identical with that used in the preparation of 3.

To a stirred suspension of $LiAlH_4$ (3.8 g, 0.105 mol) in 125 ml of anhydrous $Et_2O$ was added dropwise *trans*-2-phenylcyclohexyl azide (24) (0.063 mol, theoretically) in 50 ml of anhydrous $Et_2O$ to afford 10.1 g (83%) of 4.

The hydrochloride salt of 4 was prepared from the free base. The solid was recrystallized ($C_6H_6$), mp 238° dec (lit.[23] mp 249–251°).

The methanesulfonate salt of 4 was prepared from the free base. The solid was recrystallized ($C_6H_6$), mp 156°. *Anal.* ($C_{13}H_{21}NO_3$) C, H, N.

General Procedure for Preparation of Isopropyl Analogs. The amine salt was converted to the free amine by the use of a strong base ion-exchange column (Amberlite IRA-400) or by adding the amine salt to a saturated $NH_3$–$CHCl_3$ solution, filtering the ammonium salt, and evaporating the solvent to yield the free amine. The free amine was dissolved in absolute EtOH containing 5% MeOH and to this solution was added a 4 *M* excess amount of $Me_2CO$. The solution was subjected to hydrogenation over Adams platinum catalyst at 32 psi at 25° for 12 hr. The catalyst and the solvent were removed to afford the isopropyl analog as the free amine, which was dissolved in $Et_2O$. The hydrochloride salt was prepared by addition of saturated HCl–$Et_2O$ solution to the ethereal solution. The salt was removed by filtration and recrystallized from the appropriate solvent.

*erythro*-2-Isopropylamino-3-phenylbutane Hydrochloride (6). This compound was recrystallized from $CHCl_3$–hexane, mp 181.5–182.5°. *Anal.* ($C_{13}H_{22}ClN$) C, H, N.

*threo*-2-Isopropylamine-3-phenylbutane Hydrochloride (5). This compound was recrystallized from MeOH–hexane, mp 228°. *Anal.* ($C_{13}H_{22}ClN$) C, H, N.

*cis*-2-Phenylisopropylaminocyclohexane Hydrochloride (7). This compound was recrystallized from $C_6H_6$, mp 228°. *Anal.* ($C_{15}H_{24}ClN$) C, H, N.

*trans*-2-Phenylisopropylaminocyclohexane Hydrochloride (8). This compound was recrystallized from $C_6H_6$, mp 213–215°. *Anal.* ($C_{15}H_{24}ClN$) C, H, N.

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# A Conformational Study of Phenethylamine Receptor Sites. 2. Synthesis of *dl*-2-Amino-3-phenyl-*trans*-decalins and *dl*-2-Isopropylamino-3-phenyl-*trans*-decalins

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*Received March 31, 1972*

The syntheses of the four possible *dl*-2-amino-3-phenyl-*trans*decalin isomers, **1–4**, and the four possible *dl*-2-isopropylamino-3-phenyl-*trans*-decalin isomers, **5–8**, are described. The results of the toxicity and behavioral studies are described.

In a previous report from these laboratories it was shown that when the phenethylamine structure was incorporated into a semirigid system the erythro configuration appeared to be required for an increase in motor activity similar to that which is found with the parent compound amphetamine.[1] Since a marked difference in activity with a change in configuration was observed, an investigation of rigid analogs which represent various fixed conformations of the *threo*- and *erythro*-β-methylamphetamines was undertaken.

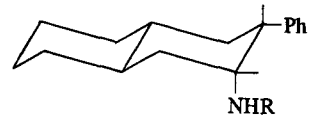
The synthesis of the four racemic isomers of *dl*-2-amino-3-phenyl-*trans*-decalin, **1–4**, afford two compounds with the threo configuration (**1** and **4**) and two compounds with the erythro configuration (**2** and **3**). The *N*-isopropyl-β-methylamphetamine analogs, **5–8**, were prepared since the substitution of an isopropyl group in the parent compound, amphetamine, results in greater specificity for anorexic effect and the hypothesis is offered that different conformations may be required at the various effector or metabolic sites.

The synthesis of 2(e)-amino-3(e)-phenyl-*trans*-decalin (**1**) and 2(a)-amino-3(e)-phenyl-*trans*-decalin (**2**) was initiated with the oxidation of commercially available *trans*-2-decalol (**9**) to *trans*-2-decalone (**10**) utilizing Jones reagent according to the procedure of Ramsey.‡

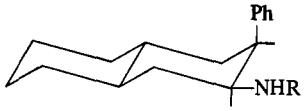
†Taken in part from the dissertation presented by T. L. Pazdernik, Aug 1971, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

‡A. Ramsey, Ph.D. Thesis, University of Kansas, 1968.

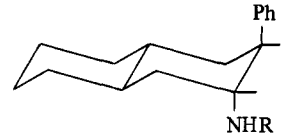
1, R = H
5, R = -CH(CH$_3$)$_2$



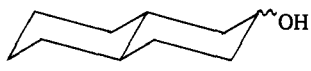
2, R = H
6, R = -CH(CH$_3$)$_2$



3, R = H
7, R = -CH(CH$_3$)$_2$



4, R = H
8, R = -CH(CH$_3$)$_2$



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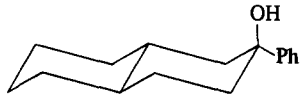
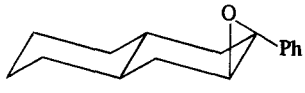


11

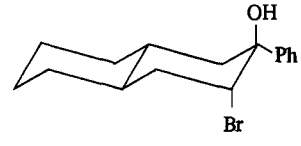
12

The reaction of **10** with phenyllithium, according to the procedure of Smissman and Gastrock,[2] afforded the alcohol **11**. Dehydration of **11** utilizing *p*-toluenesulfonic acid in refluxing benzene afforded 2-phenyl-$\Delta^2$-*trans*-octalin (**12**).

