Reversal of reserpine effects of compounds **1**, **8**, and **9** were tested. Reserpine (25 mg/kg) was injected subcutaneously to groups of mice (five per group); 3 hr later the compounds were injected intraperitoneally in doses of 10, 20, and 30 mg/kg. Controls were injected with DL-amphetamine (20 mg/kg ip) which caused complete reserpine reversal, *i.e.*, arousal from sedated state and cessation of ptosis. This reversal lasted for at least 3 hr and after that period the animals again returned to the sedated state. Compound **9** (20 mg/kg) showed a very slight, delayed, and short-lasting reserpine reversal.

Antagonistic action to pressor activity of epinephrine was tested as follows. Epinephrine (1–2 μg/kg) was administered to cats (2.5–3.5 kg) and when the blood pressure returned to control level the test substance was administered. Five minutes later epinephrine was injected and the effects were compared.

Gross behavioral changes were conducted on mice. Substances were administered intraperitoneally into groups of five animals for each dose level and changes were noted. Observations were made for not more than 24 hr after injection.

**Antibacterial Tests.**—Compound **1** was tested for antibacterial activity on the following bacteria and fungi: *Staphylococcus aureus* 209P (Oxford), *S. aureus* 183, *Bacillus cereus*, *B. cereus I*, *Escherichia coli* W, *E. coli* WI, *E.* $O_{111}B_4H_{12}$, *E. coli* $O_{119}B_2H_6$, *Salmonella typhimurium*, *Shigella flexneri* 4b 5412, *Candida albicans*, and *Cryptococcus neoformans* A. The bacteria and the fungi ($1 \times 10^4$ and $1 \times 10^6$) were added in drops (0.02 ml) to Petri dishes containing the growth media, composed of Agar 3 (containing peptone, yeast extract, beef extract, dextrose, and buffer pH 7) or Saboraud agar and 0.4% yeast extract. Control experiments were carried out wherein the bacteria or the fungi were grown in the absence of the compound investigated. Phenethylamine hydrochloride did not inhibit growth at concentrations of 1000 μg/ml, while **1** inhibited growth of the above bacteria at 500 μg/ml, of *C. neoformans* A at 1000 μg/ml, and of *C. albicans* at 500 μg/ml ($10^4$) and 1000 μg/ml ($10^6$).

Compound **10** was tested for antibacterial activity in the above growth media and on addition of 50% human or sheep blood to the growth media. The results are summarized in Table IV. It is seen that **10** inhibited most of the bacteria tested at a concentration of 100 μg/ml, but in the presence of blood the activity was lower. Compound **10** did not inhibit the growth of *C. albicans* and *C. neoformans* A at concentrations of 100 or 200 μg/ml.

TABLE IV
ANTIBACTERIAL ACTIVITY[a] OF *p*-TRIMETHYLSILYLMETHYLPHENETHYLAMINE HYDROCHLORIDE (**10**)

| Type of bacteria or fungi | Concn of compd,[b] μg/ml | Inhib of growth Concn of bacteria $10^4$ | Inhib of growth Concn of bacteria $10^6$ | Inhib in presence of 50% human blood[c] Concn of bacteria $10^4$ | Inhib in presence of 50% human blood[c] Concn of bacteria $10^6$ |
|---|---|---|---|---|---|
| *S. aureus* 209P (Oxford) | 100 | + − | + + | + + | − |
| | 200 | + − | + + | + + | + + |
| *S. aureus* 183 | 100 | − | − | − | − |
| | 200 | + + | + + | + + | + |
| *B. cereus* | 100 | + + | + + | − | − |
| | 200 | + + | + + | + | − |
| *B. cereus* (streptomycin resistant) | 100 | − | − | | − |
| | 200 | | + + | | − |
| *E. coli* $O_{111}B_4H_{12}$ | 100 | + + | + + | − | − |
| | 200 | + + | + + | + + | + + |
| *E. coli* $O_{119}B_4H_{12}$ | 100 | + + | + + | − | − |
| | 200 | + + | + + | + + | + + |
| *S. typhimurium* | 100 | − + | + − | − | − |
| | 200 | − + | + + | − | − |
| *Shigella flexneri* 4b 5412 | 100 | + + | + + | − | − |
| | 200 | + + | + + | + + | + + |
| *Candida albicans* | 100 | − | − | − | − |
| | 200 | + | − | − | − |
| *Cr. neoformans* "A" | 1000 | − | − | − | − |
| | 200 | − | − | + | − |

[a] ++, complete inhibition; +, partial inhibition; −, no inhibition. [b] No inhibition was observed at a concentration of 50 μg/ml. [c] With *C. albicans* and *Cr. neoformans* "A" 50% sheep blood was used.

**Acknowledgment.**—We wish to thank Dr. H. Edery and Dr. Y. Grunfeld of the Israel Institute for Biological Research, Ness-Ziona, and the Pharmacological Institute of the National Council for Research and Development for carrying out the pharmacological tests. Likewise, our thanks are due to Dr. M. Aharonson and his staff at the Israel Institute for Biological Research, Ness-Ziona, for carrying out the bacteriological tests. This research was partly supported by "Yissum" Research Development Co.

