent.

Method C. Condensation of the Chloroquinolines with Dimethyl- and Methylamine or Ammonia. A mixture of the chloroquinoline and excess amine or ammonia (15 equiv) in methanol was heated in a Parr pressure reaction bomb at 110–120 °C for 15 to 20 h. Usually the desired product precipitated after evaporation of the excess amine at room temperature.

Method D. Catalytic Hydrogenolysis of Chloroquinolines. 7-(Dimethylamino)carbostyril (12). 4-chloro-7-(dimethylamino)carbostyril (**11**) (2.2 g, 0.01 mol) was dissolved in 25 mL of H_2O containing 5 g of KOH, with addition of 5 mL of ethanol to make a clear solution. To the solution was added 0.5 g of Raney nickel, and hydrogen was allowed to pass through the solution with shaking. After 3 h the reaction mixture was filtered from the catalyst. Neutralization with HCl gave a crystalline product. Recrystallization from acetone gave 1.7 g of **12**: ^{1}H NMR (Me_2SO-d_6) δ 2.97 (s, 6 H, NMe_2), 6.61 (s, H-8), 6.71 (d, H-6), 6.82 (d, H-4), 7.46 (d, H-5), 7.77 (d, H-3). Anal. ($C_{11}H_{12}N_2O$) C, H, N. Hydrogenolysis of the rest of the chloro derivatives was done with 5% Pd/C in glacial acetic acid solution. 2,7-Quinolinediamine (**22**) was prepared by hydrogenation of **20** by use of activated Raney nickel as catalyst in acetone solution.

Method E. 4-Chloro-7-(dimethylamino)carbostyril (11). A mixture of 2.4 g (0.01 mol) of 2,4-dichloro-7-(dimethylamino)quinoline (**6**) and 15 mL of 6 N HCl was refluxed for 1 h. During reflux a red color, which developed at the start of the reaction, disappeared by the end of the reaction. The reaction mixture was diluted with water and neutralized with NaOH solution, whereupon a yellow crystalline product was obtained. Recrystallization from alcohol gave 2.2 g of **11**: ^{1}H NMR (Me_2SO-d_6) δ 3.01 (s, 6 H, NMe_2), 6.90 (s, H-8), 7.18 (s, H-3), 7.25 (d, H-6), 7.84 (d, H-5). Anal. ($C_{11}H_{11}ClN_2O$) C, H, N.

***N*^{2},*N*^{2}-Dimethyl-2,7-quinolinediamine (23).** A mixture of 0.2 g (0.001 mol) of **21** and 1.2 g of $SnCl_2$ in 5 mL of concentrated HCl was heated with stirring at 80 °C for 12 h. The reaction mixture was diluted with water and neutralized with NaOH solution. The product obtained was recrystallized from ether, giving 0.1 g of **23**: ^{1}H NMR ($CDCl_3$) δ 2.97 (s, 6 H, NMe_2), 5.32 (s, NH_2), 6.61 (s, H-8), 6.71 (d, H-6), 6.82 (d, H-4), 7.46 (d, H-5), 7.77 (d, H-3). Anal. ($C_{11}H_{13}N_3$) C, H, N.

Method F. *N*^{7},*N*^{7}-Dimethyl-2,7-quinolinediamine (14). A mixture of 2.6 g (0.01 mol) of 2-chloro-7-(dimethylamino)quinoline (**13**) and 15 g of phenol was allowed to heat at 140 °C. Dry ammonia was passed through the solution at 180–200 °C for 6 h. The mixture was treated with a strong NaOH solution and then extracted with chloroform. The chloroform was evaporated, and the product obtained was recrystallized from hexane to give 0.62 g of **14**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 6 H, NMe_2), 6.61 (s, H-8), 6.71 (d, H-6), 6.81 (d, H-4), 7.42 (d, H-5), 7.69 (d, H-3). Anal. ($C_{11}H_{13}N_3$) C, H, N.

4-Methyl-2,7-quinolinediamine Hydrochloride (29). A mixture of 0.4 g (0.002 mol) of **27** and 10 mL of 15% HCl was refluxed for 1 h. The reaction mixture was neutralized with NH_4OH solution after which most of the product stayed in solution. The solution was filtered and cooled, whereupon a yellow crystalline material was obtained. Recrystallization from ethanol gave 0.3 g of **29**. Anal. ($C_{10}H_{11}N_3$·HCl) C, H, N.

