Sodium-Independent [^{3}H]γAbu Binding Assay. The Na-independent binding of [^{3}H]γAbu was determined in crude synaptic membrane-rich fractions of rat brain as described by Enna and Snyder[10] with only minor modifications. Briefly, whole rat brain was homogenized in 15 volumes of ice-cold 0.32 M sucrose using a Teflon–glass homogenizer. By differential centrifugation,[10] the homogenate was fractionated into a crude synaptic membrane pellet that was frozen at −20 °C for at least 18 h prior to use.

The frozen synaptic membrane pellet was resuspended (1 mg/1 mL) in 0.05 M Tris–citrate buffer (pH 7.1) containing 0.05% Triton X-100.[13] The suspension was incubated at 37 °C for 30 min and then centrifuged at 48000*g* for 10 min (4 °C). The 48000*g* pellet was resuspended in 0.05 M Tris–citrate buffer (pH 7.1), and aliquots of the suspension were incubated with 8.0 nM [^{3}H]γAbu (36.1 Ci/mmol) for 5 min at 4 °C in the presence and absence of various concentrations (concentration range of each agent tested was 1 nM to 1 mM) of known γAbu receptor agonists, antagonists, or (±)-1. Following incubation, the suspension was centrifuged at 48000*g* for 15 min. The resulting pellets were dissolved in Soluene-350 (Packard Instrument Co.), and the radioactivity was assayed in Dimilume-30 (Packard Instrument Co.) with a Packard liquid scintillation spectrometer equipped with automatic standardization.

Nonspecific Na-independent binding was determined in the presence of excess unlabeled γAbu (5×10^{-5} M). Total specific Na-independent γAbu binding was obtained by reducing the total bound radioactivity by an amount equal to that not displaced by excess unlabeled γAbu. The IC_{50} value for each agonist, antagonist, or (±)-1 was obtained by plotting the total specific Na-independent binding (as a percentage of control) at each concentration of agonist, antagonist, or (±)-1.[18] All experiments were performed in triplicate. Total protein in the synaptic membrane fraction was determined by the biuret method.[19] Statistical significance ($p = 0.05$) was determined by Student's t test.

Acknowledgment. The authors express their appreciation to Mrs. Kathleen Ice for her excellent technical assistance in the pharmacological studies.

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Structure–Activity Relationships of Pyrrole Amidine Antiviral Antibiotics. 2. Preparation of Mono- and Tripyrrole Derivatives of Congocidine

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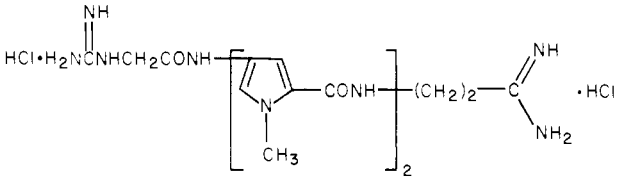
Representatives of three types of congocidine (1) analogues were synthesized. These were tested for cytotoxicity, inhibition of herpes simplex virus (HSV) replication in cultured cells, and effects on the synthesis of HSV DNA in isolated nuclei in vitro, as well as on DNA synthesis by purified HSV DNA polymerase. All synthesized tripyrrole derivatives of congocidine were less cytotoxic and more active than the parent drug in all the three antiviral tests.

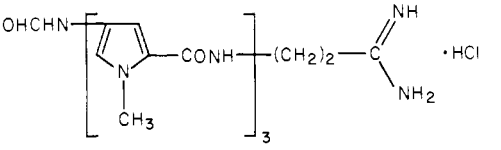
Congocidine (1) is a basic oligopeptide isolated from the fermentation medium of *Streptomyces chromagens* and *Streptomyces umbifaciens*.[2,3] The chemical structure of 1 was established by a series of degradations and a total



congocidine (1)

synthesis.[4,5] An antibiotic named netropsin was isolated from a fermentation medium of *Streptomyces netropsis*[6] and different chemical structures were assigned to it.[7-9] In 1964, the correct chemical structure of netropsin was established by proving its identity to congocidine.[10] Still, there are several cases (e.g., ref 11) where a wrong chemical structure is given for congocidine (or netropsin).[11]

