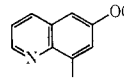
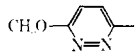
TABLE IV
AMIDES OF PANTOYLTAURINE (10)

No.	R	Mp, °C	Yield, %	Purifn solvent	$[\alpha]D^{a}$ deg	Formula[b]
10a	C_6H_4F-*p*	104–105	49	EtOAc–Et_2O[c]	+37.2	$C_{14}H_{21}FN_2O_5S$
b	C_6H_2-4-Cl-2,5-$(OMe)_2$	95–97	35	do[d]	+30.5	$C_{16}H_{25}ClN_2O_7S$
c	C_6H_2-5-Cl-2,4-$(OMe)_2$	139–140	40	do[e]	+25.0	$C_{16}H_{25}ClN_2O_7S$
d	C_6H_3-2,5-F_2	125	46	do[c]	+34.6	$C_{14}H_{20}F_2N_2O_5S$
e	C_6H_3-2,4-F_2	79–80	52	do[d]	+30.6	$C_{14}H_{20}F_2N_2O_5S$
f		117–118	46	CH_2Cl_2–Et_2O[d]	+30.9	$C_{18}H_{25}N_3O_6S$
g		162–165	26	EtOH–Et_2O[f]	+16.9	$C_{12}H_{20}N_4O_5S$
h			25	*g*	+38.8	$C_{13}H_{23}N_4O_6S$
i	1-Adamantyl	150–151	38	$CHCl_3$–Et_2O	*h*	$C_{18}H_{32}N_2O_5S$

[a] C = 1–2%, temp, 22–25°, 95% EtOH. [b] All compounds were analyzed for C, H, N.[12] [c] Crystallized after purification by chromatography on silicic acid (100 mesh) and eluted with EtOAc. [d] Eluted with 50:50 EtOAc–C_6H_6. [e] Eluted with 95:5 EtOAc–MeOH. [f] Eluted with 3:1 $CHCl_3$–MeOH; [g] Eluted with 9:1 EtOAc–MeOH; the gum failed to crystallize. [h] It showed zero rotation.

which was triturated with Et_2O. The solid was filtered and recrystallized.

Compounds **10f–h** were prepared following the conditions used for the preparation of amides of ω-methylpantoyltaurines. However, in the case of **10g** the K salt was heated with the lactone **8** for 24 hr and after neutralization with dilute HCl the solution was evaporated to dryness and the residue extracted with EtOH. The extract was evaporated to a brown gum. Trituration with EtOH gave a beige solid which was removed by filtration. The filtrate was concentrated and chromatographed in the usual way.

Synthesis and Microbiological Properties of Some Substituted Derivatives of 3-Amino-3,4-dihydrocarbostyril[1]

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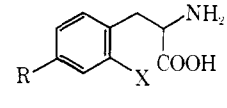
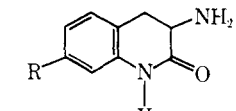
The synthesis and microbiological properties of several reduction products of *o*-nitrophenylalanine have been previously described to afford some rather interesting structure–activity relationships. For example, *o*-aminophenylalanine specifically and competitively antagonizes the utilization of phenylalanine for the growth of *Escherichia coli*, whereas its corresponding lactam, 3-amino-3,4-dihydrocarbostyril, also causes growth inhibitions to *E. coli* and *Leuconostoc dextranicum* that are reversed by phenylalanine but in a noncompetitive manner.[3] Another reductive cyclization product, 3-amino-3,4-dihydro-1-hydroxycarbostyril, was demonstrated to exert potent inhibitory activity against the growth of *E. coli*, *L. dextranicum*, and *L. mesenteroides*, and its toxicity is not appreciably affected by natural extracts or protein hydrolysates.[4] Our studies on tyrosine analogs demonstrated that 2-aminotyrosine VI is a specific and competitive antagonist of tyrosine for *E. coli* and *L. dextranicum*, while 2-amino-4-methoxyphenylalanine V is an effective growth inhibitor of *L. dextranicum* but not of *E. coli*.[5]

As an extension of this work, the 1-hydroxy-7-methoxy-III, 1,7-dihydroxy-IV, 7-methoxy-VII, and 7-hydroxy-VIII substituted derivatives of 3-amino-3,4-dihydrocarbostyril were prepared and examined for microbiological growth-inhibitory properties in *E. coli*, and *L. dextranicum* as subsequently described.

