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 *para*-chloro 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.

TABLE II

RELATIVE INHIBITORY PROPERTIES OF SOME N-PANTOYL-AMINES FOR *Lactobacillus arabinosus* AND *Leuconostoc mesenteroides*

$HOCH_2C(CH_3)_2CHOHCONHR$ R	Inhibition Index[a] *L. arabinosus*[b]	Inhibition Index[a] *L. mesenteroides*[c]
Benzyl-	25,000	10
p-Chlorobenzyl-	2,000	2
p-Nitrobenzyl-	2,000	10
m-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	4
p-Aminophenethyl-	10,000	500
Phenylpropyl-[e]	2,000	25
p-Nitrophenylpropyl-	1–2,000	50–100
o-Nitrophenylpropyl-	2,000	20–40
N-Anilinopropyl-	2,000	20
N-Pyrrolylpropyl-	...	200
Phenylbutyl-[e]	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 μg./ml. for *L. arabinosus*, and 0.1 and 0.5 μg./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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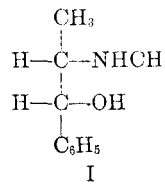
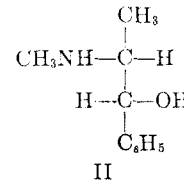
It is generally accepted that the amino group, the alcoholic hydroxyl group and the benzene ring are the three major points involved in the interaction of adrenergic drugs and their receptors. With this in mind we have studied the stereochemical relationship of the diastereoisomers D(−)ephedrine (I) and D(−)pseudoephedrine (II), whose configurations have been established by Freudenberg, *et al.*[1,2]

Inspection of these formulas reveals that the carbon



I



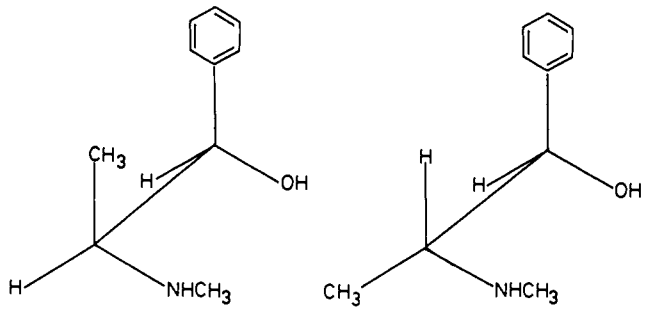
II

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.

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

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



D(−)Ephedrine D(−)Pseudoephedrine

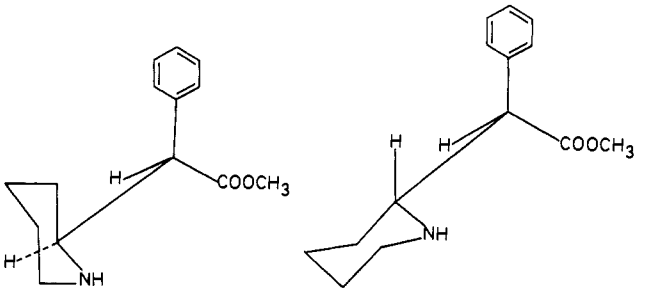
Fig. 1.—Relationship of the functional groups in the D-diastereoisomers, ephedrine and pseudoephedrine (preferred conformations not implied).

At this dose level D(−)pseudoephedrine produced no pressor response whatever, and in fact, produced a small, transient drop in blood pressure. D(−)Ephedrine produced a rise in blood pressure of approximately 70 mm. If the test animal was pretreated with D(−)pseudoephedrine and given D(−)ephedrine one-half hour later, there was no pressor response, indicating that, at these doses, D(−)pseudoephedrine is capable of completely blocking the pressor effect of D(−)ephedrine.