Congocidine has very interesting biological activities, such as antibacterial,[12] antiparasitic,[2,3,10] and antiviral. As an antiviral drug, congocidine inhibits the multiplication of DNA viruses, such as vaccinia virus,[5,13] HSV,[14] and SFV,[15] and reteroviruses, such as RSV,[16] RuLV,[17] and FeLV.[18] Congocidine and distamycin A[19] (2) are the major



distamycin A (2)

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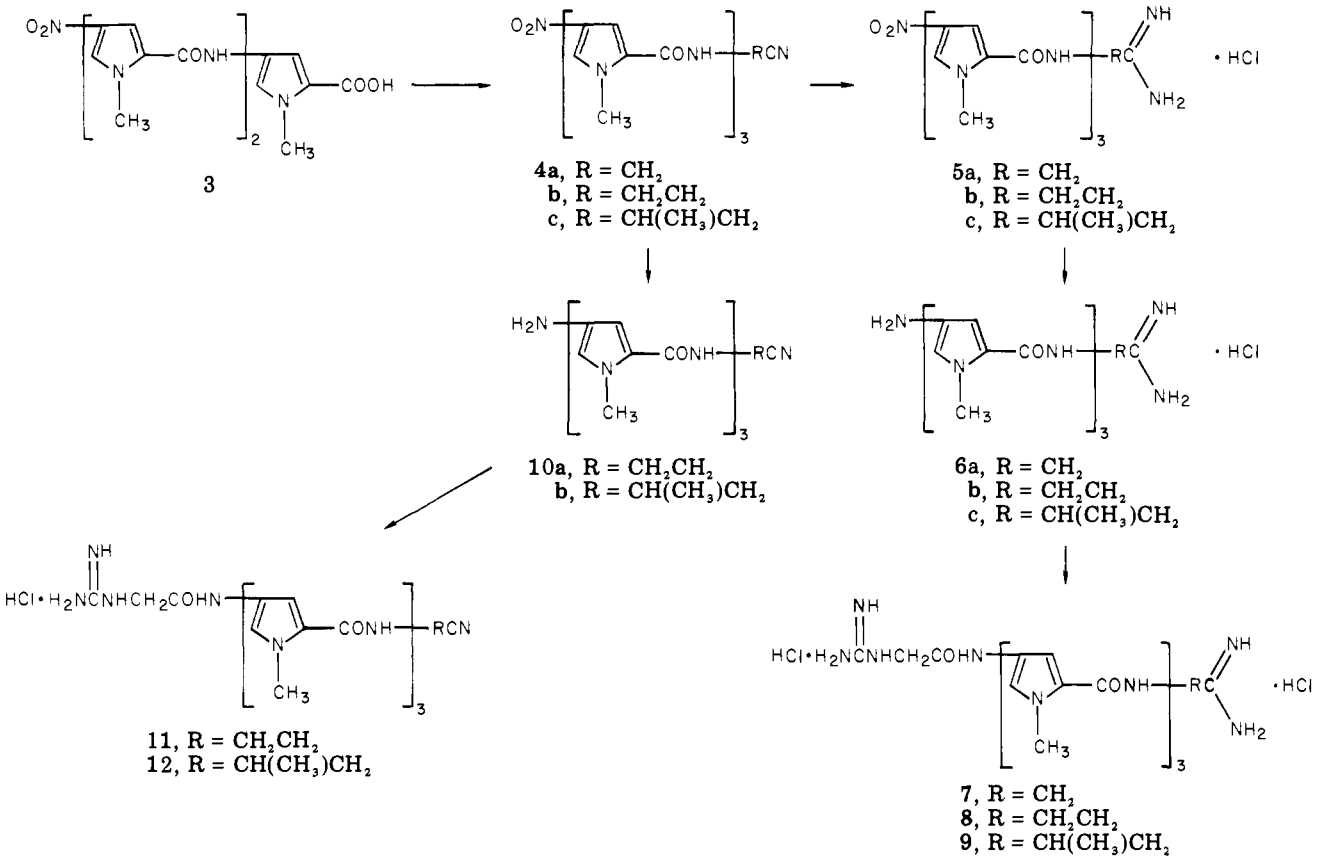
Scheme I



components of a group of pyrrole amidine antiviral antibiotics. The mechanism of the antiviral activity of these two compounds is very similar.[20,21] A very limited amount of information is available on the structural requirements for the antiviral activity of congocidine. Replacement of the *N*-methylpyrrole ring in congocidine by analogue moieties, such as thiophene, pyridine, and benzene, leads to reduction of the antiviral and antiparasitic activities.[22] Replacement of the guanidinoacetyl side chain by an amine moiety causes a reduction in the binding of congocidine to DNA.[23]

