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.* ($C_{16}H_{14}N_2$) 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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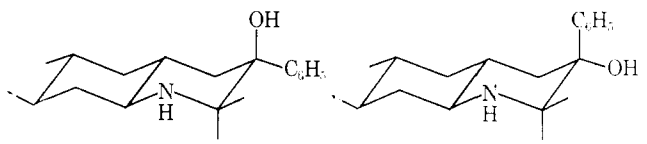
The synthesis of the four possible 3-isopropylamino-2-phenyl-*trans*-2-decalols (**5**–**8**) is described. These four *dl* compounds, *N*-isopropylnorephedrine (**3**), and *N*-isopropylnor-ψ-ephedrine (**4**) were assayed for their ability to potentiate D-(−)-norepinephrine in the contraction of the 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

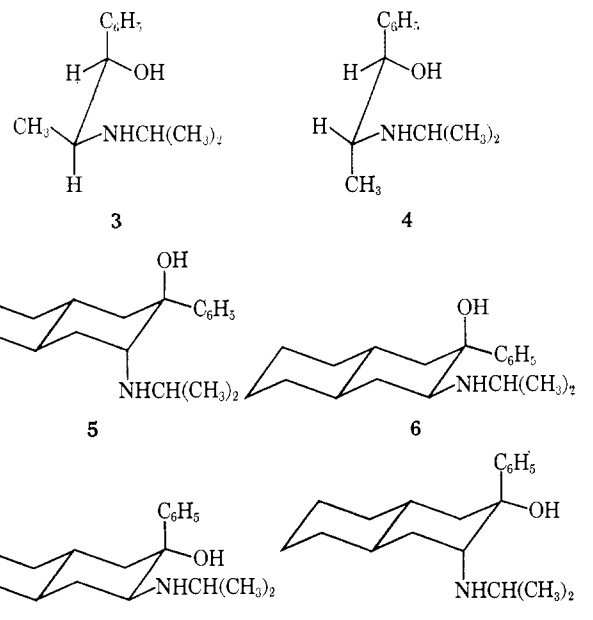


1 **2**

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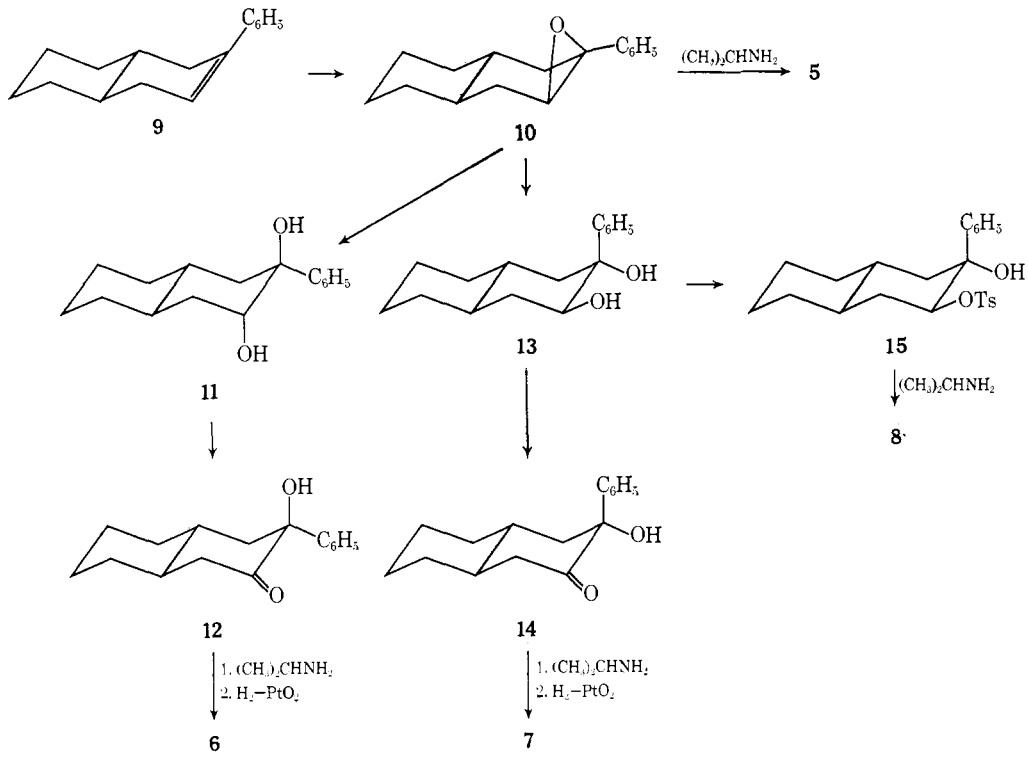
(1) E. E. Smissman and G. S. Chappell, *J. Med. Chem.*, **12**, 429 (1969).

