Experimental Section[9]

Synthesis of Compounds 3–11.—Paraformaldehyde (0.01 mol) and a secondary amine (0.01 mol) were refluxed in EtOH solution for 2 hr. The intermediate **2** (R = H) (0.01 mol) was then added to the reaction mixture and refluxing was continued for 6–8 hr. The solvent was evaporated and the residue, if solid, was recrystallized. Bases which did not crystallize were converted into the dihydrochloride salts by treatment in Et_2O with dry HCl. For physical data, see Table I.

Acknowledgments.—The author wishes to express his appreciation to Dr. T. Darby, Mr. L. Wiemeler, and Mr. C. Shannon of the Pharmacology Department of Abbott Laboratories, North Chicago, Ill., for pharmacological investigations and permission to use their data.

(9) All melting points were taken with the Thomas–Hoover capillary melting point apparatus. Microanalyses were performed at the Microanalytical Laboratories of Abbott Laboratories, North Chicago, Ill. Ir spectra were recorded on a Beckman IR-8 infrared spectrophotometer.

Antimalarials. Antagonists of Pantothenic Acid[1]

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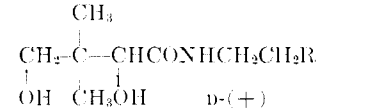
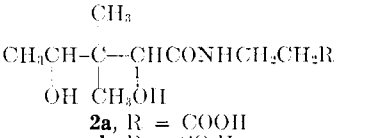
The antimalarial activity of some pantothenic acid antagonists (**1b,c,d**) is well documented.[2,3] However, at the time the antimalarial activity of **1b** was discovered, it was observed that the only analogs that acted as pantothenic acid antagonists were those which retained unchanged the pantoic acid portion (*i.e.*, $HOCH_2C(CH_3)_2CHOHCOOH$) of the pantothenic acid (**1a**). Since then this has been found to be incorrect. ω-Methylpantothenic acid (**2a**) is in fact the most inhibiting analog of pantothenic acid. Similarly ω-methylpantoyltaurine (**2b**) is more inhibitory than pantoyltaurine.[4] It was therefore considered of interest



D-(+)

1a, R = COOH **1c**, R = $SO_2NHC_6H_5$
b, R = COC_6H_5 **d**, R = SC_6H_5, SOC_6H_5, $SO_2C_6H_5$



2a, R = COOH
b, R = SO_3H

to test variously substituted amides of pantoyltaurine[5] (**10**) and ω-methylpantoyltaurine (**9**) as potential antimalarials. The compounds were synthesized according to Scheme I.

The variously substituted sulfamoylethylphthalimides (**5**, Table I) and the corresponding 2-aminoethanesulfonamides (**6**, Table II) were conveniently synthesized by following the previously described procedure for such compounds.[5] Although most of the amides of pantoyltaurine (**10**, Table IV) were obtained by the direct condensation of **6** with D-(−)-pantolactone (**8**) without solvent,[6] the same procedure failed in the synthesis of **9** (Table III). They were successfully obtained, however, by heating a mixture of the K salt of the sulfonamides **6** with the lactone **7** in a melt at 115–120°. A similar method was used in the preparation of **10** (**f**, **g**, **h**). The final compounds **9** and **10** were obtained as crystals only after great difficulty, usually following chromatography and then standing for days. Similar to the experience of Winterbottom, *et al.*,[5] we have found these compounds to have a pronounced tendency to form supersaturated solutions or to separate as oils even when seeded and cooled slowly.

Biological Results.—The compounds were screened for potential antimalarial activity in mice[8] infected with *Plasmodium berghei* and chicks[7] with *P. gallinaceum* by subcutaneous administration in a single dose. They were also evaluated against blood induced *P. gallinaceum* infections in mosquitoes[8] (*Aedes aegypti*).

None of the compounds submitted were considered active at the 640 mg/kg dose level. Even the lead compound from the World War II program, *i.e.*, **10**, R = *p*-C_6H_4Cl, is inactive in the present chick screen.[9] In our opinion the nonreproducibility of its activity lies in the present test procedure as the drug-diet method[10] was used before.

