A Conformational Study of β-Phenethanolamine Receptor Sites. II. The Syntheses of the *dl*-3-Phenyl-3-hydroxy-*trans*-decahydroquinolines

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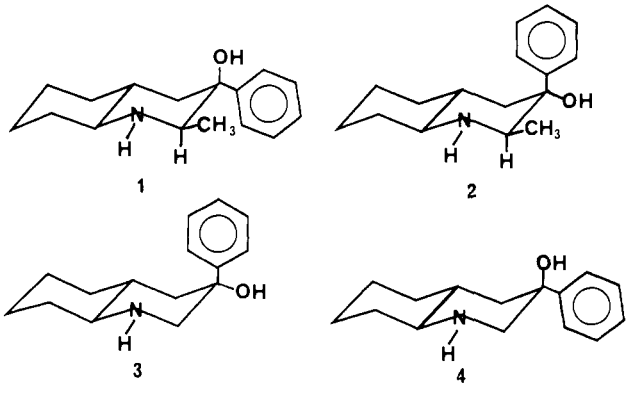
trans-Decahydro-3(e)-quinolinol (**5**) was treated with $(CF_3CO)_2O$ to give the amido ester. Selective cleavage of the ester gave the trifluoroacetamide of *trans*-decahydro-3(e)-quinolinol (**6**). This amido alcohol (**6**) was oxidized by the Moffatt–Pfitzner procedure to give the trifluoroacetamide of *trans*-decahydro-3-quinolone (**7**). Addition of PhLi to the amido ketone (**7**) gave 3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**3**) as the only isomer. N-Methyl-*trans*-decahydro-3(e)-quinolinol was oxidized by the Moffatt–Pfitzner procedure to give N-methyl-*trans*-decahydro-3-quinolone (**8**). PhLi was added to this ketone to give a 5:1 mixture of N-methyl-3(e)-phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (**13**) and N-methyl-3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**14**). The major isomer (**13**) having the equatorial phenyl group was demethylated using diethyl azodicarboxylate to give 3(e)-phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (**4**). The stereochemistry was assigned on the basis of nmr and ir spectra. The results of vas deferens assays are discussed.

The basic postulate that different conformations of a biologically active agent might be preferred at each type of receptor site (metabolic, effector, transport, etc.) has received support as the result of incorporation of the acetylcholine moiety in the conformationally rigid *trans*-decalin.[2]

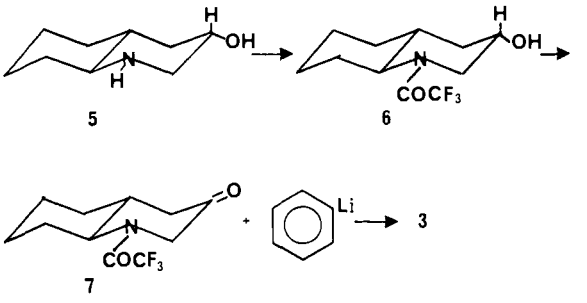
A similar approach was employed in investigation of the conformational requirements of the β-phenethanolamine receptor sites by the syntheses of the four possible 3-amino-2-phenyl-*trans*-2-decalols.[3] All four of these isomers as *d,l* pairs possessed equal activity in the vas deferens preparation of Patil and coworkers.[4] The resolution of these four compounds into their optical antipodes and testing of the resolved materials in reserpinized preparations is now under investigation.

The 3-amino-2-phenyl-*trans*-2-decalols provided two conformations of each, the *erythro* and *threo* configurations with respect to the ephedrines. The syntheses of two *d,l* pairs of isomeric 2-methyl-3-phenyl-3-hydroxy-*trans*-decahydroquinolines (**1**, **2**) will provide the remaining analogous noneclipsed conformations of the *erythro* and *threo* configurations. The demethyl analogs **3** and **4** are the subject of this paper.



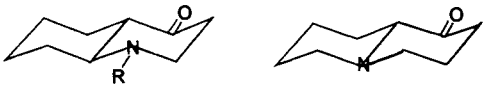
trans-Decahydro-3(e)-quinolinol (**5**) was prepared by the catalytic reduction of 3-quinolinol in THF with Raney Ni.[5] The trifluoroacetamide of *trans*-decahydro-3(e)-quinolinol (**6**) was prepared to protect the basic amine during subsequent reactions. Oxidation of the amido alcohol **6** using the DMSO–dicyclohexylcarbodiimide method[6] with pyridinium trifluoroacetate as the proton source gave the trifluoroacetamide of *trans*-decahydro-3-quinolone (**7**) in 80% yield (Scheme I).

