(5) J. Greenberg, D. J. Taylor, and E. S. Josephson, *J. Infect. Dis.*, **88**, 163 (1951).
(6) N. L. Drake and Y. T. Pratt, *J. Am. Chem. Soc.*, **73**, 544 (1951).
(7) E. S. Josephson, D. J. Taylor, J. Greenberg, and A. P. Ray, *Proc. Soc. Exp. Biol. Med.*, **76**, 700 (1951).
(8) E. S. Josephson, J. Greenberg, D. J. Taylor, and H. L. Bami, *J. Pharmacol. Exp. Ther.*, **103**, 7 (1951).
(9) S. Kawai, J. Kosaka, and M. Hatano, *Proc. Jpn. Acad.*, **30**, 774 (1954).
(10) F. E. King, N. G. Clark, and P. M. H. Davis, *J. Chem. Soc.*, 3012 (1949).
(11) W. F. Gum, Jr., and M. M. Joullié, *J. Org. Chem.*, **32**, 53 (1967).
(12) J. Habermann, *Chem. Ber.*, **11**, 1038 (1878).
(13) W. F. Gum, Jr., M. R. W. Levy, and M. M. Joulié, *J. Chem. Soc.*, 2282 (1965), reported a similar unusual oxidative demethylation during attempts to nitrate some substituted 1,4-dimethoxybenzenes.
(14) G. Charles, *Bull. Soc. Chim. Fr.*, **5**, 1559 (1963).
(15) J. Klicnar, M. Vavra, P. Vetesnik, and S. Panusova, *Sb. Ved. Pr., Vys. Sk. Chemickotechnol. Pardubice*, **18**, 15 (1968); *Chem. Abstr.*, **72**, 66896q (1970).
(16) G. M. Bennett and G. H. Willis, *J. Chem. Soc.*, 1960 (1928).
(17) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967). The authors thank the staff of the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for transmitting the test results provided by Dr. L. Rane, University of Miami.
(18) L. Rane and D. S. Rane, *Proc. Helminthol. Soc. Wash.*, **39**, 283 (1972).
(19) E. M. Kampouris, *J. Chem. Soc. C*, 1235 (1967).
(20) M. Chaykovsky, M. H. Lin, and A. Rosowsky, *J. Org. Chem.*, **37**, 2018 (1972). The authors thank Dr. Chaykovsky et al. for a prepublication copy of this paper.
(21) L. Rubenstein, *J. Chem. Soc.*, 2003 (1925).

Synthesis and Antibacterial Activities of Some Chloro Analogs of 3-Amino-3,4-dihydro-1-hydroxycarbostyril

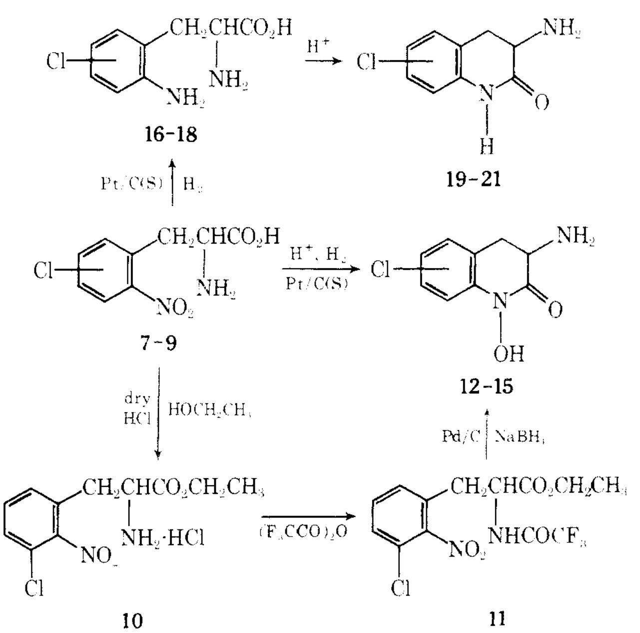
Alvie L. Davis,* William H. Chambers, Don H. Kelley, David A. Fell, John R. Haynes, Karen L. Hulme, Larry D. Gage, and Tommy J. McCord