A few of the compounds were also tested by Dr. Trager in his *in vitro* system with *P. coatneyi* in monkey erythrocyte suspension, in a medium containing calcium pantothenate.[11] Compound **9b** was found to be as active as **10** (R = *p*-C_6H_4Cl) and **10f** much more active than the latter.

Experimental Section[12]

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories and Galbraith Laboratories, Inc. The uv, ir, and nmr spectra were as expected for the assigned structures.

2-Phthalimidoethanesulfonyl chloride (**4**) was prepared according to the procedure of Winterbottom, *et al.*[5] mp 160–162°.

(1) This investigation was supported by the U.S. Army Medical Research and Development Command Contract No. DA-49-193-MD-2879. This paper is Contribution No. 722 from the Army Research Program on Malaria and was the subject of a preliminary report at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

(2) (a) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, J. W. Edwards, Ann Arbor, Mich., 1946, p. 250; (b) *ref 2a*, p 174; see also pp 138–140.

(3) For leading references and biological rationale see E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Med. Chem.*, **11**, 1071 (1968).

(4) (a) W. Drell and M. S. Dunn, *J. Amer. Chem. Soc.*, **68**, 1868 (1946); (b) *ibid.*, **70**, 2058 (1948); (c) *ibid.*, **76**, 2804 (1954).

(5) R. Winterbottom, J. W. Clapp, W. H. Miller, J. P. English, and R. O. Roblin, *J. Amer. Chem. Soc.*, **69**, 1393 (1947).

(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(7) Chicks (9–12 days old) were infected (intravenously) with a standard inoculum to produce a disease fatal to 100% of untreated controls within 3–4 days. Candidate compounds were dissolved or suspended in peanut oil and administered either subcutaneously or *per os* immediately after infection. A 100% increase in survival time was considered to be the minimum effective response to the antimalarial activity of the drug. Chicks surviving 30 days are recorded as cures.

(8) E. J. Gerberg, L. T. Richards, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

(9) Personal communication from Drs. Strube and B. Poon of WRAIR.

(10) Reference 2, p 491; test procedure 0-1.

(11) W. Trager, *Trans. N. Y. Acad. of Sci.*, **28**, 1094 (1966).

(12) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

SCHEME I

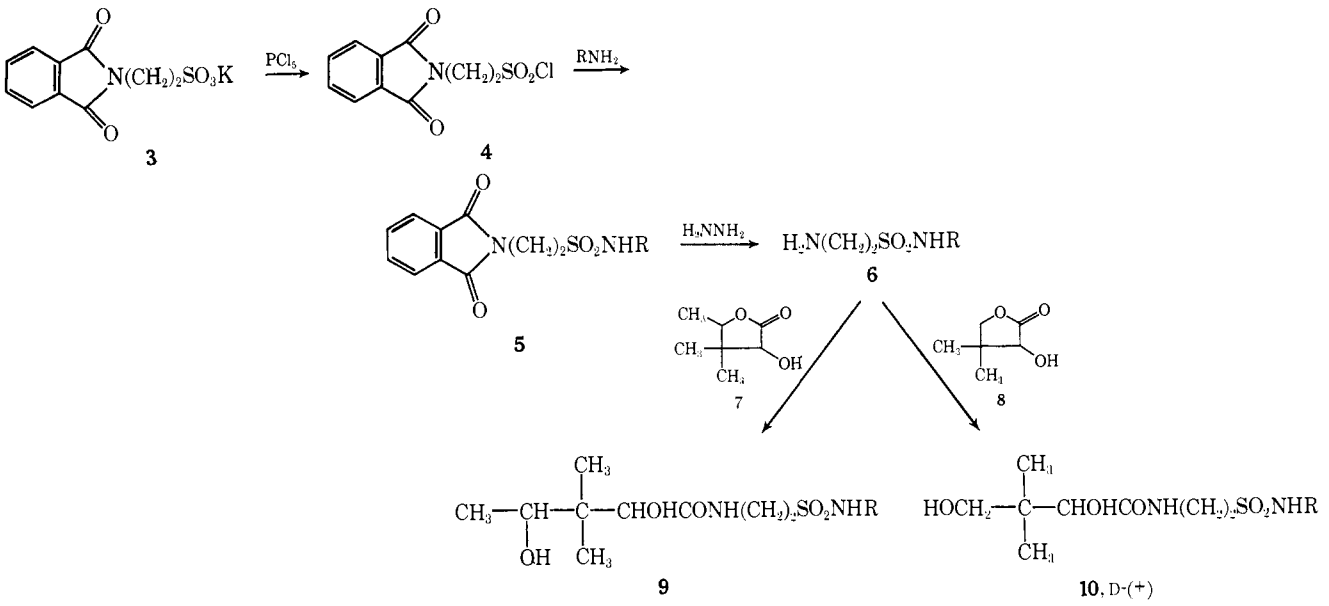
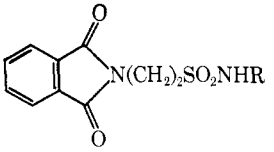
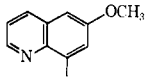
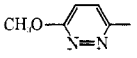
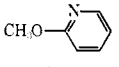