Congocidine and distamycin A are very similar in their chemical structures. They are mainly different in the number (n) of pyrrole rings. For congocidine, $n = 2$; for distamycin A, $n = 3$. When distamycin A (tripeptide) is converted into tetra- or pentapeptide analogues, the antiviral activity against some viruses is increased.[24,25] At the same time, the cytotoxicity is somewhat reduced, indicating that the antiviral and cytotoxic activities are separable.

Similar mono- and dipeptidic homologues of distamycin A proved to be more toxic and less effective than the parent drug.[24,25] The fact that the dipeptide congocidine demonstrates antiviral activity led us to challenge the effect of "n" on antiviral activity in the congocidine series. So, we decided to synthesize mono- and tripyrrolic derivatives of congocidine and test them for antiviral activity. Additionally, four other tripyrrole side-chain derivatives of congocidine were prepared and tested.

Chemistry. We recently described a new total synthesis of distamycin A.[26] The essential novel feature of this synthesis is that it employs the acid **3** as a key intermediate which can readily be used for the synthesis of different side-chain tripyrrole derivatives of congocidine as well as a distamycin A.[27] We now report the use of **3** for the synthesis of a tripyrrole homologue of congocidine and two types of side-chain analogues. In addition, we report a synthesis of a monopyrrole homologue of congocidine.

(a) The tripyrrole homologue of congocidine was prepared from the acid **3** in a manner similar to the preparation of distamycin A and its derivatives (Scheme I).[26,27] The only difference was in the last step of the synthesis. In this step the nitro group of **5b** was hydrogenated over Pd catalyst, giving the free amine **6b**, which without isolation was converted to the desired tripyrrole congocidine (**8**) by reaction with glycocyamine hydrochloride (**13**)[28] and DCC. Two side-chain analogues, compounds **7** and **9**, of the tripyrrole congocidine (**8**) were prepared in the same way (Scheme I). Compound **7** has an amidino side chain

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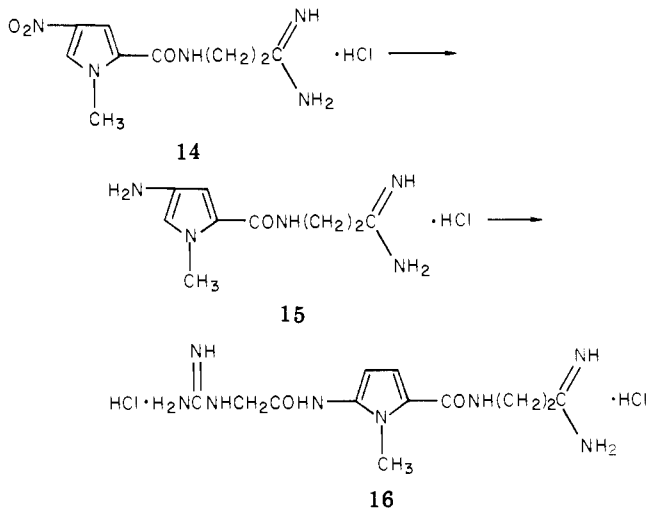
Scheme II



14

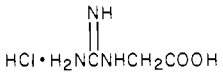
15

16

which is derived from an α-amino acid (glycine), while compounds **8** and **9** have amidino side chains which are derived from β-amino acids (β-alanine and β-amino-β-methylpropionic acid, respectively).

The NMR and mass spectra of compounds **7–9** fully support the structures indicated (see Experimental Section).

