N-Pantoyl-(substituted-phenyl)alkylamines, Inhibitory Analogs of Pantothenic Acid^{1,2}

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The syntheses of nineteen new N-pantoyl-(substituted-phenyl)alkylamines were accomplished by the condensation of the appropriate amines with pantolactone. Using *Lactobacillus arabinosus* 17–5 and *Leuconostoc mesenteroides* P-60 as the test organisms, all of the derivatives were found to be competitive inhibitors of the utilization of pantothenic acid. For *L. mesenteroides*, a *p*-chloro substituent increased the inhibitory activity of the parent N-pantoyl(phenylalkyl)amines; whereas, a *p*-nitro substituent appreciably increased the activity only with the highest homolog prepared. In contrast, for *L. arabinosus*, either a chloro or a nitro group enhanced the activity of the lowest homolog, N-pantoylbenzylamine, but did not appreciably affect the other homologs.

In contrast to the relatively limited number of structural changes in the pantoyl group which have produced effective antagonists of pantothenic acid,4-7 many variations of the β -alanine moiety of pantothenic acid have been found to produce inhibitory analogs.⁸ Among this latter type of analog, a number of Npantoyl derivatives of alkylamines are of interest since a variation in biological activity with change in carbon chain length has been observed,⁹ and, more recently, a series of N-pantoyl- ω -phenylalkylamines have been found to be particularly effective antagonists (especially the N-pantoyl- ω -phenylheptylamine derivative) of pantothenic acid.¹⁰ In a study to determine whether or not the introduction of various substituents on the terminal phenyl groups of these ω -phenylalkylamine derivatives would increase the inhibitory activity, a number of N-pantovl derivatives of benzene ring substituted ω -phenylalkylamines were prepared in which chloro, nitro, and amino groups were introduced as substituents on the ring.

Experimental¹¹

Organic Syntheses. Intermediate Amines.—A number of the amines utilized in this study were available commercially; others were prepared and/or characterized through the sources indicated: *p*-chlorobenzyl-,¹² *o*-chlorobenzyl-,¹² *p*-nitrobenzyl-,¹³

(5) T. Wieland and E. F. Möller, Ber., 81, 316 (1948).

m-nitrobenzyl-, 14 p-aminobenzyl-, 15 p-chlorophenethyl-, 16 p-nitrophenethyl-, 17 and N-phenylpropane-1, 3-diamine. 18

N-[p-Nitrophenyl)propyl]phthalimide.—Nitration of 118 g. of (3-bromopropyl)benzene by a previously reported procedure yielded 43.4 g. of (3-bromopropyl)-p-nitrobenzene, b.p. 128-132° (0.2 mm.), n²⁰D 1.5830.¹⁹ An infrared spectrum of this product indicated a strong absorption band at 9.02 μ and a moderate band at 12.47 μ which were absent in the *ortho* isomer described subsequently. These spectral data are in agreement with those previously reported for the o- and p-nitrotoluenes.²⁰ To a solution of 29.3 g. of potassium phthalimide in 100 ml. of N,N-dimethylformamide was added 35 g. of p-(3-bromopropyl)nitrobenzene with efficient stirring over a 2 hr. period, and the reaction mixture then was heated at 100° for about 1 hr. After cooling, 500 ml. of water was added, and the resulting mixture was extracted with 200 ml. of chloroform. The organic phase was recovered, washed successively with 10% sodium hydroxide solution and saturated sodium chloride solution, and finally dried over calcium sulfate. The solvent was removed in vacuo, and, after crystallization from ethanol, there was recovered 40.5 g. of product, m.p. 131-132°

Anal. Calcd. for $C_{17}H_{14}N_2O_4$: N, 9.03. Found: N, 9.20.