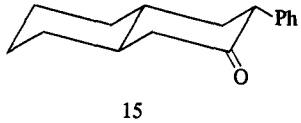
3(e)-Phenyl-*trans*-decalin 2,3-oxide (**13**) was prepared from the $\Delta^2$ olefin **12** *via* the bromohydrin **14** according to the procedure of Smissman and Gastrock.[2] Acid-catalyzed rearrangement of the epoxide **13** afforded 3(e)-phenyl-*trans*-2-decalone (**15**).



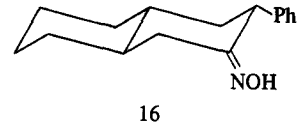
13



14



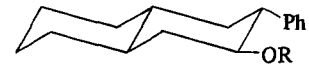
15



16

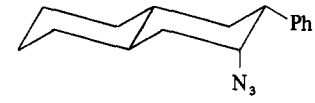
Treatment of 3(e)-phenyl-*trans*-2-decalone (**15**) with hydroxylamine hydrochloride and sodium acetate in ethanol produced the corresponding oxime **16**. The reduction of **16** with lithium aluminum hydride in tetrahydrofuran afforded excellent yields of 2(e)-amino-3(e)-phenyl-*trans*-decalin (**1**), whereas reduction of **16** with the reducing reagent, sodium bis(2-methoxyethoxy)aluminum hydride, resulted in the formation of a mixture of **1** and 2(a)-amino-3(e)-phenyl-*trans*-decalin (**2**). The nmr spectrum of the hydrochloride salt of **1** showed absorptions at $\delta$ 3.70 ($W_{1/2}$ = Hz) indicative of an axial C-2 methine proton and at $\delta$ 2.95 ($W_{1/2}$ = 18 Hz) indicative of an axial C-3 methine proton.

The reduction of the ketone **15** with lithium aluminum hydride gave 3(e)-phenyl-*trans*-2(e)-decalol (**17**). The nmr spectrum of **17** showed absorptions at $\delta$ 3.50 ($W_{1/2}$ = 18 Hz) indicative of an axial C-2 methine proton and at $\delta$ 2.40 ($W_{1/2}$ = 18 Hz) indicative of an axial C-3 methine proton. The reactions of **17** with *p*-toluenesulfonyl chloride in pyridine afforded the corresponding tosylate **18** and, with methanesulfonyl chloride in pyridine, the corresponding mesylate **19**.



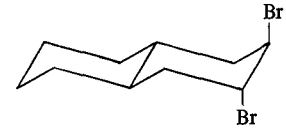
17, R = H
18, R = OTs
19, R = OMs

The treatment of **18** with sodium azide in dimethylformamide resulted in the formation of 3(e)-phenyl-*trans*-decalin 2(a)-azide (**20**). The azide **20** was immediately reduced with lithium aluminum hydride to produce 2(a)-amino-3(e)-phenyl-*trans*-decalin (**2**). The nmr spectrum of **2** shows absorption for the C-2 methine proton at $\delta$ 3.25 ($W_{1/2}$ = 6 Hz). The peak half-width of the C-2 proton indicates an equatorial orientation of this proton which is in agreement with the expected inversion of configuration at C-2 during the SN2 displacement with sodium azide.



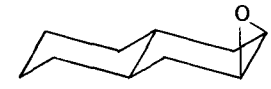
20

The syntheses of 2(e)-amino-3(a)-phenyl-*trans*-decalin (**3**) and 2(a)-amino-3(a)-phenyl-*trans*-decalin (**4**) were initiated by the conversion of 2(a),3(a)-dibromo-*trans*-decalin (**21**)



21

22

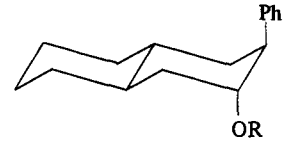


23

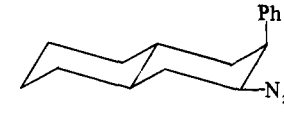
to *trans*-$\Delta^2$-octalin (**22**) according to the procedure of Johnson, *et al.*[3]

*trans*-$\Delta^2$-Octalin (**22**) was epoxidized according to the procedure of Johnson, *et al.*,[3] to yield *trans*-decalin 2,3-epoxide (**23**).

The epoxide **23** was opened with phenyllithium, according to the procedures developed in the butane and cyclohexane systems,[1] to give excellent yields of 3(a)-phenyl-*trans*-2(a)-decalol (**24**). The nmr spectrum of **24** showed absorptions at $\delta$ 4.35 ($W_{1/2}$ = 7 Hz) indicative of an equatorial C-2 methine proton and at $\delta$ 3.15 ($W_{1/2}$ = 9 Hz) indicative of an equatorial C-3 methine proton. 3(a)-Phenyl-*trans*-decalin 2(a)-tosylate (**25**) and 3(a)-phenyl-*trans*-decalin 2(a)-mesylate (**26**) were synthesized by treating **24** with *p*-toluenesulfonyl chloride and methanesulfonyl chloride in pyridine, respectively.



24, R = H
25, R = OTs
26, R = OMs

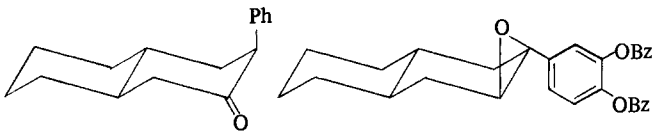


27

The reaction of **25** with sodium azide in dimethylformamide resulted in the formation of the azide **27**. Lithium aluminum hydride reduction of the azide **27** resulted in the formation of 2(e)-amino-3(a)-phenyl-*trans*-decalin (**3**). Inversion of stereochemistry during the nucleophilic displacement reaction with sodium azide was verified by the nmr

spectrum of the hydrochloride salt of **3**. Absorption at δ 3.95 ($W_{1/2}$ = 20 Hz) indicates axial orientation of the C-2 methine proton.