Department of Chemistry, Abilene Christian College, Abilene, Texas, 79601. *Received January 16, 1975*

The effects of a chloro substituent upon the microbiological activities of 3-amino-3,4-dihydro-1-hydroxycarbostyril were determined. The 5-, 6-, and 7-chloro analogs were synthesized by reductive cyclizations of the appropriately chloro-substituted *o*-nitrophenylalanines, while the 8-chloro analog was obtained from the *N*-trifluoroacetyl-3-chloro-2-nitrophenylalanine ethyl ester. All of these compounds were observed to inhibit the growth of *Escherichia coli* 9723, *Leuconostoc dextranicum* 8086, and *Lactobacillus plantarum* 8014. The relative inhibitory activities of the chloro analogs were 7-Cl > 6-Cl > 8-Cl > 5-Cl in *E. coli* and 7-Cl > 6-Cl > 8-Cl = 5-Cl in *L. dextranicum* and *L. plantarum*. In each of the three microorganisms, the 7-Cl analog was a more effective growth inhibitor than the parent unsubstituted compound. The growth inhibitory activities of this class of compounds were demonstrated to be much more effective than those of the four corresponding lactams, the 5-, 6-, 7-, and 8-chloro analogs of 3-amino-3,4-dihydrocarbostyril.

Since our earliest report on the synthesis and potent antibacterial activity of the cyclic hydroxamic acid, 3-amino-3,4-dihydro-1-hydroxycarbostyril,[1] we have studied the structure–activity relationships of its 7-hydroxy and 7-methoxy derivatives,[2] its optically active forms,[3] and its lower condensed-ring homolog, 3-amino-1-hydroxy-2-indolinone.[4] The purpose of this paper was to further these studies by determining the effects upon microbiological activity of a chloro substituent at each of the benzenoid positions of the cyclic hydroxamic acid. Accordingly, the four isomeric chloro-substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils **12–15** were synthesized and their relative growth inhibitory activities were determined and compared with those of the unsubstituted parent compound in *Escherichia coli* 9723, *Lactobacillus plantarum* 8014, and *Leuconostoc dextranicum* 8086. The corresponding four chloro-substituted lactams were also studied for their activities in these microorganisms.

Chemistry. The desired chloro-substituted cyclic hydroxamic acids **12–15** and lactams **19–21** were synthesized either directly or indirectly by reductive cyclization of the appropriately chloro-substituted *o*-nitrophenylalanines **7–9**. A major portion of the synthetic work in this study involved the preparation of the requisite chloro-2-nitrophenylalanines (**7–9**) by the usual acetamidomalonic ester method as previously described for the synthesis of 5-chloro-2-nitrophenylalanine.[5]



The 5-Cl (**12**), 6-Cl (**13**), and 7-Cl (**14**) analogs of 3-amino-3,4-dihydroxy-1-hydroxycarbostyril were obtained in good yield by reductive cyclization of the hydrochloride salts of the respective chloro-2-nitrophenylalanines under acidic conditions of catalytic hydrogenation. In order to prevent hydrogenolysis of the chloro groups, platinum on carbon (sulfided)[6] was used as the catalyst. On the other hand, when the 3-chloro-2-nitrophenylalanine hydrochloride was catalytically hydrogenated under the same experimental conditions, only the corresponding lactam, 3-amino-8-chloro-3,4-dihydrocarbostyril (**21**), was obtained rather than the desired 8-Cl cyclic hydroxamic acid **15**.

The remaining 8-Cl analog **15** was synthesized by an indirect method from compound **7**, in which the amino acid was converted first to its ethyl ester hydrochloride **10** and then to the *N*-trifluoroacetyl derivative **11**. Reduction of the latter compound with sodium borohydride and palladium/charcoal according to the method of Coutts and coworkers[7] gave 3-amino-8-chloro-3,4-dihydro-1-hydroxycarbostyril (**15**) in low yield.

In accord with the method previously described for the synthesis of 3-amino-6-chloro-3,4-dihydrocarbostyril,[5] the 5-Cl, 7-Cl, and 8-Cl lactams **19–21** were prepared by cyclization of the corresponding chloro-substituted 2-aminophenylalanines **16–18**. The latter compounds (**16–18**) were obtained by catalytic hydrogenation of the free bases of the chloro-2-nitrophenylalanines **7–9** under neutral conditions.