Since D(−)pseudoephedrine itself did not produce any pressor response it was assumed that this was a true blockade and that cross-tachyphylaxis was not involved. This was borne out by the finding that D(−)pseudoephedrine given at the peak of the pressor response to D(−)ephedrine caused an immediate return of the blood pressure to normal. These effects were not obtained when the other ephedrine isomers (L(+)ephedrine, L(+)pseudoephedrine) were tested under the same conditions.

In a further series of experiments, it was found that pretreatment with D(−)pseudoephedrine blocked the pressor effect of tyramine and amphetamine, and augmented the pressor response of norepinephrine. In these respects the action of D(−)pseudoephedrine appears very similar to that reported for methylphenidate.[3,4] Methylphenidate (methyl-α-phenyl-2-piperidine acetate) contains two asymmetric carbon atoms, and therefore can exist in two diastereoisomeric forms, *erythro* and *threo*. When methylphenidate is represented as in Fig. 2, the resemblance to the isomers of ephedrine becomes apparent. This resemblance led us to make the assumption that the active racemate of methylphenidate is the *threo* racemate, and this has been stated by Druey,[5] recently. Although the absolute configurations of the isomeric methylphenidates are not known, we have drawn the *threo* enantiomorph which is configurationally identical to D(−)pseudoephedrine because the action of methylphenidate is essentially the same as the action of D(−)pseudoephedrine.

Burn and Rand[6] have demonstrated that ephedrine, tyramine, amphetamine, and certain other sympathomimetic amines act by releasing norepinephrine from



erythro-Methylphenidate *threo*-Methylphenidate

Fig. 2.—Relationship of the functional groups in the D-diastereoisomers of methylphenidate (preferred conformations not implied).

storage sites. Muskus, *et al.*,[7] have suggested recently that ephedrine and norephedrine are compounds which have indirect activity (release of norepinephrine from storage sites) as well as direct activity (at effector site). The experiments described in this note indicate that D(−)pseudoephedrine blocks the pressor effects of ephedrine regardless of whether these effects are indirectly or directly produced. Investigations are being carried out to determine the exact nature of this blocking action.

Experimental

Preparation of the Isomers of Ephedrine.—Ephedrine alkaloid (Merck) was converted into a mixture of four isomers by boiling in *p*-cymene in the presence of sodium methoxide.[8,9] The two racemates were obtained by fractional crystallization. (±)-Ephedrine was resolved through formation of the (+)-mandelate salts according to Manske and Johnson.[10] (±)-Pseudoephedrine was resolved through formation of the (+)-tartrate salts according to Späth and Göhring.[11] These resolutions were carried out primarily to obtain L(+)ephedrine, and D(−)pseudoephedrine, neither of which is commercially available. D(−)Ephedrine was obtained from Merck and Company, and L(+)pseudo ephedrine from L. Light and Company, Ltd., England.

Acknowledgment.—This research was supported in part by a grant from the Development Fund of the Ohio State University.

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A Hydroxamic Acid Analog of Cortisone

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August 8, 1962

Numerous modifications have been carried out on the 21-hydroxymethylene grouping in the corticoid series[1]

(1) For leading references, see R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **26**, 1223 (1961); also H. D. Brown, A. R. Matzuk, D. R. Hoff and L. H. Sarett, *J. Org. Chem.*, **27**, 961 (1962); M. Marx and L. L. Smith, U. S. Patent 3,020,275 (Feb. 6, 1962); W. S. Allen and M. J. Weiss, *J. Org. Chem.*, **26**, 4153 (1961); H. D. Brown, A. R. Matzuk, D. R. Hoff and L. H. Sarett, *J. Org. Chem.*, **26**, 5052 (1961); J. Tóth, Z. Tuba and L. Szporny, *Nature*, **191**, 607 (1961); E. J. Agnello and G. D. Laubach, U. S. Patent 2,920,999 (Jan. 12, 1960); E. J. Agnello, R. Pinson, S. K. Figdor, G. M. K. Hughes, H. W. Ordway, B. M. Bloom and G. D. Laubach *Experientia*, **16**, 357 (1960).