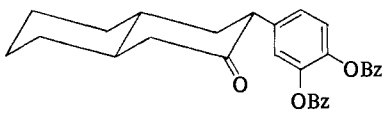
3(a)-Phenyl-*trans*-2-decalone (**28**) was considered to be an important intermediate in the synthesis of 3(a)-amino-3(a)-phenyl-*trans*-decalin (**4**). Borchardt§ was able to rearrange 2(e)-(3′,4′-dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**29**) to a mixture of 3(e)-(3′,4′-dibenzyloxyphenyl)-*trans*-2-decalone (**30**) and 3(a)-(3′,4′-dibenzyloxyphenyl)-*trans*-2-decalone (**31**) with slight heating in the presence of dimethyl sulfoxide. When this rearrangement was attempted using epoxide **13**, only the equatorial isomer **15** and starting material were obtained.



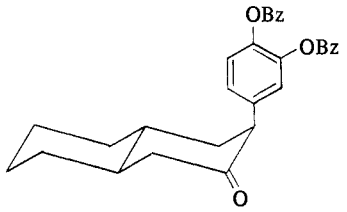

**28**




**29**




**30**

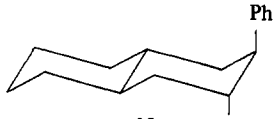



**31**

Excellent yields of 3(a)-phenyl-*trans*-2-decalone (**28**) were obtained by oxidizing the alcohol **24** with *N*-bromosuccinimide in aqueous acetone solution in the cold. The temperature was maintained below 15° during work-up to prevent isomerization to the equatorial isomer **15**. The nmr spectrum of **28** showed C-3 methine absorption at δ 3.80 ($W_{1/2}$ = 9 Hz) indicative of an equatorial proton at C-3.

The ketone **28** was reduced with lithium aluminum hydride to afford 3(a)-phenyl-*trans*-2(e)-decalol (**32**). The nmr spectrum of **32** showed absorptions at δ 3.95 ($W_{1/2}$ = 18 Hz) indicative of an axial C-2 methine proton and at δ 3.35 ($W_{1/2}$ = 9 Hz) indicative of an equatorial C-3 methine proton. The tosylate **33** was prepared and purified without difficulty from **32**; however, the mesylate **34** when recrystallized from hexane eliminated methanesulfonic acid readily to give 2-phenyl-$\Delta^2$-*trans*-octalin (**12**).

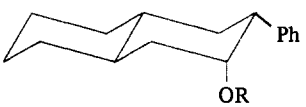

**32**, R = H
**33**, R = OTs
**34**, R = OMs



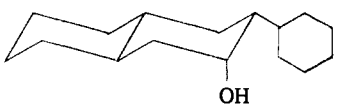

**35**

Treatment of the tosylate **33** with sodium azide in dimethylformamide resulted in the formation of a mixture of approximately 40% of the desired azide **35** and 60% of 2-phenyl-$\Delta^2$-*trans*-octalin (**12**). The infrared spectrum of the mixture showed azide absorption at 2095 $cm^{-1}$. The mixture containing the azide **35** and $\Delta^2$ olefin **12** was reduced with lithium aluminum hydride to produce a mixture of 3(a)-amino-3(a)-phenyl-*trans*-decalin (**4**) and the $\Delta^2$ olefin **12**. The mixture was dissolved in methanol and the $\Delta^2$ olefin **12** crystallized from the methanolic solution. The amine **4** was isolated as the methanesulfonate salt. The nmr spectrum of the methanesulfonate salt showed absorption at δ 4.05 ($W_{1/2}$ = 13 Hz) indicative of an equatorial methine proton at C-2 and at δ 3.45 ($W_{1/2}$ = 6 Hz) indicative of an equatorial methine proton at C-3. These assignments verify the inversion of configuration at C-2 during the nucleophilic displacement with sodium azide.

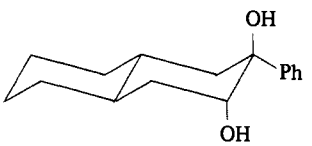
Several methods were investigated before a satisfactory procedure was developed for the synthesis of the final isomeric decalol **36**. Augustine[4] reported that reduction of




**36**, R = H
**39**, R = OTs
**40**, R = OMs




**37**




**38**

cyclohexanones utilizing platinum oxide under acidic conditions results in the formation of axial alcohols. When these conditions were applied to 3(e)-phenyl-*trans*-2-decalone (**15**) at 30 psi at 25°, the compound obtained was 3(e)-cyclohexyl-*trans*-2(a)-decalol (**37**). When this reaction was performed at atmospheric pressure, there was obtained a mixture of starting material and **37**. The nmr spectrum of **37** shows equatorial C-2 methine absorption at δ 4.55 ($W_{1/2}$ = 7 Hz).

The use of iridium tetrachloride as a catalyst in combination with trimethyl phosphite in a modified Meerwein-Pondorf reduction has also been reported to yield axial alcohols.[5] However, when this procedure was utilized to reduce ketone **15**, starting material was obtained.

3(e)-Phenyl-*trans*-2(a)-decalol (**36**) was finally prepared by opening the epoxide **13** according to the procedure of Berti, *et al.*,[6] to yield diol **38**, which was subjected to Raney nickel hydrogenolysis according to the procedure of Garbish[7] to yield the decalol **36**. The nmr spectrum of **36** showed absorptions at δ 4.00 ($W_{1/2}$ = 6 Hz) indicative of a C-2 equatorial methine proton and at δ 2.80 ($W_{1/2}$ = 18 Hz) indicative of a C-3 axial methine proton. The tosylate **39** and the mesylate **40** were prepared from **36**.