SCHEME I



Infrared bands at 5.75 and 5.92 μ verified the presence of a ketone and trifluoroacetamide, respectively.

Phenylation of the amido ketone **7** using either PhMgBr or PhLi gave 3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**3**) as the only product. The exclusive addition of the phenyl group to **7** was quite surprising in light of previously reported results. Garbisch and Patterson[7] found an axial to equatorial phenyl ratio of 2.5:1 when PhMgBr was added to 4-*t*-butylcyclohexanone. Smissman and Steinman[8] reported the equatorial phenyl group to predominate over the axial phenyl group by a 6:1 ratio when PhMgBr was added to N-methyl-*trans*-decahydro-4-quinolone (**8**), while Mistryukov, *et al.*,[9] found a 4:1 ratio of equatorial to



8 R = CH_3
9 R = PhCO

10

(1) Taken in part from the dissertation presented by G. S. Chappell, Oct 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

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

(3) E. E. Smissman and W. H. Gastrock, *ibid.*, 11, 860 (1968).

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

(5) E. E. Smissman and G. S. Chappell, *J. Med. Chem.*, **12**, 432 (1969).

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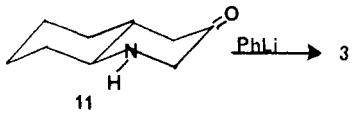
(7) E. Garbisch, Jr., and D. Patterson, *ibid.*, **85**, 3228 (1963).

(8) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).

(9) E. Mistryukov, N. Aronova, and V. Kucherov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1514 (1962).

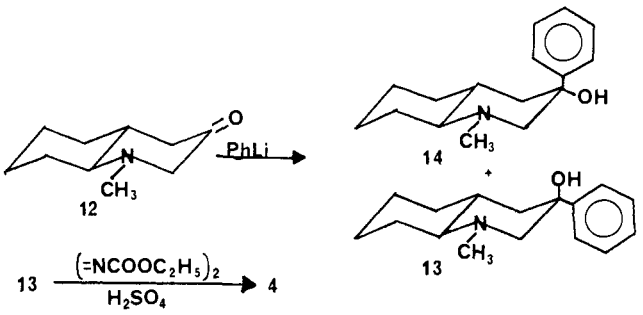
axial phenyl group with the same ketone (**8**) using PhLi. N-Benzoyl-*trans*-decahydro-4-quinolone (**9**) gave predominantly equatorial phenyl product with PhLi.[9] 1-Ketoquinolizidine (**10**) was allowed to react with PhMgBr to give a 2.5:1 equatorial:axial phenyl ratio.[10]

When PhLi was allowed to react with *trans*-decahydro-3-quinolone (**11**), the axial phenyl compound **3** was the only product. This indicated that the axial addition of the phenyl group did not result from the presence of the trifluoroacetamide function.



N-Methyl-*trans*-decahydro-3(e)-quinolinol[5] was oxidized with the DMSO–dicyclohexylcarbodiimide–H_3PO_4 reagent[6] using the procedure of Albright and Goldman[11] to give N-methyl-*trans*-decahydro-3-quinolone (**12**). Addition of PhLi to this ketone gave N-methyl-3(e)-phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (**13**) and N-methyl-3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**14**) in a 5:1 ratio (Scheme II). The stereochemistry of these isomers was assigned on the basis of ir and nmr data.

SCHEME II



The ir spectrum of **13** exhibited a strong OH absorption at 2.86 μ which was attributed to intramolecular H bonding and is in accord with the reported values of 2.86 and 2.87 μ for OH$\cdots$N absorption.[10,12] Intramolecular H bonding is possible only with an axial alcohol at C-3. The other isomer (**14**) showed a free OH absorption at 2.78 μ and intermolecular H-bonded absorption at 2.94 μ. These values corresponded well with the reported values of 2.76 and 2.92 μ, respectively, for *trans*-1-hydroxy-1-phenylquinolizidine.[9]

The aromatic region in the nmr spectrum of **14** was split into multiplets at δ 7.80 and 7.30 in a ratio of 2:3. This same 2:3 effect was observed with similar axial phenyl compounds in the decalin series when the amino group, two carbons removed, was in an equatorial conformation.[3] The aromatic region in the nmr of **13** showed a multiplet at δ 7.40 as was observed with similar compounds having an equatorial phenyl group and the amino group two carbons removed in either an axial or equatorial conformation.