7-(Dimethylamino)-2-methyl-4(1*H*)-quinolone (34). A mixture of 13.6 g (0.1 mol) of *N,N*-dimethyl-*m*-phenylenediamine and 13 g (0.1 mol) of ethyl acetoacetate in 200 mL of benzene was refluxed for 7 h with a water separator. The benzene was distilled, and the oily residue obtained was heated at 255 °C in phenyl ether for 0.5 h. The solid obtained was then separated after cooling and washed with petroleum ether. Recrystallization from ethanol gave 6.5 g of **34**: ^{1}H NMR (Me_2SO-d_6) δ 2.39 (s, Me), 2.98 (s, 6 H, NMe_2), 6.11 (s, H-3), 6.72 (s, H-8), 6.95 (d, H-6), 7.92 (d, H-5). Anal. ($C_{12}H_{14}N_2O$) C, H, N.

Virus and Cells. The source of cells and HSV-1 (HF strain), the routine growth and passage of KB and BHK 21/4 cells, the propagation and titration of virus, and techniques for the enumeration of cells and detection of mycoplasma contamination have been described previously.[24]

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Inhibition of HSV-1 Replication. The effect of drugs on virus replication was measured as described previously[25] by treating duplicate cultures of HSV-1-infected KB cells for 20 h with one of five or six half-log dilutions of test compound. Virus titers were determined by enumeration of macroscopic plaques in BHK 21/4 cells seeded with serial dilutions of the disrupted KB cell cultures.

Cytotoxicity Determinations. Biochemical cytotoxicity measurements were made as detailed earlier[26] with logarithmically growing KB cells planted in scintillation vials. Two sets of duplicate cultures were treated for 20 h with one of five or six half-log dilutions of drug. One set of cultures was used to determine drug effects on protein synthesis as measured both by Lowry assays and incorporation of ^{3}H-labeled amino acids into acid-precipitable material. The other was used to determine drug effects on DNA synthesis as measured by diphenylamine assay and incorporation of [^{3}H]thymidine.

Data Analysis. Dose–response relationships were constructed by linearly regressing log drug concentrations against the percent inhibition values derived for viral replication, incorporation of [^{3}H]thymidine, incorporation of ^{3}H-labeled amino acids, and net synthesis of total protein or total DNA. I_{50} concentrations were calculated from the regression lines by using methods previously described.[25] Samples containing 10 μg/mL *ara*-A were included in all assays as positive controls. Results from sets of assays were rejected whenever inhibition by *ara*-A deviated from its mean response by more than 1.5 standard deviations. I_{50} concentrations for cytotoxicity presented in the tables are the mean values of the four I_{50} concentrations for effects on protein and DNA synthesis.

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Synthesis and Antiviral Activity of Novel N-Substituted Derivatives of Acyclovir†

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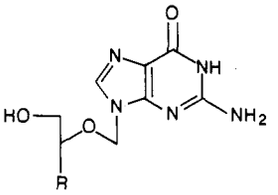
Novel N-substituted derivatives of acyclovir (**1a**) were synthesized and evaluated for their antiviral, antimetabolic, and antitumor cell properties in vitro. Monomethylation of **1a** at positions 1, 7, and N-2 gave compounds **2–4**, respectively. When positions 1 and N-2 were linked together by an isopropeno group, the tricyclic 9-[(2-hydroxyethoxy)methyl]-1,*N*-2-isopropenoguanine (**5**) was obtained. Compound **5** was then further methylated at positions N-2 and 7 to give **6** and **7**, respectively. None of the new acyclovir derivatives showed any appreciable antimetabolic or antitumor cell activity. However, compounds **2** and **5** exhibited a marked antiherpetic activity. Their activity spectrum was similar to that of acyclovir, and their selectivity as inhibitors of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) was at least as great as, if not greater than, that of acyclovir.

The potent and selective antiherpetic activity of the acyclic analogue of guanosine, 9-[(2-hydroxyethoxy)-methyl]guanine (acyclovir, **1a**),[1,2] has generated much interest in the synthesis of new congeners. Modifications of the acyclic side chain of **1a** have given rise to several new compounds with significant selective antiviral activity,[3–14] 9-(1,3-dihydroxy-2-propoxymethyl)guanine (**1b**)[3–8] being the acyclovir derivative that has been most extensively pursued for its antiviral properties[15] (for recent reviews on acyclic guanosine analogues, see ref 16 and 17). Modifications of the guanine moiety of acyclovir have received relatively minor attention and yielded few compounds with appreciable antiviral activity. Only the 8-substituted derivatives, i.e. 8-amino-, 8-bromo-, 8-iodo-, and 8-methylacyclovir have proven to be active antiherpetic agents in vitro.[18]



1a, R = H
b, R = CH_2OH

Acyclovir owes its antiherpetic selectivity to a specific phosphorylation by the virus-encoded deoxythymidine

† Abbreviations used: HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; VV, vaccinia virus; VSV, vesicular stomatitis virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; SHV-1, suid herpesvirus type 1; BHV-1, bovid herpesvirus type 1; EHV-1, equid herpesvirus type 1 ; TK^-, deficient in thymidine kinase inducing activity; PRK, primary rabbit kidney; HEL, human embryonic lung.

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