Microbiological Studies. The inhibitory activities of the four chloro-substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils in *E. coli* 9723, *L. dextranicum* 8086, and *L. plantarum* 8014 were summarized in Table I. As a basis for comparing the inhibitory activities of these chloro analogs with the unsubstituted parent compound and related derivatives, aspergillic acid[8,9] was again used as the standard in the microbiological assays under the conditions described in the Experimental Section.

All of chloro cyclic hydroxamic acids were effective in inhibiting the growth of each of three microorganisms at relatively low concentrations, and they were in general more inhibitory in *L. plantarum* than the other two assay organisms. It was also observed that the relative inhibitory effects of the analogs vary with the position of the chloro substituent. The relative inhibitory activities of the chloro analogs were 7-Cl > 6-Cl > 8-Cl = 5-Cl, and this order was the same for each microorganism, with the single exception that the 8-Cl > 5-Cl in *E. coli*.

In every instance, the 7-Cl analog was several-fold more effective than the parent compound as a growth inhibitor. Furthermore, the 6-Cl analog was more effective, equally effective, and less effective than the parent compound in inhibiting the growth of *E. coli, L. plantarum,* and *L. dextranicum,* respectively. As growth inhibitors, , the 5-Cl and 8-Cl cyclic hydroxamic acids were appreciably less effective than the unsubstituted compound.

The four chloro-substituted lactams were also tested for their activities in the same microorganisms and as a group they were much less effective growth inhibitors than the chlorocarbostyrilhydroxamic acids as indicated in Table I. At concentrations of 200 μg/ml, both the 5-Cl (**19**) and 8-Cl (**21**) lactams were inactive in *E. coli* and active in *L. plantarum* as growth inhibitors, whereas the 5-Cl was active and the 8-Cl was inactive in inhibiting the growth of *L. dextranicum.* The 6-Cl,[5] like the 5-Cl analog, inhibited the growth of only the latter two microorganisms, but the 6-Cl was about three times more effective than the 5-Cl isomer as a growth inhibitor. All three of the microorganisms were inhibited by the 7-Cl (**20**) analog, and once again it was the most effective inhibitor of its class.

From this structure–activity study, it was found that the substitution of a chloro group affects the growth inhibitory activity of 3-amino-3,4-dihydro-1-hydroxycarbostyril and the degree of activity was dependent on the position in the benzene ring. A chloro substitutent at the 7 position produces an analog with increased inhibitory activity over the parent compound. And since the chloro-substituted carbostyrilhydroxamic acids were far more effective than the lactams as growth inhibitors, the most significant structural feature in this type of heterocyclic compound for producing antibacterial activity still appeared to be the presence of the hydroxamate grouping.

Table I. Microbiological Activities of Some Chloro Analogs of 3-Amino-3,4-dihydro-1-hydroxycarbostyril and Related Compounds

Compound	MIC, μg/ml[a] *E. coli*	*L. dextranicum*	*L. plantarum*
Parent compound	1	1	0.6
5-Cl (**12**)	40	10	6
6-Cl (**13**)	0.4	2	0.6
7-Cl (**14**)	0.2	0.4	0.2
8-Cl (**15**)	20	10	6
Aspergillic acid[b]	10	2	20
5-Cl (**19**)	>200	200	200
6-Cl[c]	>200	60	60
7-Cl (**20**)	60	20	6
8-Cl (**21**)	>200	>200	200

[a]Minimum inhibitory concentration. [b]See ref 8 and 9. [c]See ref 5.

Experimental Section

General. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Where analyses are indicated only by symbols of the elements, analytical results obtained by those elements were within ±0.4% of the theoretical values.

