Potentiation of Phenethylamine in Mice. PEA hydrochloride (10 mg/kg sc) was given to mice pretreated 18 h beforehand with reserpine, 5 mg/kg sc. In combination with inhibitors of the B form of MAO (but not with those of the A form), PEA caused an awakening effect and tremor in these mice. The test compounds were injected intraperitoneally 1 h prior to the injection of phenethylamine, and the mice were observed in the 30-min period thereafter. The lowest dose producing potentiation of the phenethylamine effect was determined.

Potentiation of the 5-HTP Syndrome in mice was determined as described by Ross et al.[28] The test compound was injected 1 h prior to intravenous injection of *dl*-5-HTP, 90 mg/kg.

Blood pressure response to tyramine was studied in conscious rats via a permanent catheter introduced into the abdominal aorta, by a method to be described elsewhere.[29] Tyramine was given orally in a dose of 10 mg/kg 2 h before oral administration of the test compound in various doses and also 1 h after the test compound. The arterial blood pressure was monitored for 1 h after administration of tyramine, with a Statham P23 Db transducer, and recorded on a polygraph.

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Acknowledgment. The authors thank Kristina Luthman and Eva Annerwall for their assistance in the synthetic procedures and Lennart Schmidt, Dr. Lars-Olof Lindbom, and Ann-Charlotte Holm for their assistance in the pharmacological work. Financial support to A.C. from Apotekare C.D. Carlssons stiftelse, Lennanders fond, Magnus Bergwalls stiftelse, and Astras forskningsfond is gratefully acknowledged.

Registry No. 1, 16719-32-7; 1 (base), 16719-33-8; 2, 85506-92-9; (*R*)-2, 85506-94-1; (*R*)-2 (base), 85506-93-0; (*S*)-2, 85506-96-3; (*S*)-2 (base), 85506-95-2; 3, 82086-61-1; 3 (base), 73586-40-0; 4, 85507-19-3; 5, 75166-24-4; 5 (base), 73586-38-6; 6, 85506-98-5; 7, 85507-00-2; 8, 85507-02-4; 9, 85507-03-5; 10, 85507-04-6; 10 (base), 70882-08-5; 11, 85507-05-7; 11 (base), 73586-41-1; 12, 85507-06-8; 12 (base), 73586-42-2; 13, 85507-08-0; 13 (base), 85507-07-9; 14, 85507-09-1; 14 (base), 85507-20-6; 15, 85507-10-4; 15 oxalate, 85507-23-9; 18, 34905-12-9; 19, 34905-11-8; 20, 85507-11-5; 21, 85507-12-6; 22, 85507-13-7; 23, 85507-14-8; 24, 85507-15-9; 25, 85507-16-0; 26, 85507-17-1; 27, 85507-18-2; (*S*)-(+)-2,3-pentadien-1-ol, 85507-21-7; 5-methoxy-3-pentyn-2-ol mesylate, 85507-22-8; α,*N*-dimethylphenethylamine, 7632-10-2; *N*-methyl-3-(2,4-dichlorophenoxy)propylamine, 85507-24-0; *N*-methylindanamine, 2084-72-2; 2,3-butadienol, 18913-31-0; (*R*)-(−)-2,3-pentadien-1-ol, 65032-23-7; *N*-methylbenzylamine, 103-67-3; benzylamine, 100-46-9; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; MAO, 9001-66-5.

Synthesis and Antiviral Activity of Distamycin A Analogues: Substitutions on the Different Pyrrole Nitrogens and in the Amidine Function

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Received September 20, 1982

Several new analogues of the antiviral antibiotic distamycin A were synthesized and assayed for their effects on influenza and herpes simplex virus. The new compounds **5b–j** ($R_{1\text{-}3}$ = H, CH_3, and C_2H_5, $R_{4,5}$ = H and CH_3) were obtained via stepwise prepared formylated trimeric benzyl 4-aminopyrrole-2-carboxylates **3a–h**, which after catalytic hydrogenolysis were coupled as *N*-succinimidyl esters directly with the proper β-aminopropionamidine, unsubstituted or substituted with one or two methyl groups in the amidine function. Most of the new analogues did not exhibit significant effects on the viruses studied, but three compounds (**5f–h**) displayed activity on herpes virus as demonstrated in plaque formation and virus yield assays. Elevated cytotoxicity was simultaneously observed for **5g** and **5h**. For compound **5f**, a partial separation of antiherpes activity and cytotoxicity was accomplished. The differences in antiherpes activity did not correspond to the differences in the inhibition of herpes virus DNA polymerase.

The antiviral antibiotic distamycin A continues to be of interest both from chemical and biological points of view, and the present standpoint in regards to its mechanism of action has recently been briefly outlined.[1] Shortly before we submitted our paper dealing with a novel synthesis of distamycin A,[2] two other papers, unnoticed by us, describing new analogues appeared.[3,4] Of all the numerous distamycin derivatives hitherto synthesized, only very few seem to have higher antiviral activity than the parent compound.

Chemistry. The present paper describes the preparation of several new distamycin analogues utilizing our previous general synthetic approach[2] (Scheme I). The new analogues were either substituted on the amidine nitrogen with one or two methyl groups, as in **5i** and **5j**, or modified on the pyrrole nitrogen. In **5b–e**, one or all methyl groups were replaced by ethyl, whereas **5f–h** possessed one unsubstituted pyrrole nitrogen. The introduction of the protecting *tert*-butyloxycarbonyl (Boc) group on the intermediate unstable aminopyrrolecarboxylic acids with Boc-F afforded **1a–c** in acceptable yields and offered no special problems. Compounds **1a–c** were conveniently esterified via their cesium salts with benzyl bromide in DMF and provided benzyl (Bzl) esters **1d–f** in excellent yields. After conventional deprotection, the resulting amino analogues were acylated with the appropriate acid **1a–c** by using 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) as dehydrating agent to give the corresponding dimers **2a–f**. In this connection it was observed that the otherwise good yield in this condensation was significantly

