cooling gave 3.12 g (28%), mp 115–131°. Recrystallization from pet ether (60°–110°) and sublimation [150°(0.1 mm)] gave 1.23 g (15%), mp 143–148° (sinters at 135°). An analytical sample was prepared by recrystn from MeCN: nmr ($CDCl_3$) δ 8.83 (d, 1, J = 2.5 Hz, H-2), 7.86 (q, 1, J = 2.5 Hz, nonequiv H-4 of diastereomers): 7.32 (s, 2), 4.85 (d, 0.41, J = 5 Hz), 4.56 (d, 0.59, J = 8 Hz), 4.21 (s, 2, NH,OH), 2.75 (s, 3), 2.46 (s, 3), 2.7 (m, 3), 1.45 (m, 6).

L(S)- and D(R)-3-Amino-1-phenylpyrrolidines. Stereoselective Antagonists for Histamine and Acetylcholine Receptors *in Vitro*

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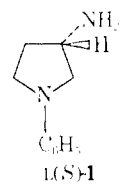
Studies leading to the synthesis of L(*S*)-3-amino-1-phenylpyrrolidine (1) and related L(*S*)- and D(*R*)-3-ethylamino analogs 11 are described. An ORD investigation is presented which defines the absolute configurations of intermediates and final products. Biological evaluation *in vitro* of racemic 11 shows both antihistaminic and anticholinergic activities. Pure L(*S*)-11 exhibits a tenfold increase in antihistamine potency over D(*R*)-11. Essentially all of the anticholinergic activity is found in the D(*R*)-11 enantiomorph. Other preliminary biological data obtained *in vivo* are also discussed.

Among biologically active compounds the arrangement of atoms >NCCR, where R = aryl, acyl-X, aryl-X, or some heterocycle and X = C, O, or N, is of major importance. This unit is found in such agonists as acetylcholine and norepinephrine; antagonists having a similar arrangement of atoms are exemplified by the cholinergic blocking agents and antihistamines. In other words, many autonomic drugs may be generally classified as β-aminoethyl analogs.

As part of a program designed to synthesize compounds of known absolute configuration for purposes of characterizing biological receptors on the basis of their stereoselective affinity towards various enantiomorphs, we explored a synthesis for optically pure L(*S*)-3-amino-1-phenylpyrrolidine analogs (**1**). This compound contains the units H_2N–C*–CN(Ph)– and H_2N–C*–C–CN(Ph)– with an asymmetric center (C*) located on the C α to the $-NH_2$ group. In this communication we report the synthesis of **1** from L(*S*)-aspartic acid (**2**), an optical rotatory dispersion investigation which defines the structures and absolute configurations of intermediates and final products, and some of our preliminary biological results *in vivo* and *in vitro* with two selected enantiomorphic analogs of **1**.



L(S)-1

Results and Discussion

Synthetic Aspects.—L(*S*)-Aspartic acid (**2**) serves as starting material. Initially, **2** was converted in 80% yield to the carbobenzoxy (Cbz) derivative (**3a**) through reaction with benzyl chloroformate in the presence of MgO in H_2O.[1] Derivatization of the amino group is required in order to render the amino N less nucleophilic and prevent its participation in subsequent reactions. The Cbz group was first investigated since it is easily removed under conditions employing mineral acid or by catalytic hydrogenation.[1,2] The Cbz derivative **3a** is converted into the corresponding anhydride **4a** by heating in Ac_2O. Reaction of anhydride **4a** with $PhNH_2$ in abs EtOH affords a mixture of α- and β-anilides (**5a** and **6a**), respectively.[3,4] The β-anilide **6a** is readily separated from the α isomer by selective crystallization from EtOH.[3,5] Heating the anilide mixture with Ac_2O affords Cbz-L(*S*)-α-amino-*N*-phenylsuccinimide (**7a**) in 70% yield. However, all attempts to remove the Cbz group under a variety of reaction conditions either afforded starting **7a** or products resulting from hydrolysis of the imide ring. Hydrogenation over Pd[2] in abs MeOH afforded the diketopiperazine dimer **8**; similar results were obtained by hydrogenation over Pd in HOAc–H_2O or EtOH–HOAc under analogous conditions.

Since the Cbz group proved difficult to remove without destruction of the imide system, we resorted to use of the *tert*-butyloxycarbonyl (Boc) group which is more easily hydrolyzed under acidic conditions.[6] Reaction of L(*S*)-aspartic acid (**2**) with *tert*-butyl azidoformate affords the Boc derivative **3b**. Heating **3b** in AcOH affords the anhydride **4b**. Reaction of **4b** with $PhNH_2$ in abs EtOH leads to the intermediate α- and β-anilides (**5b** and **6b**), respectively, in a combined yield of 40%. The anilide mixture is heated with Ac_2O affording the desired Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**). Reaction of **7b** in CF_3CO_2H, followed by treatment with Amberlite IRA-400 ion-exchange resin ($RN(CH_3)_3^+Cl^-$) yields a mixture of the HCl salts of imide **9** and anilide **10**. However, short reaction of Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**) with HCl gas in $CHCl_3$–C_6H_6 (3:1) affords L(*S*)-α-amino-*N*-phenyl-

* To whom correspondence should be addressed.

(1) M. Bergman and L. Zervas, *Ber.*, **65**, 1192 (1932).