The *N*-isopropyl analogs **5-8** were prepared by reductive amination of acetone with the primary amines **1-4**.

**Biological Results.** The toxicity of the decalin isomers **1-4** and their isopropyl derivatives **5-8** were determined according to the procedure outlined previously.[1] The results are listed in Table I.

The effects of these compounds on behavioral changes were determined as previously described.[1] The results are tabulated in Table II.

As with the previous work,[1] conformational changes resulted in different behavioral patterns. In these preliminary studies the only behavioral effect which appears to be correlated to a unique conformation is the prevalence of

§ R. Borchardt, Ph.D. Thesis, University of Kansas, 1970.

Table I. Toxicity of Phenethylamine-Like Compounds

| Compound | Approximate $LD_{50}$,[c] mg/kg |
|---|---|
| Decalins | |
| Ph = e, N = e (1)[b] | 28 |
| Ph = e, N = a (2)[b] | 28 |
| Ph = a, N = e (3)[b] | 28 |
| Ph = a, N = a (4)[b] | 23 |
| Isopropyldecalins | |
| Ph = e, N = e (5)[a] | 19 |
| Ph = e, N = a (6)[a] | 12 |
| Ph = a, N = e (7)[a] | 14 |
| Ph = a, N = a (8)[a] | 14 |

[a]Hydrochloride salt. [b]Methanesulfonate salt. [c]D. E. S. Campbell and W. Richter, *Acta Pharmacol. Toxicol.*, 25, 345 (1967).

Table II. Behavioral Study of Phenethylamine-Like Compounds

| Compound | Dose, mg/kg[c] | Duration, hr | MA[d] |
|---|---|---|---|
| Decalins | | | |
| Ph = e, N = e (1)[a] | 25 | 4–5 | – |
| Ph = e, N = a (2)[a] | 50 | 5–6 | – |
| Ph = a, N = e (3)[a] | 50 | 1–2 | – |
| Ph = a, N = a (4)[a] | 25 | 1–3 | – |
| Isopropyldecalins | | | |
| Ph = e, N = e (5)[b] | 25[e] | 1–2[e] | 0[e] |
| Ph = e, N = a (6)[b] | 50[e] | 1[e] | 0[e] |
| | 100[e] | | |
| Ph = a, N = e (7)[b] | 25 | 1–3 | – |
| Ph = a, N = a (8)[b] | 50 | 1–3 | – |

[a]Methanesulfonate salt. [b]Hydrochloride salt. [c]Minimal dose required for changes in motor activity. [d](+) = increased motor activity; (–) = decreased motor activity; (0) = no change in motor activity. [e]Changes in behavior without changes in motor activity.

lachrymation in the isomers which have the amino group and the phenyl group in the trans-anti conformation, such as the axial positions in the decalin ring (**4** and **8**) or in those compounds which could easily obtain this trans-anti conformation (amphetamine and the butane analogs).[1]

The absence of the increased motor activity in all of the decalin isomers was unexpected. It was expected that at least one of the erythro conformers, **2** or **3**, in the aminodecalin series and **6** or **7** in the isopropylaminodecalin series would show an increase in motor activity based on the observations in the semirigid system.[1] The reason for the erythro isomers' increasing motor activity in the semirigid systems but not in the rigid systems is not clear but may be due to a difference in the mechanism of action.

A study of the hexane–water and octanol–water partition coefficients gave no correlation with the observed activities.

Resolution of these compounds into their optically active antipodes and a detailed biological study of these compounds will be the subject of a future report.

## Experimental Section#

*trans*-**2-Decalone (10).** Commercially available *trans*-2-decalol (9) (50.2 g, 0.32 mol) was oxidized according to the procedure of Ramsey,‡ utilizing Jones Reagent to yield 45.4 g (93.5%) of 10, bp 60–68° (0.4 mm) [lit.‡ 60° (0.5 mm)].

**2-Phenyl-$\Delta^2$-*trans*-octalin (12).** 2-Phenyl-$\Delta^2$-*trans*-octalin (12) was prepared according to the procedure of Smissman and Gastrock,[2] utilizing lump Li (4.00 g, 0.51 g-atom), $C_6H_5Br$ (45.0 g, 0.29 mol), and $Et_2O$ as a solvent. The resulting alcohol was dehydrated using *p*-TsOH in $C_6H_6$ affording 27.8 g (50.5%) of 12, mp 53–56° (lit.[2] 56–68°).

**2(e)-Phenyl-*trans*-decalin 2,3-Oxide (13).** 2(e)-Phenyl-*trans*-decalin 2,3-oxide (13) was prepared according to the procedure of Smissman and Gastrock,[2] utilizing 2-phenyl-$\Delta^2$-*trans*-octalin (12) (25.8 g, 0.122 mol), $H_2SO_4$ (13.7 g, 0.14 mol), $H_2O$ (15 ml), and dioxane (75 ml). The resulting bromohydrin 14 was treated with $Na_2CO_3$ (38 g) in 250 ml of $H_2O$ affording 15.6 g (56%) of 13, mp 101–102° (lit.[2] 99–101°).

**3(e)-Phenyl-*trans*-2-decalone (15).** 3(e)-Phenyl-*trans*-2-decalone (15) was prepared according to the procedure of Smissman and Gastrock,[2] utilizing 2(e)-phenyl-*trans*-decalin 2,3-oxide (13) (12.0 g, 0.050 mol), *p*-TsOH (12 g), and $C_6H_6$ as a solvent, to yield 6.3 g (52.5%) of 15, mp 99–101° (lit.[2] 101–102°).

**3(e)-Phenyl-*trans*-2-decalone Oxime (16).** 3(e)-Phenyl-*trans*-2-decalone oxime (16) was prepared from 3(e)-phenyl-*trans*-2-decalone (15), mp 235° (lit.[2] 235–237°).