Chloro-2-nitrobenzyl Bromides (1–3). These compounds were synthesized according to the procedure described previously for the preparation of 5-chloro-2-nitrobenzyl bromide.[5] As a general method, 95 g (0.53 mol) of *N*-bromosuccinimide and 2 g (0.008 mol) of dibenzoyl peroxide were added in small increments to a solution of 85 g (0.49 mol) of the appropriate chloro-2-nitrotoluene in 200 ml of anhydrous CCl_4 under reflux conditions over a period of 10 hr. The reaction mixture was filtered to remove the succinimide, and the filtrate was reduced to 0.5 of its original volume by evaporation of the solvent in vacuo. Upon chilling the remaining solution at −17°, the crystalline bromide which separated was filtered and washed with *n*-hexane. Analytical samples were recrystallized from 95% EtOH. The melting points, yields, and analytical data are given in Table II.

Ethyl 2-Acetamido-2-(chloro-2′-nitrobenzyl)malonates (4–6). These compounds were prepared in a manner similar to that described for the synthesis of ethyl 2-acetamido-2-(5′-chloro-2′-nitrobenzyl)malonate.[5] In a typical procedure, 25.2 g (0.1 mol) of the appropriate chloro-2-nitrobenzyl bromide was added to a solution of 21.7 g (0.1 mol) of ethyl acetamidomalonate in 100 ml of Mg-dried EtOH containing 2.3 g (0.1 mol) of Na. After the reaction mixture had stirred at 25° for 1 hr, an equal volume of water was added to cause precipitation of the product. The solid was collected on a filter, washed with water, and dried. Recrystallization of the product from 95% EtOH gave analytical samples (Table II).

Chloro-2-nitrophenylalanines (7–9). For the synthesis of these compounds, the same reaction procedure was followed as reported previously for the preparation of 5-chloro-2-nitrophenylalanine hydrochloride.[5] A mixture of 14 g (0.036 mol) of the ethyl 2-acetamido-2-(chloro-2′-nitrobenzyl)malonate and 150 ml of concentrated HCl was refluxed for 24 hr. On cooling to 25°, the product separated as the HCl salt. It was filtered, washed with acetone, and dried in vacuo over P_2O_5. An aqueous solution of the HCl salt was converted to the free base by adjusting the pH to 7 with concentrated NH_4OH. The melting points, yields, and analyses of the free bases are given in Table II.

3-Chloro-2-nitrophenylalanine Ethyl Ester Hydrochloride (10). A solution of 4.4 g (0.018 mol) of **7** in 100 ml of saturated ethanolic HCl was refluxed for 1–2 hr and then chilled at −17° for several hours, and the addition of Et_2O resulted in the isolation of

Table II. Physical Constants, Yields, and Analytical Data of Compounds Prepared in This Study

Compd	Position of Cl	Mp, °C	Yield, %	Formula	Analyses
		Chloro-2-nitrobenzyl Bromides			
1	3	62–63	61	$C_7H_5NO_2BrCl$	C, H
2	4	40–41	70	$C_7H_5NO_2BrCl$	C, H
3	6	50–52	64	$C_7H_5NO_2BrCl$	C, H
		Ethyl 2-Acetamido(chloro-2′-nitrobenzyl)malonates			
4	3′	156–157	78	$C_{16}H_{19}N_2O_7Cl$	C, H, N
5	4′	139–140	62	$C_{16}H_{10}N_2O_7Cl$	C, H, N
6	6′	127–128	65	$C_{16}H_{19}N_2O_7Cl$	C, H, N
		Chloro-2-nitrophenylalanines[a]			
7	3	236–238	90	$C_9H_9N_2O_4Cl$	C, H, N
8	4	232–233	94	$C_9H_9N_2O_4Cl$	C, H, N
9	6	211–213	76	$C_9H_9N_2O_4Cl$	C, H, N
		3-Aminochloro-3,4-dihydro-1-hydroxycarbostyrils[b]			
12	5	284–288	66	$C_9H_9N_2O_2Cl \cdot HCl$	C, H, N
13	6	206–207	63	$C_9H_9N_2O_2Cl$	C, H, Cl
14	7	202–203	73	$C_9H_9N_2O_2Cl$	C, H, Cl
15	8	168–169	26	$C_9H_9N_2O_2Cl$	C, H, N
		2-Aminochlorophenylalanines			
16	3	206–207	84	$C_9H_{11}N_2O_2Cl$	C, H, N
17	4	191–192	93	$C_9H_{11}N_2O_2Cl$	C, H, N
18	6	197–200	97	$C_9H_{11}N_2O_2Cl$	C, H, N
		3-Aminochloro-3,4-dihydrocarbostyrils			
19	5	335–340	66	$C_9H_9N_2OCl \cdot HCl$	C, H, N
20	7	173–174	85	$C_9H_9N_2OCl$	C, H, N
21	8	304–305	76	$C_9H_9N_2OCl \cdot HCl$	C, H, N

[a]Yields based on HCl salts. [b]Yields based on HCl salts except that of 15 which was based on free base.