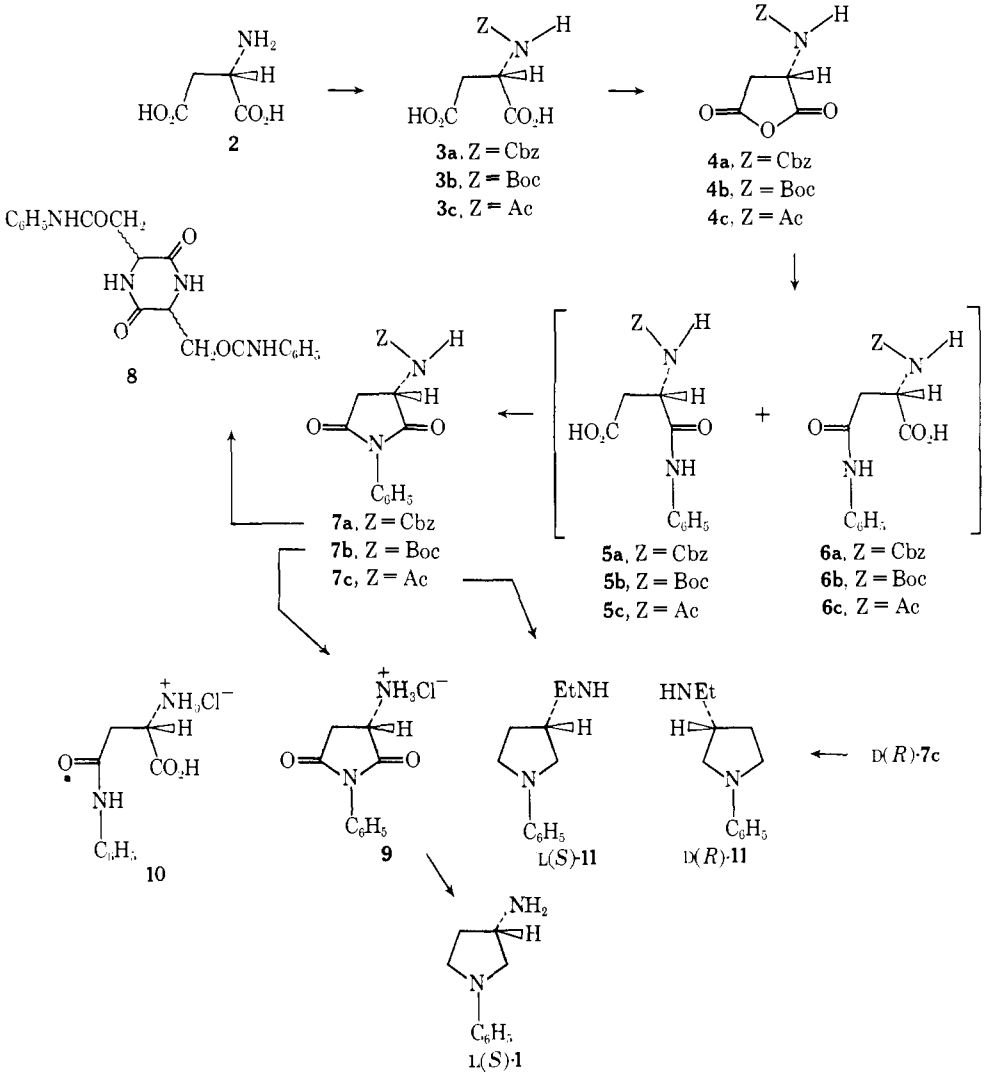
(2) E. Sondheimer and R. W. Holley, *J. Amer. Chem. Soc.*, **76**, 2467 (1954).

(3) C. C. Barker, *J. Chem. Soc.*, 453 (1953).

(4) J. Kovacs, H. N. Kovacs, I. Konyves, J. Csazar, T. Vaja, and H. Mix, *J. Org. Chem.*, **26**, 1084 (1961).

(5) F. E. King and E. A. A. Kidd, *J. Chem. Soc.*, 2976 (1951).

(6) R. Schwyzer, B. Iselin, H. Kappler, B. Riniker, and H. Zuber, *Helv. Chim. Acta*, **46**, 1975 (1963).



succinimide·HCl (**9**). The free amine is liberated from its salt **9** by treatment with 2% $NaHCO_3$ solution. LAH reduction of hydrochloride **9** affords L(*S*)-3-amino-1-phenylpyrrolidine (**1**). This successful synthesis of **1** and **9** allows for the preparation of numerous derivatives, having either the L(*S*) or D(*R*) abs configuration, for biological investigations.

In this report we discuss the antagonist activity of the enantiomorphic Et analogs of L(*S*)-**1**, namely, L(*S*)- and D(*R*)-**11**, on H_1 receptors of the guinea pig ileum. The preparation of L(*S*)-3-ethylamino-1-phenylpyrrolidine (**11**) from L(*S*)-aspartic acid (**2**) is described below; synthesis of D(*R*)-**11** from D(*R*)-**2** is similar. The HBr salt of L(*S*)-**2** is heated with Ac_2O affording the acetyl anhydride **4c**. This could be hydrolyzed to the corresponding α-acetamido-L(*S*)-aspartic acid (**3c**) for characterization purposes. Anhydride **4c** is converted into the imide L(*S*)-α-acetamido-*N*-phenylsuccinimide (**7c**) by a sequence of reactions previously described for the preparation of the Boc derivative **7b**. Reduction of **7c** with LAH affords L(*S*)-**11**. Distilled amines are dissolved in very dil HCl; aliquots of known concentration are taken and dissolved in the appropriate buffer. The solutions are biologically evaluated the same day after distillation.

Optical Rotatory Dispersion (ORD).—α-Amino acids of the L configuration, when examined in acid medium, show a long wavelength peak at 225 mμ, crossover at 210–212 mμ, and a trough at 195–200 mμ.[7] The Cotton effect corresponds to the $n \rightarrow \pi^*$ transition of the CO_2H chromophore. Since D-amino acids exhibit a similar Cotton effect, but of opposite sign, the ORD may readily be correlated with the abs configuration of amino acids in solution.

The Cbz, Boc, and Ac derivatives of L(*S*)-Asp (**3a**, **b**, and **c**, respectively) exhibit negative anomalous ORD curves with a trough between 240 and 245 mμ. These ORD curves correspond to the $n \rightarrow \pi^*$ transitions of the CO group for the Cbz, Boc, and acetamido functions (curves B in Figures 1, 2, and 3, respectively).[8] The β-anilides (**6a**, **b**, and **c**, curves C) of these 3 *N*-substituted aspartic acids exhibit negative plain curves in the region 270–300 mμ. This increase in intensity of the ORD curve reflects the influence of the anilide chromophore on the asymmetric center.[9] The Cbz, Boc, and Ac derivatives of L(*S*)-α-amino-*N*-phenylsuccinimide exhibit negative Cotton effects (curves A) with troughs near 245 mμ. This corresponds to the $n \rightarrow \pi^*$ transition for the Cbz, Boc, and AcCO groups.[8] The decrease in intensity of the trough at 245 mμ characterizes the anilide

(7) (a) W. Caffield, *Chem. Ind. (London)*, 1460 (1964); (b) D. W. Urry and H. Eyring, *J. Amer. Chem. Soc.*, **86**, 4574 (1964); (c) J. C. Craig and S. K. Roy, *Tetrahedron*, **21**, 391 (1965).

(8) N. Sakota, *Nippon Kagaku Zasshi*, **89**, 425 (1968).

(9) I. Fric, V. S. Spirko, and K. Blaha, *Collect. Czech. Chem. Commun.*, **33**, 4008 (1968).