(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).

SCHEME I



series.[4] The reaction scheme is shown in Scheme I utilizing 2-phenyl-Δ^2-*trans*-octalin (**9**) as the principal starting material.

The epoxide **10** was converted into 3(a)-isopropylamino-2(e)-phenyl-*trans*-2(a)-decalol (**5**) by refluxing with *i*-$PrNH_2$ in EtOH. By the previously reported procedures,[4] **10** was opened to give the diols **11** and **13**. The diaxial diol **11** could be oxidized to the ketol, **12**, which was then refluxed in the presence of excess *i*-$PrNH_2$ in C_6H_6. The resulting oily product was reduced to produce 3(e)-isopropylamino-2(e)-phenyl-*trans*-2(a)-decalol (**6**).

The diol **13** could be carried through the same sequence of reactions to give 3(e)-isopropylamino-2(a)-phenyl-*trans*-2(e)-decalol (**7**).

The fourth decalin analog, **8**, was prepared from the diol **13** by converting it into the monotosylate, **15**. When refluxed with an EtOH soln of *i*-$PrNH_2$, the desired compound was obtained.

Biological Data.—Neither the *dl*-erythro compound, **3**, nor the *dl*-threo compound **4** at 10^{-4} *M* showed any effect on the normal or reserpinized rat vas deferens. The pD_2 of D-(−)-norepinephrine (NE) was increased slightly by both **3** and **4** (6.4 to 6.6) at 10^{-4} *M*. At this concentration maximal response was increased by 50%. When the concentration was increased to 10^{-3} *M*, the pD_2 was lowered from 6.4 to 6.1 but the increased maximal response of the vas deferens was still observed. Similar effects were observed on guinea pig seminal vesicles. Spontaneous movement of rabbit jejunum was inhibited at 10^{-4} *M*. The effect of D-(−)-norepinephrine on rabbit aortic strip was blocked at 10^{-4} *M*. A short-lasting (1 min) fall of blood pressure in both the dog and rat was observed after the administration of 20 mg/kg with both agents. The erythro compound, **3**, gave a 30-mm decrease while the threo compound **4**, was more effective. Phenoxybenzamine increased the effect. The fall of blood pressure was partially antagonized by β-blocking agent. The decalin analog **6** showed very strong potentiation of NE on the vas deferens of the rat and the guinea pig and the seminal vesicles of the guinea pig. The pD_2 of NE was raised from 6.4 to 7.4 and the maximal response increased by 30% at 10^{-4} *M*. At this concentration, there is essentially no agonist response from **6**. At 10^{-3} *M*, **6** blocks high doses of NE while still potentiating the lower doses.

The effect of NE on rabbit aortic strip was blocked by **6** at 10^{-4} *M* and the spontaneous movement of the rabbit jejunum was inhibited at 10^{-5} *M*. A dose of 20 mg/kg caused a fall (−40 mm) in the blood pressure of the dog and the rat (short lasting). Phenoxybenzamine increased the effect.

Compound **5** was similar in all effects to **6** but somewhat less effective; the pD_2 of NE on rat vas deferens increased from 6.4 to 7.0 the maximal response increased by 25%.

Compound **7** was similar to **6** qualitatively but was much less effective. There was no potentiation of NE response on the rat vas deferens although the maximal response was increased by 25%. Compound **8** was far less effective on all parameters reported for the preceding compounds. More complete pharmacology on the racemic and optically active will be reported in the future.

No definite conclusions can be offered at this time, however, it is interesting to note that all of the compounds tested except **8** can have the phenyl ring gauche to the amino function. In **8** they are staggered. This compound had very little activity.

