at −30°. After hydrolysis, a soln of the crude alcohol in CH_2Cl_2 was passed through a column of Florisil and the product was crystd from hexane–CH_2Cl_2 to give 2.3 g (70%) of **5**, mp 140–142°. Recrystn yielded the analytical sample, mp 142.2–143.0°, with little loss. *Anal.* ($C_{21}H_{18}O$) C, H.

5-Acetoxymethyl-7,12-dimethylbenz[*a*]anthracene (6). By treatment of **5** with Ac_2O in pyridine and recrystn of the product from hexane–CH_2Cl_2 there was obtained **6**, mp 136.0–137.5°, in high yield. *Anal.* ($C_{23}H_{20}O_2$) C, H.

5,7,12-Trimethylbenz[*a*]anthracene (7). A soln of 0.3 ml of PBr_3 in 10 ml of THF was added slowly to a soln of 0.10 g of **5** in 7 ml of THF. After 2 hr, the mixt was poured on ice and a THF soln of the crude product was treated with LAH in THF. The product thus obtd was purified by chromatography and crystn from hexane to yield **7**, mp 128.0–129.5°, in 32% yield. A better product, mp 129–130°, was obtd by ring closure of **18** as described above for the synthesis of **12**. *Anal.* ($C_{21}H_{18}$) C, H. The 1:1 TENF complex of **7**, black elongated prisms, mp 238–239° dec., was prepd. *Anal.* ($C_{34}H_{22}N_4O_9$) C, H, N.

In an alternate synthesis of **7**, the Grignard reagent from 1-bromo-4-methylnaphthalene (Aldrich Co.) was added to phthalic anhydride to yield *o*-(4-methyl-1-naphthoyl)benzoic acid (**15**), mp 171.5–173.0°, in 61% yield essentially as described for the preparation of *o*-(1-naphthoyl)benzoic acid.[19,20] *Anal.* ($C_{19}H_{14}O_3$) C, H. Treatment of **15** with MeMgBr essentially as described for the synthesis of 3-methyl-3-(1-naphthyl)phthalide[18] yielded 3-methyl-3-(4-methyl-1-naphthyl)phthalide (**16**), mp 147–149°, in 57% yield as colorless platelets from EtOH–PhH. *Anal.* ($C_{21}H_{16}O_2$) C, H. Reduction of **16** as for **9** above yielded 87% of *o*-(2-[4-methyl-1-naphthyl]ethyl)benzoic acid (**17**), mp 189–192° [*Anal.* ($C_{20}H_{18}O_2$) C, H], which was converted into *o*-(2-[4-methyl-1-naphthyl]ethyl)-acetophenone (**18**), mp 110–111.5°, in 70% yield as described in **11** above. *Anal.* ($C_{21}H_{20}O$) C, H. By treatment with PPA at 110° for 35 min, **18** was converted to **7**, identical with the sample of **7** prepd as described above. The TENF derivs were also identical.

5-Methylmercapto-7,12-dimethylbenz[*a*]anthracene (8). A soln of 1.0 ml of $SOCl_2$ in 20 ml of $CHCl_3$ was added during 15 min to a stirred mixt of 1.0 g of **5** in 50 ml of $CHCl_3$. After a further 30 min, the mixt was treated with ice and the crude chloromethyl compd, isolated rapidly and dissolved in 20 ml of dry THF, was added to a suspension of $NaSCH_3$ in THF at −10° prepd with NaH. After several hours at −10° and overnight at room temp, the crude product was chromatogd on Florisil using hexane–PhH (5:1) to yield 0.76 g (69%) of **8** as pale yellow prisms, mp 104.5–106.0°, from hexane–CH_2Cl_2. *Anal.* ($C_{22}H_{20}S$) C, H, S. The TENF complex (1:1) of **8** melted at 167–169° and formed black elongated prisms. *Anal.* ($C_{35}H_{24}N_4O_9S$) C, H, N, S.

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Notes

Preparation and Antimicrobial Properties of the D and L Forms of 3-Amino-3,4-dihydro-1-hydroxycarbostyril†

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Even though a large amount of work has been previously reported on the interesting biological activities displayed by both the natural and synthetic hydroxamic acids,[1-3] no study has appeared on the structure–activity relationships of enantiomeric hydroxamate compounds. Interest in such a study stems from our previous work on the unusual chemical and microbiological properties of racemic 3-amino-3,4-dihydro-1-hydroxycarbostyril.[4,5] As an extension of this work, we now report the preparation of the title compounds and a comparative study of the stereochemical effects on their inhibitory activities.