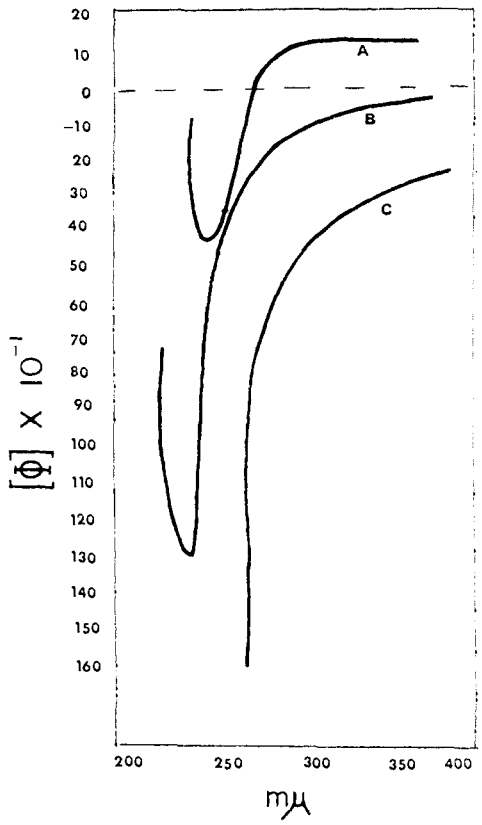


Figure 1.—ORD spectra of the Cbz derivatives taken in MeOH: (A) Cbz-L(*S*)-α-amino-*N*-phenylsuccinimide (**7a**, *c* 0.012); (B) *N*-Cbz-L(*S*)-Asp (**3a**, *c* 0.010); (C) *N*-Cbz-L(*S*)-Asp β-anilide (**6a**, *c* 0.095).

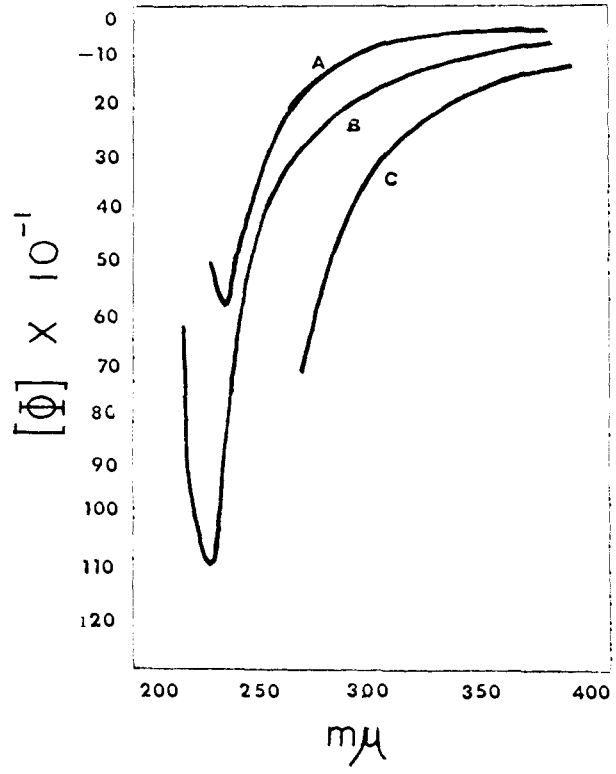


Figure 2.—ORD spectra of the Boc derivatives taken in MeOH: (A) Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**, c 0.010); (B) *N*-Boc-L(*S*)-Asp (**3b**, c 0.011); (C) *N*-Boc-L(*S*) Asp β-anilide (**6b**, *c* 0.011).

to imide conversion, correlates the spectra for these compounds with the L(*S*) absolute configuration, and suggests the CO chromophore of the protecting group to have a greater influence on the ORD than does the *N*-phenylimide function.

Removal of the Boc group affords L(*S*)-α-amino-*N*-phenylsuccinimide, the ORD spectrum of which, either as the free base (curve C, Figure 4) or HCl salt (**9**, curve D, Figure 4), exhibits a negative Cotton effect with a trough at 320–330 mμ. This large shift in the ORD curve to a longer λ reflects the removal of the CO chromophore and corresponds to electronic transitions for the *N*-phenylimido chromophore.[10] Imide hydrolysis, which may take place during protecting group removal, is easily detected since the resulting L(*S*)-aspartic acid β-anilide·HCl exhibits the expected positive rotatory dispersion (curve A, Figure 4). This is similar to the ORD observed for L(*S*)-α-aminosuccinic acid·HCl (curve B)[11] and occurs at approximately the same λ (although opposite in sign) observed for the imide. These studies substantiate the applicability of the synthetic schemes for the preparation of substituted and unsubstituted L(*S*)- or D(*R*)-α-aminosuccinimides. LAH reduction of L(*S*)-**9** affords L(*S*)-**1** exhibiting a plain positive ORD curve (see Experimental Section). Reduction of L(*S*)-**7c** and D(*R*)-**7c** afford L(*S*)-**11** and D(*R*)-**11**, respectively, exhibiting enantiomorphic ORD spectra (see Experimental Section).

Biological Aspects.—The antihistaminic and anticholinergic activity *in vitro* for racemic, L(*S*)-, and D(*R*)-3-ethylamino-1-phenylpyrrolidine (**11**) is determined employing the method of Magnus on the isolated guinea pig ileum. These results are listed in Table I. At histamine concentrations between 1.0×10^{-8} to 1.0×10^{-7} *M*, L(*S*)-**11** at 1.0×10^{-6} to 5.0×10^{-5} *M* or D(*R*)-**11** at 1.0×10^{-5} to 5.0×10^{-4} *M* displace the agonist dose–response curve to the right. The calculated pA_2 values[12] (Table I) show L(*S*)-**11** to possess approximately 10 times greater antihistaminic potency than D(*R*)-**11**.

TABLE I

ANTIHISTAMINIC AND ANTICHOLINERGIC ACTIVITY *in Vitro* FOR RACEMIC, L(*S*)-, AND D(*R*)-**11**[a]

Compd	Antihistaminic activity pA_2	Anticholinergic activity pA_2
Rac-11	5.0–5.8	3.0
L(*S*)-11	5.92	Too weak to be calculated
D(*R*)-11	4.92	3.5–4.0
Antazoline[b]	7.67	5.47

[a] Data obtained *in vitro* on the guinea pig ileum. [b] J. J. Reuse, *Brit. J. Pharmacol.*, **3**, 174 (1948).

It is well known that for maximum antihistaminic activity compounds of type **12**, where X = N, CO, or saturated C, are necessary.[13] It appears that strong-

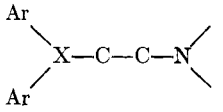
(10) (a) C. Djerassi, E. Lund, E. Bunnenburg, and J. C. Sheehan, *J. Org. Chem.*, **26**, 4509 (1961); (b) in H_2O this trough for the HCl salt **9** appears at 280 mμ. Wavelengths of $n \rightarrow \pi^*$ bands are generally found to decrease (blue-shift) with the increase in the polarity of the solvent. See M. Kasha, *Discuss. Faraday Soc.*, **9**, 14 (1950), and H. J. McConnell, *J. Chem. Phys.*, **20**, 700 (1952).

(11) J. Sterni, Y. S. R. Krishna Prasad, and J. A. Schellman, *Tetrahedron*, **13**, 176 (1961).