With the stereochemistry at C-3 of **13** and **14** firmly established, **3** was N-methylated using the procedure of Minato and Nagaski.[13] The nmr and ir spectra of the N-methylated product were identical with those of **14**. This proved that **3** possessed an axial phenyl group and an equatorial OH group.

3(e)-Phenyl-3(a)-hydroxyl-*trans*-decahydroquinoline (**4**) was prepared by the demethylation of **13** utilizing diethyl azodicarboxylate.[14]

The axial phenyl isomer **3** and the equatorial phenyl isomer **4** were assayed in the vas deferens preparation.[4] Neither agent contracted the vas deferens at a concentration of 10^{-4} *M*. The lack of an α-stimulatory response can be assumed to be due to the fact that both **3** and **4** are analogs of isoproterenol. The compounds were also assayed in the presence of D(−)-norepinephrine. Each sample was assayed in four different preparations. With each compound, a potentiation of the contractile response over that obtained with D(−)-norepinephrine was noted although no agonist response was found with either compound alone. The potentiation with the isomer **3** was essentially linear at all dose levels (Figure 1); however, with the isomer **4** (Figure 2) the sensitization of the preparation became marked at the higher concentrations and was no longer parallel to the response of the control. This sensitization has been reported with other compounds.[15,16]

The preparation of **1** and **2**, the optical resolution of **3** and **4**, and more detailed pharmacology of these compounds is presently under investigation.

Experimental Section[17]

Trifluoroacetamide of *trans*-Decahydro-3(e)-quinolinol (6).—*trans*-Decahydro-3(e)-quinolinol[5] (**5**) (5.5 g, 35 mmoles), C_6H_6 (100 ml), and K_2CO_3 (15 g) were cooled in ice while $(F_3CCO)_2O$ (20 ml) was added slowly with rapid stirring. Stirring was continued for 1 hr after the addition. The solution was filtered and the solvent was removed *in vacuo* leaving an oil. The oil was dissolved in MeOH and methanolic KOH was added until the pH was approximately 9. The solvent was removed *in vacuo* to give an oily solid. It was chromatographed on alumina (Woelm, neutral, activity I, 200 g) and eluted with EtOAc to give 6.7 g of white solid. One recrystallization from MeOH–EtOAc gave 6.0 g (68%) of **6**: mp 109–110°; ir ($CHCl_3$), 2.77, 2.89, 3.34, 3.41, 3.51, 5.95 μ; nmr ($CDCl_3$), δ 4.13 ($W_{1/2}$ = 20 cps, axial proton at C-3), 3.60 (multiplet, C*H*$_2$ at C-2, and C*H* at C-10). *Anal.* ($C_{11}H_{16}F_3NO_2$) C, H, N.

Trifluoroacetamide of *trans*-Decahydro-3-quinoline (7).—Compound **6** (5.25 g, 21 mmoles) was dissolved in C_6H_6 (30 ml) and DMSO (30 ml, dried over Molecular Sieves 4A). Pyridine (1.68 ml, 21 mmoles), CF_3CO_2H (0.84 ml, 11 mmoles), and dicyclohexylcarbodiimide (13.0 g, 63 mmoles) were added and the mixture was allowed to stand at room temperature for 24 hr. Et_2O (400 ml) was added followed by oxalic acid (5.67 g, 63 mmoles) dissolved in CH_3OH. When gas evolution ceased, H_2O (150 ml) was added and the solution was filtered. The Et_2O layer of the filtrate was separated and washed twice ($NaHCO_3$, H_2O), dried ($MgSO_4$), and filtered, and the solvent was removed *in vacuo* to give an oily solid. A small amount of Et_2O (50 ml) was added and the solid was filtered. The Et_2O extract was chromatoqraphed on alumina (Woelm, neutral activity I, 200 g) and eluted with C_6H_6. Recrystallization of the product from petroleum ether (60–70°) gave 3.7 g (70%) of the desired ketone **7**: mp 63–64°; ir ($CHCl_3$), 3.31, 3.42, 3.51, 5.75, 5.92 μ; nmr ($CDCl_3$), δ

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(14) A. Makriyannis, Ph.D. Thesis, University of Kansas, 1967.
(15) J. E. Besse, *J. Pharmacol. Exptl. Therap.*, **154**, 224 (1966).
(16) A. Tye, P. N. Patil, and J. B. LaPidus, *ibid.*, **155**, 24 (1967).
(17) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Ir data (μ) were recorded on Beckmann IR8 and IR10 spectrophotometers. Nmr data (ppm, δ) were recorded on Varian Associates Model A-60, A-60A, and HA-100 spectrophotometers (TMS). Microanalyses were conducted by Midwest Microlob, 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.