# A Conformational Study of β-Phenethanolamine Receptor Sites. I. The Syntheses of the 3-Amino-2-phenyl-*trans*-2-decalols[1]

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The synthesis of the four possible 3-amino-2-phenyl-*trans*-2-decalols (**1**–**4**) is described. The results of adrenergic α-receptor site stimulation are recorded.

In any biologically active agent which possesses more than one type of action or which is metabolized by more than one pathway, the possibility exists that the approach and binding to a receptor site will require or favor a specific conformation for each effector site, metabolic site, transport, etc. The first attempt to illustrate this postulate involved the use of analogs of acetylcholine in the decalin system and was successful.[3] The application of a similar system to the β-phenethanolamines involves somewhat more complex chemistry but a similar approach.

LaPidus and coworkers[4] have demonstrated that a steric relationship exists among the enantiomorphs of ephedrine and ψ-ephedrine with regard to agonist and

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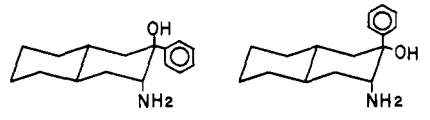
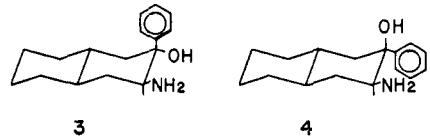
(2) Taken in part from the dissertation presented by W. H. Gastrock, Feb 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(3) E. E. Smissman, W. L. Nelson, J. B. LaPidus, and J. L. Day, *J. Med. Chem.*, **9**, 458 (1966).

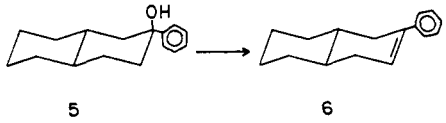
(4) J. B. LaPidus, A. Tye, P. Pail, and B. A. Modi, *ibid.*, **6**, 76 (1963).

antagonist action. Their observations have been made on nonrigid systems and thus no conclusions can be reached concerning conformational preference. It was the goal of the initial work in these laboratories to prepare rigid analogs of ephedrine and ψ-ephedrine which have fixed conformations. Compounds **1** and **3** represent two conformers of *erythro* configuration and compounds **2** and **4** represent conformers of *threo* configuration.

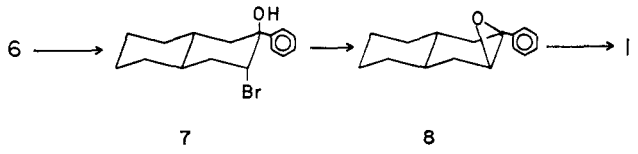



The synthesis of the four conformationally rigid systems **1**, **2**, **3**, and **4** involved the use of the common intermediate 2-phenyl-$\Delta^2$-*trans*-octalin (**6**). The latter was prepared from commercially available *trans*-2-decalol which was oxidized to *trans*-2-decalone. This ketone could be converted to the carbinol **5** by treatment with either phenylmagnesium bromide or phenyllithium and then to the desired **6** by dehydration (eq 1).



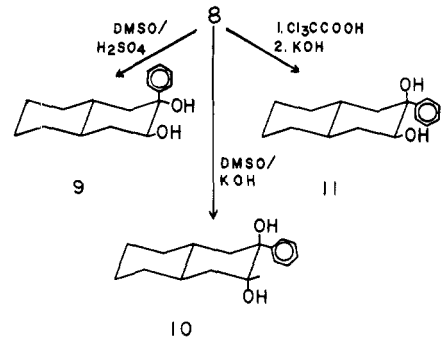

Compound **1**, 3(a)-amino-2(e)-phenyl-*trans*-2(a)-decalol, was prepared by the conversion of the olefin **6** to 2(e)-phenyl-*trans*-decalin 2,3-oxide (**8**) by treatment with *m*-chloroperbenzoic acid or in better yields by initial treatment with N-bromosuccinimide in aqueous dioxane to form the bromohydrin **7** which could be converted to the epoxide by treatment with sodium carbonate (eq 2). The epoxide **8**, on treatment with




liquid ammonia under pressure, afforded the desired **1**. The nmr spectrum of **1** showed a multiplet at δ 3.10 ($W_{1/2}$ = 6 cps), which is consistent with an equatorial methine proton at C-3 coupling with two methylene protons at C-4 ($J_{ae} = J_{ee}$ = 2–4 cps).

An alternate pathway to **1** involved the procedure of Bordwell and Garbisch.[5] The olefin **6** was treated with acetic anhydride and 70% nitric acid to yield 3(a)-nitro-2(e)-phenyl-*trans*-2(a)-decalol acetate along with an olefinic nitro material. The former compound could be hydrolyzed and reduced to the desired **1**; however, this procedure was inferior to the epoxide opening method.

The epoxide **8**, under conditions similar to those utilized by Berti, Macchia, and Macchia,[6] could be made to yield 2(a)-phenyl-*trans*-decalin-2(e),3(e)-diol (**9**), 2(e)-phenyl-*trans*-decalin-2(a),3(a)-diol (**10**), or 2(e)-phenyl-*trans*-decalin-2(a),3(e)-diol (**11**) (eq 3).