The catalytic hydrogenation of 4-methoxy-2-nitrophenylalanine (I) and 2-nitrotyrosine (II) under rather exacting conditions of acidity gave the reduction cyclization products, 3-amino-3,4-dihydro-1-hydroxy-7-methoxycarbostyril (III) and 3-amino-3,4-dihydro-1,7-dihydrocarbostyril (IV), respectively. Alternatively, 2-amino-4-methoxyphenylalanine (V) and 2-aminotyrosine (VI),[5] were cyclized intramolecularly by treatment with acid to form their corresponding lactams,



I, R = OCH_3; X = NO_2
II, R = OH; X = NO_2
V, R = OCH_3; X = NH_2
VI, R = OH; X = NH_2



III, R = OCH_3; Y = OH
IV, R = OH; Y = OH
VII, R = OCH_3; Y = H
VIII, R = OH; Y = H

3-amino-3,4-dihydro-7-methoxycarbostyril (VII) and 3-amino-3,4-dihydro-7-hydroxycarbostyril (VIII), re-

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(2) Taken in part from the M. S. Thesis of J. W. Hughes, Abilene Christian College, Abilene, Texas, May, 1969.

(3) A. L. Davis, R. Lloyd, J. Fletcher, and T. J. McCord, *Arch. Biochem. Biophys.*, **102**, 48 (1963).

(4) A. L. Davis, O. H. P. Choun, D. E. Cook, and T. J. McCord, *J. Med. Chem.*, **7**, 632 (1964).

(5) A. L. Davis, J. W. Zaun, P. C. Reeves, R. L. Hance, and T. J. McCord, *ibid.*, **9**, 828 (1966).

spectively. VIII was prepared also by the demethylation of VII using concentrated HBr under reflux.

The various substituted derivatives of 3-amino-3,4-dihydrocarbostyril thus prepared were isolated as their HCl salts. These compounds decomposed at their melting points and gave a positive ninhydrin reaction. Unlike the lactams VII and VIII, the cyclic hydroxamates III and IV gave the characteristic violet color with $FeCl_3$.

The microbiological activities of III, IV, VII, and VIII compared to that of the previously reported 3-amino-3,4-dihydro-1-hydroxycarbostyril[4] using *E. coli* 9723 and *L. dextranicum* 8086 as the test organisms are shown in Table I. In each case, the 1-hydroxy substituted compound is completely inhibitory to the growth of both microorganisms at a concentration level of 2 μg/ml. Of the other 3-amino-3,4-dihydrocarbostyrils tested, only the 7-methoxy derivative showed appreciable biological activity and inhibited the growth of *E. coli* and *L. dextranicum* at concentration levels of 60 and 200 μg/ml, respectively.

TABLE I
RELATIVE MICROBIOLOGICAL ACTIVITIES OF SOME SUBSTITUTED 3-AMINO-3,4-DIHYDROCARBOSTYRILS

Substituted 3-amino-3,4-dihydrocarbostyrils	Microorganism, μg/ml[a]	
	E. coli	*L. dextranicum*
3-Amino-3,4-dihydro-1-hydroxycarbostyril	2	2
III	2	2
IV	2	2
VII	60	200
VIII	>200[b]	>200[b]

[a] Minimal concentration required for complete inhibition of growth. [b] Maximum concentration at which compound was tested in the assay medium.

This preliminary study of the microbial activity of the carbostyril compounds in two microorganisms showed that the more inhibitory derivatives were uniformly those containing the cyclic hydroxamate linkage, –N(OH)–CO–.

Experimental Section[6]

3-Amino-3,4-dihydro-1-hydroxy-7-methoxycarbostyril·HCl (III).—A solution of 500 mg of I[5] in 75 ml of 50% aq MeOH was acidified to pH 1.0 by the dropwise addition of concd HCl and then treated with an aq slurry of 50 mg of Pt black. The resulting mixture was agitated under 3.18 kg/cm² of H_2 for 30 min at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to cause precipitation. The solid was filtered to yield 300 mg (58%) of III, mp 246° dec. The product gave an intense purple color with 10% $FeCl_3$ solution and R_f values of 0.38 and 0.89 in 1-BuOH–AcOH–H_2O (3:1:1) and 65% pyridine, respectively; major ir absorption bands, 3.3–3.5 (broad), 6.0, 6.7–6.8, 7.8, and 9.7 μ. *Anal.* ($C_{10}H_{12}N_2O_3$·HCl) C, H, N.