TABLE I

SUBSTITUTED SULFAMOYLETHYLPHTHALIMIDES (5)



No.	R	Mp, °C	Yield, %	Purifn solvent[a]	Formula	Analyses[b]
5a	C_6H_5	141–143[c]		A	$C_{16}H_{14}N_2O_4S$	
b	C_6H_4Cl-*p*	151–153[c]		B	$C_{16}H_{13}ClN_2O_4S$	
c	C_6H_4F-*p*	161–163	51	A	$C_{16}H_{13}FN_2O_4S$	C, H, N
d	C_6H_4Me-*p*	168–170[c]		A	$C_{17}H_{16}N_2O_4S$	
e	C_6H_4OMe-*p*	148–149[c]		B	$C_{17}H_{16}N_2O_5S$	
f	C_6H_2-4-Cl-2,5-$(OMe)_2$	194–196	50	C	$C_{18}H_{17}ClN_2O_6S$	C, H, N
g	C_6H_2-5-Cl-2,4-$(OMe)_2$	188–192	57	B	$C_{18}H_{17}ClN_2O_6S$	C, H, N
h	C_6H_3-2,5-F_2	157–159	53	A	$C_{16}H_{12}F_2N_2O_4S$	C, H, N
i	C_6H_3-2,4-F_2	162–163	49	A	$C_{16}H_{12}F_2N_2O_4S$	C, H, N
j		208–209	83	B	$C_{20}H_{17}N_3O_5S$	C, H, N
k		205–207[c]		B	$C_{14}H_{12}N_4O_4S$	
l		178–180	35	B	$C_{15}H_{14}N_4O_5S$	C, H, N
m		150–152	59	A	$C_{16}H_{15}N_3O_5S$	C, H, N
n	1-Adamantyl	190–191		A	$C_{20}H_{24}N_2O_4S$	C, H, N

[a] A, EtOH; B, AcOH; C, Me_2CO–H_2O. [b] See ref 12. [c] See ref 5.

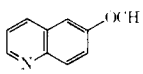
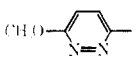
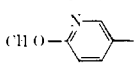
Substituted Sulfamoylethylphthalimides (5, Table I).—All the compounds except **5m** were prepared by adding slowly 0.1 mol of finely powdered 2-phthalimidoethanesulfonyl chloride (4) to a stirred and ice-cooled mixture of 0.1 mol of the amine in 80 ml of dry pyridine. After the reaction mixture had been stirred for 1 hr at room temperature, it was poured into excess 15% HCl with stirring and the precipitate was filtered and washed (H_2O). After drying the solid was crystallized from an appropriate solvent. Compound **5m** was prepared by heating a mixture of 19.8 g (0.16 mol) of 5-amino-2-methoxypyridine and 22.8 g (0.08 mol) of finely powdered 2-phthalimidoethanesulfonyl chloride (4) in 64 ml of refluxing PhH for 1 hr. The precipitate that had formed during the reaction was filtered off, stirred with 600 ml of 10% $NaHCO_3$ solution, filtered, and washed (H_2O). After drying the solid was crystallized from EtOH.