3-(*p*-Nitrophenyl)propylamine.—A solution containing 40.5 g. of N-[3-(*p*-nitrophenyl)propyl]phthalimide, 25.9 g. of 64% hydrazine solution, and 200 ml. of methanol was heated under reflux for about 5 hr. After cooling, 100 ml. of water was added, the methyl alcohol was distilled from the mixture, and 100 ml. of concd. hydrochloric acid was added. The resulting solution was heated under reflux for about 16 hr., cooled to 0°, and filtered. The filtrate was adjusted to pH 10 with 10% sodium hydroxide solution. The oil phase which separated was taken up in ether, dried over calcium sulfate, and, after removal of the solvent, fractionally distilled to yield 10 g. of product, b.p. 98-104° (0.07 mm.), n^{20} p 1.5654.

Anal. Caled. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.72; N, 15.55. Found: C, 60.18; H, 6.56; N, 16.00.

An infrared spectrum of this compound showed strong absorption bands at $9.02 \ \mu$ and $12.52 \ \mu$. The N-acetyl derivative was prepared in the usual manner with acetic anhydride, m.p. 72-73°.

tion of the lower boiling components from the nitration products

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⁽¹⁾ This investigation was assisted in part by a PHS research grant (CY-5779), National Institutes of Health, National Cancer Institutes, Public Health Service.

⁽²⁾ Predoctoral Fellow (10,364) National Institute of Allergy and Infectious Diseases, United States Public Health Service. Taken in part from the Ph.D. dissertation of E. D. Parker, University of Texas, June, 1962.

 ⁽³⁾ Portions of this paper were taken from the M.S. thesis of T. J. Cogdell. The University of Texas, January, 1962.

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of (3-bromopropyl)benzene yielded 23.8 g. of o-(3-bromopropyl)nitrobenzene, b.p. 94–98° (0.05 mm.), n^{20} p 1.5728. The reported values are 114° (0.75 mm.), n^{21} p 1.573.¹⁹ Reaction of 21 g. of potassium phthalimide and 20 g. of o-(3-bromopropyl)nitrobenzene in the presence of 100 ml. of N,N-dimethylformamide, as described for the preparation of the *para* isomer, gave 20.7 g. of product, m.p. 119–121° (recrystallized from carbon tetrachloride).

Anal. Caled. for C₁₇H₁₄N₂O₄: N, 9.03. Found: N, 9.34.

3-(*o*-Nitrophenyl)propylamine.—A sample of 20.6 g. of N-[3*o*-nitrophenyl)propyl]phthalimide was treated with 6.7 g. of 65% hydrazine by the procedure previously indicated for the *para* isomer, and on fractional distillation there was recovered 4.15 g. of product, b.p. $101-103^{\circ}$ (0.07 mm.), $n^{20}p$ 1.5546.

4.15 g. of product, b.p. $101-103^{\circ}(0.07 \text{ mm.})$, n^{20} J.5546. Anal. Caled. for C₉H₁₂N₂O₂: C, 59.99; H, 6.72; N, 15.55. Found: C, 60.22; H, 7.38; N, 15.54.

4-(*o*-**Nitrophenyl**)**butyronitrile**.—The nitration of 25 g. of 4phenylbutyronitrile, patterned after a previously reported technique for the lower homolog,²¹ produced a reaction mixture which was fractionally distilled to yield both the *ortho* and *para* isomers as subsequently described. There was recovered 6.5 g. of 4-(*o*-nitrophenyl)butyronitrile, b.p. 172–176° (2.5 mm.), n^{27} D 1.5458, which possessed a strong infrared absorption peak at 12.7 μ .

Anal. Caled. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.84; H, 5.63; N, 14.57.

4-(*p*-Nitrophenyl)butyronitrile.—Fractional distillation of the nitration mixture previously described for the preparation of 4-(*o*-nitrophenyl)butyronitrile also produced 13.9 g. of the higher boiling *para* isomer, b.p. 188–189° (2.5 mm.), n^{27} D 1.5513, which had a strong infrared absorption band at 9.0 μ .²²

Anal. Caled. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.31; N, 15.02.