3-Amino-3,4-dihydro-7-methoxycarbostyril·HCl (VII).—A 500-mg sample of V[5] was suspended in 30 ml of H_2O, and solution was effected by adjusting the pH to 1 by the dropwise addition of 2 *N* HCl. After the solution was heated for 20 min, powdered charcoal was added and the mixture was filtered. On concentrating the filtrate to 10 ml by evaporation of the solvent *in vacuo*, a white solid precipitated. There was obtained 340 mg (63%) of VII, mp 296–297°; R_f values 0.38 and 0.88 in 1-BuOH–AcOH–H_2O (3:1:1) and 65% pyridine, respectively; major ir absorption bands, 3.5, 5.9, 6.7, 6.9, 7.8, 8.6, 9.7, and 11.6 μ. *Anal.* ($C_{10}H_{12}N_2O_2$·HCl) C, H, N.

3-Amino-3,4-dihydro-1,7-dihydroxycarbostyril·HCl (IV).—To a solution of 4.1 g of II·HCl[5] in a minimal amount of hot 50% aq MeOH was added an aqueous slurry of 50 mg of Pt black and 0.5 ml of concd HCl. The mixture was shaken under 3.18 kg/cm² of H_2 for 1.5 hr at room temperature. After removal of the catalyst by filtration, the product was recovered from the filtrate by precipitating with the addition of an equal vol of concd HCl to yield 2.8 g (75%) of IV, dec at 260–272°. This compound gave an intense purple color with 10% $FeCl_3$ solution and R_f values of 0.27 and 0.90 in 1-BuOH–AcOH–H_2O (3:1:1) and 65% pyridine, respectively; major ir absorption bands, 3.0–3.5 (broad), 6.0, 6.2, 6.8, and 7.7 μ. *Anal.* ($C_9H_{10}N_2O_3$·HCl) C, H, N.

3-Amino-3,4-dihydro-7-hydroxycarbostyril·HCl (VIII). Method A.—A mixture of 2.1 g of VI[5] in 50 ml of 95% EtOH and 50 ml of concd HCl was heated with stirring. The solution was evaporated to dryness by removal of the solvent under reduced pressure. The residue was dissolved in 95% EtOH, and powdered charcoal was added. After removal of the charcoal by filtration, the solvent was evaporated to 0.1 of its original vol and the product which separated was recovered to give 1.6 g (70%) of VIII, mp 297–298° dec. In 1-BuOH–AcOH–H_2O (3:1:1) and 65% pyridine, the R_f values were 0.27 and 0.88, respectively; major ir absorption bands, 2.9–3.5 (broad), 5.9, 6.7, 7.1, and 7.6 μ. *Anal.* ($C_9H_{10}N_2O_2$·HCl) C, H, N.

Method B.—A sample of 150 mg of VII was refluxed in 50 ml of 48% HBr for 12 hr. The reaction mixture was reduced to dryness by removal of the acid *in vacuo* leaving a residue which was dissolved in a minimal amount of H_2O. The resulting solution was neutralized by the addition of concentrated NH_4OH, and after chilling in the refrigerator, a solid formed. The solid was filtered, washed with cold H_2O, and dissolved in 2 ml of concd HCl. Upon cooling in the refrigerator, there was obtained 60 mg (35%) of VIII. The melting point, R_f values, and ir spectrum of this sample were identical with those of the product prepared by method A.

Microbiological Assays.—For *E. coli* 9723, a previously described inorganic salts medium[7] was employed, and the organism was incubated at 37° for about 16 hr. For *L. dextranicum* 8086, the same assay procedure was employed as previously reported.[4] The carbostyril derivatives were dissolved in sterile H_2O and added aseptically to the previously autoclaved tubes. In all assays the amount of growth was determined photometrically at 625 mμ with a Bausch and Lomb Spectronic 20 spectrophotometer in terms of absorbance readings of the turbid culture medium against a blank of uninoculated medium set at zero absorbance.

(6) All melting points are corrected. The R_f values were determined using the ascending technique of paper chromatography in the solvents indicated, and ninhydrin reagent was used for development of the spots. Uv absorption spectra were obtained on a Bausch and Lomb Spectronic 505 recording spectrophotometer, at concentrations of 10 μg/ml in aq solutions at pH 2, 7, and 10 in the 200–350-mμ region. The pH of each sample was adjusted by the dropwise addition of concd HCl or 2 *N* NaOH. Ir spectra were determined using a Beckman IR-8 spectrophotometer (KBr). Elemental analyses were performed by the 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.

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Antiprotozoal Quinones. IV. 2-Amino-1,4-naphthoquinone Imines as Potential Antimalarials[1]

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Investigation of the chemical and biological properties of the 2-amino-1,4-naphthoquinone imines (**1**) has been rather limited. Several of these quinones have

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