2-Aminoethanesulfonamides (6, Table II).—A mixture of 0.04 mol of the appropriate sulfamoylethylphthalimide (**5**) in 25–100 ml of EtOH and 2.4 g (0.04 mol) of 85% hydrazine hydrate was heated at reflux for 3 hr. The solvent was removed under vacuum and the residue was suspended in warm H_2O and acidified to congo red with the minimum amount of 10% HCl. The mixture was stirred, cooled in an ice bath, and filtered. The filtrate was concentrated to dryness to give the hydrochloride. The salt was added to boiling EtOH and neutralized with 1 equiv of a freshly

TABLE II

2-AMINOETHANESULFONAMIDES (6)

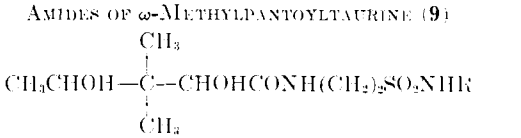
$H_2N(CH_2)_2SO_2NHR$

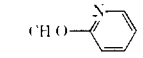
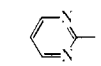
No.	R	Mp, °C	Yield, %	Purification solvent[a]	Formula	Analyses[b]
6a	C_6H_5	123–125[c]		A	$C_8H_{12}N_2O_2S$	
b	C_6H_4Cl-*p*	160–161[c]		B	$C_8H_{11}ClN_2O_2S$	
c	C_6H_4F-*p*	125–128	68	A	$C_8H_{11}FN_2O_2S$	C, H, N
d	C_6H_4Me-*p*	129–131[c]		A	$C_9H_{14}N_2O_2S$	
e	C_6H_4OMe-*p*	177–178[c]		B	$C_9H_{14}N_2O_3S$	
f	C_6H_2-4-Cl-2,5-$(OMe)_2$	158–160	43	A	$C_{10}H_{15}ClN_2O_4S$	C, H, N
g	C_6H_2-5-Cl-2,4-$(OMe)_2$	164–167	41	A	$C_{10}H_{15}ClN_2O_4S$	C, H, N
h	C_6H_3-2,5-F_2	170–171	39	A	$C_8H_{10}F_2N_2O_2S$	C, H, N
i	C_6H_3-2,4-F_2	168–170	55	A	$C_8H_{10}F_2N_2O_2S$	C, H, N
j		197–199	40	A	$C_{12}H_{13}N_3O_3S$	C, H, N
k		220–222[c] dec		B	$C_6H_{10}N_4O_2S$	
l		215–217 dec	38	B	$C_7H_{12}N_4O_3S$	C, H, N
m		140–142	46	A	$C_8H_{13}N_3O_3S$	C, H, N
n	1-Adamantyl	159–160		C	$C_{12}H_{22}N_2O_2S$	C, H, N

[a] A, EtOH; B, water; C, EtOAc. [b] See ref 12. [c] See ref 5.

TABLE III

AMIDES OF ω-METHYLPANTOYLTAURINE (9)



No.	R	Mp, °C	Yield, %	Purification solvent	Formula[a]
9a	C_6H_5	110–112	10	EtOAc–Et_2O[b]	$C_{15}H_{24}N_2O_5S$
b	C_6H_4Cl-*p*	142–144	24	do	$C_{15}H_{23}ClN_2O_5S$
c	C_6H_4F-*p*	117–119	17	do	$C_{15}H_{23}FN_2O_5S$
d	C_6H_4Me-*p*	116–118	23	do	$C_{16}H_{26}N_2O_5S$
e	C_6H_4OMe-*p*	92–94	11	do[c]	$C_{16}H_{26}N_2O_6S$
f	C_6H_2-4-Cl-2,5-$(OMe)_2$	123–124	17	do[c]	$C_{17}H_{27}ClN_2O_7S$
g	C_6H_2-5-Cl-2,4-$(OMe)_2$	128–130	14	do[c]	$C_{17}H_{27}ClN_2O_7S$
h	C_6H_3-2,5-F_2	113–115	17	do[c]	$C_{15}H_{22}F_2N_2O_5S$
i	C_6H_3-2,4-F_2	97–102	29	$CHCl_3$–Et_2O[c]	$C_{15}H_{22}F_2N_2O_5S$
j		95–97	9	EtOAc–Et_2O[c]	$C_{15}H_{23}N_3O_6S$
k[e]		148–150	39	MeOH–EtOAc[d]	$C_{14}H_{22}N_4O_5S$