4.4 g (90%) of product, mp 186–187°. Anal. ($C_{11}H_{13}N_2O_4Cl \cdot HCl$) C, H, N.

N-Trifluoroacetyl-3-chloro-2-nitrophenylalanine Ethyl Ester (11). Compound **10** (2.12 g, 0.008 mol) was suspended in 50 ml of EtAc and treated with 0.68 g (0.007 mol) of Et_3N followed by 2.72 g (0.013 mol) of trifluoroacetic anhydride. The reaction mixture was stirred for 12 hr at 25° and washed with saturated aqueous $NaHCO_3$ and then H_2O. After separating and drying the organic layer over anhydrous Na_2SO_4, it was concentrated in vacuo to about 25 ml and brought to cloudiness by the addition of *n*-hexane. Upon cooling at 0° for several hours, there was recovered 2.0 g (80%) of product, mp 79–81°. Anal. ($C_{13}H_{12}N_2O_5F_3Cl$) C, H, N.

3-Aminochloro-3,4-dihydro-1-hydroxycarbostyrils (12–14). Method A. Except for **7**, 1.0 g (0.004 mol) of the HCl salt of the chloro-2-nitrophenylalanine was dissolved in 10 ml of 50% aqueous MeOH and 1 drop of concentrated HCl was added. Hydrogenation of this solution was carried out in the presence of 50 ml of Pt/C(sulfided)[6] catalyst at 3.67 kg/cm^2 of H_2 pressure for 3 hr. The catalyst was collected on a filter-cel mat and addition of 10 ml of concentrated HCl to the filtrate resulted in separation of the HCl salt of the product. While **12** was analyzed as the HCl salt, analytical samples of **13** and **14** were obtained as the free bases by adjusting the pH of their aqueous HCl salt solutions to 7 with concentrated NH_4OH (Table II). These compounds gave the characteristic color reaction (violet) with $FeCl_3$ reagent.

3-Amino-8-chloro-3,4-dihydro-1-hydroxycarbostyril (15). Method B. The reductive cyclization procedure was similar to that previously reported.[7] To a mixture of 120 mg of 5% Pd/C suspended in 40 ml of 0.5 *N* methanolic NaOH solution and 1 ml of H_2O was added 1.05 g (0.0028 mol) of compound **11**. After N_2 was passed through the mixture for 5 min, a solution of 213 mg of $NaBH_4$ (0.0056 mol) in 12 ml of 0.1 *N* NaOH was added dropwise and stirring was continued for 0.5 hr. The catalyst was collected by filtering and the filtrate was neutralized with concentrated HCl and reduced in vacuo to a small volume and extracted with $CHCl_3$. After drying over anhydrous Na_2SO_4, the solvent was evaporated in vacuo. The residue was dissolved in a solution of 0.5 g of NaOH in 10 ml of 60% MeOH. After standing at 25° for 1 hr, the solution was neutralized with concentrated HCl and the solvent was evaporated in vacuo. The residue was leached with 70 ml of acetone and filtered to remove the insoluble material. The filtrate was concentrated in vacuo to about 30 ml and 2 drops of H_2O were added. Upon cooling at 0° for 12 hr, a product weighing 150 mg was collected (Table II). This compound gave a violet $FeCl_3$ test.

2-Aminochlorophenylalanines (16–18). Using the same method of preparation for 2-amino-5-chlorophenylalanine as described in previous work,[5] a solution of 1.0 g (0.004 mol) of the chloro-2-nitrophenylalanine (free base) in 200 ml of 50% aqueous MeOH was hydrogenated at 3.67 kg/cm^2 of H_2 pressure in the presence of Pt/C (sulfided) catalyst for 5 hr. Concentration of the filtrate from the catalyst in vacuo to a small volume and cooling at 0° yielded the crystalline product. Analytical samples were recrystallized from 95% EtOH (Table II).