4-(*p*-Aminophenyl)butylamine.—Catalytic hydrogenation of 5 g. of 4-(*p*-nitrophenyl)butyronitrile in the presence of acetic anhydride was patterned after a previously reported technique,²³ and, after alkaline hydrolysis of the diacetyl derivative, there was recovered 1.9 g. of the diamine, b.p. 111-114° (0.15 mm.); diacetyl derivative, m.p. 152-153°, reported m.p. 154-155°;²¹ dibenzoyl derivative, m.p. 218-220°, reported m.p. 224-225°.²¹

4-(o-Aminophenyl)butylamine.—Catalytic hydrogenation of 5 g, of 4-(o-nitrophenyl)butyronitrile using the same procedure as for the corresponding *para* isomer yielded 2.3 g, of product, b.p. 115° (0.25 mm.). The dibenzoyl derivative was prepared in the usual manner, m.p. 178–183°.

Anal. Caled. for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.50. Found: C, 77.15; H, 6.55.

N-[5-(p-Nitrophenyl)pentyl] benzamide.—Using the procedures previously described for the propyl homolog, a direct separation of the isomeric products resulting from the nitration of (5bromopentyl)benzene and/or its conversion to the corresponding amines using potassium phthalimide, with subsequent hydrolysis failed to yield pure isomeric products. Thus, 3.7 g. of the mixed 5-(nitrophenyl)-pentylamines was treated with 5 g. of benzoyl chloride in the presence of 3.6 g. of triethylamine and 20 ml. of benzene, and the reaction mixture was heated at about 65° for 1 hr. The resulting mixture was washed successively with 10%hydrochloric acid and 10% sodium hydroxide, and the organic phase then was dried over sodium sulfate. Upon addition of Skellysolve B (b.p. 60 to 70°) there was obtained 1.6 g. of product which was recrystallized from methanol, m.p. 123-125°. This material possessed strong infrared absorption bands at 9.00 and 12.47 μ which is indicative of p-substituted nitroaromatic derivatives.20

Anal. Caled. for C₁₈H₂₀N₂O₃: N, 8.96. Found: N, 8.86.

5-(p-Nitrophenyl)pentylamine, obtained through acid hydrolysis of 1 g. of this benzamide derivative, possessed an infrared spectrum which was almost identical with the lower homolog, 3-(p-nitrophenyl)propylamine, and this semi-purified sample was used in the subsequent condensation with pentolactone.

5-(Chlorophenyl)pentylamine.--(5-Bromopentyl)benzene (33.4 g.) was treated with chlorine gas (15.6 g.) in the dark at 0°, and the resulting chlorophenyl product (14.6 g.) then was condensed with potassium phthalimide. The resulting oily phthalimide

derivative finally was decomposed with hydrazine to yield 4.9 g. of a mixture of o- and p-chlorophenyl-pentylamines as evidenced by infrared absorption studies, and this mixture of products was subsequently condensed with pantolactone to yield the material which was studied as a pantothenic acid antagonist.

p-(3-Aminopropyl) aniline Dihydrochloride.—Using a Parr lowpressure hydrogenation apparatus, 2.42 g. of 3-(p-nitrophenyl)propylamine, 100 ml. of glacial acetic acid, and about 1 g. of Raney nickel were placed under 2.8 kg./cm.² of hydrogen pressure and shaken for 8 hr. The catalyst was removed by filtration, the filtrate was saturated with hydrogen chloride, and the resulting solution was reduced to about one-half volume. Upon cooling, the precipitated product was filtered and recrystallized from ethyl acetate–ethanol to yield 1.9 g. of product, m.p. 266° dec.

Anal. Caled. for $C_9H_{14}N_2$ ·2HCl: N, 12.55. Found: N, 12.64. **1-(3-Aminopropy)pyrroline.**—To a stirred, ice-cold solution of 75 ml. each of propane-1,3-diamine and benzene was added dropwise 12.5 g. of *cis*-1,4-dichloro-2-butene in 50 ml. of benzene, and, after stirring at the ice-bath temperature for several hr., the reaction mixture was placed in the refrigerator overnight. This solution then was treated with 25 ml. of 40% solution hydroxide and stirred for 1 hr. at room temperature. The organic phase was separated and finally dried over solium hydroxide pellets. After filtering, the solvent was removed and the residue was distilled *in vacuo* to yield 6.6 g. of product, b.p. 39° (1.5 mm.), n^{25} D 1.4833.