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(1) (a) Gale, E. F.; Cundliffe, E.; Reynolds, P. E.; Richmond, M. H.; Waring, M. J. "The Molecular Basis of Antibiotic Action", 2nd ed.; Wiley: New York, 1981; p 345. (b) Hahn, F. E. In "Inhibitors of DNA and RNA Polymerases"; Sarin, P. S.; Gallo, R. C., Eds.; Pergamon Press: Oxford, 1980; p 225.
(2) Grehn, L.; Ragnarsson, U. *J. Org. Chem.* 1981, 46, 3492.
(3) Gendler, P. L.; Rapoport, H. *J. Med. Chem.* 1981, 24, 33.
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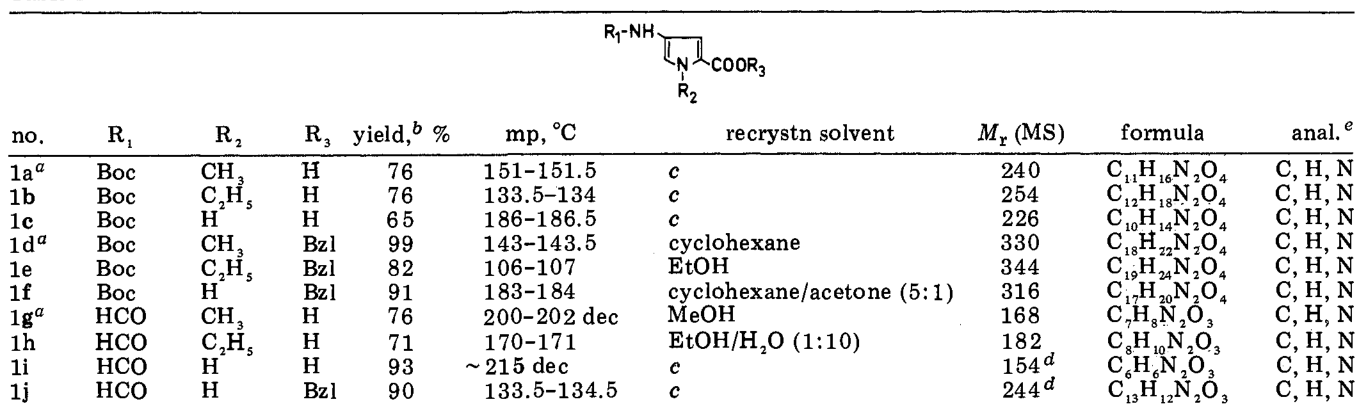
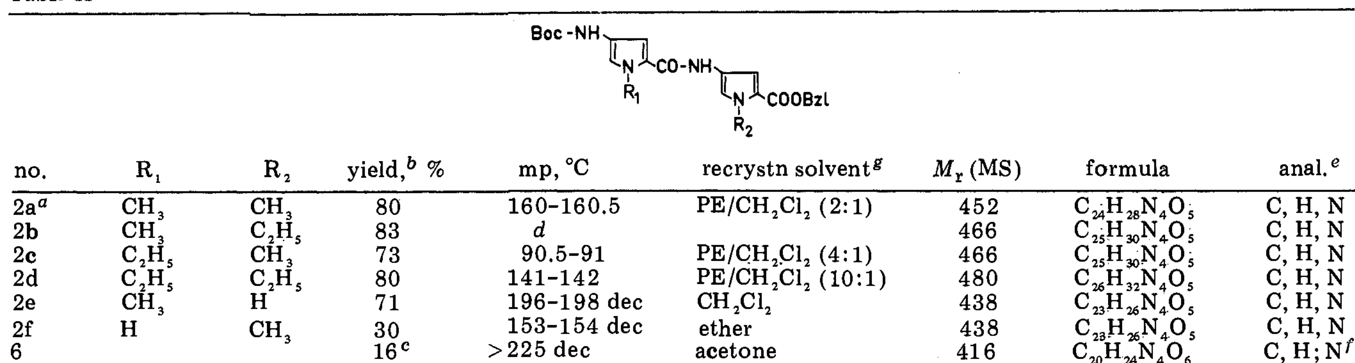
Table I



no.	R_1	R_2	R_3	yield,[b] %	mp, °C	recrystn solvent	M_r (MS)	formula	anal.[e]
1a[a]	Boc	CH_3	H	76	151-151.5	*c*	240	$C_{11}H_{16}N_2O_4$	C, H, N
1b	Boc	C_2H_5	H	76	133.5-134	*c*	254	$C_{12}H_{18}N_2O_4$	C, H, N
1c	Boc	H	H	65	186-186.5	*c*	226	$C_{10}H_{14}N_2O_4$	C, H, N
1d[a]	Boc	CH_3	Bzl	99	143-143.5	cyclohexane	330	$C_{18}H_{22}N_2O_4$	C, H, N
1e	Boc	C_2H_5	Bzl	82	106-107	EtOH	344	$C_{19}H_{24}N_2O_4$	C, H, N
1f	Boc	H	Bzl	91	183-184	cyclohexane/acetone (5:1)	316	$C_{17}H_{20}N_2O_4$	C, H, N
1g[a]	HCO	CH_3	H	76	200-202 dec	MeOH	168	$C_7H_8N_2O_3$	C, H, N
1h	HCO	C_2H_5	H	71	170-171	EtOH/H_2O (1:10)	182	$C_8H_{10}N_2O_3$	C, H, N
1i	HCO	H	H	93	~215 dec	*c*	154[d]	$C_6H_6N_2O_3$	C, H, N
1j	HCO	H	Bzl	90	133.5-134.5	*c*	244[d]	$C_{13}H_{12}N_2O_3$	C, H, N

[a] Data from ref 2. [b] Crude. [c] See Experimental Section. [d] Mass spectrum not recorded. [e] ±0.3%.

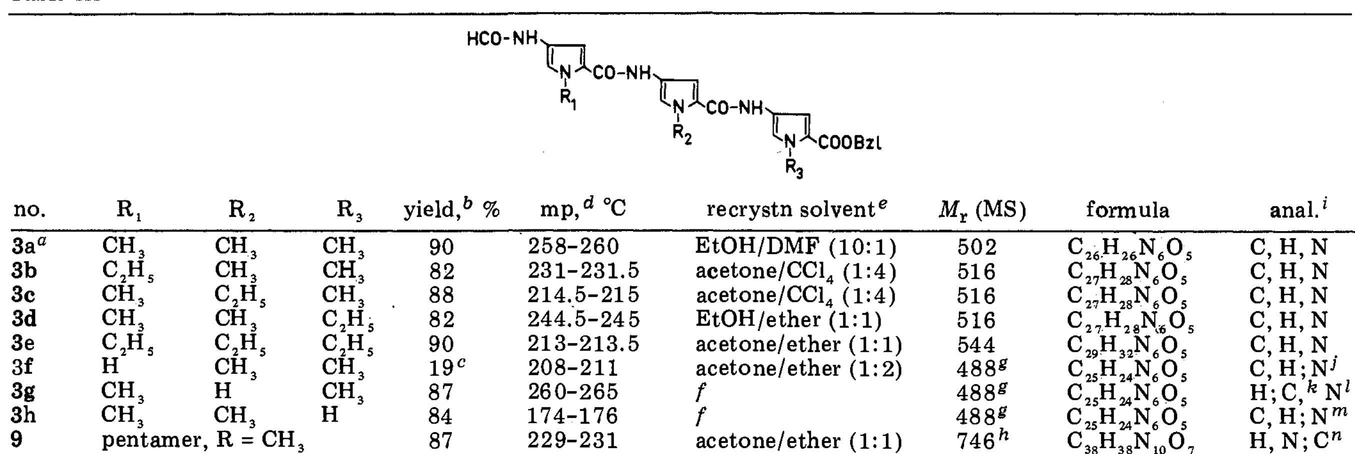
Table II



no.	R_1	R_2	yield,[b] %	mp, °C	recrystn solvent[g]	M_r (MS)	formula	anal.[e]
2a[a]	CH_3	CH_3	80	160-160.5	PE/CH_2Cl_2 (2:1)	452	$C_{24}H_{28}N_4O_5$	C, H, N
2b	CH_3	C_2H_5	83	*d*		466	$C_{25}H_{30}N_4O_5$	C, H, N
2c	C_2H_5	CH_3	73	90.5-91	PE/CH_2Cl_2 (4:1)	466	$C_{25}H_{30}N_4O_5$	C, H, N
2d	C_2H_5	C_2H_5	80	141-142	PE/CH_2Cl_2 (10:1)	480	$C_{26}H_{32}N_4O_5$	C, H, N
2e	CH_3	H	71	196-198 dec	CH_2Cl_2	438	$C_{23}H_{26}N_4O_5$	C, H, N
2f	H	CH_3	30	153-154 dec	ether	438	$C_{23}H_{26}N_4O_5$	C, H, N
6			16[c]	>225 dec	acetone	416	$C_{20}H_{24}N_4O_6$	C, H; N[f]

[a] Data from ref 2. [b] Crude; calculated from crude amine. [c] Side product in the preparation of 2f. Yield calculated from 1c. [d] Not obtained crystalline. The isolated crisp foam softened at 85-90 °C. [e] ±0.4%. [f] N: calcd, 13.5; found, 12.8. [g] PE = petroleum ether.