[a] All compounds were analyzed for C, H, N.[12] [b] Crystallized after purification by chromatography on silicic acid (100 mesh) and eluted with EtOAc. [c] Eluted with 50:50 EtOAc–C_6H_6. [d] Eluted with 3:1 EtOAc–MeOH. [e] The 2-amino-*N*-(2-pyrimidyl)ethanesulfonamide used in the preparation of **9k** was prepared according to ref 13.

prepared KOEt solution. The solution was filtered hot. Cooling the filtrate gave the solid which was crystallized from the indicated solvents.

α-Hydroxy-β,β-dimethyl-γ-valerolactone (7) was prepared according to the method of Drell and Dunn,[4b] mp 58–60°.

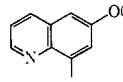
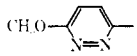
Amides of ω-Methylpantoyltaurines (9, Table III).—To a mixture of 0.02 mol of the requisite 2-aminoethanesulfonamide (**6**) in EtOH, an EtOH solution containing 1 equiv of freshly prepared KOEt was added. After refluxing for 0.5–1 hr, the solution was cooled and EtOH was removed under vacuum. The K salt thus obtained was further dried overnight *in vacuo*. The solid was powdered and heated with 0.021–0.03 mol of α-hydroxy-β,β-dimethyl-γ-valerolactone (**7**) at 110–120° for 4–5 hr with occasional stirring. The residue was dissolved in the minimum quantity of H_2O and neutralized with dilute HCl. It was extracted with EtOAc, dried, and evaporated to leave a gum which was chromatographed through a column of silicic acid (100 mesh) with the indicated solvent system and followed by tlc. The later fraction which showed only one spot on tlc, was concentrated *in vacuo* to leave a gum which was crystallized from the indicated solvents.

Amides of Pantoyltaurine (10, Table IV).—Compounds **10a–e** were prepared by heating a mixture of 0.01 mol of the appropriate 2-aminoethanesulfonamide (**6**) and 1.4 g (0.108 mol) of D-(−)-pantolactone (**8**) in a melt at 115–120° for 2–4 hr with occasional stirring. The resulting clear viscous liquid was chromatographed and crystallized as described above.

Compound **10i** was prepared by adding 0.01 mol of freshly prepared KOEt solution in EtOH to a mixture of 2.44 g (0.01 mol) of 2-amino-*N*-(1-adamantyl)-ethanesulfonamide in EtOH. After refluxing for 0.5 hr, 2 g (0.0154 mol) of **8** was added. After the solution had refluxed for 4 hr the solvent was removed under vacuum and the residue was dissolved in H_2O. The solution was neutralized and then was extracted with EtOAc. The combined extracts were washed (H_2O), dried, and evaporated to leave a solid

(13) J. F. Mead, M. M. Rapport, A. E. Snear, J. T. Maynard, and J. B. Koepfli, *J. Biol. Chem.*, **163**, 465 (1946).

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	$C_{16}H_{23}ClN_2O_7S$
c	C_6H_2-5-Cl-2,4-$(OMe)_2$	139–140	40	do[e]	+25.0	$C_{16}H_{23}ClN_2O_7S$
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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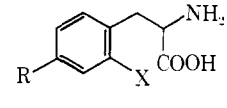
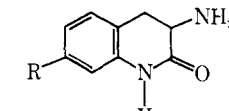
The synthesis and microbiological properties of several reduction products of *o*-nitrophenylalanine have been previously described to afford some rather interesting structure–activity relationships. For example, *o*-aminophenylalanine specifically and competitively antagonizes the utilization of phenylalanine 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.

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