(12) (a) H. O. Schild, *Brit. J. Pharmacol.*, **4**, 277 (1949); *ibid.*, **2**, 189 (1947); (b) A. S. F. Ash and H. O. Schild, *ibid.*, **27**, 427 (1966).

(13) For a review see D. T. Witiak in "Medicinal Chemistry," A. Burger, Ed., Wiley, New York, N. Y., 1970, chapter 65.

est competitive antagonism occurs when at least one ring is capable of assuming a position 5–6 Å from the



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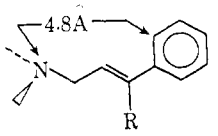
amino N. While utilization of two aromatic rings affords compounds which are most potent as antihistamines, reports in the literature suggest one ring and its relative distance from the aliphatic N to be the major contributor to antihistaminic activity on H_1 receptors.[13] For example, *N*,*N*-dimethyl-2-halogeno- and hydroxyphenethylamines show relatively high antihistaminic activity.[14] Studies by Casy and Ison,[15] employing semirigid 2-butene analogs of type **13**, also suggest the amine to ortho aromatic position distance of 4.8 Å to be particularly significant for antihistaminic activity. This distance (in antihistamines) is related to the amine to imidazole N distance in the staggered conformation of histamine (**14**). A second aromatic ring (R in **13**) is



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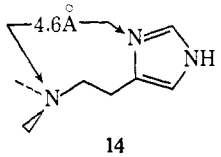


14

assumed to bind to an additional receptor area outside the histamine receptor site thereby affording a compound with greater affinity and blocking activity.

The data obtained with stereoisomeric pyrrolidines **11** are of particular interest since these compounds contain only one aromatic ring appropriately placed at a distance of about 5 Å from the aliphatic N. Their activity *in vitro* may be compared with an antihistamine (antazoline)[16] of intermediate activity on the guinea pig ileum (Table I). Understandably, the pyrrolidine analogs **11** are not as potent as other standard drugs (*i.e.*, diphenhydramine, $pA_2 = 8.14$; chlorpheniramine, $pA_2 = 8.82$)[17] which have two aromatic rings and presumably greater affinity for antihistamine receptor sites.

Prior to the results described in this study, stereoselective antihistaminic activity had only been observed when the asymmetric center was located α to the aromatic ring functions; in other words, the asymmetric unit is located on the C β to the aliphatic N.[18] This is observed for the dextrorotatory isomer of dimethylaminoethyl 4-methylbenzhydryl ether which is 4 times as active as the levorotatory enantiomorph. Similarly, the *d* forms of carbinoxamine, pheniramine, chlorpheniramine, and brompheniramine are the more potent enantiomorphs.[19] With isothipendyl, where the asymmetric center is located β to the aromatic rings (α to NMe_2) resolution affords *d* and *l* enantiomorphs exhibiting less activity than the original *dl* pair.[19b] Also, in promethazine (asymmetric center α to NMe_2) *d* and *l* isomers are reported to have the same toxicity and activity.[20] These observations have led to the suggestion that regions adjacent to H_1 histamine receptors are asymmetric[13] since the receptor affinity for aryl groups, presumably binding to extrahistamine–receptor sites, is influenced by the asymmetry of the C to which they are bonded. Results with D(*R*)– and L(*S*)–**11** show asymmetry at the C α to the amino group in an appropriately constructed antihistamine also influences the receptor–drug interaction. Although further work is necessary, if the same antihistamine binding site is involved with the pyrrolidines and classical antihistamines, these results will have to be considered when attempting to "map" the structural features of the antihistamine receptor.[15,21]

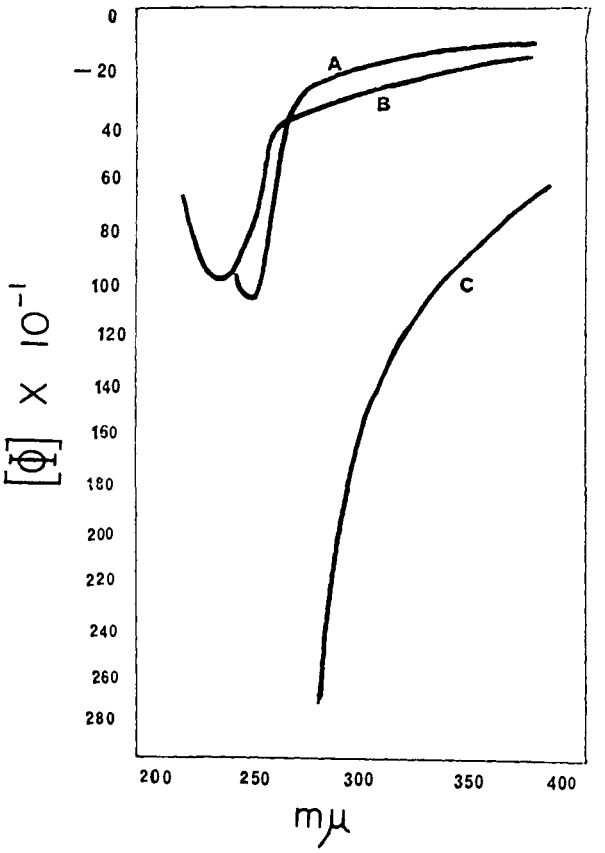


Figure 3.—ORD spectra of acetyl derivatives taken in MeOH: (A) Ac-L(*S*)-α-amino-*N*-phenylsuccinimide (**7c**, *c* 0.111; (B) *N*-Ac-L(*S*)-Asp (**3c**, *c* 0.111); (C) *N*-Ac-L(*S*)-Asp β-anilide (**6c**, *c* 0.042).

Classical antihistamines, like antazoline (Table I), are generally less active antagonists for AcCh. The same is true for the pyrrolidines **11**. However, stereoselective activity is again observed. Whereas the L(*S*) isomer is the most active antagonist for histamine, the D(*R*) isomer has nearly all of the antichlorinergic activity *in vitro*. In addition, at higher doses both isomers have cholinergic agonist activity. L(*S*)-**11** (1.0×10^{-6} and 5.0×10^{-5} *M*) and D(*R*)-**11** (1.0×10^{-4} and 5.0×10^{-4} *M*) isomers exhibit a slow sustained contractile response (up to 18–25% of the maximal contraction) of

(14) J. D. P. Graham and M. A. Karrar, *J. Med. Chem.*, **6**, 103 (1963).
(15) A. F. Casy and R. R. Ison, *J. Pharm. Pharmacol.*, **22**, 270 (1970).
(16) J. J. Reuse, *Brit. J. Pharmacol.*, **3**, 174 (1948).
(17) P. B. Marshall, *ibid.*, **10**, 270 (1955).
(18) (a) M. J. Jarrousse and M. T. Regnier, *Ann. Pharm. Fr.*, **9**, 321 (1951); (b) A. F. Harms and W. Th. Nauta, *J. Med. Pharm. Chem.*, **2**, 57 (1960).
(19) (a) A. P. Roszkowski and W. M. Grovier, *Pharmacologist*, **1**, 60 (1959); (b) F. E. Roth, *Chemotherapia*, **3**, 120 (1961); (c) F. E. Roth and W. M. Grovier, *Amer. J. Pharmacol.*, **124**, 347 (1958); (d) R. T. Brittain, P. F. D'Arcy, and J. H. Hunt, *Nature (London)*, **183**, 734 (1959); (e) A. Shafi'ee and G. Hite, *J. Med. Chem.*, **12**, 266 (1969).
(20) L. Toldy, L. Vargha, I. Toth, and J. Borsey, *Acta Chim. Acad. Sci. Hung.*, **19**, 273 (1959).
(21) G. Hite and A. Shafi'ee, *J. Pharm. Sci.*, **56**, 1041 (1967).