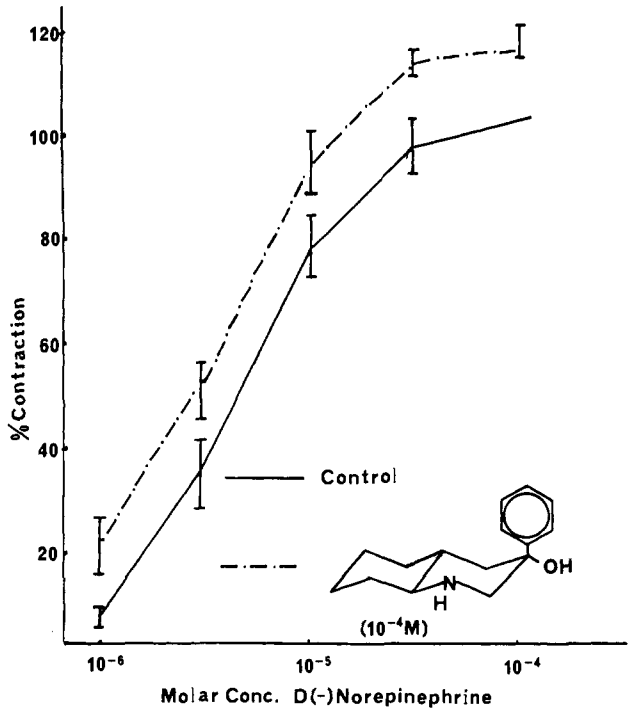

Figure 1.

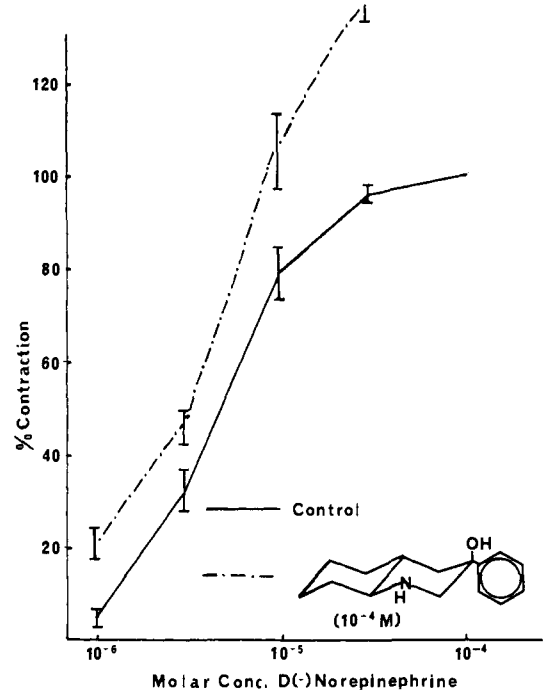

Figure 2.

4.32 (J_{gem} = 18 cps, equatorial proton at C-2), 3.90 (doublet, J_{gem} = 18 cps, axial proton at C-2), 3.73 ($W_{1/2}$ = 23 cps, axial proton at C-10). *Anal.* ($C_{11}H_{14}F_3NO_2$) C, H, N.