**2(e)-Amino-3(e)-phenyl-*trans*-decalin (1).** To a stirred suspension of $LiAlH_4$ (1.14 g, 0.03 mol) in 100 ml of THF was added dropwise 3(e)-phenyl-*trans*-2-decalone oxime (16) (6.0 g, 0.0247 mol). The solution was stirred at reflux for 24 hr. Excess $LiAlH_4$ was decomposed with "wet" $Et_2O$ followed by $H_2O$. The inorganic salts were removed and the organic layer was washed with $H_2O$ and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 4.1 g (72.5%) of 1.

The hydrochloride salt of 1 was prepared from the free base. The solid was recrystallized (MeOH–EtOAc): mp 305° dec; nmr ($CF_3COOH$) $\delta$ 3.70 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 CH), 2.95 (m, 1 H, $W_{1/2}$ = 18 Hz, C-3 CH). *Anal.* ($C_{16}H_{24}ClN$) C, H, N.

The methanesulfonate salt was prepared and recrystallized ($C_6H_6$), mp 207°.

**3(e)-Phenyl-*trans*-2(e)-decalol (17).** To a stirred suspension of $LiAlH_4$ (12.5 g, 0.33 mol) in 200 ml of anhydrous $Et_2O$ was added dropwise 3(e)-phenyl-*trans*-2-decalone (15) (19.0 g, 0.083 mol) in 300 ml of anhydrous $Et_2O$. After the addition was complete, the solution was stirred at reflux for 4 hr. Excess $LiAlH_4$ was decomposed with "wet" $Et_2O$ followed by $H_2O$. The inorganic salts were removed and the $Et_2O$ layer was washed with $H_2O$ and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the resulting solid was recrystallized (hexane) to afford 16.0 g (84%) of 17: mp 110°; nmr ($CCl_4$) 3.50 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 CH). *Anal.* ($C_{16}H_{22}O$) C, H.

**3(e)-Phenyl-*trans*-decalin 2(e)-Tosylate (18).** To 3(e)-phenyl-*trans*-2(e)-decalol (17) (2.5 g, 0.011 mol) in 50 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added *p*-TsCl (4.1 g, 0.022 mol). The solution was stirred for 16 hr at 25° and then poured into 300 ml of ice–$H_2O$. The precipitate was washed with $H_2O$ and dried under reduced pressure to afford 4.1 g (97.5%) of 18: mp 162° dec; nmr ($CDCl_3$) $\delta$ 4.64 (m, 1 H, $W_{1/2}$ = 20 Hz, C-2 CH). *Anal.* ($C_{23}H_{28}O_3S$) C, H.

**3(e)-Phenyl-*trans*-decalin 2(e)-Mesylate (19).** To 3(e)-Phenyl-*trans*-2(e)-decalol (17) (0.9 g, 0.004 mol) in 25 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added methanesulfonyl chloride (0.9 g, 0.008 mol). The solution was stirred for 1 hr and then placed in the refrigerator for 12 hr. This solution was poured into 300 ml of ice–$H_2O$ and the resulting solid was recrystallized ($Me_2CO$) to afford 1.1 g (84%) of 19: mp 142°; nmr ($CDCl_3$) 4.65 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 CH), 2.75 (m, 1 H, $W_{1/2}$ = 20 Hz, C-3 CH). *Anal.* ($C_{17}H_{24}O_3S$) C, H.

**3(e)-Phenyl-*trans*-decalin 2(a)-Azide (20).** To 3(e)-phenyl-*trans*-decalin 2(e)-tosylate (18) (1.0 g, 0.0026 mol) in 50 ml of DMF was added $NaN_3$ (0.3 g, 0.0052 mol) in 5 ml of $H_2O$. The solution was stirred for 30 hr at 95°. $H_2O$ was added to the solution and it was extracted several times with $Et_2O$. The combined $Et_2O$ fractions were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 0.5 g of crude azide 20, which was used without further purification.

**2(a)-Amino-3(e)-phenyl-*trans*-decalin (2).** To a stirred suspension of $LiAlH_4$ (0.13 g, 0.0035 mol) in 30 ml of anhydrous $Et_2O$ was added 3(e)-phenyl-*trans*-decalin 2(a)-azide (20) (0.0026 mol) in 10 ml of anhydrous $Et_2O$. The solution was stirred for 2 hr after the addition was complete. Excess $LiAlH_4$ was decomposed with "wet" ether followed by $H_2O$. The inorganic salts were removed and the $Et_2O$ layer was washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 0.45 g (84%) of 2: nmr ($CDCl_3$) $\delta$ 3.25 (m, 1 H, $W_{1/2}$ = 6 Hz, C-2 CH), 2.85 (m, 1 H, $W_{1/2}$ = 20 Hz, C-3 CH).

#Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckmann IR-10 spectrophotometer and nmr data on Varian Associates Model A-60A and T-60 spectrometers (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on the F & M Model 185 C, H, N analyzer, University of Kansas, Lawrence, Kan. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

The hydrochloride salt of **2** was prepared from the free base. The solid was recrystallized (MeOH–$Et_2O$), mp 130–131°. *Anal.* ($C_{16}H_{24}ClN$) C, H, N.

The methanesulfonate salt of **2** was recrystallized ($C_6H_6$), mp 228°.

*trans*-$\Delta^2$-Octalin (**22**). *trans*-$\Delta^2$-Octalin (**22**) was prepared according to the procedure of Johnson, *et al.*,[3] utilizing 2(a),3(a)-dibromo-*trans*-decalin (**21**) (35.5 g, 0.12 mol), Zn (78 g, 1.20 g-atoms), and absolute EtOH as a solvent affording 12.8 g (79%) of **22**.