Table III



no.	R_1	R_2	R_3	yield,[b] %	mp,[d] °C	recrystn solvent[e]	M_r (MS)	formula	anal.[i]
3a[a]	CH_3	CH_3	CH_3	90	258-260	EtOH/DMF (10:1)	502	$C_{26}H_{26}N_6O_5$	C, H, N
3b	C_2H_5	CH_3	CH_3	82	231-231.5	acetone/CCl_4 (1:4)	516	$C_{27}H_{28}N_6O_5$	C, H, N
3c	CH_3	C_2H_5	CH_3	88	214.5-215	acetone/CCl_4 (1:4)	516	$C_{27}H_{28}N_6O_5$	C, H, N
3d	CH_3	CH_3	C_2H_5	82	244.5-245	EtOH/ether (1:1)	516	$C_{27}H_{28}N_6O_5$	C, H, N
3e	C_2H_5	C_2H_5	C_2H_5	90	213-213.5	acetone/ether (1:1)	544	$C_{29}H_{32}N_6O_5$	C, H, N
3f	H	CH_3	CH_3	19[c]	208-211	acetone/ether (1:2)	488[g]	$C_{25}H_{24}N_6O_5$	C, H; N[j]
3g	CH_3	H	CH_3	87	260-265	*f*	488[g]	$C_{25}H_{24}N_6O_5$	H; C,[k] N[l]
3h	CH_3	CH_3	H	84	174-176	*f*	488[g]	$C_{25}H_{24}N_6O_5$	C, H; N[m]
9	pentamer, R = CH_3			87	229-231	acetone/ether (1:1)	746[h]	$C_{38}H_{38}N_{10}O_7$	H, N; C[n]

[a] Data from ref 2. [b] Crude; calculated from crude amine. [c] Yield after chromatography (crude product impure). [d] Decomposition. [e] Active carbon if colored. [f] See Experimental Section. [g] Mass spectrum not recorded. [h] No molecular ion peak in the 12-eV mass spectrum. [i] ±0.4%. [j] N: calcd, 17.3; found, 16.4. [k] C: calcd, 61.5; found, 60.7. [l] N: calcd, 17.3; found, 16.7. [m] N: calcd, 17.3; found, 16.8. [n] C: calcd, 61.1; found, 60.6.

Scheme I

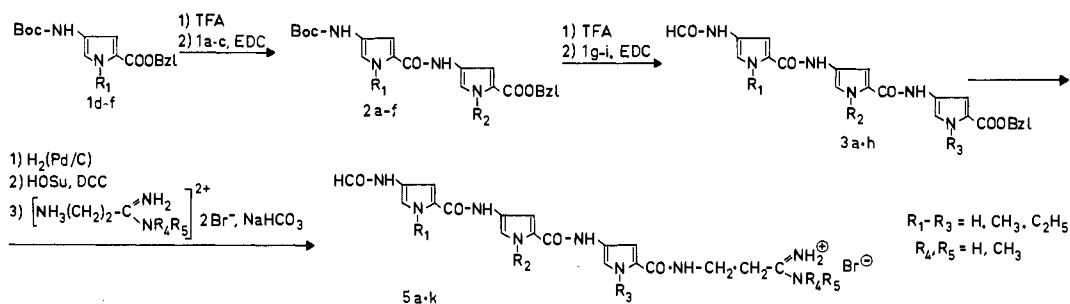


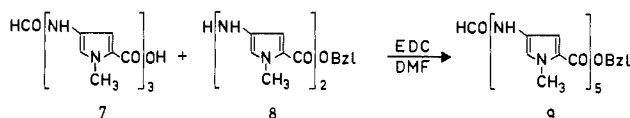
Table IV

$R_1R_2N\text{-}CH_2\text{-}CH_2\text{-}C(=NH_2^{\oplus}X^{\ominus})NR_3R_4$

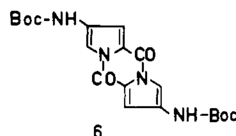
no.	R_1	R_2	R_3	R_4	X	yield,[a] %	mp, °C	recrystn solvent	formula	anal.
4a	Ts	H	CH_3	H	Cl	84[b]	217-217.5	EtOH	$C_{11}H_{17}N_3O_2S\cdot HCl$	C, H, N
4b	Ts	H	CH_3	CH_3	Cl	86[b]	235.5-236	EtOH	$C_{12}H_{19}N_3O_2S\cdot HCl$	C, H, N
4c	Ts	CH_3	H	H	Cl	60[c]	162.5-163		$C_{11}H_{17}N_3O_2S\cdot HCl$	C, H, N
4d	H	H	CH_3	H	Br	87	205.5-206	EtOH	$C_4H_{11}N_3\cdot 2HBr$	C, H, N, Br
4e	H	H	CH_3	CH_3	Br	86	199-199.5	EtOH	$C_5H_{13}N_3\cdot 2HBr$	C, H, N; Br[d]
4f	H	CH_3	H	H	Br	86	143.5-144	EtOH	$C_4H_{11}N_3\cdot 2HBr$	C, H, N

[a] Crude. [b] Calculated from imidate HCl. [c] Calculated from nitrile. Physical data for $Ts(CH_3)N(CH_2)_2CN$: mp 107-107.5 °C; ^1H NMR (acetone-d_6) δ 7.74 (d, 2 H), 7.45 (d, 2 H), 3.37 (perturbed t, 2 H), 2.83 (s, 3 H), 2.80 (perturbed t, 2 H), 2.44 (s, 3 H). Anal. ($C_{11}H_{14}N_2O_2S$) C, H, N. [d] Br: calcd, 57.7; found, 57.1.

Scheme II



decreased when **1c** was employed as the acid component. Instead, substantial amounts of the symmetrical dimer **6**

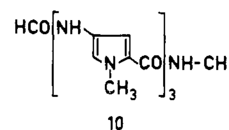


could be isolated from the crude reaction mixture together with the desired **2f**. This side reaction is not unexpected, since such pyrrocolls have been detected earlier when pyrrole-2-carboxylic acids with unprotected 1-nitrogens were treated with dehydrating agents.[5] Evidently, the nitrogen site requires suitable protection for obtaining optimal yields in such cases.

The pyrrole backbone in **2a–f** was further extended by repetition of the deprotection–coupling sequence, now using the readily obtainable formyl derivatives **1g–i** as acylating components. With the exception of **3f**, the yields of **3a–h** were consistently satisfactory. The reason for this is obviously the same as for **2f**, but no attempts were made to isolate the pyrrocoll dimer corresponding to **1i** in this case. Also, higher oligomers are accessible by this synthetic strategy. Thus, trimer **7** was attached to dimer **8**, yielding pentamer **9**, using the same reaction conditions (Scheme II).

The cleavage of the benzyl function in **3a–h** and **9** was effected in a straightforward manner by catalytic hydrogenolysis under standard conditions. The resulting acids then reacted smoothly with *N*-hydroxysuccinimide (HOSu) in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC), and in these conversions the yields were generally fair. It was, however, noticed that the acid corresponding to **3h**, having an unsubstituted pyrrole nitrogen adjacent to the carboxy function, underwent an undesired side reaction during this activation, thus paralleling the behavior of **1c** and **1i** (see discussion above).

The final step in our scheme, the attachment of the aliphatic side chain, proceeded satisfactorily on treatment of the active esters with the appropriate β-aminopropionamidine derivatives **4d–e** or unsubstituted compound under the influence of sodium bicarbonate. Also, the active ester derived from **9** afforded the known analogue **5k** under these conditions.[6] It was found that the introduction of substituents into the amidine moiety, as in **4d** and **4e**, was not detrimental to the yields in these acylations, giving **5i** and **5j**. In contrast to this, the isomer **4f**, having a substituted amino group, gave only traces of the corresponding distamycin analogue under the same conditions, and this may be at least partly due to steric interactions. Among the various substances formed in this reaction, we could isolate the methyl amide **10** as the major product.



Biology. At the enzymatic level, very small differences in inhibition were observed for herpes simplex virus type 1 (HSV-1) DNA polymerase, and cellular DNA polymerase α when compounds **5a–k** were compared (Table VI). The inhibition was more effective when $(dT)_n(rA)_{12-18}$ was used as template instead of activated DNA for DNA polymerase α, and this is in agreement with earlier findings.[7] The inhibitory effect of distamycin A on HSV-1 DNA polymerase was also comparable to that reported earlier using a similar DNA template concentration.[8] The avian myeloblastosis virus (AMV) reverse transcriptase activity was only slightly influenced with $(rA)_n(dT)_{12-18}$ as template/primer, whereas reactions directed by $(dC)_n(dG)_{12-18}$ or $(rC)_n(dG)_{12-18}$ remained unaffected. This template dependence has earlier been observed with distamycin analogues.[9,10] The most active compounds, **5f,g,h**, can be regarded as isomers of nordistamycin A.