Anal. Calcd. for $C_7H_{14}N_2$: N, 22.22. Found: N, 21.94. A sample of this diamine was converted to the *dipicrate* salt in the usual manner, m.p. 199–204° dec.

Anal. Calcd. for $C_{19}H_{20}N_8O_{14}$: N, 19.17. Found: N, 19.21. N-Pantoyl-(substituted)amines.—Most of the pantothenic acid analogs were prepared by heating a stoichiometric mixture of p-pantolactone and the appropriate amine under dry nitrogen in a tightly stoppered tube or flask.^{9,10,24,25} The particular conditions for each of the different types of amines are indicated in Table I. In general, one of two sets of conditions was utilized for the initial condensation, but minor variations were necessary in the recovery procedure for some of the derivatives.

Method A.—A sample of about 1 g. of the amine and a M equiv. weight of pantolactone were combined and heated in an oil bath (at 100 or 180°) for about 8 hr. The reaction mixtures usually solidified on standing at room temperature; however, in some instances several weeks were required before crystallization of the product began. The resulting solid was recrystallized from suitable solvents, usually ethyl acetate:Skellysolve B, using a seed crystal from the original material to induce crystallization. In those instances where the reaction product failed to crystallize from a number of different solvent systems, the residue was analyzed directly after heating *in vacuo* for several hr. both to remove the volatile amine and to sublime away the unreacted pantolactone.

Method B.—An alternate generalized procedure for preparing these pantothenic acid analogs involved mixing stoichiometric equiv. of the amine and pantolactone, then heating the mixture in a bath at the proper temperature to insure homogeneity of the sample. The resulting reaction mixture then was placed in an oven at 65–70° overnight and finally heated at 100° for about 1 hr. Following this, the mixture was heated at about 100° for several hr. *in vacuo* to remove the unreacted amine and pantolactone. The resulting product then was allowed to stand at room temperature for solidification (frequently a matter of weeks) and subsequent crystallization.

N-Pantoyl-2-(p-aminophenyl)ethylamine.—A 1-g. sample of N-pantoyl-p-nitrophenethylamine in 25 ml. of acetic acid was shaken in the presence of about 1 g. of Raney nickel catalyst under 2.8 kg./cm.² of hydrogen for about 20 hr. After filtration, the solvent was removed in vacuo, and the residue was dissolved in ethyl acetate and dried over sodium sulfate. The drying agent was recovered and Skellysolve B added to induce turbidity. After standing at room temperature there was recovered 0.45 g. of material, m.p. 94–96°. This product did not depress the melting point of N-pantoyl-p-aminophenethylamine prepared by the method indicated in Table I.

Microbiological Assays.—Microbial assays with Lactobacilius arabinosus 17-5 were made in a previously reported 26 assay