*trans*-Decalin 2,3-Epoxide (**23**). The procedure used was essentially that of Hibbert and Burt.[8] as reported by Johnson, *et al.*,[3] utilizing *trans*-$\Delta^2$-octalin (**22**) (11.0 g, 0.086 mol), 87% *m*-chloroperbenzoic acid, and $CHCl_3$ as a solvent yielding 10.6 g (82%) of **23**, bp 123° (26 mm) [lit.[3] 105° (21 mm)].

3(a)-Phenyl-*trans*-2(a)-decalol (**24**). To lump Li (0.490 g, 0.07 g-atom) in 30 ml of anhydrous $Et_2O$, under a $N_2$ atmosphere, was added bromobenzene (5.2 g, 0.030 mol) at such a rate as to maintain reflux. After addition was complete, the solution was stirred for 4 hr. The solution was cooled in an ice bath and *trans*-decalin 2,3-epoxide (**23**) (5.0 g, 0.030 mol) was added. Then the solution was refluxed for 4 hr and stirred at 25° for 12 hr. $H_2O$ was added dropwise and the aqueous solution was extracted several times with $Et_2O$. The combined $Et_2O$ fractions were washed with saturated NaCl solution and $H_2O$ and dried ($MgSO_4$). The solvent was removed to afford 6.7 g of a light yellow oil. Chromatography on silica gel, eluting with hexane–EtOAc (9:1), afforded 6.0 g (87%) of **24**. The oil was crystallized (hexane): mp 83–84°; nmr ($CDCl_3$) δ 4.35 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH), 3.15 (m, 1 H, $W_{1/2}$ = 9 Hz, C-3 CH). *Anal.* ($C_{16}H_{22}O$) C, H.

3(a)-Phenyl-*trans*-decalin 2(a)-Tosylate (**25**). To a 3(a)-phenyl-*trans*-2(a)-decalol (**24**) (4.0 g, 0.017 mol) in 100 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added *p*-TsCl (7.0 g, 0.036 mol). The solution was stirred for 1 hr and then placed in the refrigerator for 48 hr. This solution was poured into 300 ml of ice–$H_2O$ and the aqueous solution was extracted several times with $Et_2O$. The combined $Et_2O$ fractions were washed with 10% HCl solution and saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the resulting solid was recrystallized (hexane–$Me_2CO$) affording 5.5 g (85%) of **25**: mp 93°; nmr ($CDCl_3$) δ 5.15 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH), 3.25 (m, 1 H, $W_{1/2}$ = 10 Hz, C-3 CH). *Anal.* ($C_{23}H_{28}O_3S$) C, H.

3(a)-Phenyl-*trans*-decalin 2(a)-Mesylate (**26**). The procedure was identical with that used in the preparation of **19**. To 3(a)-phenyl-*trans*-2(a)-decalol (**24**) (14.4 g, 0.063 mol) in 100 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added methanesulfonyl chloride (14.4 g, 0.126 mol) to afford 18.0 g (84%) of **26**: mp 85°; nmr ($CDCl_3$) δ 5.35 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH), 3.40 (m, 1 H, $W_{1/2}$ = 9 Hz, C-3 CH). *Anal.* ($C_{17}H_{24}O_3S$) C, H.

3(a)-Phenyl-*trans*-decalin 2(e)-Azide (**27**). The procedure was identical with that used in the preparation of **20**. To 3(a)-phenyl-*trans*-decalin 2(a)-tosylate (**25**) (4.5 g, 0.012 mol) in 150 ml of DMF was added $NaN_3$ (2.5 g, 0.038 mol) in 10 ml of $H_2O$ to afford 3.7 g of crude azide **27**, which was used without further purification.

2(e)-Amino-3(a)-phenyl-*trans*-decalin (**3**). To a stirred suspension of $LiAlH_4$ (1.0 g, 0.05 mol) in 75 ml of anhydrous $Et_2O$ was added dropwise 3(a)-phenyl-*trans*-decalin 2(e)-azide (**3**) (0.0117 mol) in 15 ml of anhydrous $Et_2O$. The solution was stirred for 4 hr. After addition was complete excess $LiAlH_4$ was decomposed with "wet" $Et_2O$ followed by $H_2O$. The inorganic salts were removed and the $Et_2O$ layer was washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 1.8 g (64%) of **3**.

The hydrochloride salt was recrystallized (MeOH–$Et_2O$): mp 293–295° dec; nmr ($CF_3COOH$) δ 3.95 (m, 1 H, $W_{1/2}$ = 20 Hz, C-2 CH), 3.55 (m, 1 H, $W_{1/2}$ = 8 Hz, C-3 CH). *Anal.* ($C_{16}H_{24}ClN$) C, H, N.

The methanesulfonate salt was recrystallized (EtOAc), mp 174–180° dec.

3(a)-Phenyl-*trans*-2-decalone (**28**). To 3(a)-phenyl-*trans*-2(a)-decalol (**24**) (14.0 g, 0.06 mol) in 500 ml of $Me_2CO$, cooled in an ice bath, was added dropwise *N*-bromoacetamide (16.5 g, 0.120 mol) in 100 ml of $H_2O$. The solution was stirred for 12 hr at 25°. Excess 20% $Na_2SO_3$ solution was added and the $Me_2CO$ was removed *in vacuo*. The aqueous solution was extracted several times with $Et_2O$. The combined $Et_2O$ fractions were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed *in vacuo*, below 5°, affording an oil, which was chromatographed on silica gel, eluting with hexane–EtOAc (9:1), affording 11.5 g (86.5%) of **28**. The oil was crystallized (hexane): mp 97°; ir (liquid film) 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) 3.8 (m, 1 H, $W_{1/2}$ = 9 Hz, C-3 CH).