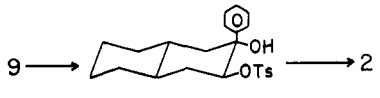



The nmr spectrum of **9** showed methine absorption at δ 3.75 (quartet, $J_{aa}$ = 11 cps, $J_{ae}$ = 5 cps). The coupling constants correspond to one axial–axial coupling (10–12 cps) and one axial–equatorial coupling (2–4 cps) showing that the methine proton is axial. An interesting pattern was observed in the nmr spectrum of **9** in the aromatic region. It was found that the aromatic protons were separated into two multiplets at δ 7.75 and 7.35; the downfield signal integrated for two protons and the upfield signal integrated for three protons. This type of aromatic absorption had not been observed in any of the previously mentioned compounds, which either exhibited a broad singlet or a multiplet. There is obviously a deshielding effect on the *ortho* protons of the axial aromatic ring.

The nmr spectrum of **10** showed methine proton absorption at δ 3.68. The peak half-width (7 cps) indicated that the proton at C-3 was equatorial, the peak resulting from one axial–equatorial interaction (2–4 cps) and one equatorial–equatorial interaction (2–4 cps).

The nmr spectrum of **11** showed methine proton absorption at δ 3.99 ($W_{1/2}$ = 19 cps). The peak half-width corresponds to one axial–axial coupling (10–12 cps) and one axial–equatorial coupling (2–4 cps) indicating the methine proton to be axial. The aromatic protons appear as a multiplet at δ 7.40.

The second conformational analog, 3(a)-amino-2(a)-phenyl-*trans*-2(e)-decalol (**2**), was prepared from 2(a)-phenyl-*trans*-decalin-2(e),3(e)-diol 3-tosylate (**12**) by allowing this compound to react with ammonia under pressure. The tosylate **12** was prepared from the diol **9** by treatment with *p*-toluenesulfonyl chloride (eq 4).

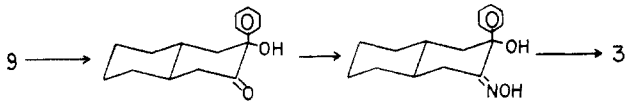



The nmr spectrum exhibited methine absorption at δ 3.83 ($W_{1/2}$ = 6 cps). The peak half-width is consistent with one equatorial–equatorial coupling (2–4 cps) and one axial–equatorial coupling (2–4 cps), indicating that the methine proton at C-3 is equatorial.

(5) F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, **28**, 1765 (1963).

(6) G. Berti, B. Macchia, and F. Macchia, *Tetrahedron Letters*, 3421 (1965).

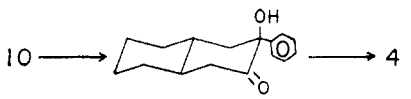
3(e)-Amino-2(a)-phenyl-*trans*-2(e)-decalol (**3**) was obtained by the oxidation of the diol **9** to 3(e)-hydroxy-3(a)-phenyl-*trans*-2-decalone **13**, conversion to the oxime **14**, and catalytic reduction (eq 5). This reduction was




13 14

stereoselective and no axial amino function was detected. The nmr spectrum exhibited methine absorption at $\delta$ 3.00 ($W_{1/2}$ = 19 cps) and two multiplets for the aromatic protons at $\delta$ 7.70 and 7.34. The peak half-width corresponds to one axial-axial coupling (10–12 cps) and one axial-equatorial coupling (2–4 cps), indicating that the methine proton at C-3 is axial. The aromatic absorption is the same as that observed for the *trans* diequatorial glycol (**9**), therefore the equatorial hydroxyl or amine grouping at C-3 has a deshielding effect on the *ortho* protons of the axial phenyl group.

Compound **4**, 3(e)-amino-2(e)-phenyl-*trans*-2(a)-decalol, was prepared by the oxidation of the diol **10** to 3(a)-hydroxy-3(e)-phenyl-*trans*-2-decalone (**15**) and catalytic reduction in the presence of ammonia (eq 6).

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Attempts to prepare a crystalline oxime of the ketone **15** failed; however, the above reduction gave only the equatorial amino function. In the nmr spectrum of **4** there was no visible absorption for the methine proton at C-3, therefore it was apparently obscured by ring absorption ($\delta$ 1.0–2.0). The methine proton was observed to shift when trifluoroacetic acid was added, the methine proton appearing at $\delta$ 3.55 ($W_{1/2}$ = 10 cps). The position of the methine proton could not be assigned solely on the basis of the peak half-width, but comparison with the three other isomeric amino alcohols (**1**, **2**, **3**) indicates the structure of the product to be **4**.

The four compounds **1**–**4** were submitted for testing in the vas deferens preparation reported by Patil, LaPidus, and Tye.[7] With all of the *dl* pairs at concentrations of $3 \times 10^{-4}$ and $1 \times 10^{-4}$ *M* the response was equivalent to norepinephrine in concentrations of $3 \times 10^{-6}$ and $1 \times 10^{-6}$ *M*. This can be assumed to be due to a mixture of both direct and indirect action with the compounds acting in a nonspecific manner to release norepinephrine.