(4) E. E. Smissman and W. H. Gastrock, *J. Med. Chem.*, **11**, 860 (1968).

Experimental Section[5]

2-Phenyl-*trans*-decalin 2,3-Oxide (10).—This compound was prepared by the method of Smissman and Gastrock[4] from 2-phenyl-Δ^2-*trans*-octalin (**9**) in 56% yield.

3(a)-Isopropylamino-2(e)-phenyl-*trans*-2(a)-decalol·HCl (5).—To a soln of 2(e)-phenyl-*trans*-decalin 2,3-oxide (**10**) (8.0 g, 0.024 mole) in 150 ml of abs EtOH was added 55 ml of *i*-$PrNH_2$. The mixture was refluxed for 9 days after which an additional 15 ml of *i*-$PrNH_2$ was added and reflux continued for an additional 8 days. Excess amine and EtOH were removed and the residue was treated with 10% HCl and filtered. The acid extract was washed with Et_2O, made alkaline with aq KOH, and extracted with Et_2O. The extract was washed with H_2O, dried (Na_2SO_4), and filtered and the solvent removed. The residue was dissolved in EtOH and treated with ethereal HCl. The HCl salt was filtered, washed (Et_2O), and recrystd (EtOH–Et_2O) to give the desired product (2.75 g, 25%) mp 227–229° dec. The ir and nmr were consistent with the structure. The nmr (CF_3COOH) δ 3.82 ($W_{1/2}$ = 6 Hz) indicated an equatorial methine proton at C-3. *Anal.* ($C_{19}H_{30}ClNO$) C, H, N.

3(e)-Isopropylamino-2(e)-phenyl-*trans*-2(a)-decalol·HCl (6).—A soln of 3(a)-hydroxy-3(e)-phenyl-*trans*-2-decalone, (**12**) (1.95 g, 0.008 mole) in 100 ml of C_6H_6 and 20 ml of *i*-$PrNH_2$ was refluxed for 48 hr. The solvent was removed and the residue was dissolved in 40 ml of abs EtOH and hydrogenated (PtO_2) at atmospheric pressure (25°) for 24 hr. The catalyst and solvent were removed to give an oily residue which was treated with ethereal HCl. The salt was filtered, washed (Et_2O), and recrystd (Me_2CO–Et_2O) to give 1.4 g (56%) of **6**, mp 227–228° dec. Ir was consistent with functional groups expected; nmr (CF_3COOH) δ 3.8 ($W_{1/2}$ = 12 Hz, axial C-3-C-H). *Anal.* ($C_{19}H_{30}ClNO$) C, H, N.

3(a)-Isopropylamine-2(a)-phenyl-*trans*-2(e)-decalol·HCl (8).—To a soln of 2(a)-phenyl-*trans*-decalin-2(e),3(e)-diol 3-tosylate (5.0 g, 0.012 mole) in 100 ml of abs EtOH was added 55 ml of *i*-$PrNH_2$ and the mixture was refluxed for 9 days after which an additional 20 ml of *i*-$PrNH_2$ was added and the soln refluxed an additional 8 days. Solvent and excess amine were removed and residue was dissolved in pet ether (bp 60–68°) and filtered. The filtrate was taken to dryness to give an oil which was then dissolved in Me_2CO and treated with ethereal HCl. The salt was filtered, washed (Et_2O), and recrystd (Me_2CO–Et_2O) to give 1.95 g (44%) of **8**, mp 282–285° dec; nmr (CF_3COOH) δ 5.0 ($W_{1/2}$ = 3, equatorial C—3C**H**). *Anal.* ($C_{19}H_{30}ClNO$) C, H, N.

3(a)-Hydroxy-3(e)-phenyl-*trans*-2-decalone (12).—The procedure used was essentially that of Borchardt.[6] A mixture of 2(e)-phenyl-*trans*-decalin-2(a),3(a)-diol (**11**) (39.0 g, 0.158 mole) in 660 ml of Me_2CO and *N*-bromoacetamide (NBA) (33.0 g, 0.24 mole) in 330 ml of H_2O was stirred at 25° for 6 hr. The crude product was crystd [$CHCl_3$–pet ether (bp 60–68°)] to yield 31.0 g (81%) of **12**, mp 167–168°.