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SYNY	THESIS OF	f Some	N-PANT	OYL-(SUBST	ituted)amines, H	IOCH ₂ C(CH ₃) ₂ CH	IOHCON	$_{ m HR}$		
		Temp.,	Yield,	М.р.,	Empirical				Found, %		
\mathbf{R}	Method	°C.	%	°C.	formula	С	H	N	С	н	N
p-Chlorobenzyl-	Α	100	50	109-111	$C_{13}H_{18}ClNO_3$	57.47	6.68	5.15	57.52	6.45	5.02
o-Chlorobenzyl-	Α	180	55	86-87	$C_{13}H_{18}ClNO_5$	57.47	6.68	5.15	57.37	6.50	4.98
p-Nitrobenzyl-	В	70	81	126 - 127	$C_{13}H_{18}N_2O_5$	55.31	6.43	9.93	55.87	6.67	10.16
m-Nitrobenzyl-	в	70	80	Oil	$C_{13}H_{18}N_2O_5$	55.31	6.43		55.54	6.09	
p-Aminobenzyl-	В	70	52	77-80	$C_{13}H_{20}N_2O_3$	61.88	7.99	11.11	61.88	7.85	10.87
p-Chlorophenethyl-	Α	100	65	100-101	$C_{14}H_{20}ClNO_3$	58.84	7.05	4.94	59.02	7.36	4.86
p-Nitrophenethyl-	в	70	60	97 - 98	$C_{14}H_{20}N_2O_5$	56.74	6.80	9.45	56.95	6.75	9.11
p-Aminophenethyl-	B	70^{a}	71	94 - 96	$\mathrm{C}_{14}\mathrm{H}_{22}\mathrm{N}_{2}\mathrm{O}_{3}$	63.13	8.33	10.52	63.26	8.54	10.72
o-Nitrophenethyl-	в	70^{b}	78	Oil	$C_{14}H_{20}N_2O_5$	56.74	6.80		56.61	6.61	
3-(p-Nitrophenyl)propyl-	Α	70	41	Oil	$C_{15}H_{22}N_2O_5$	58.05	7.15	9.02	58.59	7.16	8.77
3-(o-Nitrophenyl)propyl-	Α	70	50	Oil	$\mathrm{C_{15}H_{22}N_2O_5}$	58.05	7.15	9.02	58.35	7.09	9.39
3-(m-Aminophenyl)propyl-	- A	100	35	Oil	$\mathrm{C_{15}H_{24}N_{2}O_{3}}$			10.00			10.17
4-(p-Aminophenyl)butyl-	В	70	82	71 - 72	$\mathrm{C_{16}H_{26}N_2O_3}$	65.27	8.90	9.52	65.23	8.78	9.58
4-(o-Aminophenyl)butyl-	В	70	75	Oil	$C_{16}H_{26}N_2O_3$	65.27	8.90	9.52	65.62	8.89	9.74
5-(p-Nitrophenyl)pentyl-	Α	70	63	Oil	$\mathrm{C_{17}H_{26}N_2O_5}$			8.27			7.97
5-(x-Chlorophenvl)pentyl-	¢ A	160	51	Oil	C ₁₇ H ₂₆ ClNO ₃	62.28	8.00	4.27	62.38	7.74	4.22
$C_6H_5NH(CH_2)_3$ -	В	60	77	78-79	$\mathrm{C_{15}H_{24}N_2O_3}$	64.26	8.63	9.99	64.26	8.58	10.21
N(CH ₂) ₃ -	в	60	76	94–96	$C_{13}H_{24}N_2O_4$	60.91	9.44		60.73	9.70	

TABLE I

^a Also prepared via reduction of corresponding nitro compound. ^b Heated at 100° for 3 hr. ^c Infrared studies indicate that this compound is primarily the para derivative, but ortho contamination is evident.

medium except that a solution containing 11 g./l. of commercial vitamin-free, salt-free casein hydrolysate (Nutritional Biochemicals Corporation, Cleveland, Ohio) was used instead of the acid-hydrolyzed casein described in the reference. The calcium pantothenate was omitted from the vitamin supplement and added as indicated in the tables. This modified medium was also used for Leuconostoc mesenteroides P-60, except that in addition the Salts A concentration was increased four-fold. All of the test samples were autoclaved in the assay medium. The assay tubes were incubated at 30° for the time interval indicated in the tables, and the amount of growth, measured in terms of galvanometer readings, was determined in a turbidimeter²⁷ which was so adjusted that distilled water read 0 and an opaque object 100. The measurements were made in the portion of the scale in which the dry weight of cells and galvanometer readings were almost linear. All of the toxicity data for comparison of inhibitory activity of the individual compounds were based on essentially complete inhibition of growth.