(b) Analogues in which the β-aminopropionamidine side chain is replaced by a β-aminoalkylnitrile moiety were prepared in order to verify the requirement of an amidine side chain for the antiviral activity in the congocidine series. Two compounds were prepared. The known nitro nitrile[26] (**4b**) was catalytically reduced to the amino nitrile (**10a**), which with glycocyamine hydrochloride (**13**) in the



glycocyamine hydrochloride (13)

presence of DCC (Scheme I) gave the desired guanidino nitrile (**11**). The guanidino nitrile (**12**) was prepared in the same fashion from the nitro nitrile (**4c**).

(c) The monopeptide homologue of congocidine (**16**) was prepared from the known nitro amidine (**14**)[24] in a way similar to that described previously (Scheme II). The nitro amidine (**14**)[24] was catalytically reduced to the amino amidine (**15**), which was reacted with glycocyamine hydrochloride (**13**) in the presence of DCC (Scheme II), giving the desired congocidine.

The final synthetic products were submitted for antiviral testing. Their activities were compared to that of the parent drug congocidine and distamycin A.

Virology. The antiviral activity of congocidine and its derivatives was studied in cell cultures infected with herpes simplex virus (HSV) type 1. The present investigation was done using four different techniques. These techniques were (a) cytotoxicity test, (b) inhibition of HSV in cultured cells, (c) effects on the synthesis of HSV DNA in isolated nuclei in vitro, and (d) effects on HSV DNA polymerase activity in vitro using activiated calf thymus DNA as a template. All the details of these techniques were given in our previous paper in this series.[27]

Results

Cytotoxicity of Congocidine Derivatives. The results revealed that congocidine (**1**) was toxic to the cultured cells at a concentration of 5 mcg/mL. The minimal toxic concentration for compounds **2**, **8**, **9**, **7**, and **16** was 25, 25, 10, 100, and 25 mcg/mL, respectively. Compound **12** had no toxic effect on the cells at 200 mcg/mL. The maximal nontoxic concentration for all the compounds in this series is presented in Table I.

Table I. Toxicity of Plaque Inhibition by Congocidine Derivatives

no.	max nontoxic concn,[a] mcg/mL	% inhibn of virus[b]
1	5	98.1
2	25	99.7
7	100	99.7
8	25	99.7
9	10	99.3
11	50	93.14
12	⩾400[c]	90.9
16	25	92.6

[a] Toxic effect is regarded as cell death within 2 days of incubation of cultured cells with the drug at 37 °C. The maximal nontoxic concentration is defined here as the nontoxic drug concentration whose twofold increase causes toxicity. [b] The titer of virus progeny produced in untreated infected cells and in cells treated with each of the distamycin derivatives was determined by plaque assay on BSC-1 cells. The virus yield by infected cells is taken as 100%, and the yield of virus from infected treated cells is related to the yield from untreated infected cells. Compound 12 was tested at a concentration of 200 mcg/mL. The rest were tested at their maximum nontoxic concentration. [c] The designation "⩾400" indicated that at 400 mcg/mL of the drug was not toxic.

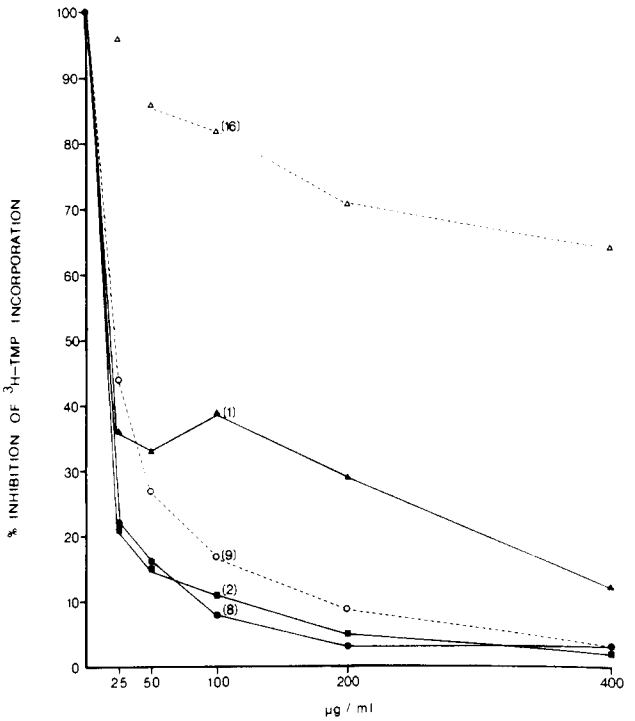


Figure 1. Percent inhibition of [^{3}H]thymidine monophosphate (^{3}H-TMP) into DNA of nuclei of cells infected by herpes simplex virus as function of drug concentration.