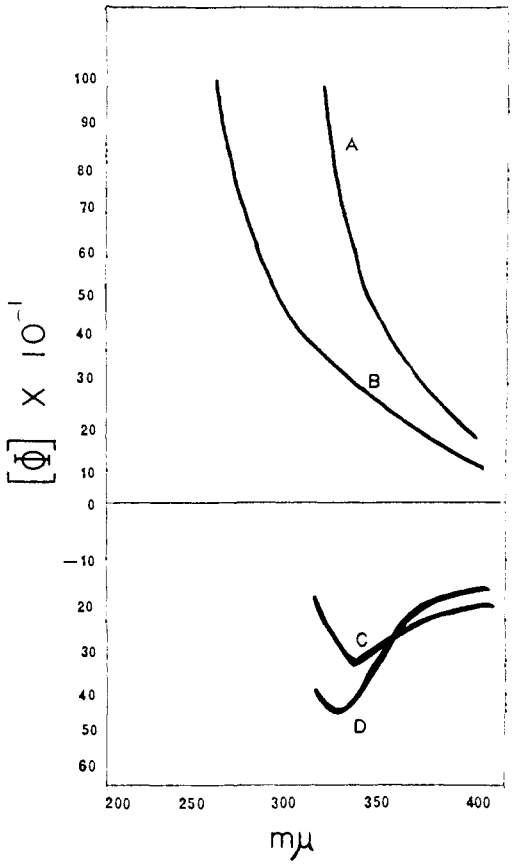


Figure 4.—ORD spectra of the nonderivatized amino series: (A) L(*S*)-Asp β-anilide·HCl (**10**, MeOH, *c* 0.066); (B) L(*S*)-Asp·HCl (**2**, H_2O, *c* 0.143); (C) L(*S*)-α-amino-*N*-phenylsuccinimide (free base of **9**, MeOH, *c* 0.111); (D) L(*S*)-α-amino-*N*-phenylsuccinimide·HCl (**9**, MeOH, *c* 0.042).

the guinea pig ileum which reaches the peak after 10 min. This shows that in addition to their blocking effects both isomers exhibit cholinergic activity. In this case the L(*S*) enantiomorph is about 10 times more potent than the D(*R*) isomer.

Cholinergic stimulants have been shown to induce hypothermia in mice, a response easily quantified. Thirty minutes after an ip dose of 20 mg/kg (which produced no grossly observable behavioral effects), S and 5% drops in rectal temperature are produced by the L(*S*)- and D(*R*)-**11** isomers, respectively; at 60 min temperatures are 5 and 2% below normal (Table II). These results suggest the L(*S*) isomer may also possess the greater cholinomimetic potency (*in vivo*), but additional work is required to rule out hypothermia resulting from other pharmacological mechanisms.

TABLE II

L(*S*)- AND D(*R*)-3-ETHYLAMINO-1-PHENYLPYRROLIDINE (**11**) INDUCED HYPOTHERMIA IN MALE MICE[a]

Compd	T_0	T_{30}	T_{60}
L(*S*)-**11**	38.1 ± 0.5 (100)	35.0 ± 0.6[b,c] (92)	36.2 ± 0.6[d,e] (95)
D(*R*)-**11**	38.2 ± 0.5 (100)	36.4 ± 0.5[b,c] (95)	37.5 ± 0.2[e,f] (98)

[a] Values are expressed as the mean temp ± S. D. in each treatment group of 5 mice. Values in parenthesis represent the percentage of predrug (T_0) temperatures. [b] $p < 0.001$ [L(*S*) T_{30} *vs.* T_0; D(*R*) T_{30} *vs.* T_0]. [c] $p < 0.01$ [L(*S*) T_{30} *vs.* D(*R*) T_{30}. [d] $p < 0.005$ [L(*S*) T_{60} *vs.* T_0]; [e] $p < 0.005$ [L(*S*) T_{60} *vs.* D(*R*) T_{60}]. [f] $p < 0.02$ [D(*R*) T_{60} *vs.* T_0].

Toxicities for these compounds in mice are approximately equal. The LD_{50} for L(*S*)- and D(*R*)-**11** are 38 and 45 mg/kg, respectively. At toxic doses, the animals exhibit hyperexcitability and convulsions prior to death.

Experimental Section[22]

Cbz-L(*S*)-Asp (3a) is prepared by the method of Bergman and Zervas[1] from L-Asp (**2**) and benzyl chloroformate affording crystals (80%) of **3a**, mp 118–120°, lit.[1] mp 116°.

Cbz-L(*S*)-Asp anhydride (4a) is prepared from L-**3a** by reaction in Ac_2O affording crystals (82%) mp 90–92°, lit.[1] mp 87°.

Cbz-L(*S*)-Asp α- and β-Anilides (5a and 6a).—Cbz-L(*S*)-Asp anhydride (**4a**, 11.8 g, 4.3×10^{-2} mole) was added to a soln of 9.33 g (0.10 mole) of $PhNH_2$ in abs EtOH. The mixture became warm and a precipitate was formed after 0.5 hr. The mixture was acidified with HCl. The ppt was sepd by filtration, dissolved in 5% $NaHCO_3$, and extd with Et_2O. The aq soln was acidified, the ppt removed, washed with H_2O, and dried under reduced pressure at 30°. This afforded 10.2 g (50%) of a mixture of *N*-Cbz-L(*S*)-Asp α- and β-anilides. Repeated crystn from 95% EtOH affords *N*-Cbz-L(*S*)-Asp β-anilide mp 166–168°. *Anal.* ($C_{18}H_{18}N_2O_5$) C, H, N.