These results will be examined further by resolving compounds **1**–**4** into their optical antipodes and by utilizing the resolved materials and the *dl* isomers in a reserpinized vas deferens preparation.[8]

## Experimental Section[9]

***trans*-2-Decalone.**—Commercially available *trans*-2-decalol (Koch-Light, England) (100 g, 0.65 mole) was recrystallized from petroleum (bp 60–70°); the solid was filtered and washed with cold petroleum ether (60–70°) affording pure *trans*-2-decalol in 70% yield, mp 73–75° (lit.[10] mp 75°). *trans*-2-Decalol (81.0 g, 0.53 mole) was oxidized according to the procedure of Nelson[11] utilizing Jones reagent to yield 77 g (95%) of *trans*-2-decalone; oxime mp 75–76° (lit.[12] mp 76°).

**2-Phenyl-$\Delta^2$-*trans*-octalin (6). a. Grignard Method.**—Using the procedure of Szmuszkovicz,[13] *trans*-2-decalone (65.0 g, 0.425 mole) was treated with PhMgBr, formed from Mg turnings (12.0 g, 0.49 g-atom) and $C_6H_5Br$ (71.5 g, 0.47 mole) in dry $Et_2O$. The semisolid residue, obtained following the work-up, was dissolved in 300 ml of toluene, and 40 g of $KHSO_4$ was added. The mixture was heated at reflux for 12 hr, using a Dean–Stark trap to collect $H_2O$. The $KHSO_4$ was removed by filtration and the solvent was evaporated at reduced pressure. The residue was recrystallized from MeOH–$CHCl_3$ affording 57 g (63%) of **6**: mp 57–59°; nmr ($CCl_4$), $\delta$ 7.21 (broad singlet, aromatic), 5.97 ($W_{1/2}$ = 10 cps, vinyl proton).

**b. Phenyllithium Method.**—To lump Li (10.7 g, 1.54 g-atoms), cut in small pieces, in 400 ml of dry $Et_2O$ was added $C_6H_5Br$ (121 g, 0.77 mole) dropwise at such a rate as to maintain reflux. The mixture was stirred for 4 hr after addition was complete and to the stirred solution *trans*-2-decalone (107 g, 0.7 mole) was added dropwise. The mixture was stirred for 12 hr at room temperature. $H_2O$ was added and the mixture was extracted with $Et_2O$. The organic phase was washed (5% HCl, $H_2O$, saturated NaCl) and dried ($MgSO_4$). The dessicant was removed by filtration and the solvent was evaporated at reduced pressure. The residue was dissolved in 400 ml of toluene and 1 g of *p*-toluenesulfonic acid was added. The solution was heated at reflux, using a Dean–Stark trap to collect the $H_2O$. The toluene solution was washed ($H_2O$) and the solvent was removed at reduced pressure. The residue was recrystallized from MeOH–$CHCl_3$ affording 70 g (47%) of **6**, mp 56–58°.

Concentration of the mother liquor yielded an oil which exhibited nmr absorption at $\delta$ 5.97 ($W_{1/2}$ = 10 cps) and 5.78 ($W_{1/2}$ = 4 cps). The oil was apparently a mixture of $\Delta^1$- and $\Delta^2$-octalins which could not be separated by chromatography or distillation.

**2(e)-Phenyl-*trans*-decalin 2,3-Oxide (8). a. *m*-Chloroperbenzoic Acid.**—To (**6**) (11.0 g, 0.052 mole) in 100 ml of $CHCl_3$, cooled to 0°, was added 80% *m*-chloroperbenzoic acid (11.2 g, 0.052 mole) dissolved in 150 ml of $CHCl_3$. The reaction was maintained at 0–5° during the addition and was stirred for 12 hr at room temperature. Upon cooling the *m*-chlorobenzoic acid precipitated and was removed by filtration. The filtrate was washed (5% $NaHCO_3$, NaI solution, $Na_2SO_3$ solution, $H_2O$, and saturated NaCl). The organic phase was dried ($MgSO_4$). Evaporation of the solvent at reduced pressure gave a semisolid, which was recrystallized from petroleum ether (28–30°) affording 2.57 g (22%) of epoxide **8**: mp 98–100°; ir ($CHCl_3$), 3.34, 3.42, 3.51, 6.24, 6.70, 6.93, 10.24, 11.55, 11.95, 12.10, 14.48 $\mu$; nmr ($CCl_4$), $\delta$ 7.19 (singlet, aromatic) 2.90 (doublet, $J$ = 5 cps, methine proton at C-3). *Anal.* ($C_{16}H_{20}O$) C, H.

Chromatography of the filtrate on silica gel (Merck 0.05–0.20 mm), eluting with cyclohexane–EtOAc (10:1), afforded an additional 4.6 g (39%) of **8** and two oils which have been tentatively identified as 2(e)-phenyl-*trans*-decalin-2(a),3(a)-diol 3-*m*-chlorobenzoate and 2(e)-phenyl-*trans*-decalin-2(a),3(a)-2-ethyl ether.

**b. From Bromohydrin.**—To **6** (25.8 g, 0.122 mole) in 75 ml of dioxane was added a solution of $H_2SO_4$ (13.7 g, 0.14 mole) in 15 ml of $H_2O$ and the mixture was cooled below 20°. N-Bromosuccinimide (23.2 g, 0.13 mole) was added while stirring at 20° and the mixture was stirred 12 hr at room temperature. $H_2O$ was added and the mixture was extracted with several portions of $Et_2O$. The organic phase was washed ($H_2O$) until neutral and

(7) P. N. Patil, J. B. LaPidus, and A. Tye, *J. Pharmacol. Exptl. Therap.*, **155**, 1 (1967).