The D- and L-3-amino-3,4-dihydro-1-hydroxycarbostyrils, III and IV, were obtained by catalytic hydrogenation of the corresponding D and L forms of the *o*-nitrophenylalanine hydrochloride salts, I and II, under acidic conditions[4] as depicted in the accompanying reactions. Since the reductive cyclization of I and II proceeds with retention of stereochemical configuration about the α-symmetric C atoms, the resulting enantiomers of the cyclic hydroxamic acid, III and IV, respectively, are configurationally equiv at the 3 position in the carbostyril ring system. Consequently, the requisite starting materials, I and II, were obtained by resolution of racemic *o*-nitrophenylalanine as its *N*-Ac derivative with brucine under the conditions described in the Experimental Section. The provisional assignment of the D and L

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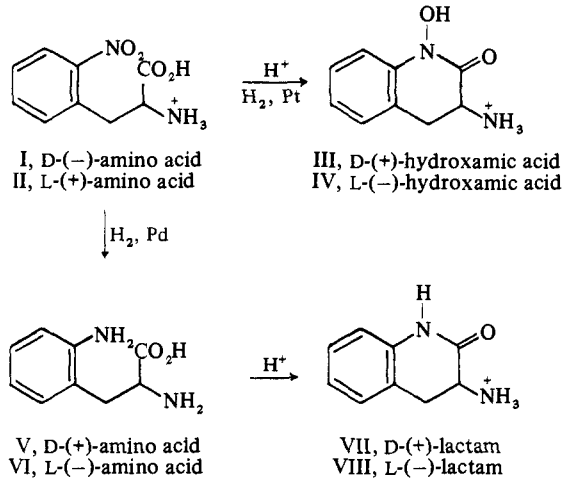

I, D-(−)-amino acid
II, L-(+)-amino acid
III, D-(+)-hydroxamic acid
IV, L-(−)-hydroxamic acid
V, D-(+)-amino acid
VI, L-(−)-amino acid
VII, D-(+)-lactam
VIII, L-(−)-lactam

configurations to the HCl salts of (−)- and (+)-*o*-nitrophenylalanine, I and II, respectively, was attributed to the water-to-acid rotation shifts of the former in a negative direction, and of the latter in a positive direction in accordance with the Cough-Lutz-Jirgensons rule.[6]

Affirmation of the configurational assignment and establishment of optical purity of I and II were accomplished by conversion of their free bases to the corresponding D and L forms of *o*-aminophenylalanine, V and VI, by catalytic hydrogenation under neutral conditions[7] and subsequent microbiological assay with *Escherichia coli*. The reduction of NO_2 to NH_2 on the benzene ring, proceeds with retention of stereochemical configuration about the α-asymmetric C atom of the alanine side chain. Under the assay conditions described in the Experimental Section, the (−)-*o*-aminophenyl-L-alanine (VI) inhibits completely the growth of this test organism at a concn level of 0.3 μg/ml, whereas (+)-*o*-aminophenyl-D-alanine (V) is devoid of any inhibitory activity up to a level of 600 μg/ml. This stereospecific inhibitory action of (−)-*o*-aminophenylalanine against the growth of *E. coli* affirms not only its own L configuration, but also that of the (+)-*o*-nitrophenylalanine from which it was derived. Also, this biological result indicates a purity of better than 99.9% for the D isomer; *i.e.*, there is less than 0.1% of the L isomer present. For complete growth inhibition of *E. coli*, a level of 0.6 μg/ml is required by the racemic compound, which is 0.5 as toxic as the L isomer. In the presence of 0.3 μg/ml of L-phenylalanine, the amounts of the L form and racemic *o*-aminophenylalanine were increased 1000-fold, (*i.e.*, concn levels of 300 and 600 μg/ml, resp) for complete inhibition of growth. Even if the L form contains a trace of the D form, such a possible impurity does not interfere with the observed microbiological response over a 1000-fold range of increasing concentration.

In order to obtain related enantiomers of the carbostyril ring system, both the *o*-aminophenyl-D- and -L-alanines, V and VI, were converted separately in acidic soln to their corresponding lactams, the D- and L-3-amino-3,4-dihydrocarbostyrils (VII and VIII), respectively. These lactams, VII and VIII, were also of biological interest because of their configurational equivalence with the corresponding enantiomeric hydroxamates, III and IV, under study.