Inhibition of HSV Replication in Cultured Cells. All the congocidine derivatives were tested for their ability to inhibit HSV replication at their maximal nontoxic concentration (Table I). The results in Table I show that compounds **7–9** inhibited the virus replication by 99.5%. The results demonstrated that these three compounds showed greater effect on HSV replication than that of the parent drug (**1**) and was equal to the inhibition demonstrated by distamycin A (**2**).[27]

Effects of Congocidine Derivatives on the Synthesis of HSV DNA in Isolated Nuclei in Vitro. In this

Table II. Inhibition of DNA Synthesis and DNA Polymerase Activity

	% inhibn of DNA synthesis in vitro: drug concn, mcg/mL					% inhibn of HSV DNA polymerase act.: drug concn, mcg/mL				
no.	25	50	100	200	400	25	50	100	200	400
2	79	85	89	95	98	20	62	85	98	99
1	64	67	61	71	88	30	61	78	90	93
7						39	83	89	99	99
8	78	84	92	97	97	25	64	93	94	99
9	56	73	83	91	97	26	59	83	96	97
11	56	68	78	87	89	12	35	68	79	91
16	4	14	18	29	36	17	10	27	28	67

study the effect of different congocidine derivatives was measured (Figure 1, Table II). Compounds 8 and 9 had the most marked effect (97% inhibition at a concentration of 400 mcg/mL). These tripyrrole congocidine derivatives and distamycin A showed the greatest inhibition in all concentrations used. These results were similar to the effect of the compounds in this series on the virus replication. The results illustrated in Figure 1 show that compounds 8, 9, and distamycin A exhibited the best inhibition of the tested derivatives.

Effects of Distamycin Derivatives on DNA Synthesis by HSV DNA Polymerase. The effect of the different compounds on HSV DNA synthesis by the viral DNA polymerase under in vitro conditions resembled that obtained with isolated infected nuclei. The results in Figure 2 and Table II show that compounds 7–9 and distamycin A were the best inhibitors of the viral DNA polymerase activity.

Discussion and Conclusions

The three tripyrrole derivatives of congocidine and distamycin A were the most active compounds in all the three antiviral tests. The least cytotoxic of these four compounds was 7, which was 4 times less cytotoxic than distamycin A and 20 times less cytotoxic than the parent drug congocidine. This phenomenon indicates the possibility of a separation between the cytotoxicity and the antiviral activity. In all the tests we checked, the tripyrrole derivatives of congocidines (7–9) were more potent and less cytotoxic than congocidine and its monopyrrole homologue (16). A nice correlation between the increased number of pyrrole rings (n) in the molecule (from one to three) and the increased antiviral activity was demonstrated in the congocidine series. The amidino derivatives of congocidine were more active than their nitrile analogues.

Experimental Section

Chemistry. General Chemical Methods. Unless otherwise stated, the following apply. UV measurements were made using EtOH or DMF as solvents. IR spectra were taken in KBr pellets. ^{1}H NMR data were determined in Me_2SO-d_6 with sodium 3′-(trimethylsilyl)propionate-d_4 as external standard. TLC was performed on 0.3-mm silica gel plates which were developed with Ehrlich reagent (2% N,N-dimethylaminobenzaldehyde in 6 N HCl) or by irradiation at 254 nm. The eluents used were BuOH/AcOH/H_2O, 40:10:50 (solvent system I), and MeOH/i-PrOH/AcOH/H_2O, 50:20:10:5 (solvent system II). Mass spectra (MS) were obtained by direct inlet method at 80 eV; in several cases, the techniques of field desorption was used.[29] Elemental analyses data for compounds 7–9 and 11 are not given due to irreproducible results obtained for these sensitive decomposable compounds.