3-Aminochloro-3,4-dihydrocarbostyrils (19–21). These compounds were prepared by a procedure patterned after that used for the synthesis of 3-amino-6-chloro-3,4-dihydrocarbostyril.[5] A 100-mg (0.0005 mol) sample of the 2-aminochlorophenylalanine was dissolved in 10 ml of concentrated HCl. On standing at 25° for 1 hr, the desired product separated as the HCl salt, which was filtered, washed with acetone followed by ether, and dried in vacuo over P_2O_5. In the case of **20**, an aqueous solution of the HCl salt was treated with concentrated NH_4OH to pH 7 to give the free base. Melting points, yields, and analyses are given in Table II.

Microbiological Assays. For the assays with *E. coli* (ATCC 9723) the procedure[10] and the inorganic salts–glucose medium[11] were the same as those previously described. For *L. dextranicum* (ATCC 8086), a previously described assay procedure and basal medium[12] were used except that histidine, phenylalanine, and tyrosine were omitted; 0.2 μg/ml of calcium pantothenate and 0.02 μg/ml of pantethine were added, and the phosphate (salts A) concentration was increased fourfold. The same assay procedure and basal medium[12] was used for *L. plantarum* (ATCC 8014, *L. arabinosus* 17-5) except that histidine was omitted from the basal medium.

The compounds (10 mg) were dissolved in sterile H_2O (10 ml) at 25°. From these solutions, serial dilutions were made and added aseptically to the previously autoclaved assay tubes without heating. After inoculation, the assay tubes with *E. coli* were incubated at 37° for 16 hr and with *L. dextranicum* and *L. plantarum* at 30° for 24 hr. In all assays the amount of growth was determined spectrometrically at 625 mμ with a Baush and Lomb Spectronic 20 spectrophotometer in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at 0 absorbance. For each assay, appropriate controls were performed and reproducible results of the minimum inhibitory concentrations of compounds were obtained on repeating the assay 12 times.

Acknowledgments. The support of this work in part by research grants (R-285 and R-286) from the Robert A. Welch Foundation, Houston, Texas, and in part by a Cottrell College Science Grant from Research Corporation, New York, N.Y., is gratefully acknowledged.

References and Notes

(1) A. L. Davis, O. H. P. Choun, D. E. Cook, and T. J. McCord, *J. Med. Chem.*, **7**, 632 (1964).
(2) A. L. Davis, J. W. Hughes, R. L. Hance, V. L. Gault, and T. J. McCord, *J. Med. Chem.*, **13**, 549 (1970).
(3) A. L. Davis, D. R. Smith, D. C. Foyt, J. L. Black, and T. J. McCord, *J. Med. Chem.*, **15**, 325 (1972).
(4) A. L. Davis, D. R. Smith, and T. J. McCord, *J. Med. Chem.*, **16**, 1043 (1973).
(5) T. J. McCord, D. H. Kelley, J. A. Rabon, D. C. Foyt, and A. L. Davis, *J. Heterocycl. Chem.*, **9**, 119 (1972).
(6) F. S. Dovell and H. Greenfield, *J. Am. Chem. Soc.*, **87**, 2767 (1965).
(7) R. T. Coutts, G. Mukherjee, R. A. Abramovitch, and M. A. Brewster, *J. Chem. Soc. C*, 2207 (1969).
(8) E. C. White and J. H. Hill, *J. Bacteriol.*, **45**, 433 (1943).
(9) H. Jones, G. Rake, and D. Hamre, *J. Bacteriol.*, **45**, 461 (1943).
(10) F. W. Dunn, J. M. Ravel, and W. Shive, *J. Biol. Chem.*, **219**, 810 (1956).
(11) E. H. Anderson, *Proc. Natl. Acad. Sci. U.S.A.*, **32**, 120 (1946).
(12) J. M. Ravel, L. Woods, B. Felsing, and W. Shive, *J. Biol. Chem.*, **206**, 391 (1954).