Results and Discussion

In order to prepare the desired pantothenic acid analogs through a direct condensation of pantolactone $(\alpha$ -hydroxy- β , β -dimethyl- γ -butyrolactone), the syntheses of properly substituted amines were necessary. Indeed, a major portion of the synthetic work in this study concerned the synthesis and proof of purity of the requisite amines. In general, two routes of synthesis were utilized, (a) a condensation of the appropriate alkyl halide with potassium phthalimide, then hydrolysis of the substituted phthalimide, or (b) the catalytic hydrogenation of the appropriate nitrile.

The structures of the nitrophenylalkylamines were based on infrared spectra of either carefully purified intermediate reaction products, or of the amines themselves. The stage at which an effective separation of isomers could be accomplished varied with the derivative. In several instances, fractional distillation provided a satisfactory technique; whereas, in other cases fractional recrystallization of solid intermediates proved to be the most satisfactory route. Previous studies on the characteristic absorption spectra of the isomeric nitro substituted toluenes²⁰ have shown the absorption

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bands at 9.02 and 12.47 μ to be associated with the *para* isomer, and absorption bands at 6.37 and 12.75 μ to characterize ortho substitution. In addition to the infrared spectra, in several instances appropriate intermediates were examined for homogeneity using vapor phase chromatographic techniques. The attempted separation of the isomeric forms of the 5-(chlorophenyl)pentyl derivatives was unsuccessful. The product isolated contained both the ortho and para derivatives as evidenced by infrared spectra, as well as by an alkaline potassium permanganate oxidation²⁸ which vielded a mixture of o- and p-chlorobenzoic acids. This mixture of amines was also condensed with pantolactone in order to compare the relative biological activity with other homologs.

A thermal condensation of the appropriate amine with pantolactone, as indicated in the accompanying equation, produced 19 new N-pantoyl-(substituted)phenylalkyl amines, and of these derivatives, 10 were obtained as crystalline products (Table I). In those $CH_2C(CH_3)_2CHOHCO + RNH_2 \longrightarrow$

HOCH₂C(CH₃)₂CHOHCONHR

cases in which a fusion reaction mixture failed to yield a solid product, several attempts were made to obtain a crystalline sample using different solvent systems to dissolve and reprecipitate the sample. Even though a number of the samples could not be crystallized, the semi-solid materials resulting from these treatments produced compounds giving the anticipated elemental analysis for the corresponding condensation product.

Using two microörganisms, Lactobacillus arabinosus and Leuconostoc mesenteroides, the inhibitory properties of these pantothenic acid analogs were determined in media containing two different concentrations of pantothenic acid. All of the derivatives were competitively reversed by the vitamin, but there were significant differences in the inhibition indices (ratio of analog to vitamin necessary for essentially complete inhibition of growth) for the two assays, the analogs being uniformly more inhibitory to growth of L.

(28) C. K. Ingold and E. H. Ingold, J. Chem. Soc., 127, 870 (1925).

TABLE II

mesenteroides than to L. arabinosus (Table II). For purposes of comparison, the inhibitory properties of the corresponding unsubstituted-phenylalkylamine derivatives are also included in Table II.

For L. mesenteroides, the substitution of a parachloro group increases the growth inhibitory activity of N-pantoyl(phenylalkyl)amines several fold and is independent of the chain length of the alkyl group. This is in contrast to the substitution of the nitro group in the para position which enhances the inhibitory activity of only the highest homolog. Other modifications in the phenyl grouping of the amines synthesized in this study produced derivatives possessing less activity than the parent compound. For L. arabinosus, both nitro and chloro substituents on the aromatic ring of the lower alkyl homologs produced analogs with increased inhibitory activity over the parent compound. In general, however, no unusual increased inhibitory properties were found in the various substituted phenylalkylamine derivatives over that of the parent unsubstituted analog for either of these microörganisms.