(8) P. N. Patil, J. B. LaPidus, D. Cambell, and A. Tye, *ibid.*, **155**, 13 (1967).

(9) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR8 spectrophotometer, and nmr data on a Varian Associates Model A-60 spectrophotometer (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(10) W. G. Dauben, R. C. Ewen, and C. Mannerskawtz, *J. Am. Chem. Soc.*, **76**, 4422 (1954).

(11) W. L. Nelson, Ph.D. Thesis, University of Kansas, 1965.

(12) W. Hückel, *Ann.*, **441**, 1 (1925).

(13) J. Szmuszkovicz and E. J. Modest, *J. Am. Chem. Soc.*, **72**, 566 (1950).

dried ($MgSO_4$). The $Et_2O$ was evaporated at reduced pressure to yield 38 g of crude bromohydrin; nmr ($CCl_4$), δ 4.24 ($W_{1/2}$ = 6 cps, equatorial methine proton at C-3). The crude bromohydrin was dissolved in 250 ml of MeOH and a solution of 38 g of $Na_2CO_3$ in 250 ml of $H_2O$ was added and the mixture was heated at reflux for 14 hr. The MeOH was evaporated and the resulting solid was removed by filtration and recrystallized from MeOH affording 15.6 g (56%) of (**8**), mp 99–101°.

**3(a)-Amino-2(e)-phenyl-*trans*-2(a)-decalol (1).**—Compound **8** (5.0 g, 0.02 mole) was placed in a steel bomb cooled in Dry Ice–$Me_2CO$ and *ca.* 100 ml of liquid $NH_3$ was added. The bomb was sealed and heated at 180° for 8 hr. After cooling to room temperature, the pressure was released and the bomb was opened. The residue was dissolved in $CHCl_3$ and this solution was filtered to remove solid impurities. The solvent was evaporated and the resulting solid was recrystallized from petroleum ether (60–70°) affording 3 g (60%) of **1**: mp 148–149°; ir ($CHCl_3$), 2.77, 2.96 (w), 3.41, 3.50, 6.25, 6.35, 6.70, 6.91, 10.00, 14.40 μ (w); nmr ($CDCl_3$), δ 7.37 (multiplet, aromatic protons), 3.10 ($W_{1/2}$ = 6 cps, equatorial methine proton at C-3). *Anal.* ($C_{16}H_{23}NO$) C, H, N.

**3(a)-Nitro-2(e)-phenyl-*trans*-2(a)-decealol Acetate.**—The procedure of Bordwell and Garbisch[5] was followed. To 35 ml of $Ac_2O$ at room temperature was added 70% $HNO_3$ (5.2 g, 0.058 mole) and the mixture was stirred for 15 min. The mixture was cooled to −10° in an ice–salt bath and **6** (6.3 g, 0.029 mole) in 20 ml of $Ac_2O$ and 10 ml of $Et_2O$ was added, maintaining the temperature 0°. The reaction was stirred for an additional 30 min at −10° and poured into $H_2O$. The aqueous solution was extracted with $Et_2O$ and the $Et_2O$ extracts were washed (5% $NaHCO_3$ solution, $H_2O$, and saturated NaCl). Drying ($MgSO_4$) and removal of the $Et_2O$ afforded a brown oil. Chromatography on silica gel (Merck 0.05–0.20 mm) afforded an oil and a solid. The oil exhibited ir absorption at 3.30, 3.42, 3.50, 6.10, 6.25, 6.52, 6.91, 7.41 μ and is most likely olefinic nitro material. The solid was recrystallized from MeOH affording 0.5 g (6.0%) of the desired product: mp 147–148°; ir ($CHCl_3$), 3.30, 3.42, 3.50, 5.73, 6.48, 6.70, 6.91, 7.33, 8.3, 9.69, 9.9, 10.08, 11.35 μ; nmr ($CHCl_3$), δ 7.34 (singlet, aromatic protons), 5.08 ($W_{1/2}$ = 7 cps, equatorial methine proton at C-3), 2.00 (singlet, $CH_3COO$). *Anal.* ($C_{18}H_{23}NO_4$) C, H, N.

**2(a)-Phenyl-*trans*-decalin-2(e),3(e)-diol (9).**—The procedure used is similar to that of Berti and coworkers.[6] To 400 ml of 75% aqueous DMSO was added 10 ml of concentrated $H_2SO_4$ and **8** (10.0 g, 0.044 mole). The mixture was stirred 16 hr at room temperature. Excess $H_2O$ was added and the resulting solid was removed by filtration and washed ($H_2O$). The wet solid was dissolved in $Et_2O$, the $Et_2O$ solution was washed with $H_2O$, the solution was dried ($MgSO_4$), and the solvent was evaporated. The solid residue was recrystallized from petroleum ether (60–70°) affording 5.6 g (52%) of the desired diol **9**: mp 120–130°; ir ($CHCl_3$), 2.79, 291, 3.32, 3.42, 3.50, 6.25, 6.70, 6.90, 9.70, 10.64, 14.30 μ; nmr ($CDCl_3$), δ 7.75 (multiplet, aromatic *ortho*-protons), 7.30 (multiplet, aromatic *meta* and *para* protons), 3.75 (quartet, $J_{aa}$ = 11 cps, $J_{ae}$ = 5 cps, axial methine at C-3).