The effects of the various distamycin analogues on influenza virus multiplication are summarized in Table IX. Evidently, no antiviral activity was found for the structural modifications, with the possible exceptions **5f** and **5k**, where a slight effect could be noticed. In contrast to this, the inhibition of HSV-1 multiplication measured both as plaque formation (Table VII) and as yield of virus (Table VIII) showed considerable structure dependence. Obviously, compounds **5f–h**, all having one unsubstituted pyrrole nitrogen, were more potent in the plaque test than

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(7) Wähnert, U.; Zimmer, Ch.; Luck, G.; Pitra, Ch. *Nucleic Acids Res.* **1975**, *2*, 391.

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(9) Hahn, F. E. In "Antibiotics III. Mechanism of Action of Antimicrobial and Antitumor Agents"; Springer: Berlin, 1975; pp 79–100.

(10) Zimmer, Ch. *Prog. Nucleic Acid Res. Mol. Biol.* **1975**, *15*, 285.

the other structures, and **5h** was the most active inhibitor. In the virus yield assay, these three compounds reduced the virus yield over 90% at 10 μM concentration. Again, compound **5h** seemed to be the most effective inhibitor. Triplicate experiments with distamycin A showed only a slight effect on the virus yield at 10 μM concentration.

The cytotoxicities of the new distamycin analogues are compiled in Table X. It appears that the toxicity toward cells are of the same magnitude or lower than that of distamycin A (**5a**), with the notable exceptions **5g** and **5h**. Thus, the higher activity of these two analogues toward HSV-1 virus is accompanied with a considerably enhanced cellular toxicity. It is also interesting to note that the isomer **5f**, which possesses an antiviral activity similar to that of **5h** (Tables VII and VIII), exhibits a cellular toxicity of the same magnitude as that of the parent distamycin A. This observation indicates that it may be possible to separate the antiviral and cytotoxic effects.

Considering the small differences in inhibition of HSV-1 DNA polymerase, it seems likely either that the primary target for the inhibition of virus multiplication by compounds **5f–h** is not the DNA polymerase or that these compounds penetrate cells more easily than distamycin A (**5a**). The latter explanation may be supported by the higher cellular toxicity observed for **5g** and, especially for **5h**. It is also possible that herpes virus infection facilitates an increased penetration of cells by distamycin analogues in analogy with what has been reported for other inhibitors penetrating preferably virus-infected cells.[11] It is generally accepted that distamycin A complexes with DNA, and a model for this interaction has been proposed. It is suggested that the complex is stabilized by hydrogen bonds and, considering this hypothesis briefly outlined recently,[1a] the complex between **5f–h** and DNA is conceivably further stabilized by interaction between the DNA helix and the pyrrole nitrogen lacking an alkyl substituent. If the hydrogen-bonding ability of the distamycin analogue correlates with the antiviral activity, one might hope that novel structural modifications with additional hydrogen-bonding sites could give more active derivatives. However, to obtain a clinically useful drug it is necessary to reduce the cytotoxicity.

In this connection it should be mentioned that the pentameric analogue **5k** was earlier claimed to be about ten times more active than distamycin A in certain assays and less toxic to host cells.[12] In the HSV-1 plaque formation test (Table VII), however, the activity of **5k** was of the same order as that of **5a**. Comparisons of **5k** with **5a** in the other assays indicated only slight differences, with the possible exception that **5k** exhibited lower cytotoxicity than several other analogues, including **5a** (Table X). A partial separation of antiviral activity and cytotoxicity has been reported for a compound related to congocidine.[8]

In conclusion, as a result of this study it appears that analogues of distamycin A with methyl substituents in the amidine function, as well as such ones with an unsubstituted amidine side chain but with ethyl substituents on one or all of the pyrrole nitrogens, offer little promise of increased effects on HSV-1 and influenza virus. Increased activities in cell culture systems of the former virus were obtained with three analogues, all with one unsubstituted pyrrole nitrogen. In two of these cases, however, the improved antiherpes activity was accompanied with elevated cytotoxicity. For the remaining compound **5f**, a partial separation of the two effects was accomplished.

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Experimental Section

Ethyl 1-ethylpyrrole-2-carboxylate was prepared from ethyl iodide and ethyl pyrrole-2-carboxylate by analogy with the previously described 1-methyl analogue.[13] The yield of crude product, obtained as a yellow oil, was 96%. Distillation afforded a colorless liquid: bp 94.5–95 °C (9 mm); TLC (CH_2Cl_2) gave one spot; M_r = 167 (mass spectrum); ^1H NMR (acetone-d_6) δ 7.04 (q, 1 H), 6.87 (q, 1 H), 6.08 (q, 1 H), 4.36 (q, 2 H), 4.24 (q, 2 H), 1.33 (t, 3 H), 1.31 (t, 3 H), $J_{3,4}$ = 3.9 Hz, $J_{4,5}$ = 2.7 Hz, $J_{3,5}$ = 2.0 Hz. Anal. ($C_9H_{13}NO_2$) C, H, N.

Ethyl 1-Ethyl-4-nitropyrrole-2-carboxylate. The previous ester was nitrated in concentrated nitric acid as described for the 1-methyl analogue.[13] The yield of crude product was 68%. An analytical sample was chromatographed (CH_2Cl_2; silica gel) and recrystallized from ethanol (10 mL/g) to give white, thick needles: mp 70.5–71 °C; TLC (CH_2Cl_2) gave one spot; M_r = 212 (mass spectrum); ^1H NMR (acetone-d_6) δ 8.05 (d, 1 H), 7.33 (d, 1 H), 4.51 (q, 2 H), 4.33 (q, 2 H), 1.45 (t, 3 H), 1.36 (t, 3 H), $J_{3,5}$ = 2.1 Hz, both $J_{C_2H_5}$ = 7.1 Hz. Anal. ($C_9H_{12}N_2O_4$) C, H, N.

1-Ethyl-4-nitropyrrole-2-carboxylic Acid. The crude nitrated ester was hydrolyzed as described for the 1-methyl analogue.[2] The yield of pure acid, obtained as tan needles, was 60% after recrystallization from EtOH–H_2O (1:7) (decolorizing carbon). An analytical sample was chromatographed [CH_2Cl_2/acetone/HOAc (40:10:1, v/v/v)] and recrystallized as above to give pale yellow needles: mp 199–200 °C dec; TLC (system above) gave one spot; M_r = 184 (mass spectrum); ^1H NMR (acetone-d_6) δ 8.06 (d, 1 H), 7.36 (d, 1 H), 4.51 (q, 2 H), 1.45 (t, 3 H), COO*H* not visible, $J_{3,5}$ = 2.1 Hz, $J_{C_2H_5}$ = 7.1 Hz. Anal. ($C_7H_8N_2O_4$) C, H, N.