3(a)-Phenyl-*trans*-2(e)-decalol (**32**). To a stirred suspension of $LiAlH_4$ (0.55 g, 0.015 mol) in 30 ml of anhydrous $Et_2O$ was added dropwise 3(a)-phenyl-*trans*-2-decalone (**28**) (1.8 g, 0.008 mol) in 10 ml of anhydrous $Et_2O$. The solution was stirred for 12 hr at 25°. Excess $LiAlH_4$ was decomposed with "wet" $Et_2O$ followed by $H_2O$. The inorganic salts were removed and the $Et_2O$ layer was washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed and the resulting oil crystallized (hexane) to afford 1.6 g (87.5%) of **32**: mp 94°; nmr ($CDCl_3$) δ 3.95 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 CH), 3.35 (m, $W_{1/2}$ = 9 Hz, C-3 CH). *Anal.* ($C_{16}H_{22}O$) C, H.

3(a)-Phenyl-*trans*-decalin 2(e)-Tosylate (**33**). To 3(a)-phenyl-*trans*-decalin-2(e)-decalol (**32**) (5.6 g, 0.024 mol) in 95 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added *p*-TsCl (9.1 g, 0.048 mol) to afford 7.6 g (82%) of **33**: mp 98° dec; nmr ($CDCl_3$) δ 4.90 (m, 1 H, $W_{1/2}$ = 16 Hz, C-2 CH) 3.35 (m, 1 H, $W_{1/2}$ = 7 Hz, C-3 CH). *Anal.* ($C_{23}H_{28}OS$) C, H.

3(a)-Phenyl-*trans*-decalin 2(e)-Mesylate (**34**). To 3(a)-phenyl-*trans*-2(e)-decalol (**32**) (10.3 g, 0.045 mol) in 200 ml of anhydrous $C_5H_5N$, cooled in a ice bath, was added methanesulfonyl chloride (10.3 g, 0.09 mol) to afford 12.0 g (90%) of **34**, which decomposed on attempted recrystallization (hexane): nmr ($CDCl_3$) δ 5.15 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 CH), 3.60 (m, 1 H, $W_{1/2}$ = 8 Hz, C-3 CH).

3(a)-Phenyl-*trans*-decalin 2(a)-Azide (**35**). To 3(a)-phenyl-*trans*-decalin 2(e)-tosylate (**33**) (20.0 g, 0.051 mol) in 750 ml of DMF was added $NaN_3$ (10.0 g, 0.154 mol) in 70 ml of $H_2O$. The solution was stirred for 20 hr at 75°. $H_2O$ was added and the solution was extracted several times with $Et_2O$. The combined $Et_2O$ fractions were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 15.2 g of a gummy precipitate which contained approximately 40% of the desired azide **35** and 60% of 2-phenyl-$\Delta^2$-*trans*-octalin (**12**). This mixture was used for the next reaction without further purification.

2(a)-Amino-3(a)-phenyl-*trans*-decalin (**4**). To a stirred suspension of $LiAlH_4$ (9.5 g, 0.25 mol) in 250 ml of anhydrous $Et_2O$ was added dropwise 15.2 g of a mixture containing approximately 40% 3(a)-phenyl-*trans*-decalin 2(a)-azide (**35**) and 60% of 2-phenyl-$\Delta^2$-*trans*-octalin (**12**) in 100 ml of anhydrous $Et_2O$. The solution was stirred for 12 hr. Excess $LiAlH_4$ was decomposed with "wet" $Et_2O$ followed by $H_2O$. The inorganic salts were removed and the $Et_2O$ layer was washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 10.8 g of a white gummy precipitate which was dissolved in MeOH. The 2-phenyl-$\Delta^2$-*trans*-octalin (**12**) crystallized from the MeOH solution and was removed by filtration. The MeOH was removed to afford 4.2 g of an oil which was the desired amine.

The methanesulfonate salt of **4** was recrystallized (absolute EtOH–$CHCl_3$): mp 161–163°; nmr ($CDCl_3$) δ 4.05 (m, 1 H, $W_{1/2}$ = 13 Hz, C-2 CH), 3.45 (m, 1 H, $W_{1/2}$ = 6 Hz, C-3 CH). *Anal.* ($C_{17}H_{27}NO_3S$) C, H, N.

3(e)-Cyclohexyl-*trans*-2(a)-decalol (**37**). To 2(e)-phenyl-*trans*-2-decalone (**15**) (2.28 g, 0.01 mol) in 50 ml of glacial AcOH containing 10 drops of concentrated HCl solution was added 120 mg of $PtO_2$. The solution was placed on the Parr shaker for 8 hr at 30 psi at 25°. The $PtO_2$ and the solvent were removed to afford 2.1 g of an oil. The oil was crystallized (hexane) to afford 2.0 g (85%) of **37**: mp 90°; nmr ($CDCl_3$) 4.55 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH). *Anal.* ($C_{16}H_{28}O$) C, H.

2(e)-Phenyl-*trans*-decalin-2(a),3(a)-diol (**38**). The procedure of Berti, *et al.*,[6] was followed, utilizing 2(e)-phenyl-*trans*-decalin 2,3-oxide (**13**) (6.5 g, 0.028 mol), KOH (9.1 g), and 110 ml of 85% DMSO solution as a solvent yielding 5.1 g (74%) of **38**, mp 115–117° (lit.[2] 118–119°).

3(e)-Phenyl-*trans*-2(a)-decalol (**36**). A mixture of 2(e)-phenyl-*trans*-decalin-2(a),3(a)-diol (**38**) (2.46 g, 0.01 mol), W-2 Raney Ni (40 g), and 150 ml of EtOH was stirred for 2.5 hr at 50°. The Raney Ni was removed by filtration and washed with hexane. $H_2O$ was added and the aqueous layer was washed several times with hexane. The combined hexane layers were washed with saturated NaCl solution and dried ($MgSO_4$). The solvent was removed to afford 2.35 g of an oil. The oil was chromatographed on silica gel, eluting with $CHCl_3$, to yield 2.0 g (87%) of **36** after crystallization (hexane): mp 55°; nmr ($CDCl_3$) δ 4.0 (m, 1 H, $W_{1/2}$ = 6 Hz, C-2 CH). *Anal.* ($C_{16}H_{22}O$) C, H.