Cbz-L(*S*)-α-amino-*N*-phenylsuccinimide (7a).—The mixture of *N*-Cbz-L(*S*)-Asp α- and β-anilides (**5a** and **6a**, 2.8 g, 8.0×10^{-2} mole) and 20 ml of Ac_2O was heated on steam bath for 1 hr. The Ac_2O and HOAc were removed under reduced pressure and crystallization of the resulting syrup was induced by addition of PhH. Recrystallization from abs EtOH afforded 1.9 g (70%) of crystals: mp 160–162°; nmr (DMSO-*d*, δ), 7.35 (multiplet, 10 H, Ph), 5.10 (singlet, 2 H, CH), 7.97 (doublet, 1 H, NH); $J_{NH-\alpha-CH}$ = 7.00 Hz. The ABX portion of the nmr spectrum[23] (aliceylic protons) is found in Table III. *Anal.* ($C_{18}H_{16}N_2O_4$), C, H, N.

***N*-Boc-L(*S*)-Asp (3b).**—L(*S*)-Asp (**2**, 13.3 g, 0.10 mole) was dissolved in 75 ml of 2 *N* NaOH and added to a soln of 17.7 g (0.12 mole) of *tert*-butyl azidoformate in 25 ml of MeOH. Et_3N (14 ml) in 25 ml of MeOH was added dropwise and stirred at 40° for 2 hr and then at room temp for 15 hr. The soln was taken to pH 7 with 2 *N* HCl and the MeOH was removed under reduced pressure. The acidified aq residue was extd with Et_2O, dried (Na_2SO_4), and concd under reduced pressure. The residue, after shaking with pet ether, afforded 10.6 g (40%) of crystals, mp 124–126°. *Anal.* ($C_9H_{15}O_6N$), C, H, N.

***N*-Boc-L(*S*)-Asp Anhydride (4b).**—*N*-Boc-L(*S*)-Asp (**3b**, 2.15 g, 1.0×10^{-2} mole) was added to 30 ml of Ac_2O and heated on a steam bath for 30 min. The Ac_2O and the HOAc were removed under reduced pressure. The syrupy liquid was crystd upon addition of Skellysolve B affording 1.5 g (64%) of crystals, mp 108–110°. *Anal.* ($C_9H_{13}O_5N$) C, H, N.

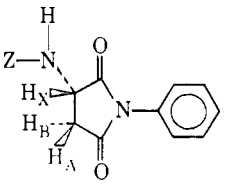
Boc-L(*S*)-Asp α- and β-Anilides (5b and 6b).—*N*-Boc-L(*S*)-Asp anhydride (**4b**, 2.15 g, 1.0×10^{-2} mole) was added to a soln of 1.86 g (2.0×10^{-2} mole) of $PhNH_2$ in 20 ml of abs EtOH. The mixture was stirred at room temp for 15 hr and acidified with 1 *N* HCl. A syrupy material was deposited which crystallized on standing for 24 hr at room temp. The crystals were dissolved in 5% $NaHCO_3$ and the excess $PhNH_2$ was removed by extraction with Et_2O. After being stored at 0° for 24 hr the aq layer was acidified with 1 *N* HCl affording 1.2 g (40%) of a ppt containing **5b** and **6b**, respectively. Recrystallization from 95% EtOH afforded **6b**, mp 148–150°. The purity of the β-anilide was confirmed by ir analysis, by paper chromatography, and by use of ninhydrin reagent.[4,5] *Anal.* ($C_{15}H_{20}N_2O_5$) C, H, N.

***N*-Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (7b).**—The mixture of α- and β-anilides (**5b** and **6b**, respectively, 3.05 g, 1.0×10^{-2} mole) was heated on a steam bath for 1 hr. The Ac_2O

(22) Melting points were taken on a calibrated Thomas-Hoover melting point apparatus. Ir spectra were recorded utilizing a Perkin-Elmer 257 spectrophotometer. ORD spectra were taken utilizing the Durrum-Jasco ORD/CD instrument. Nmr spectra were recorded on a Varian A60A spectrometer. Chemical shifts in DCCl₃ and DMSO-*d* were recorded downfield from internal TMS. Chemical shifts in D_2O were recorded downfield from internal sodium 3-(trimethyl)propylsulfonate. Elemental analyses were performed by Clark Microanalytical Labs, Urbana, Ill.

(23) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 21–25.

TABLE III
ABX CALCULATED SPECTRA[a] FOR SUCCINIMIDE DERIVATIVES



Compd	Z	ppm			Hz			Solvent[b]
		δ_{H_A}	δ_{H_B}	δ_{H_X}	$J_{AB(gem)}$	$J_{AX(cis)}$	$J_{BX(trans)}$	
7a	Cbz	2.91	2.96	4.63	18.00	11.90	5.20	DMSO-*d*
7b	Boc	3.01	3.03	4.33	18.00	9.03	6.97	$DCCl_3$
7c	Ac	2.88	2.95	4.58	18.00	10.67	4.74	DMSO-*d*
9	HCl salt	3.31	3.35	4.78	18.50	9.36	5.14	D_2O[c]
9	Free base	2.83	2.85	3.99	18.00	8.74	5.76	$DCCl_3$

[a] Calcd according to ref 23. [b] The chemical shifts are expressed in parts per million downfield from internal TMS. [c] The chemical shift is expressed in parts per million downfield from internal sodium 3-(trimethylsilyl)propylsulfonate.[22]

and HOAc were removed under reduced pressure. Crystallization of the resulting syrupy liquid was induced by addition of PhH. Recrystallization from EtOH afforded 1.5 g (51%) of crystals: mp 166–168°; nmr ($DCCl_3$, δ), 7.40 (multiplet, 5 H, Ph), 1.45 [singlet, 9 H, $(CH_3)_3C$], 5.61 (doublet, 1 H, CONH, $J_{NH,\alpha-CH}$ = 7.0 Hz). The ABX portion[23] of the nmr spectrum (alicyclic protons) is found in Table III. *Anal.* ($C_{15}H_{18}N_2O_4$) C, H, N.

L(*S*)-α-Amino-*N*-phenylsuccinimide·HCl (9).—*N*-Boc-L(*S*)-α-amino-*N*-phenylsuccinimide (**7b**, 1.45 g, 5.0×10^{-3} mole) was dissolved in a mixture of $HCCl_4$–PhH (3:1). Gaseous HCl was passed through the soln with continuous stirring. After 10 min a white crystalline compd began to ppt. After standing at room temp for 2 hr the crystals were filtered and recrysd from MeOH–EtOH (1:3) affording 6.8 g (75%) crystals: mp 248–250; nmr (D_2O, δ), 7.50 (multiplet, 5 H, Ph). The ABX portion of the nmr spectrum[23] (alicyclic protons) is found in Table III. *Anal.* ($C_{10}H_{11}N_2O_2Cl$) C, H, N, Cl.