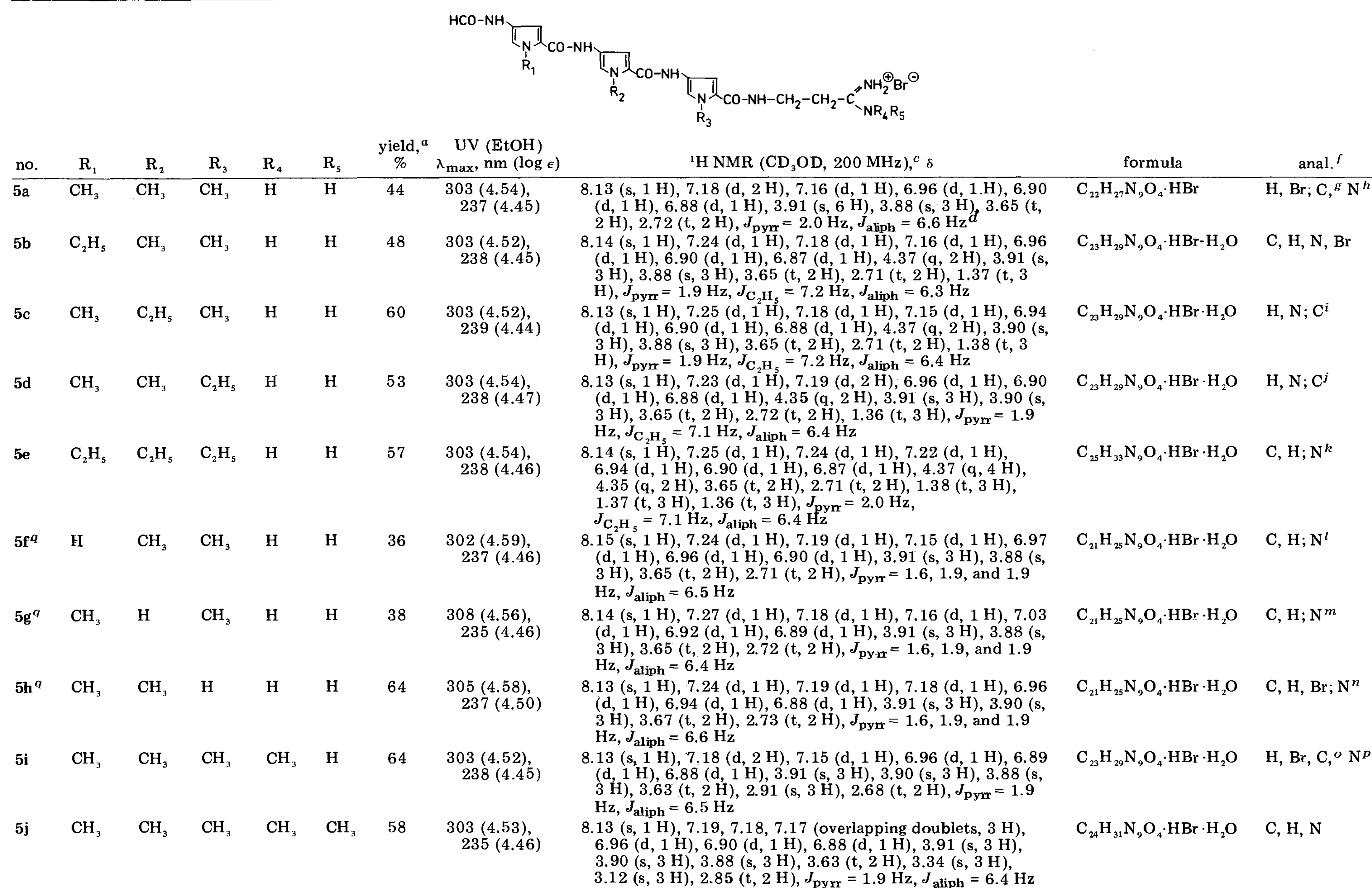
4-[(*tert*-Butyloxycarbonyl)amino]-1-substituted-pyrrole-2-carboxylic Acids (1b and 1c) and Their Benzyl Esters (1e and 1f). The preparation of the acids from 1-ethyl-4-nitropyrrole-2-carboxylic acid (above) and 4-nitropyrrole-2-carboxylic acid, respectively, follows the detailed procedure given for **1a**.[2] The purified acids were obtained as white powders. The crude acids were converted to the corresponding benzyl esters according to the method of preparation for **1d**.[2] Pure **1e** and **1f** were white crystalline substances. For yields and physical data, see Table I.

Benzyl 4-(Formylamino)pyrrole-2-carboxylate (1j). Crude benzyl 4-aminopyrrole-2-carboxylate (obtained in 91% yield from **1f** as described for the deprotection of **1d**[2]) (2.17 g, 10 mmol) in dry DMF (30 mL) was treated with formic acid (1.40 g, 30 mmol). To the reaction mixture was then added DCC (2.27 g, 11 mmol) in small portions with rapid stirring at room temperature. After the mixture was stirred overnight, the precipitated urea was filtered off and rinsed with some DMF. The filtrate was evaporated to dryness at reduced pressure below 40 °C, and the brownish oil was dissolved in acetone (10 mL). After filtration it was diluted with CH_2Cl_2 (20 mL) and subjected to column chromatography [CH_2Cl_2–acetone (2:1, v/v)] on silica gel. The yield of **1j**, obtained as a colorless oil which soon solidified, was 2.22 g (90%). An analytical sample was recrystallized from acetone/ether (1:10, ~100 mL/g) to give white fluffy crystals (Table I).

4-(Formylamino)-1-substituted-pyrrole-2-carboxylic Acids (1h and 1i). Compound **1h** was synthesized from the corresponding nitro derivative by analogy with **1g**.[2] Since **1h** was rather soluble in organic solvents, the washing of the crude product with methanol and ether was omitted. Recrystallized **1h** was obtained as white fluffly crystals. Attempts to prepare **1i** similarly gave a rather low yield of impure product. This was probably due to the higher solubility of this analogue in aqueous media. Therefore, **1i** was instead conveniently obtained from **1j**. Thus, **1j** (1.03 g, 4.22 mmol) in dry DMF (50 mL) was hydrogenated for 2 h at 60 psi at room temperature in the presence of Pd (5% on C). When the reaction was complete, the catalyst was removed by filtration, and the resulting pale yellow filtrate was taken to complete dryness at reduced pressure below 40 °C. The grayish solid residue was thoroughly triturated with dry ether, and the insoluble part was rinsed with several portions of dry ether and dried in vacuo at 50 °C for 20 h. The yield of crude, chromatographically pure 1 was 0.57 g (93%). An analytical sample was prepared by dissolving

(13) Grehn, L. *Chem. Scr.* **1978**, *13*, 67.