3(e)-Phenyl-*trans*-decalin 2(a)-Tosylate (**39**). To 3(e)-phenyl-*trans*-2(a)-decalol (**36**) (0.69 g, 0.003 mol) in 15 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added *p*-TsCl (1.1 g, 0.06 mol) to afford 0.9 g (88%) of **39**: mp 134° dec; nmr ($CDCl_3$) δ 4.80 (m, 1 H, $W_{1/2}$ = 8 Hz, C-2 CH). *Anal.* ($C_{23}H_{28}O_3S$) C, H.

3(e)-Phenyl-*trans*-decalin 2(a)-Mesylate (40). To 3(e)-phenyl-*trans*-2(a)-decalol (36) (0.69 g, 0.003 mol) in 10 ml of anhydrous $C_5H_5N$, cooled in an ice bath, was added methanesulfonyl chloride (0.69 g, 0.006 mol) to afford 0.70 g (80%) of 40: mp 115°; nmr ($CDCl_3$) 4.80 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH). *Anal.* ($C_{17}H_{24}O_3S$) C, H.

General Procedure for Preparation of Isopropyl Analogs. The amine salt was converted to the free amine by the use of a strong base ion-exchange column (Amberlite IRA-400) or by adding the amine salt to a saturated $NH_3$–$CHCl_3$ solution, filtering the ammonium salt, and evaporating the solvent to yield the free amine. The free amine was dissolved in absolute EtOH containing 5% MeOH and to this solution was added a 4 *M* excess amount of $Me_2CO$. The solution was subjected to hydrogenation over Adams platinum catalyst at 32 psi at 25° for 12 hr. The catalyst and the solvent were removed to afford the isopropyl analog as the free amine, which was dissolved in $Et_2O$. The hydrochloride salt was prepared by the addition of saturated HCl-$Et_2O$ solution to the etheral solution. The salt was removed by filtration and recrystallized from the appropriate solvent.

2(e)-Isopropylamino-3(e)-phenyl-*trans*-decalin Hydrochloride (5). This compound was recrystallized from $Me_2CO$-hexane, mp 117°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(a)-Isopropylamino-3(e)-phenyl-*trans*-decalin Hydrochloride (6). The compound was recrystallized from $CH_3CN$, mp 295–300°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(e)-Isopropylamino-3(a)-phenyl-*trans*-decalin Hydrochloride (7). This compound was recrystallized from $CHCl_3$, mp 280°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(a)-Isopropylamino-3(a)-phenyl-*trans*-decalin Hydrochloride (8). This compound was recrystallized from $C_6H_6$–EtOAc, mp 227°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

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# Conformational Aspects of Systems Related to Acetylcholine. 5. Syntheses of the *dl*-2(e)-Methyl-, *dl*-3(e)-Methyl-, and *dl*-2(e),3(e)-Dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin Halides

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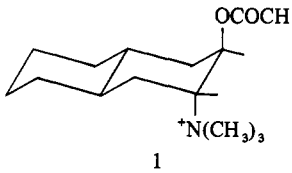
The syntheses of the *dl*-2(e)-methyl-, *dl*-3(e)-methyl-, and *dl*-2(e),3(e)-dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin halides (5–7) are described. These three compounds were assayed for their muscarinic activity and as substrates for AChE.

In previous reports from these laboratories, the synthesis and testing of conformationally rigid analogs of acetylcholine (ACh) in the *trans*-decalin series and the *trans*-decahydroquinoline series were discussed.[1–4] These compounds were prepared in an attempt to determine the conformational requirements for ACh at the muscarinic, nicotinic, and esterase receptor sites. The compounds having the acetoxy and the ammonium functions in a staggered conformation, 1 and 2, were substrates for acetylcholineesterase (AChE)



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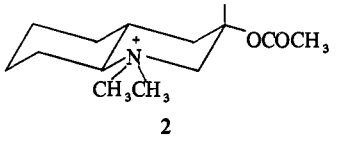
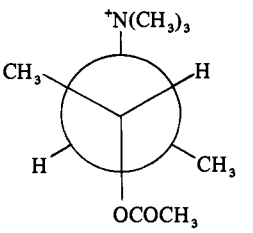


2

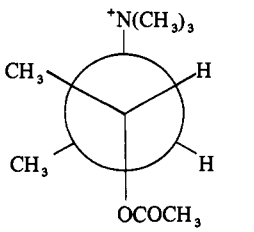
while the compounds in a gauche conformation did not undergo significant hydrolysis with AChE. The diaxial analog in the decalin series, 1, also exhibited the greatest amount of muscarinic activity in the series. Similar studies[5,6] with systems incapable of a truly staggered conformation show maximum activity with the partial eclipse conformations having a dihedral angle ~120° rather than with the total eclipse conformation having a dihedral angle ~0° with respect to the acetoxy and quaternary nitrogen.

Cocolas, *et al.*,[7] have proposed a model for muscarinic and hydrolytic sites which is dependent on a tight three-dimensional fit of cholinergic molecules between the agonist and hydrolytic sites. This proposal is similar to that of Chothia[8] who has based his receptor site conformational preferences on crystallographic studies.[9–12]

The postulates offered by the above authors are not in agreement with the observations previously reported from this laboratory.[1,3] With *dl-erythro*- and *dl-threo*-α,β-dimethylacetylcholines (3 and 4) muscarinic activity of 3 was markedly greater than that of 4 while the erythro isomer 3



3



4

†Taken in part from the dissertation presented by G. R. Parker, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.