Concentration of the filtrate afforded a small amount of impure diol and 2.9 g (29%) of 3(e)-phenyl-*trans*-2-decalone, mp 101–102°.

**3(e)-Phenyl-*trans*-2-decalone.**—To **8** (4.0 g, 0.018 mole) in 100 ml of $C_6H_6$ was added 4 g of *p*-toluenesulfonic acid and the mixture was heated at reflux for 12 hr. The $C_6H_6$ solution was washed (5% $NaHCO_3$ solution, $H_2O$, and saturated NaCl) and dried ($MgSO_4$), the solvent was evaporated at reduced pressure, and the resulting solid was recrystallized from petroleum ether (60–70°) affording 2.55 g (64%) of 3(e)-phenyl-*trans*-2-decalone: mp 101–102°; ir ($CHCl_3$), 3.31, 3.40, 3.48, 5.86, 6.24, 6.68, 6.91, 8.60, 11.60, 14.50 μ; nmr ($CCl_4$), δ 7.16 (multiplet, aromatic), 3.50 (quartet, $J_{aa}$ = 12 cps, $J_{ae}$ = 6 cps, axial methine at C-3). *Anal.* ($C_{16}H_{20}O$) C, H.

Oxime, mp 236–237. *Anal.* ($C_{16}H_{21}NO$) C, H, N.

**2(e)-Phenyl-*trans*-decalin-2(a),3(a)-diol (10).**—The procedure of Berti and coworkers[6] was followed. Compound **8** (10.0 g, 0.044 mole) was dissolved in 200 ml of 85% aqueous DMSO, and KOH (14 g, 0.044 mole) was added. The mixture was heated at reflux for 19 hr. Excess $H_2O$ was added and the resulting solid was removed by filtration and washed with $H_2O$. The wet solid was dissolved in $Et_2O$ and the $Et_2O$ solution was washed ($H_2O$) and dried ($MgSO_4$), and the solvent was evaporated. Recrystallization of the solid from petroleum ether (60–70°) afforded 9.8 g (91%) of colorless needles: mp 118–119°; ir ($CHCl_3$), 2.78, 2.90, 3.32, 3.42, 3.51, 6.70, 6.92, 9.64, 9.97, 10.30, 14.30 μ; nmr ($CDCl_3$), δ 7.40 (multiplet, aromatic), 3.68 ($W_{1/2}$ = 7 cps, equatorial methine proton at C-3). *Anal.* ($C_{16}H_{22}O_2$) C, H.

**2(e)-Phenyl-*trans*-decalin-2(a),3(e)-diol (11).**—The procedure used is essentially that of Berti and coworkers.[6] To anhydrous trichloroacetic acid (3.3 g, 0.02 mole) in 75 ml of $C_6H_6$ was added **8** (2.0 g, 0.009 mole) and the solution was stirred for 18 hr at room temperature. The $C_6H_6$ solution was washed (10% $Na_2CO_3$ solution, $H_2O$, and saturated NaCl). The solvent was removed and the residue was dissolved in a solution of 2 g of KOH in 50 ml of EtOH. The mixture was heated at reflux for 2 hr and excess $H_2O$ was added. The solid was removed by filtration, washed, and dried. Recrystallization from petroleum ether (60–70°) afforded 0.9 g (50%) of **11**: mp 142–143°; ir ($CHCl_3$), 2.80, 2.90, 3.32, 3.41, 3.50, 6.25, 6.71, 6.91, 9.65, 10.28, 10.64, 14.30 μ; nmr ($CDCl_3$), δ 7.40 (multiplet, aromatic protons), 3.99 ($W_{1/2}$ = 19 cps, axial methine proton at C-3). *Anal.* ($C_{16}H_{22}O$) C, H.

**3(a)-Hydroxy-3(e)-phenyl-*trans*-2-decalone (15). a. Pfitzner–Moffatt Method.**[14]—To **10** (0.85 g, 0.0034 mole) in 5 ml of anhydrous DMSO was added a solution of anhydrous pyridine (0.27 ml, 0.0034 mole) and trifluoroacetic acid (0.14 ml, 0.0017 mole) in 5 ml of anhydrous $C_6H_6$. Dicyclohexylcarbodiimide (3.3 g, 0.016 mole) was added and the mixture was allowed to stand for 19 hr. The reaction mixture was diluted with 50 ml of $Et_2O$ and 1.6 g of oxalic acid in 15 ml of MeOH was added. After cessation of gas evolution 50 ml of $H_2O$ was added and the dicyclohexylurea was removed by filtration. The filtrate was washed (5% $NaHCO_3$, $H_2O$, and saturated NaCl) and dried ($MgSO_4$), and the solvent was evaporated. The residue was crystallized from petroleum ether (60–70°) affording 0.10 g (12%) of ketone **15**: mp 167–169°; ir ($CHCl_3$), 2.80, 3.33, 3.42, 3.40, 5.86, 6.26, 6.70, 6.92, 14.40 μ; nmr ($CDCl_3$), δ 7.31 (singlet, aromatic protons). *Anal.* ($C_{16}H_{20}O_2$) C, H.