Table V



no.	R_1	R_2	R_3	R_4	R_5	yield,[a] %	UV (EtOH) λ_{max}, nm (log ϵ)	^{1}H NMR (CD_3OD, 200 MHz),[c] δ	formula	anal.[f]
5a	CH_3	CH_3	CH_3	H	H	44	303 (4.54), 237 (4.45)	8.13 (s, 1 H), 7.18 (d, 2 H), 7.16 (d, 1 H), 6.96 (d, 1 H), 6.90 (d, 1 H), 6.88 (d, 1 H), 3.91 (s, 6 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.72 (t, 2 H), J_{pyrr} = 2.0 Hz, J_{aliph} = 6.6 Hz[d]	$C_{22}H_{27}N_9O_4 \cdot HBr$	H, Br; C,[g] N[h]
5b	C_2H_5	CH_3	CH_3	H	H	48	303 (4.52), 238 (4.45)	8.14 (s, 1 H), 7.24 (d, 1 H), 7.18 (d, 1 H), 7.16 (d, 1 H), 6.96 (d, 1 H), 6.90 (d, 1 H), 6.87 (d, 1 H), 4.37 (q, 2 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.71 (t, 2 H), 1.37 (t, 3 H), J_{pyrr} = 1.9 Hz, $J_{C_2H_5}$ = 7.2 Hz, J_{aliph} = 6.3 Hz	$C_{23}H_{29}N_9O_4 \cdot HBr\text{-}H_2O$	C, H, N, Br
5c	CH_3	C_2H_5	CH_3	H	H	60	303 (4.52), 239 (4.44)	8.13 (s, 1 H), 7.25 (d, 1 H), 7.18 (d, 1 H), 7.15 (d, 1 H), 6.94 (d, 1 H), 6.90 (d, 1 H), 6.88 (d, 1 H), 4.37 (q, 2 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.71 (t, 2 H), 1.38 (t, 3 H), J_{pyrr} = 1.9 Hz, $J_{C_2H_5}$ = 7.2 Hz, J_{aliph} = 6.4 Hz	$C_{23}H_{29}N_9O_4 \cdot HBr \cdot H_2O$	H, N; C[i]
5d	CH_3	CH_3	C_2H_5	H	H	53	303 (4.54), 238 (4.47)	8.13 (s, 1 H), 7.23 (d, 1 H), 7.19 (d, 2 H), 6.96 (d, 1 H), 6.90 (d, 1 H), 6.88 (d, 1 H), 4.35 (q, 2 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.65 (t, 2 H), 2.72 (t, 2 H), 1.36 (t, 3 H), J_{pyrr} = 1.9 Hz, $J_{C_2H_5}$ = 7.1 Hz, J_{aliph} = 6.4 Hz	$C_{23}H_{29}N_9O_4 \cdot HBr \cdot H_2O$	H, N; C[j]
5e	C_2H_5	C_2H_5	C_2H_5	H	H	57	303 (4.54), 238 (4.46)	8.14 (s, 1 H), 7.25 (d, 1 H), 7.24 (d, 1 H), 7.22 (d, 1 H), 6.94 (d, 1 H), 6.90 (d, 1 H), 6.87 (d, 1 H), 4.37 (q, 4 H), 4.35 (q, 2 H), 3.65 (t, 2 H), 2.71 (t, 2 H), 1.38 (t, 3 H), 1.37 (t, 3 H), 1.36 (t, 3 H), J_{pyrr} = 2.0 Hz, $J_{C_2H_5}$ = 7.1 Hz, J_{aliph} = 6.4 Hz	$C_{25}H_{33}N_9O_4 \cdot HBr \cdot H_2O$	C, H; N[k]
5f[q]	H	CH_3	CH_3	H	H	36	302 (4.59), 237 (4.46)	8.15 (s, 1 H), 7.24 (d, 1 H), 7.19 (d, 1 H), 7.15 (d, 1 H), 6.97 (d, 1 H), 6.96 (d, 1 H), 6.90 (d, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.71 (t, 2 H), J_{pyrr} = 1.6, 1.9, and 1.9 Hz, J_{aliph} = 6.5 Hz	$C_{21}H_{25}N_9O_4 \cdot HBr \cdot H_2O$	C, H; N[l]
5g[q]	CH_3	H	CH_3	H	H	38	308 (4.56), 235 (4.46)	8.14 (s, 1 H), 7.27 (d, 1 H), 7.18 (d, 1 H), 7.16 (d, 1 H), 7.03 (d, 1 H), 6.92 (d, 1 H), 6.89 (d, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.72 (t, 2 H), J_{pyrr} = 1.6, 1.9, and 1.9 Hz, J_{aliph} = 6.4 Hz	$C_{21}H_{25}N_9O_4 \cdot HBr \cdot H_2O$	C, H; N[m]
5h[q]	CH_3	CH_3	H	H	H	64	305 (4.58), 237 (4.50)	8.13 (s, 1 H), 7.24 (d, 1 H), 7.19 (d, 1 H), 7.18 (d, 1 H), 6.96 (d, 1 H), 6.94 (d, 1 H), 6.88 (d, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.67 (t, 2 H), 2.73 (t, 2 H), J_{pyrr} = 1.6, 1.9, and 1.9 Hz, J_{aliph} = 6.6 Hz	$C_{21}H_{25}N_9O_4 \cdot HBr \cdot H_2O$	C, H, Br; N[n]
5i	CH_3	CH_3	CH_3	CH_3	H	64	303 (4.52), 238 (4.45)	8.13 (s, 1 H), 7.18 (d, 2 H), 7.15 (d, 1 H), 6.96 (d, 1 H), 6.89 (d, 1 H), 6.88 (d, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.63 (t, 2 H), 2.91 (s, 3 H), 2.68 (t, 2 H), J_{pyrr} = 1.9 Hz, J_{aliph} = 6.5 Hz	$C_{23}H_{29}N_9O_4 \cdot HBr \cdot H_2O$	H, Br, C,[o] N[p]
5j	CH_3	CH_3	CH_3	CH_3	CH_3	58	303 (4.53), 235 (4.46)	8.13 (s, 1 H), 7.19, 7.18, 7.17 (overlapping doublets, 3 H), 6.96 (d, 1 H), 6.90 (d, 1 H), 6.88 (d, 1 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.63 (t, 2 H), 3.34 (s, 3 H), 3.12 (s, 3 H), 2.85 (t, 2 H), J_{pyrr} = 1.9 Hz, J_{aliph} = 6.4 Hz	$C_{24}H_{31}N_9O_4 \cdot HBr \cdot H_2O$	C, H, N

5k	pentamer derived from 9	13[b]	308 (4.74), 238 (4.62)	8.13 (s, 1 H), 7.18–7.21 (overlapping doublets, 4 H), 7.16 (d, 1 H), 6.95–6.97 (overlapping doublets, 3 H), 6.90 (d, 1 H), 6.88 (d, 1 H), 3.92 (s, 9 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 3.65 (t, 2 H), 2.71 (t, 2 H), J_{pyrr} = 1.9 Hz, J_{aliph} = 6.6 Hz[e]

[a] Crude. [b] Low yield in chromatography due to low solubility. [c] Recorded on a Varian XL 200. NH-protons not visible. [d] Spectrum recorded on chloride. [e] Minor impurities at δ 3.50–3.60. [f] ±0.4%. [g] C: calcd, 47.0; found, 46.5. [h] N: calcd, 22.4; found, 20.9. [i] C: calcd, 46.5; found, 47.8. [j] C: calcd, 46.5; found, 44.8. [k] N: calcd, 20.3; found, 20.8. [l] N: calcd, 23.0; found, 22.0. [m] N: calcd, 23.0; found, 23.0; found, 21.8. [n] N: calcd, 23.0; found, 21.0. [o] C: calcd, 46.5; found, 45.9. [p] N: calcd, 21.2; found, 20.6. [q] Compounds 5f, 5g, and 5h could be named 1-nordistamycin A, 2-nordistamycin A, and 3-nordistamycin A, respectively. The pyrrole rings are numbered from left to right in accordance with conventions in peptide chemistry.

the product in a minimal amount of EtOH. After treatment with decolorizing carbon, the solution was diluted with dry ether. Pure **1** precipitated as a white powder (Table I).

Synthesis of Protected Dimers (2b–f). General Procedure. Crude benzyl 4-amino-1-substituted-pyrrole-2-carboxylate (obtained from the corresponding Boc analogues **1d–f** in 90–95% yield as described earlier[2]) was dissolved in dry DMF (5 mL/g) and 1 equiv of the appropriate acid (**1a–c**) was added. The resulting clear solution was then treated with solid EDC (10% excess) in small portions with rapid stirring for 10 min. After the brownish reaction mixture was stirred at 40 °C overnight, most of the DMF was evaporated at reduced pressure below 40 °C. The sirupy residue was then partitioned between CH_2Cl_2 (~100–200 mL/g of amine, EtOAc for **2e** and **2f**) and the same volume of 1 M aqueous $KHSO_4$. The organic extract was separated, and the aqueous phase was extracted once more with one-fifth of solvent volume. The combined extracts were processed as described for the synthesis of **2a**,[2] affording the crude desired product as a solid, crisp foam suitable for further work. The analytical samples were obtained by column chromatography, with CH_2Cl_2/acetone (20:1, v/v; 9:1, v/v, for **2e** and **2f**) as eluant and, when possible, recrystallization of the chromatographed material from a suitable solvent.

In the preparation of **2f**, evaporation of the EtOAc extract gave a solid residue consisting of a mixture of **2f** and **6**. Addition of cold ether (~20 mL/g residue) dissolved **2f**, and essentially pure **6** was filtered off and rinsed with small portions of cold ether. The combined filtrates were kept at −20 °C overnight, and again filtered to remove traces of precipitated **6**. Evaporation to dryness afforded crude **2f**, which could be further purified as usual. Recrystallization of **6** gave bright yellow crystals. Yields, recrystallization solvents, and physical data for **2b–f** and **6** are summarized in Table II.