The most significant variable in producing biological activity in this type of pantothenate derivative still appears to be the chain length of the amine grouping; however, this does not preclude the possibility that the presence of a chemically reactive center on the phenyl moiety could produce a non-competitive antagonist. These differential toxicities for different species of microörganisms might prove of some benefit in chemotherapy since it should be possible to prepare an analog which would specifically inhibit pathogenic organisms without affecting the desirable bacteria in the intestinal flora. RELATIVE INHIBITORY PROPERTIES OF SOME N-PANTOYL-AMINES FOR Lactobacillus arabinosus and Leuconostoc mesenteroides

	Inhibition Index ^a					
HOCH ₂ C(CH ₃) ₂ CHOHCONHR	<i>L</i> .	<i>L</i> .				
R	$arabinosus^{b}$	mesenteroides ^c				
Benzyl-	25,000	10				
p-Chlorobenzyl-	2,000	2				
p-Nitrobenzyl-	2,000	10				
<i>m</i> -Nitrobenzyl-	5,000	40				
o-Chlorobenzyl-	10,000	$200 \ 400$				
$Phenethyl-^{d}$	2,000	25				
o-Nitrophenethyl-	1,000	100				
p-Nitrophenethyl-	1,000	50 - 100				
p-Chlorophenethyl-	2,000	-1				
p-Aminophenethyl-	10,000	500				
Phenylpropyl- ^e	2, 0 00	25				
p-Nitrophenylpropyl-	1-2,000	50-100				
o-Nitrophenylpropyl-	2,000	20-40				
N-Anilinopropyl-	2,000	20				
N-Pyrrolylpropyl-	• • •	200				
Phenylbutyl-"	1,000	50				
p-Aminophenylbutyl-	1,000	400				
o-Aminophenylbutyl-	1,000	100				
Phenylpentyl- ^e	1,000	25				
p-Nitrophenylpentyl-	1,000	4				
x -Chlorophenylpentyl- f	2,000	5-10				

^a Determined in duplicate or triplicate for essentially complete growth inhibition at two levels of calcium pantothenate concentrations, 0.02 and 0.1 μ g./ml. for *L. arabinosus*, and 0.1 and 0.5 μ g./ml. for *L. mesenteroides.* ^b Incubation at 30° for 17 hr. ^c Incubated at 30° for 24 hr. ^d W. Shive and E. E. Snell, *J. Biol. Chem.*, 160, 287 (1945). ^e J. D. Fissekis, C. G. Skinner and W. Shive, *J. Med. Pharm. Chem.*, 2, 47 (1960). ^f A mixture of o- and p-derivatives as indicated by infrared spectra.

Notes

Conformational Aspects of Drug Action. I. The Effects of D(-)Pseudoephedrine on the Action of Certain Pressor Amines

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It is generally accepted that the amino group, the alcoholic hydroxyl group and the benzene ring are the three major points involved in the interaction of adrenergic drugs and their receptors. With this in mind we have studied the stereochemical relationship of the diastereoisomers D(-)ephedrine (I) and D(-)pseudo-ephedrine (II), whose configurations have been established by Freudenberg, *et al.*^{1,2}

Inspection of these formulas reveals that the carbon

(1) K. Freudenberg, E. Schoffel and E. Braun, J. Am. Chem. Soc., 54, 234 (1932).



bearing the hydroxyl and the phenyl group has the same configuration in each diastereoisomer. Since the hydroxyl and phenyl groups represent two of the three groups involved in the drug receptor interaction, and since the carbon bearing the methylamino group can be rotated in space, these two isomers represent a rather special case: they can both "fit" receptors at the same three points (Fig. 1).

This observation led us to study the effects of pretreatment with D(-)pseudoephedrine on the actions of pressor amines. Anesthetized dogs, pretreated with atropine (1 mg./kg.) were used as the test animals. The hydrochloride salts of the amines were used in all cases. D(-)Pseudoephedrine was used in doses of 3.3 mg./kg. i.v., and D(-)ephedrine was used in doses of 0.33 mg./kg. i.v.

⁽²⁾ K. Freudenberg and F. Nikolai, Ann., 510, 223 (1934).