**b. Albright–Goldman Method.**[15]—To **10** (9.8 g, 0.04 mole) was added 50 ml of anhydrous DMSO and 50 ml of $Ac_2O$ and the mixture was stirred at room temperature for 24 hr. Excess $H_2O$ was added and the resulting solid was removed by filtration and washed ($H_2O$). The wet solid was dissolved in $Et_2O$, the solution was washed ($H_2O$, saturated NaCl) and dried ($MgSO_4$), and the solvent was evaporated. Recrystallization of the residue from $CHCl_3$–petroleum ether (60–70°) affording 4.85 g (49%) of ketone **15**, mp 167–168°.

**c. N-Bromoacetamide Method.**—The procedure used is essentially that of Oliveto and coworkers.[16] Compound **10** (5.9 g, 0.024 mole) was dissolved in 100 ml of $Me_2CO$ and 25 ml of $H_2O$ and the solution was cooled to 3°. A solution of N-bromoacetamide (5.0 g, 0.032 mole) in 50 ml of $H_2O$ was added dropwise maintaining a temperature of 5°. The reaction mixture was kept in a refrigerator for 5 hr and the excess oxidizing agent was destroyed by adding 20% $Na_2SO_4$ solution. Excess $H_2O$ was added and the precipitate was removed by filtration. Recrystallization from $CHCl_3$–petroleum ether (60–70°) afforded 3.45 g (58%) of ketone **15**, mp 167–168°.

**d. From 2(e)-Phenyl-*trans*-decalin-2(a),3(e)-diol (11).**—Using the procedure of Albright and Goldman,[15] 2(e)-phenyl-*trans*-2(a),3(e)-diol (**11**) (0.50 g, 0.002 mole) afforded 0.08 g (16%) of the ketone **15**, mp 167–169°.

**3(e)-Hydroxy-3(a)-phenyl-*trans*-2-decalone (14). a. Pfitzner–Moffatt Method.**[14]—Utilizing this approach **9** (2.9 g, 0.012 mole) gave an oil which would not crystallize and which would not form a solid oxime.

**b. Albright–Goldman Method.**[15]—The diol **9** (2.0 g, 0.008 mole) was treated under these conditions to give an oil which would not crystallize but which did form an oxime, mp 105–110°.

**c. N-Bromoacetamide Method.**[16]—This method, utilizing the diol **9** (1.7 g, 0.007 mole), gave 0.50 g of starting material and an oil. Chromatography of the oil on silica gel (Merck 0.05–0.20 mm), eluting with petroleum ether–EtOAc (4:1), afforded 0.59 g (35%) of oil: ir (neat), 2.88, 3.42, 3.50, 5.85, 6.25, 6.70, 6.92, 7.85, 8.19, 8.74, 8.97, 9.40, 9.79, 13.10, 14.32 μ. The oxime **14** was prepared with $HONH_2 \cdot HCl$ and NaOAc in EtOH; mp 105–110°.

**3(e)-Amino-2(a)-phenyl-*trans*-2-decalol (3).**—Compound **14** (1.2 g, 0.0046 mole) was hydrogenated at atmospheric pressure

(14) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5670 (1965).
(15) J. D. Albright and L. Goldman, *ibid.*, **87**, 4214 (1965).
(16) E. P. Oliveto, H. L. Herzog, M. A. Jevnik, H. E. Jorgensen, and E. U. Hershberg, *ibid.*, **75**, 3651 (1953).

in absolute EtOH using W-5 Raney nickel[17] catalyst. The catalyst was removed by filtration and the EtOH was evaporated at reduced pressure. The residue was recrystallized from petroleum ether (60–70°) affording 0.5 g (42%) of desired amino alcohol **3**: mp 149–151°; ir ($CHCl_3$), 2.78, 2.96, 3.33, 3.41, 3.50, 6.25, 6.35, 6.70, 6.92, 7.40, 9.85, 10.66 $\mu$; nmr ($CDCl_3$), $\delta$ 7.70 (multiplet, aromatic *ortho* protons), 7.34 (multiplet, aromatic *meta* and *para* protons), 3.00 ($W_{1/2}$ = 19 cps, axial methine proton at C-3). *Anal.* ($C_{16}H_{23}NO$) C, H, N.

**2(a)-Phenyl-*trans*-decalin-2(e),3(e)-diol 3-Tosylate (12).**—To **9** (1.05 g, 0.0043 mole), dissolved in 20 ml of anhydrous pyridine, was added *p*-toluenesulfonyl chloride (2.0 g, 0.01 mole) and the solution was allowed to stand at room temperature for 48 hr. $H_2O$ was added and the resulting oil was scratched with a glass rod to promote crystallization. The solid was removed by filtration and recrystallized from petroleum ether (60–70°) affording 1.0 g (58%) of tosylate **12**: mp 99–100°; ir ($CHCl_3$), 2.78, 3.42, 3.50, 6.27, 6.70, 6.92, 7.40, 8.55, 9.13, 9.74, 10.33, 10.82, 11.25, 11.62, 11.93 $\mu$; nmr ($CCl_3$), $\delta$ 7.2–8.0 (multiplet, aromatic protons), 4.80 (quartet, $J_{aa}$ = 11 cps, $J_{ae}$ = 6 cps, axial methine proton at C-3), 2.43 (singlet, $ArCH_3$). *Anal.* ($C_{23}H_{28}SO_4$) C, H.