The relative growth inhibitory properties of the optically active and racemic hydroxamates in *E. coli* and *Leuconostoc dextranicum* are shown in Table I. The L isomer of 3-amino-3,4-dihydro-1-hydroxycarbostyril was found to inhibit the growth of *E. coli* and *L. dextranicum* at a concn level of 0.5 μg/ml. In contrast, the D isomer of the cyclic hydroxamic acid inhibits the growth of the same 2 organisms at respective concns of 50 and 200 μg/ml. For each organism, the L enantiomer is twice as potent as the racemic modification.

Table I. Relative Growth Inhibitory Properties of the 3-Amino-3,4-dihydro-1-hydroxycarbostyrils

3-Amino-3,4-dihydro-1-hydroxycarbostyril	Microorganism, μg/ml[a]	
	E. coli	*L. dextrianicum*
L	0.5	0.5
DL	1	1
D	50	200

[a] Minimal concns required for complete inhibition of growth.

Since no bond is broken to the asymmetric α-C of *o*-nitrophenyl-D-alanine on conversion to D-3-amino-3,4-dihydro-1-hydroxycarbostyril and *o*-aminophenyl-D-alanine by catalytic hydrogenation, and an optical purity of greater than 99.9% for the latter amino acid was previously established by microbiological studies, each of the other configurationally related compounds including the D-hydroxamate would be expected to possess the same degree of optical purity. In addition, all compounds were dissolved in sterile H_2O at room temp, and the resulting solns were added aseptically to the previously autoclaved culture tubes of the microbiological assay. Therefore, the toxicity of D-3-amino-3,4-dihydro-1-hydroxycarbostyril was not ascribed to a contamination of the L isomer arising from slight racemization during synthesis or the assay procedure. Further, it would be difficult to account for the apparent differences in the inhibitory response of the D isomer for the 2 assay organisms. For example, the concn level of the D isomer was increased 100-fold above that of the L isomer for complete inhibition of growth of *E. coli*; however, a 400-fold increase of the D isomer above the L isomer was required for complete growth inhibition of *L. dextranicum*. For the 2 test organisms, the same fold increase in concn of the D isomer above that of the L isomer would have been expected if the biological response was attributed to the presence of the L isomer as an impurity with the D isomer. These biological results do not preclude enzymic inversion of D-3-amino-3,4-dihydro-1-hydroxycarbostyril on the part of both microorganisms; however, that such is the case seems unlikely in view of the failure of the same 2 organisms to cause enzymic inversion of the configurationally related *o*-aminophenyl-D-alanine. Similar cases have been found in which both optical antipodes of certain compounds possess biological activity in which one form is more effective for a given biological response than the other.[8] Thus, D-3-amino-3,4-dihydro-1-hydroxycarbostyril appears to be a growth inhibitor itself, and considerably less effective than the L isomer.

A comparison of the growth-inhibitory properties of the lactams, D- and L-3-amino-3,4-dihydrocarbostyril, and the previously reported racemic modification[7] for *E. coli* showed that the L isomer was twice as toxic as the racemate and the D form was not inhibitory even at a concn level of 600 μg/ml.

These biological results indicate that the potent growth-inhibitory activity exhibited by 3-amino-3,4-dihydro-1-hydroxycarbostyril is not restricted to the presence of the cyclic hydroxamate function alone, but some stereochemical specificity exists for optimal biological activity. Therefore, this work suggests that there are other factors to be considered in the mode of inhibitory action of certain hydroxamic acids besides the implicated role of chelation with essential metals.[1,2]

Experimental Section§

N-Acetyl-(*o*-nitrophenyl)-DL-alanine. *o*-Nitrophenyl-DL-alanine (60.0 g) was treated with 26.1 g of Ac_2O in aq 1 *N* NaOH soln at 0.5° to yield 49.0 g (80%) of product after acidification, mp 203–205° (lit. mp 205–206° *via* different procedure[4]).