***N*-Methyl-4-[*N*-methyl-4-[*N*-methyl-4-(guanidineacetamido)pyrrole-2-carboxamido]pyrrole-2-carboxamido]-pyrrole-2-carboxamidoacetamidine Dihydrochloride (7).** The nitropyrrole derivative **5a**[27] (0.5 g, 1.0 mmol) was dissolved in DMF (10 mL) and reduced at atmospheric pressure with Pd on charcoal (0.2 g). The mixture was filtered. The presumed intermediate amine (**6a**) was not purified due to instability. Glycocyamine hydrochloride (**13**) (Fluka)[28] (153 mg, 1.0 mmol) was added and then DCC (206 mg, 1 mmol) in DMF (10 mL) was gradually added under nitrogen to the solution of **6a**, and the solution was stirred at 0 °C for 1 h. Then reaction mixture was stirred at room temperature overnight and filtered. The filtrate was evaporated and the crude residue was purified by chromatography on an alumina (activity I) column (80 g). The eluant used was methanol. Crystallization from a mixture of methanol and ethyl acetate gave 7: yield 90 mg (15%); mp 216–220 °C; NMR δ 3.83 (N-CH_3 groups), 4.06 (2 H), 6.92–7.24 (aromatic H's), 7.46 (amidine and guanidine H's), 9.83, 9.89, 10.42 (amide H's); UV λ_{max} (EtOH) 240 nm (ϵ 23400), 308 (24700); IR ν 3040–3460, 1660, 1580, 1430, 1400, 1250, 1210, 1110, 1060 cm^{-1}; MS, m/e (field desorption) 489, 438, 331; TLC, a single spot using solvent systems I and II.

***β*-[*N*-Methyl-4-[*N*-methyl-4-[*N*-methyl-4-(guanidineacetamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]propionamidine Dihydrochloride (8).** This compound was prepared from the nitropyrrole **5b** as described above for the synthesis of its homologue 7. Compound 8 was obtained in 11% yield: mp 213–217 °C; NMR δ 2.72, 3.3 (2 H), 3.84 (N-CH_3 groups), 4.06 (2 H), 6.98–7.22 (aromatic H's), 8.16, 9.84, 10.15 (amide H's); UV λ_{max} (EtOH) 237 nm (ϵ 20000), 306 (25000); IR ν 3000–3460, 1650, 1570, 1450, 1400, 1230, 1200, 1100 cm^{-1}; MS, m/e (field desorption) 518, 464, 452, 435, 381; TLC, a single spot using solvent systems I and II.

***β*-[*N*-Methyl-4-[*N*-methyl-4-[*N*-methyl-4-(guanidineacetamido)pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]butyramidine Dihydrochloride (9).** This compound was prepared from the nitropyrrole **5c** as described above for the synthesis of its homologue 7. Compound 9 was obtained in 13% yield: mp 218–223 °C; NMR δ 1.33 (C-CH_3), 3.92 (N-CH_3 groups), 8.04–8.66 (aromatic H's), 9.33 (amide H's); UV λ_{max} (EtOH) 239 nm (ϵ 20000), 305 (26400); IR ν 3000–3500, 1630, 1520, 1430, 1400, 1260, 1200, 1150, 1100, 1050 cm^{-1}; MS, m/e (field desorption) 466, 381; TLC, a single spot using solvent systems I and II.