3(e)-Hydroxy-3(a)-phenyl-*trans*-2-decalone (14).—The method used was that of Borchardt.[6] To a stirred soln of 2(a)-phenyl-*trans*-decalin-2(e),3(e)-diol (**13**) (12.0 g, 0.05 mole) in a mixture of 200 ml of Me_2CO and 50 ml of H_2O was added NBA (14.0 g, 0.09 mole) in 120 ml of H_2O. The crude oil which was obtained was purified by chromatography on silica gel to give 11.0 g (87%) of the desired ketone **14** as an oil.

2(a)-Phenyl-*trans*-decalin-2(e),3(e)-diol 3-Tosylate (15).—To a soln of the diol **13** (1.05 g, 0.004 mole) in 20 ml of anhyd pyridine was added 2 g of *p*-TsCl and the soln was allowed to stand at 25° for 48 hr. On the addition of H_2O an oil separated and was extd with Et_2O. The extract was washed with 200 ml of 15% HCl and H_2O and dried (Na_2SO_4). The solvent was removed *in vacuo* to give a pale yellow oil which crystd from pet ether (bp 60–68°) to yield 1.2 g (85.7%), mp 101–103°. This compound was identical with that obtained previously,[4] however, this procedure gave greatly improved yield.

3(e)-Isopropylamino-2(a)-phenyl-*trans*-2(e)-decalol·HCl (7).—This compound was synthesized essentially by the same method utilized for **6**. The keto alcohol, **14**, (1.95 g, 0.008 mole) was treated with *i*-$PrNH_2$ and reduced. The hydrochloride **7** (1 g, 40%) had mp 253–254° dec, nmr (CF_3COOH) δ 3.85 ($W_{1/2}$ = 12 Hz, axial C-3 CH). *Anal.* ($C_{19}H_{30}ClNO$), C, H, N.

(±)-*N*-**Isopropylnorephedrine·HCl (3).**—The procedure was essentially that of Engelhardt, *et al.*[2] A soln of 5.02 g (0.033 mole) of norephedrine in 40 ml of EtOH and 12.3 ml of Me_2CO was reduced (PtO_2) at atmospheric pressures for 17 hr. The desired compound was obtained (6.5 g, 85.5%), mp 191–193°.

(±)-**Pseudonorephedrine·HCl.**—The procedure was essentially that of Müller.[3] To a soln of (±)-norephedrine·HCl (19.0 g, 0.1 mole) in 100 of H_2O and 20 ml of Ac_2O at 0° was added an excess of $NaHCO_3$ followed by 350 ml of H_2O. The $NaHCO_3$ was neutralized with AcOH and the soln heated to boiling. The (±)-*N*-acetylnorephedrine (17 g, 88%) was filtered and air-dried. This compound (12 g, 0.062 mole) was added to 25 ml of cold $SOCl_2$ and allowed to stand at 25° for 30 min. An excess of 20% Na_2CO_3 soln was added, followed by 5 ml of H_2O and the mixture was extracted with Et_2O. The extract was washed with H_2O, dried (Na_2SO_4), and filtered and the solvent removed to give a yellow liquid which was refluxed for 30 min with 50 ml of HCl (18%). The soln was cooled and the residue recrystd (EtOH–Et_2O) to yield 9.5 g (81.8%) of the product, mp 168–169°.

(±)-*N*-**Isopropylnorpseduoephedrine·HCl (4).**—(±)-Norpseudoephedrine·HCl was treated with excess cooled KOH and the free base extd with Et_2O. The procedure of Engelhardt, *et al.*,[2] was followed as for **3**, using 5.02 g (0.033 mole) of the free base to give the desired product, mp 187–188° (6.5 g, 85.5%). Admixture with pseudonorephedrine·HCl or with *N*-isopropylnorephedrine·HCl markedly lowered the melting point.

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(5) Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Ir data were recorded on Beckmann IR8 and IR10 spectrophotometers. Nmr data were recorded on Varian Associates Model A-60 and A-60A, spectrophotometers (TMS) and are reported as ppm (δ). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F and M Model 185, University of Kansas, Lawrence, Kan.

(6) R. F. Borchardt, Ph.D. Thesis, April 1970, University of Kansas, Lawrence, Kan.