Synthesis of Trimeric Analogues (3b–h) and Pentameric Compound 9. The Boc derivatives **2a–f** were deprotected with CH_2Cl_2–TFA (2:1, v/v) as described earlier[2] to give the corresponding free amines in good yields (>80%). To the crude, dry amino analogue dissolved in dry DMF (5–10 mL/g) was added a slight excess (~5%) of the appropriate formylated acid (**1g–i** and **7**). The solution was then treated with solid EDC (~1.1 equiv) in small portions with shaking. After stirring overnight at 40 °C, the resulting dark reaction mixture was slowly poured into ice-cold 1 M aqueous $KHSO_4$ with rapid stirring. The precipitated brownish solid was collected, thoroughly rinsed with, in turn, 1 M $KHSO_4$, 1 M $NaHCO_3$, and water (several portions each), and then dried in vacuo. These crude products were sufficiently pure for further synthesis, except **3f**, which required chromatographic purification before further use. Analytical specimens of all analogues were obtained by column chromatography with CH_2Cl_2–acetone (1:1, v/v) as eluant and crystallization of the chromatographed material from a suitable solvent. Compounds **3g** and **3h** were dissolved in a miminum quantity of acetone, and the pure sample precipitated on dilution with dry ether. All these compounds tenaciously retained solvents and moisture and were therefore thoroughly dried (50 °C, high vacuum overnight). General properties of **3b–h** and **9** are reported in Table III.

Deprotection of Compounds 3b–h and 9 and Activation of the Corresponding Acids. General Method. (a) Removal of Benzyl Group. Crude benzyl ester **3b–h** and **9**, dissolved in dry DMF (20–30 mL/g), was hydrogenated for 2 h at 60 psi (room temperature) over Pd (5% on C). When the reaction was complete, the catalyst was removed by filtration, and the yellowish filtrate was evaporated at reduced pressure below 40 °C, affording the pure acid as a brownish gum. The crude product could be further purified by dissolving it in a minimum quantity of ethanol. After filtration, the solution was diluted with ~10 volumes of dry ether with gentle stirring, whereupon all acids, except the one obtained from **3e**, precipitated as tan hygroscopic powders. The yield of chromatographically pure acids was, after careful drying, 85–95%. These compounds decomposed with evolution of gas between 150 and 200 °C.

(b) Preparation of *N*-Succinimidyl Esters. The purified, carefully dried acids were dissolved in dry DMF (15–25 mL/g), and the solution was cooled to 0 °C. After the addition of *N*-hydroxysuccinimide (1.1 equiv), the resulting mixture was treated

Table VI. Inhibition of Polymerase Activities by Distamycin Analogues

compd	concn, μM	% inhibition of: HSV-1 DNA polymerase	DNA polymerase α: $(dT)_n\cdot(rA)_{12-18}$	DNA polymerase α: act. DNA	AMV reverse transcriptase: $(rA)_n\cdot(dT)_{12-18}$	AMV reverse transcriptase: $(dC)_n\cdot(dG)_{12-18}$	AMV reverse transcriptase: $(rC)_n\cdot(dG)_{12-18}$
5a[a]	10	49	58	31			
	50	83	82	40	13	<5	<5
5b	10	48	60	29			
	50	83	85	42	11	<5	<5
5c	10	48	31	23			
	50	83	64	34	8	<5	<5
5d	10	52	40	26			
	50	83	73	35	11	<5	<5
5e	10	47	58	29			
	50	80	75	39	9	<5	<5
5f[b]	10	54	58	31			
	50	89	82	45	18	<5	<5
5g[b]	10	55	55	29			
	50	88	80	41	13	<5	<5
5h[b]	10	57	45	27			
	50	83	75	37	17	<5	<5
5i	10	45	50	27			
	50	76	76	38	12	<5	<5
5j	10	44	56	29			
	50	81	80	41	15	<5	<5
5k	10	56	20	17			
	50	91	56	50	39	<5	<5

[a] Distamycin A. [b] See last note to Table V.

Table VII. Effect of Distamycin Analogues on HSV-1 Plaque Formation

compd	concn, μM	% reduction in plaque formation
5a[a]	200	55
5b	200	50
5c	200	<50
5d	200	<50
5e	200	<50
5f	10	60
	50	90
	100	>90
5g	10	<50
	50	90
5h	1	<50
	5	85
	10	>90
5i	200	<50
5j	200	<50
5k	200	<50

[a] Distamycin A.

Table VIII. Reduction in HSV-1 Yield by Distamycin Analogues

compd	concn, μM	% reduction in virus yield
5a[a]	10	27
5f	10	98
5g	10	92
5h	10	99

[a] Distamycin A.

Table IX. Effect of Distamycin Analogues on Influenza Virus Plaque Formation

compd	concn, μM	% reduction in plaque formation
5a[a]	100	<50
5b	200	<50
5c	200	<50
5d	200	<50
5e	100	<50
5f	200	75
5g	200	<50
5h	100	<50
5i	100	<50
5j	100	<50
5k	200	65

[a] Distamycin A.

Table X. Cellular Toxicity of Distamycin Analogues

compd	concn, μM	% inhibn of cellular growth
5a[a]	100	69
5b	200	50
5c	200	10
5d	200	10
5e	100	15
5f	10	30
	100	50
5g	10	25
	100	75
5h	10	60
	100	98
5i	100	30
5j	200	0
5k	200	10

[a] Distamycin A.

with solid DCC (10% excess) in small portions at 0 °C with rapid stirring. The resulting dark slurry was stirred for 1 h at 0 °C and then at 40 °C overnight. After the mixture was cooled in ice for a few hours, the white precipitate was filtered off and washed with small portions of cold DMF. The combined dark filtrates were evaporated to dryness as usual, and the semisolid brownish residue was taken up in acetone (10–15 mL/g). After traces of insoluble material were removed, the solution was applied to a silica gel column, packed in CH_2Cl_2–acetone (1:1, v/v). After elution of minor quantities of colored impurities, a fraction consisting of pure *N*-succinimidyl ester was obtained. The eluate was taken to dryness, and the residual white solid was dissolved in a minimal quantity of lukewarm acetone. The resulting clear solution was then diluted with 10 volumes of dry ether, whereupon a fine powder precipitated. This was collected, rinsed with dry ether, and carefully dried. The yields of chromatographically pure active esters were between 62 and 73%, with the exception of the one corresponding to 3h, where the occurrence of various side products lowered the yield to 51%. The pure *N*-succinimidyl esters were hygroscopic substances that melted with decomposition over long

intervals in the range 150–200 °C.

Synthesis of β-Aminopropionamidine Compounds (4a–f). The amidines used in the final coupling steps, as well as their precursors, were synthesized by analogy with procedures described elsewhere, with only minor modifications.[14] Yields and physical data for these compounds are summarized in Table IV.