***β*-[*N*-Methyl-4-[*N*-methyl-4-[*N*-methyl-4-(guanidineacetamido)pyrrole-2-carboxamido]pyrrole-2-carbox-**

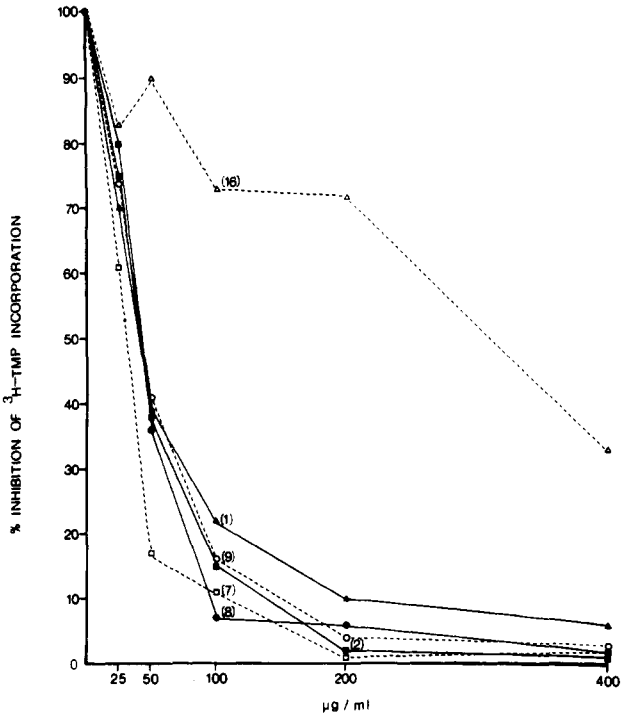


Figure 2. Percent inhibition of [^{3}H]thymidine monophosphate (^{3}H-TMP) by purfied HSV-coded DNA polymerase under in vitro conditions, using calf tymus DNA as template.

(29) H. D. Beckey and H. R. Schulten, *Angew. Chem.*, 87, 425 (1975).

amido]pyrrole-2-carboxamido]propionitrile Hydrochloride (11). This compound was prepared from the nitropyrrole **4b** as described above for the synthesis of its homologue **7**. Compound **11** was obtained in 10% yield: mp 196–199 °C; NMR δ 2.84 (2 H), 3.95 (N-CH_3 groups), 4.13 (2 H), 7.0, 7.18, 7.34 (aromatic H's), 9.85, 10.30 (amide H's); UV λ_{max} (EtOH) 244 nm (ϵ 19 900), 305 (21 400); IR ν 3040–3500, 2950, 2260, 1640, 1580, 1440, 1400, 1260, 1200, 1150, 1110, 1000, 1010 cm^{-1}; MS, *m/e* 435 (M − 100, 30), 411 (10), 314 (42), 261 (100); TLC, a single spot using solvent systems I and II.

β-[*N*-Methyl-4-[*N*-methyl-4-[*N*-methyl-4-(guanidineacetamido)pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamido]butyronitrile Hydrochloride (12). This compound was prepared from the nitropyrrole **4c** as described above for the synthesis of its homologue **7**. Compound **12** was obtained in 28% yield: mp 195–198 °C; NMR δ 1.3 (C-CH_3), 2.1, 2.82 (2 H), 3.92 (N-CH_3 groups), 408 (2 H), 6.88, 7.04, 7.22 (aromatic H's), 9.84, 10.3 (amide H's); UV λ_{max} (EtOH) 242 nm (ϵ 24 000), 305 (25 600); IR ν 3000, 3500, 2470, 2260, 1650, 1580, 1520, 1430, 1400, 1260, 1200, 1150, 1100, 1060, 1010 cm^{-1}; MS, *m/e* 449 (M − 100, 26), 328 (100), 261 (84). Anal. ($C_{25}H_{31}N_{11}O_4 \cdot HCl \cdot 2H_2O$) C, H, N, Cl; TLC, a single spot using solvent systems I and II.

β-[*N*-Methyl-4-(guanidineacetamido)pyrrole-2-carboxamido]propionamidine Dihydrochloride (16). This compound was prepared from the nitropyrrole **14** as described above for the synthesis of its homologue **7**. Compound **16** was obtained in 9.7% yield: mp 234–240 °C; NMR δ 2.7 (2 H), 3.7 (N-CH_3), 4.0 (2 H), 6.8, 7.09 (aromatic H's), 7.5, 8.4, 8.92, 10.3 (amide, amidine, and guanidine H's); UV λ_{max} (EtOH) 238 nm (ϵ 15 000), 274 (11 500); IR ν 3090–3320, 1670, 1640, 1580, 1520, 1440, 1410, 1240 cm^{-1}; MS, *m/e* 274 (M − $2NH_3$, 40), 246 (30), 220 (20), 208 (67), 192 (100); MS, *m/e* (field desorption) 291, 274, 208, 192; TLC, a single spot in TLC using solvent systems I and II. Anal. ($C_{12}H_{20}N_8O_2 \cdot 2HCl$) C, H, N, Cl.