The free base **L(*S*)-α-amino-*N*-phenylsuccinimide** was obtained by suspending the HCl salt **9** (1.13 g, 5.0×10^{-3} mole) in $HCCl_3$ (20 ml). The mixture was cooled (ice) and 2% $NaHCO_3$ soln was added dropwise until the soln became clear. The $HCCl_3$ layer was separated and the aq layer was repeatedly extracted with $HCCl_3$. The $HCCl_3$ fractions were combined, dried (Na_2SO_4), and filtered and the solvent was removed under reduced pressure affording 6.5 g (52.2%) of white crystals: mp 124–125°; nmr ($DCCl_3$, δ), 7.32 (multiplet, 5 H, Ph), 1.76 (singlet, 2 H, NH_2). The ABX portion[23] of the nmr spectrum (alicyclic protons) is found in Table III. *Anal.* ($C_{10}H_{10}N_2O_2$) C, H, N.

***N*-Ac-L(*S*)-Asp (3c)** is prepared by the method of Barker[3] from L(*S*)-Asp (**2**) and Ac_2O affording 70% crystals of **3c**, mp 140–141°, lit.[3] mp 139–140°.

***N*-Ac-L(*S*)-Asp anhydride (4c)** is prepared by the method of Kovacs and coworkers[24] from L(*S*)-Asp·HBr and Ac_2O affording 2.80 g (60%) of crystals of **4c**, mp 177–179°, lit.[23] mp 187°.

***N*-Ac-L(*S*)-Asp α- and β-Anilides (5c and 6c).**—*N*-Ac-L(*S*)-aspartic acid anhydride (**4c**, 3.14 g, 2.0×10^{-2} mole) was added to a soln (4.67 g, 1.0×10^{-2} mole) of $PhNH_2$ in 15 ml of abs EtOH. The mixture became warm and gave a clear soln which deposited crystals after 12 hr. The mixture was acidified with 1 *N* HCl, the ppt was sepd by filtration and dissolved in 5% $NaHCO_3$ soln, and the $PhNH_2$ was removed by extraction with Et_2O. The aq soln was acidified after being kept at 0° overnight. The ppt was removed by filtration, washed with H_2O, and dried under reduced pressure at 30°. This afforded a mixture of α- and β-anilides (**5c** and **6c**) of *N*-Ac-L(*S*)-Asp. Repeated recrystn from 95% EtOH afforded 3.1 g (62%) of crystals of *N*-Ac-L(*S*)-Asp β-anilide (**6c**): mp 190–192°, lit.[3] mp for the *dl*-β-anilide 188–190°; ir (KBr, cm^{-1}), 3350 (NH, stretch), 1725 (CO, stretch of the anilide), 1660 (CO, stretch of the acetamide), 1600, 1550, 770, 700 (Ph).

Ac-L(*S*)-α-amino-*N*-phenylsuccinimide (7c).—The mixture of *N*-Ac-L-Asp α- and β-anilides (**5c** and **6c**, 1.0 g, 4.0×10^{-3} mole) were heated at 95° for 1 hr with Ac_2O. The Ac_2O and HOAc were removed under reduced pressure. Crystallization of the resulting syrupy liquid was induced by addition of PhH. This crude imide, 0.55 g (70.5%), mp 160–162°, was recrystd from abs EtOH affording white crystals: mp 163–164°, lit.[3] mp for the *dl*-imide 162–164°; nmr DMSO-*d*, δ) 7.41 (multiplet, 5 H, Ph), 1.90 (singlet, 3 H, CH_3), 8.61 (doublet, 1 H, CONH). $J_{NH-\alpha-CH}$ = 7.00 Hz. The ABX portion of the nmr spectrum[23] (alicyclic protons) is found in Table III. *Anal.* ($C_{12}H_{12}N_2O_3$) C, H, N.

L(*S*)-3-Ethylamino-1-phenylpyrrolidine (11).—To a stirred suspension of LAH (0.66 g, 1.7×10^{-2} mole) in dry Et_2O (75 ml) was added 0.5 g (2.2×10^{-3} mole) of Ac-L(*S*)-α-amino-*N*-phenylsuccinimide (**7c**) suspended in Et_2O (50 ml). After addition the mixture was stirred overnight and the excess LAH decomposed by dropwise addition of ice-cold 10% NaOH. The mixture was filtered and the Et_2O filtrate was washed with H_2O, dried (Na_2SO_4), and concd under reduced pressure affording a yellow oil. The bp was not accurately determined because the compd was prepared on a small scale, approx bp 105–112° (0.025 mm). Yield after distn was 0.26 mg (64%) of a colorless oil (**11**) which turned yellow on prolonged exposure to air; glpc identical with 3-D(*R*)-ethylamino-1-phenylpyrrolidine (**11**); ir (neat, cm^{-1}), 3300 (NH, stretch), 3058 (CH stretch, Ph), 2956 (CH_2, stretch), 1605 (Ph). ORD shows a positive plain curve which is the mirror image of the curve described for D(*R*)-**11**. The nmr spectrum, which can not be analyzed by first-order principles, was in general agreement with the assigned structure. *Anal.* ($C_{12}H_{18}N_2$) C, H, N.

***N*-Ac-D(*R*)-Asp anhydride 5c** was prepared according to the method described for the L(*S*) enantiomorph in 50.5% yield, mp 175–177°. The ORD for the D(*R*) compd was the mirror image of the spectrum for the L(*S*) isomer.

***N*-Ac-D(*R*)-Asp β-anilide (6c)** was prepared according to the method described for the L(*S*) enantiomorph. After repeated crystn from abs EtOH 28.5% crystals, mp 182.5–183.5°, were obtained. The ORD for the D(*R*) compd was the mirror image of the spectrum for the L(*S*) isomer.

Ac-D(*R*)-α-amino-*N*-phenylsuccinimide 7c was prepared from the D(*R*)-α and β-anilide mixture (**5c** and **6c**), according to the method described for the L(*S*) enantiomorph in 61% yield, mp 173.5–174.5°. The ORD for the D(*R*) compd was the mirror image of the spectrum for the L(*S*) isomer.

D(*R*)-3-Ethylamino-1-phenylpyrrolidine (11) was prepared according to the method described for the L(*S*) enantiomorph in 64–65% yield. The boiling point was not accurately determined because the compd was prepared on a small scale: approx bp 105–112° (0.025 mm); glpc on 10% silicone gum rubber (UC-W98) on diaport-S (80–100 mesh), 4 ft × 0.25 inch glass column with column temp 150°, injection port temp 280°, detector temp 265°, inlet pressure of 40 psi and carrier gas (He) rate 60 ml/min showed one peak at 11.6 min; ORD (*c* 0.094, MeOH) (29°) $[\phi]_{370}$ −93.14°, $[\phi]_{340}$ −78.55°, $[\phi]_{318}$ −133.60°. *Anal.* ($C_{12}H_{18}N_2$) C, H, N.