**3(a)-Amino-2(a)-phenyl-*trans*-2(e)-decalol (2).**—Compound **12** (1.0 g, 0.0025 mole) was placed in a steel bomb and the bomb was cooled in Dry Ice–$Me_2CO$. To the bomb was added *ca.* 100 ml of liquid $NH_3$. The bomb was sealed and heated at 120° for 24 hr. The pressure was released and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was filtered and the solvent was evaporated. The residue was recrystallized from petroleum ether (60–70°) affording 0.30 g (50%) of amino alcohol **2**: mp 116–117°; ir ($CHCl_3$), 2.79, 2.97, 3.34, 3.42, 3.51, 6.25, 6.35, 6.71, 6.92, 7.40, 9.85, 10.01, 10.28, 10.67 $\mu$; nmr ($CDCl_3$), $\delta$ 7.43 (multiplet, aromatic protons), 3.83 ($W_{1/2}$ = 6 cps, equatorial methine proton at C-3). *Anal.* ($C_{16}H_{23}NO$) C, H, N.

**3(e)-Amino-2(e)-phenyl-*trans*-2(a)-decalol (4).**—Compound **15** (1.0 g 0.004 mole) was dissolved in 100 ml of absolute EtOH saturated with $NH_3$ and material was hydrogenated under 70 kg/cm² of $H_2$ using W-5 Raney Ni catalyst.[17] The catalyst was removed by filtration and the solvent was evaporated at reduced pressure. The residue was chromatographed on silica gel (Merck 0.05–0.20 mm) eluting with cyclohexane–EtOAc (1:1) affording 0.5 g (50%) of desired amino alcohol **4**: mp 146–148°; ir ($CHCl_3$), 2.78, 2.95, 3.34, 3.52, 3.51, 6.25, 6.34, 6.70, 6.92, 7.63, 8.60, 9.51, 9.66, 10.00, 10.26 $\mu$; nmr ($CDCl_3$, $CF_3CO_2H$), $\delta$ 7.46 (broad singlet, aromatic protons), 3.55 ($W_{1/2}$ = 10 cps, methine proton at C-3). *Anal.* ($C_{16}H_{23}NO$) C, H, N.

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# Synthesis and Myotrophic–Androgenic Activity of Substituted 2α,3α-Methano-5α-androstane Derivatives[1]

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The preparation and androgenic–myotrophic testing of analogs of **17** having substituents on the cyclopropyl ring were undertaken in an effort to obtain information regarding the steric and electronic requirements in the A ring of anabolic–androgenic androstanes. Treatment of 17β-hydroxyandrost-2-ene acetate with ethyl diazoacetate in the presence of anhydrous $CuSO_4$ gave 2α,3α-(β-carbethoxymethano)-5α-androstan-17β-ol acetate which was converted to a variety of substituted cyclopropane derivatives. The most potent is the aldehyde **15** which is more active than testosterone propionate in the myotrophic test and is much less androgenic.

Studies in this laboratory have resulted in the proposal[2] that anabolic–androgenic androstanes are bound to their receptor by a β-face π-bond to an $sp^2$ system in the A ring. The pronounced anabolic–androgenic activity of 2α,3α-methano-5α-androstan-17β-ol (**17**)[2] was taken as evidence for this hypothesis. Recent work[3a] on steroidal episulfides, bioisosteric with these methano steroids, has shown that the 2α,3α isomers indeed have high parenteral activity, whereas the 2β,3β isomers are essentially inactive. This is in harmony with our proposal.[3b] On the other hand, 2α,3α- and 2β,3β-steroidal difluorocyclopropanes have similar activity.[4]

To gain further information in this area, the preparation of analogs of **17** having altered electron density at the $sp^2$ centers was undertaken. If a π bond is important, the strength of the binding would be different in such analogs. Since β-face binding is assumed to be involved, the preparation of substituted cyclopropane analogs of **17** should be feasible since the substituent groups should not interfere sterically with drug receptor binding.

The synthetic plan involved the preparation of 2α,3α-carbethoxymethano-5α-androstan-17β-ol acetate (**7**) as a common intermediate for the other derivatives. This material was prepared by the reaction of 17β-hydroxyandrost-2-ene acetate[5] (**2**) with ethyl dazoacetate. Although carbene intermediates have been proposed in the reaction of diazo compounds with olefins,[6] the reaction failed when the reagents were heated at 120–180°, or were irradiated in toluene or hexane solution with a medium-pressure mercury arc. On the other hand, a 45% yield of **7** was realized when the reagents were heated in the presence of anhydrous $CuSO_4$. These results point to

(1) (a) This investigation was supported in part by a Public Health Service research grant (AM-05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. (b) Portions of this work are taken from the Ph.D. thesis of S.-Y. Cheng, University of California, San Francisco, 1966.

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