Distamycin A Analogues (5a–k). General Procedure. Pure N-succinimidyl ester (0.25 mmol) was dissolved or suspended in dry dioxane (5–10 mL) and added dropwise with vigorous agitation to a solution of β-aminopropionamidine dihydrobromide or analogue **4d** or **4e** (0.5 mmol) and $NaHCO_3$ (0.5 mmol) in dioxane–water (1:2, 15–20 ml) during 15 min. The resulting turbid reaction mixture was stirred rapidly for 1 h at room temperature and for 1–2 h at 40 °C, whereupon it became clear in most cases. The reaction was allowed to proceed at room temperature while monitoring with TLC [EtOAc/acetone/HOAc/H_2O (5:3:1:1) or EtOH/0.1 M pyridine acetate (2:1, v/v)]. If larger amounts of active ester remained after a further 3 h, the reaction mixture was treated with an additional quantity of amidine and $NaHCO_3$ (0.25 mmol of each). After the mixture was stirred overnight, pH was adjusted to ~4 with 0.3 M HBr (Br_2 free), and most of the solvents were removed at reduced pressure below 30 °C. The semisolid residue was dissolved in a small volume of ethanol and applied to a silica gel column packed in EtOH. Elution with EtOH gave minor quantities of starting active ester and some other colored impurities. Continued elution with EtOH/0.01 M HBr (Br_2 free) (5:1) gave a fraction containing the title compound, pure by TLC. When this fraction was concentrated to a small volume (10–20 mL), **5f–h** precipitated upon refrigeration. The crude products were collected, rinsed with small portions of ice-water, and dried thoroughly. Further concentration of the mother liquor and washings gave more pure product. In the case of **5a–e** and **5i–k**, the fraction was carefully taken to dryness, and the residue containing inorganic impurities was dissolved in a small volume of EtOH. The solution was chromatographed on Sephadex LH-20 with 95% EtOH as eluant. Evaporation of the pure fraction afforded the crude product as a glassy solid. Crude **5a–k** could be further purified by rechromatography on Sephadex LH-20. The analytical specimen was obtained by dissolving the chromatographed dry material in a minimum amount of 99% EtOH. The solution was filtered, and the filtrate was slowly added to 10 volumes of dry ether with rapid stirring. The precipitated white, fine-grained solid was collected by centrifugation and washed with several portions of dry ether. All analogues were very hygroscopic and required meticulous drying (50–60 °C, high vacuum, 1–2 days). TLC (systems above) indicated that all compounds were essentially pure. Compounds **5a–k** darkened rapidly when heated above 150 °C.

When the N-succinimidyl ester derived from **7** was allowed to react with **4f** under the same reaction conditions, the major product was not the expected distamycin A analogue. Instead, **10** could be isolated after a laborious workup involving chromatography: ^1H NMR (CD_3OD) δ 8.14 (s, 1 H), 7.20 (perturbed m, 3 H), 6.95 (d, 1 H), 6.88 (d, 1 H), 6.79 (d, 1 H), 3.90 (s, 6 H), 3.86 (s, 3 H), 2.84 (s, 3 H).

Enzyme Assays. Vero cells were infected with herpes simplex virus type 1 (HSV-1), strain C42.[15] HSV-1 DNA polymerase was isolated and assayed as previously described.[16] [^3H]dTTP was used as labeled substrate. Activated calf thymus DNA was used at a concentration of 200 μg/mL.

Cellular DNA polymerase α was purchased from PL Biochemicals, Inc., Milwaukee, WI, and assayed in a 100-μL reaction mixture containing 100 mM Tris-HCl (pH 8.0), 3 mM $MgCl_2$, 1 mM dithiothreitol, 40 μg of bovine serum albumin (fraction V), 100 μM dATP, dCTP, and dGTP, ~10 μM [^3H]dTTP (specific activity ~1000 cpm/pmol), 200 μg/mL of activated DNA, and 2.5 units/mL of enzyme. In the $(dT)_n\cdot(rA)_{12-18}$-directed reaction, 0.2 OD_{260}/mL and ~10 μM [^3H]dATP (specific activity ~900 cpm/pmol) were used. The reactions were incubated at 37 °C and processed as described previously.[16]

Avian myeloblastosis virus (AMV) reverse transcriptase was obtained from Boehringer Mannheim GmbH and assayed as described previously.[17] The different templates/primers were used in the following concentrations: 0.20 OD_{260}/mL of $(rA)_n\cdot(dT)_{12-18}$, 0.20 OD_{260}/mL of $(rC)_n\cdot(dG)_{12-18}$, and 0.23 OD_{260}/mL of $(dC)_n\cdot(dG)_{12-18}$. Inhibition of less than 5% has not been considered significant. The results in Table VI are presented as averages of duplicate assays.

Virus Multiplication. The effects of distamycin analogues on plaque formation and virus yield were determined with HSV-1 strain C42 and Vero cells as described earlier.[18] Inhibition of influenza A strain Victoria with MDCK cells has been described earlier.[19]

For virus titrations, inhibitions of less than 50% were not considered significant. The results are presented as averages of duplicate cell cultures. All comparisons of inhibition (Tables VII–IX) were made in experiments where the tested compounds were added to parallel cell cultures to decrease the variability due to cell condition.

Cellular Toxicity. The cellular toxicity was determined as the reduction in Vero cell proliferation during 48 h as described earlier.[20]

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Registry No. **1a**, 77716-11-1; **1b**, 85406-52-6; **1c**, 85406-53-7; **1d**, 77716-13-3; **1e**, 85406-54-8; **1f**, 85406-55-9; **1g**, 77716-18-8; **1h**, 85406-56-0; **1i**, 85406-57-1; **1j**, 85406-58-2; **2a**, 77716-15-5; **2a** (amine), 77716-19-9; **2b**, 85406-59-3; **2b** (amine), 85406-60-6; **2c**, 85406-61-7; **2c** (amine), 85406-62-8; **2d**, 85406-63-9; **2d** (amine), 85406-64-0; **2e**, 85406-65-1; **2e** (amine), 85406-66-2; **2f**, 85406-67-3; **2f** (amine), 85406-68-4; **3a**, 77716-20-2; **3b**, 85406-69-5; **3b** (acid), 85406-70-8; **3b** (N-succinimidyl ester), 85406-71-9; **3c**, 85406-72-0; **3c** (acid), 85406-73-1; **3c** (N-succinimidyl ester), 85406-74-2; **3d**, 85406-75-3; **3d** (acid), 85406-76-4; **3d** (N-succinimidyl ester), 85406-77-5; **3e**, 85406-78-6; **3e** (acid), 85406-79-7; **3e** (N-succinimidyl ester), 85406-80-0; **3f**, 85406-81-1; **3f** (acid), 85406-82-2; **3f** (N-succinimidyl ester), 85406-83-3; **3g**, 85406-84-4; **3g** (acid), 85406-85-5; **3g** (N-succinimidyl ester), 85406-86-6; **3h**, 85406-87-7; **3h** (acid), 85406-88-8; **3h** (N-succinimidyl ester), 85406-89-9; **4a**, 85406-90-2; **4b**, 85406-91-3; **4c**, 85406-92-4; **4d**, 85406-93-5; **4e**, 85406-94-6; **4f**, 85406-95-7; **5a**, 85406-96-8; **5a** (base), 636-47-5; **5b**, 85406-97-9; **5b** (base), 85406-98-0; **5c**, 85406-99-1; **5c** (base), 85407-00-7; **5d**, 85407-01-8; **5d** (base), 85407-02-9; **5e**, 85407-03-0; **5e** (base), 85407-04-1; **5f**, 85407-05-2; **5f** (base), 85407-06-3; **5g**, 85407-07-4; **5g** (base), 85407-08-5; **5h**, 85407-09-6; **5h** (base), 85407-10-9; **5i**, 85421-66-5; **5i** (base), 85407-11-0; **5j**, 85407-12-1; **5j** (base), 85407-13-2; **5k**, 85407-14-3; **5k** (base), 35967-49-8; **6**, 85407-15-4; **6** (amine), 85407-16-5; **9**, 85407-17-6; **9** (acid), 85407-18-7; **9** (N-succinimidyl ester), 85407-19-8; **10**, 85407-20-1; ethyl 1-ethylpyrrole-2-carboxylate, 85407-21-2; ethyl 1-ethyl-4-nitropyrrole-2-carboxylate, 85407-22-3; 1-ethyl-4-nitropyrrole-2-carboxylic acid, 85407-23-4; 4-nitropyrrole-2-carboxylic acid, 5930-93-8; ethyl pyrrole-2-carboxylate, 2199-43-1; benzyl 4-aminopyrrole-2-carboxylate, 85407-24-5.

Supplementary Material Available: ^1H NMR data for compounds **1a–j**, **2a–f**, **3a–h**, **4a–f**, **6**, and **9** (4 pages). Ordering information is given on any current masthead page.

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