L(*S*)-3-Amino-1-phenylpyrrolidine (1).—To a stirred suspension of LAH (228 mg, 6.0×10^{-3} mole) in Et_2O (50 ml) was gradually added 226 mg (1.0×10^{-3} mole) of L(*S*)-α-amino-*N*-phenylsuccinimide·HCl (**9**) in small portions. The stirring was continued overnight at room temp. The excess LAH was decomposed by dropwise addition of ice-cold 10% NaOH soln.

(24) T. Kovacs, H. N. Kovacs, and R. Ballina, *J. Amer. Chem. Soc.*, **85**, 1839 (1963).

The mixture was filtered and the Et_2O filtrate was washed with H_2O, dried (Na_2SO_4), and concd under reduced pressure: approx bp 90–100° (0.005 mm); yield after distn, 92 mg (56.8%); glpc on 3.8% silicone gum rubber (UC-W98) on chromosorb-W (80–100 mesh), 4 ft × 0.25 in. glass column with column temp 150°, injection port temp 280°, detector temp 260°, inlet pressure of 40 psi and carrier gas (He) rate 60 ml/min showed one peak at 3 min; ir (neat, cm^{-1}), 3344 and 3280 (NH, stretch), 1596 (NH, bending), 1566, 1505, 1483 (Ph); ORD (*c* 0.050, MeOH) (29°) $[\phi]_{380}$ +19.46°, $[\phi]_{350}$ + 29.19°, $[\phi]_{320}$ +48.65°. The nmr spectrum, which could not be analyzed by first-order analysis, was in general agreement with the assigned structure. *Anal.* ($C_{10}H_{14}N_2$) C, H, N.

Biological Aspects.—The acute toxicity of L(*S*)-3-ethylamino-1-phenylpyrrolidine (11) and the D(*R*) enantiomorph was determined in groups of 8 mice (25–30 g) 24 hr after an ip injection of the drugs. The LD_{50} was determined by the method of Litchfield and Wilcoxon.[25]

Rectal temp of mice were measured with a Y-51 Tele-thermometer (Yellow Springs Instrument Co.) equipped with a small animal probe. Temperatures were recorded immediately prior to injection of the test drugs (T'_0) and at 30 and 60 min thereafter (T'_{30} and T'_{60}, respectively).

Antihistaminic and anticholinergic activities *in vitro* were determined utilizing the isolated guinea pig ileum suspended in Kreb's soln at 37 ± 0.5° and bubbled with 95% O_2–5% CO_2. Tissues were allowed to stabilize 30 min after mounting. After 30 min either histamine or acetylcholine were given at 15-min intervals in order to construct a dose–response curve; the agonist was given 15 min before and after administration of the test drugs.

All compds were prepd and dist on the same day of the biological evaluation. Free bases were dissolved in 5 ml of 0.1 *N* HCl. A known aliquot for assay *in vitro* was dissolved in Kreb's bicarbonate soln. For work *in vivo* the HCl soln was further diluted and adjusted to about pH 6.

(25) J. F. Litchfield, Jr. and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

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A Conformational Study of β-Phenethanolamine Receptor Sites. 3. Synthesis of the 3-Isopropylamino-2-phenyl-*trans*-2-decalols

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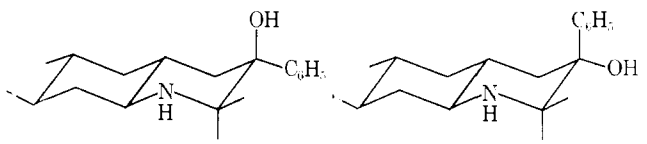
The synthesis of the four possible 3-isopropylamino-2-phenyl-*trans*-2-decalols (**5**–**8**) is described. These four *dl* compounds, *N*-isopropylnorephedrine (**3**), and *N*-isopropylnor-ψ-ephedrine (**4**) were assayed for their ability to potentiate D-(−)-norepinephrine in the contraction of the vas deferens.

In a recent report from these laboratories[1] the synthesis and preliminary testing of the *trans*-perhydroquinolines **1** and **2** were discussed. These compounds were not active as α-adrenergic receptor agonists in the

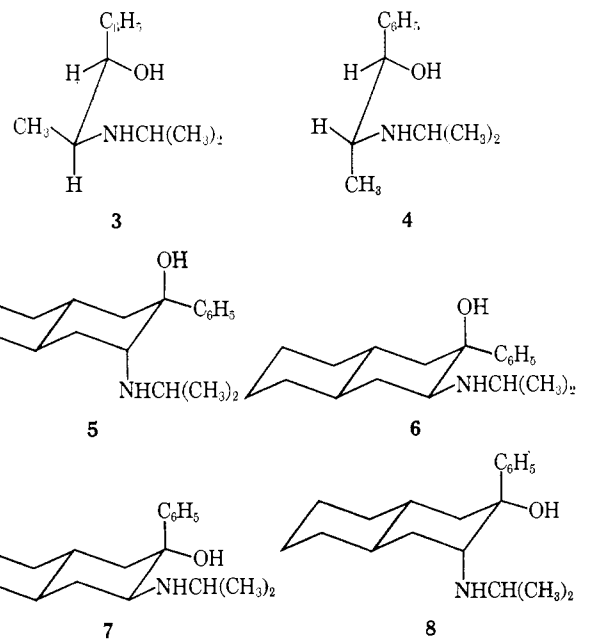


1 **2**

vas deferens assay, however, they potentiated the D-(−)-norepinephrine contraction of the vas deferens markedly. Compound **1** was considerably more effective in this sensitization than **2**, thus indicating a true steric dependency. These substances can be viewed as *N*-isopropyl derivatives of ephedrine-like compounds.

In order to study the possible mechanism and steric requirements of this potentiation it was decided to prepare and test *N*-isopropylnorephedrine(**3**), *N*-isopropylnor-ψ-ephedrine(**4**), and the four *trans*-decalin analogs, **5**, **6**, **7**, and 8.

The synthesis of (±)-*N*-isopropylnorephedrine(**3**) and (±)-*N*-isopropylnor-ψ-ephedrine was reported by Engelhardt and coworkers.[2] After preparing (±)-norpseudoephedrine from commercially available (±)-norephedrine by the method of Müller,[3] the Engelhardt procedure was followed.



3 **4**

5 **6**

7 **8**

The synthesis of the 4 possible *dl* pairs of 3-isopropylamino-2-phenyl-*trans*-2-decalols, **5**, **6**, **7**, and **8**, was accomplished by modifications of the procedures utilized in the preparation of the nor compounds in this

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(1) E. E. Smissman and G. S. Chappell, *J. Med. Chem.*, **12**, 429 (1969).

(2) E. L. Engelhardt, F. S. Crossley, and J. M. Sprague *J. Amer. Chem. Soc.*, **72**, 2718 (1950).

(3) von H. K. Müller, *Justus Liebigs Ann. Chem.*, **599**, 211 (1956).