N-Acetyl-(*o*-nitrophenyl)-D- and -L-alanine Brucinates. A mixt of 32.0 g of racemic *N*-acetyl-*o*-nitrophenylalanine, 50.0 g of recrystd brucine hydrate, and 600 ml of MeOH was continuously heated with stirring until soln was effected. The soln was concd to about 0.6 of its original vol by evapn of the MeOH *in vacuo*. After standing at −17° overnight, a cryst ppt was formed, filtered, washed with a small portion of MeOH, and dried to weigh 37.7 g. Recrystn from a minimum amt of boiling MeOH gave 31.0 g (77%) of the brucine salt of *N*-acetyl-(*o*-nitrophenyl)-D-alanine, mp 210–212° $[\alpha]^{21}D$ −26.0° (*c* 1, H_2O) and −14.2° (*c* 1, MeOH). *Anal.* ($C_{34}H_{38}N_4O_9$) C, H.

The resoln mother liquor was concd to about 0.8 of its vol by removal of MeOH *in vacuo*, and stored at −17° overnight. There was recovered 4.0 g of ppt which melted over a wide range. In order to avoid any contamination of the more sol brucinate salt by small and varying amts of the D isomer, this crop was discarded. The resulting filtrate was reduced to about 0.8 of its vol by evapn *in vacuo*, chilled at −17° overnight, and yielded 25.7 g of the *N*-acetyl-(*o*-nitrophenyl)-L-alanine brucinate. The product was dissolved in a minimum amt of boiling MeOH treated with Norite, and recrystd to yield 21.7 g (54%), mp 188–191°, after drying *in vacuo* over P_2O_5; $[\alpha]^{21}D$ −12.0° (*c* 1, H_2O) and −7.3° (*c* 1, MeOH). *Anal.* ($C_{34}H_{38}N_4O_9$) C, H.

N-Acetyl-*o*-nitrophenyl-D-alanine. A 30.9-g sample of *N*-acetyl-*o*-nitrophenyl-D-alanine brucinate was treated with 200 ml of 1 *N* NH_4OH, and the resulting mixt was extd with 100 ml of $CHCl_3$. The $CHCl_3$ layer was sepd from the aq layer, and the latter was extd twice with 40-ml portions of $CHCl_3$ to remove brucine. The aq ammonical layer was taken to dryness *in vacuo*, and the residue was dissolved in 50 ml of H_2O. The resulting soln was adjusted to pH 1 with addn of concd HCl to form a ppt. This was collected on a filter, washed with cold H_2O, and dried to yield 10.9 g (90%) of product. A sample, when recrystd from EtOH–H_2O, had mp 201–202°; $[\alpha]^{21}D$ −42.0° (*c* 1, CH_3OH). *Anal.* ($C_{11}H_{12}N_2O_5$) C, H.

N-Acetyl-*o*-nitrophenyl-L-alanine. The same prep procedure as described above was repeated using 21.6 g of *N*-acetyl-*o*-nitrophenyl-L-alanine brucinate, which was decompd with NH_3 and freed of alkaloid to give 7.1 g (84%) of product. After recrystn from EtOH–H_2O, the compd was analytically pure, mp 201–202°, $[\alpha]^{21}D$ +42.0° (*c* 1, MeOH). *Anal.* ($C_{11}H_{12}N_2O_5$) C, H.

o-Nitrophenyl-D-alanine Hydrochloride (I). A soln of 8.87 g of *N*-acetyl-*o*-nitrophenyl-D-alanine in 90 ml of concd HCl was heated under reflux for 3 hr. After the reaction mixt was allowed to chill at −17° overnight, crystals of the HCl salt separated. Filtration, washing with cold H_2O, and drying gave 5.04 g (58%) of the product. An analytical sample was obtd by recrystn from MeOH–Et_2O, mp 223–224° dec; $[\alpha]^{21}D$ −16.5° (*c* 0.5, H_2O) and $[\alpha]^{21}D$ −41.1° (*c* 0.5, 1 *N* HCl). *Anal.* ($C_9H_{10}N_2O_4 \cdot HCl$) C, H.

o-Nitrophenyl-L-alanine hydrochloride (II) was prepd exactly as described for the D isomer except that 5.40 g of *N*-acetyl-*o*-nitrophenyl-L-alanine was employed. There was recovered 3.32 g (63%) of product, which was purified by recrystn from MeOH–Et_2O, mp 223–224° dec; $[\alpha]^{21}D$ +16.3° (*c* 0.5, H_2O) and $[\alpha]^{21}D$ +41.6° (*c* 0.5, 1 *N* HCl). *Anal.* ($C_9H_{10}N_2O_4 \cdot HCl$) C, H.