Ellipticine Derivatives

Robert W. Guthrie,* Arnold Brossi, Francis A. Mennona, John G. Mullin, Richard W. Kierstead,

Chemical Research Department

and E. Grunberg

Chemotherapy Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received November 25, 1974*

Several acyloxy and alkyl derivatives of ellipticine have been prepared. In addition, a modified synthesis leading to the hitherto unobtainable 8,9-dimethoxy- and 8,9-methylenedioxyellipticines is described. Some of the derivatives described herein exhibit antitumor activity. However, none of the compounds showed activity superior to that of the naturally occurring pyridocarbazoles, ellipticine and 9-methoxyellipticine.

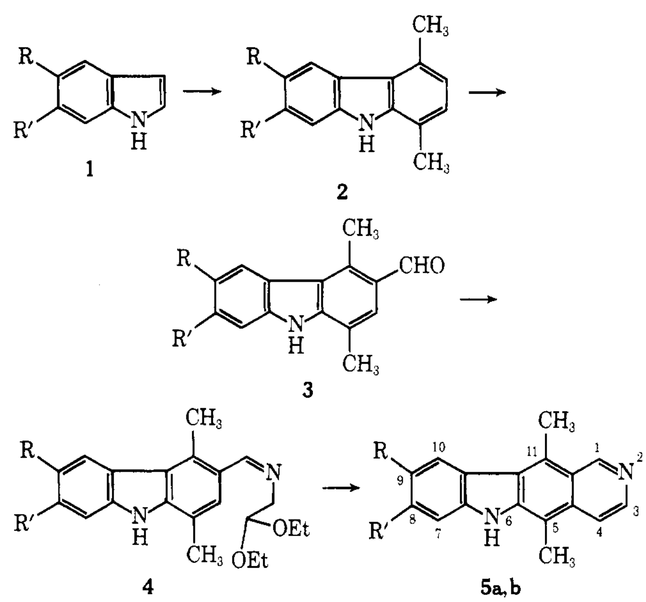
The disclosure of potentially useful tumor inhibitory[1–4] properties of the pyridocarbazole alkaloids, ellipticine **5a** and 9-methoxyellipticine **5b**, has prompted considerable interest in the compounds. These alkaloids are widely distributed in the genera *Aspidosperma*[5] and *Orchrosia*[6] and several syntheses have been elaborated in attempts to make ellipticine[1,7–10] and, more particularly, related substances[1,2,10–14] available for evaluation as chemotherapeutic agents. In the search for compounds which might exhibit similar or hopefully superior antitumor properties, it has been generally established that skeletal modifications of ellipticine diminish its antitumor effect.[11–14] Accordingly, this report describes the preparation of compounds that are peripheral modifications of the parent molecule.

Thus far, the most versatile and efficient method for the syntheses of ellipticine and its analogs has been that as shown in Scheme I developed by the Australian workers.[1] However, the rather severe conditions required to cyclize the azomethine **4** precluded the preparation of several potentially useful analogs, e.g., **5c**[14] and **5d**. It was therefore desirable to find a method that would effect the transformation **4** into **5** under milder conditions.

Jackson and Stewart[15] reported a new isoquinoline synthesis that involved cyclization of the *N*-tosyl derivative **6** using HCl in dioxane to give the *N*-tosyldihydroisoquinoline **7** and subsequent conversion of **7** to the isoquinoline **8** on treatment with KO-*t*-Bu. Modification of the existing ellipticine synthesis by the successful incorporation of this method has enabled the preparation of hitherto unattainable analogs.

Thus 5,6-methylenedioxyindole **1c** was condensed with hexane-2,5-dione to give the corresponding carbazole **2c** which was formylated and then allowed to react with ami-

Scheme I



	R	R′
a	H	H
b	OCH_3	H
c	OCH_2O	
d	OCH_3	OCH_3

noacetal to give the Schiff base **4c**.[14] Reduction of **4c** with sodium borohydride in methanol furnished the amine **9a** which when allowed to react with tosyl chloride afforded the corresponding *N*-tosyl derivative **9c**. Treatment of **9c**