Virology. The details for the virological experimental were given in our previous paper in this series.[27]

Acknowledgment. We thank Rhône-Poulene Laboratories, France, for a sample of authentic congocidine. The chemical research was partially supported by the Israeli National Council on Research and Development. The virological studies were supported in part by a grant from Dr. K. Hermann, Hermal Chemie, Hamburg, West Germany. We are indebted to Yehudit Hamburger, Yael Asher, Eynat Tavor, and Yaffa Cohen for technical assistance, Dr. B. Fridlender for his help in performing the DNA polymerase assay, and to David Linder for the mass spectra.

Book Reviews

How to Find Chemical Information. By Robert E. Maizell. Wiley, New York. 1979. xxiii + 261 pp. 15 × 23 cm. $17.95.

The author of this "guide for practicing chemists, teachers, and students" is currently Manager of Information Services for the Olin Corp. For 20 years he has had daily experience in handling chemical information sources in a number of academic and industrial positions.

In a book of this size it is impossible to describe adequately all available sources of chemical information. The author has elected to describe the more important classical sources, the more significant newer sources, and the underlying methods, principles, and keys that the chemist and engineer need to cope with the constantly changing array of sources and tools. In an effort to update his information, he includes an appendix of about 30 items, keyed to appropriate pages in the text, describing developments through 1978.

Specific major topics included in the book are: search strategy; current awareness; acquisition of chemical documents; Chemical Abstracts Service; other abstracting and indexing services; computer-based information retrieval systems; reviews; major reference books; patents; physical property data; chemical marketing and business information; process information; and, in response to the current emphasis in programs and expenditures, a chapter on toxicology, safety, and pollution. Medicinal chemical literature as such is not discussed.

Two items in the book were particularly interesting to me. In discussing the surrogate concept in literature use, the author points out that the secondary sources of information are now so numerous, complex, and ephemeral that they are used best by information science specialists. These surrogates for the laboratory chemist or project leader are valuable colleagues. The author then retreats and, in the course of half a page, makes an excellent case for exercising the greatest caution when using surrogates, and he lists several excellent reasons for a chemist doing his own literature work. Case histories of projects gone astray as the result of faulty literature work make fascinating reading. I know of one case where, because of reliance on unqualified surrogates, a major compilation was published with so many errors that the errata list was almost as long as the original document. As in so many instances in life, the use of surrogates involves trade-offs.

In a chapter describing how to locate and use physical property and related data, the author includes a section on how to evaluate data from conflicting or unevaluative sources. Appropriate officials in the FDA, EPA, and other regulatory agencies should read the 18 questions asked, answers to each of which must be given before any sane decision can be reached concerning the reliability of the data. I lived with the problem of data collection and evaluation for a period of 2 years, during which, with the help of the best available surrogates, I prepared a compilation of about 30 items for each of 900 chemicals. When collection was complete, the data and references cited were evaluated by a public health M.D., an organic chemist with 40 years experience, a fire and safety expert, and a chemical engineer who was an expert in the evaluation of physical properties. Then and only then were the data released for publication. The proper use of the chemical literature is hard, exacting, time-consuming work. There are shortcuts, but Dr. Maizell and I agree that they who use them will sooner or later wish that they had not.

Amherst, Mass. **Edward R. Atkinson**

The Porphyrins. Volume VI. Biochemistry. Part A. Edited by David Dolphin. Academic Press, New York. 1979. xxi + 932 pp. 16 × 23 cm. $90.00.

This fine volume should appeal to a very wide spectrum of readers having an interest in porphyrin chemistry. Its value is greatly enhanced by the inclusion of a substantial number of experimental procedures, a feature which should lead to its use as a laboratory source-book as well as a library text.

The first two chapters deal comprehensively with protoporphyrin biosynthesis, Chapter 1 being particularly rich in chemical information regarding the organic synthesis of biogenetic precursors in labeled form. Chlorophyll biosynthesis is covered in Chapter 3, while Chapter 4 presents a critical evaluation of enzymatic and other preparations of everything from δ-aminolevulinic acid to protoporphyrin IX. The chemistry and biochemistry of the bile pigments are extensively reviewed in Chapters 5 and 6, again with much pertinent spectroscopic and experimental detail. Chapter 7 discusses plant pigments as exemplified by phytochrome and the phycobiliproteins. Derivatives