D-3-Amino-3,4-dihydro-1-hydroxycarbostyril (III). Using a similar procedure previously described for the synthesis of racemic 3-amino-3,4-dihydro-1-hydroxycarbostyril,[4] a 1.0-g sample of *o*-nitrophenyl-D-alanine hydrochloride (I) was hydrogenated in the presence of Pt on C to give the hydrochloride of III, which was subsequently converted with NH_4OH to yield 560 mg (77%) of III, mp 202–203° dec, $[\alpha]^{21}D$ +63° (*c* 1, 0.1 *N* HCl). *Anal.* ($C_9H_{10}N_2O_2$) C, H, N.

L-3-Amino-3,4-dihydro-1-hydroxycarbostyril (IV). Repeating the same condns of catalytic hydrogenation as above a 500-mg sample of *o*-nitrophenyl-L-alanine hydrochloride (II) was converted to 290 mg (80%) of product, mp 202–203° dec, $[\alpha]^{21}D$ −64° (*c* 1, 0.1 *N* HCl). *Anal.* ($C_9H_{10}N_2O_2$) C, H, N.

o-Aminophenyl-D-alanine (V). Using the method previously described for the synthesis of racemic *o*-aminophenylalanine,[7] 500 mg of the free base of I was hydrogenated to give 230 mg (51%) of product, mp 160–163° dec, $[\alpha]^{21}D$ +55.1° (*c* 0.5, 50% MeOH). *Anal.* ($C_9H_{12}N_2O_2 \cdot 0.5H_2O$) C, H, N.

o-Aminophenyl-L-alanine (VI). By the same procedure, 400 mg of the free base of II was converted to 190 mg (55%) of product, mp 165–166° dec, $[\alpha]^{21}D$ −54.2° (*c* 0.5, 50% in MeOH). *Anal.* ($C_9H_{12}N_2O_2$) C, H, N.

D-3-Amino-3,4-dihydrocarbostyril Hydrochloride (VII). A procedure was used similar to that previously described for the synthesis of racemic 3-amino-3,4-dihydrocarbostyril hydrochloride,[7] with the exception that V was not isolated. A 370-mg sample of the free base of I was hydrogenated to give a soln of V. The catalyst was removed by filtration and the filtrate was treated with 1 ml of concd HCl. The resulting soln was taken to dryness *in vacuo* to give a solid residue. Recrystn from MeOH–Et_2O gave 245 mg (70%) of product, mp 322–323° dec, $[\alpha]^{21}D$ +127.0° (*c* 0.5, H_2O). *Anal.* ($C_9H_{10}N_2O \cdot HCl$) C, H, N.

L-3-Amino-3,4-dihydrocarbostyril Hydrochloride (VIII). In a similar manner, 230 mg of the free base of II was converted to 150 mg (69%) of product, mp 322–323° dec, $[\alpha]^{21}D$ −125.0° (*c* 0.5, H_2O). *Anal.* ($C_9H_{10}N_2O \cdot HCl$) C, H, N.

Microbiological Assays. For *E. coli* 9723 and *L. dextranicum* 8086 a similar assay procedure was used as described previously.[4] In all assays the amt of growth was detd 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 0 absorbance.

§Melting points were determined on a Thomas-Hoover apparatus and are corrected. Optical activity readings were taken with a Schmidt-Haensch precision polarimeter. Elementary 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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Inhibition of Dopamine β-Hydroxylase by 5-Phenoxymethyl-2-oxazolidinethiones

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The bioconversion of dopamine (DA) to norepinephrine (NE) in the CNS and in the sympathetic nerve network is catalyzed by dopamine β-hydroxylase, a Cu-containing enzyme.[1] Inhibition of this enzyme in the brain results in the depletion of endogenous NE while DA stores remain intact.[2,3] Although several different classes of dopamine β-hydroxylase inhibitors have been reported, each of which acts through the chelation of the Cu^{+2}, none has yet found clinical use. Their principal utility to date has been as pharmacologic tools in attempts to elucidate the respective roles of DA and NE on behavior and mental function.

The inhibition of dopamine β-hydroxylase *in vitro* and *in vivo* with alkyl and aromatic thioureas was recently described.[4] Several groups of investigators have noted the *in vivo* dopamine β-hydroxylase inhibitory activity of various mono- and disubstituted dithiocarbamates[5-8] and the resulting alterations in behavioral responses in laboratory animals concurrent with the depletion of brain NE.[7,9,10] The iso-