3(a)-Phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (3).—Li (1.5 g, 216 mg-atoms) cut into small pieces was suspended in a small amount of Et_2O and PhBr (16.96 g, 108 mmoles) in Et_2O was added slowly with stirring. After the addition was completed, the PhLi solution was cooled in an ice bath and compound **7** (2.7 g, 10.8 mmoles) was added dropwise as an Et_2O solution. Stirring and cooling was continued for 2 hr after the addition. The excess PhLi was destroyed (saturated NH_4Cl) and the Et_2O layer was separated and extracted with 3% HCl (three 70-ml portions). The combined acid extracts were made basic (K_2CO_3) and extracted (CH_2Cl_2). The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* leaving a very viscous oil. Trituration with a very small amount of EtOAc gave 2.0 g of solid. Recrystallization from EtOAc–petroleum ether (60–70°) gave 1.8 g (72%) of **3**: mp 113–114°; nmr ($CDCl_3$), δ 7.63 (multiplet, aromatic *o*-protons), 7.40 (multiplet, aromatic *m*- and *p*-protons), 3.52 (four-line multiplet, J_{gem} = 13 cps, J_{ee} = 1 cps, equatorial proton at C-2), 2.79 (doublet, J_{gem} = 13 cps, axial proton at C-2). *Anal.* ($C_{15}H_{21}NO$) C, H, N.

***trans*-Decahydro-3-quinoline (11).**—The trifluoroacetamide of *trans*-decahydro-3-quinoline (**7**) (200 mg) was heated on a steam bath with 10% H_2SO_4 until solution was effected. The solution was extracted with CH_2Cl_2 which on evaporation produced no residue. The acid solution was made basic (K_2CO_3) and extracted (CH_2Cl_2). The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* leaving a colorless oil (**11**) (75 mg, 61%) which began crystallizing and turning dark almost immediately; ir ($CHCl_3$), 3.03, 3.41, 3.50, 5.85 μ.

The amino ketone **11** (75 mg, 0.5 mmole) was quickly dissolved in Et_2O and added to ethereal PhLi. After stirring for 1 hr, the reaction mixture yielded 3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**3**).

N-Methyl-*trans*-decahydro-3-quinoline (12).—N-Methyl-*trans*-decahydro-3(e)-quinolinol[5] (1.91 g, 11 mmoles) and dicyclohexylcarbodiimide (9.82 g, 48 mmoles) were dissolved in DMSO (25 ml, dried over Molecular Sieves 4A). Crystalline H_3PO_4 (2.35 g, 24 mmoles) was added and the mixture was stirred with cooling for 2 hr. It was allowed to stand for 14 hr at 25°, during which time it became semisolid. A large quantity of CH_2Cl_2 (300 ml) was added and allowed to stand for 30 min. The solid was filtered and washed (CH_2Cl_2), extracted (H_2O), made basic (K_2CO_3), and extracted (CH_2Cl_2). The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered and the solvent was removed *in vacuo* leaving a black oil (1.5 g). The oil was chromatographed on silica gel (Brinkmann, 100 g) and eluted with 1% MeOH–$CHCl_3$. The first 300 ml of solvent eluted some impurities, and the next 600 ml gave 230 mg (12%) of the desired ketone **12**: ir (neat), 3.42, 3.51, 3.62, 5.80 μ; nmr (CCl_4), δ 3.12 (four-line multiplet, J_{gem} = 14 cps, J_{ee} = 1.5 cps, equatorial proton at C-2), 2.69 (doublet, J_{gem} = 14 cps, axial proton at C-2), 2.33 (singlet, NCH_3).

A slightly modified oxidation gave an estimated 35% yield of **12**. N-Methyl-*trans*-decahydro-3(e)-quinolinol[5] (6.71 g, 40 mmoles) and dicyclohexylcarbodiimide (24.52 g, 120 mmoles) were dissolved in DMSO (35 ml, dried over Molecular Sieves 4A). Crystalline H_3PO_4 (6.00 g, 80 mmoles) was dissolved in DMSO (25 ml) with cooling. This cool acid solution was added with C_6H_6 (50 ml, Na dry) to the alcohol solution. The reaction mixture was cooled to maintain it at 25°. It was allowed to stand overnight at 25° and afforded 4.2 g of black oil, estimated to be approximately 60% of the desired ketone **12**. This product was allowed to react with PhLi without further purification.

PhLi Reaction with N-Methyl-*trans*-decahydro-3-quinoline (12).—The purified ketone **12** (230 mg, 1.3 mmoles) dissolved in Et_2O (Na dry) was added with cooling and stirring to an Et_2O solution of PhLi (48 mmoles). After stirring for 3 hr, it was isolated in the manner previously described for PhLi reactions to give 340 mg of black oil. The oil was chromatographed by preparative tlc (Brinkmann silica gel, 2 mm thick, 20 × 40 cm) and developed with 1% MeOH–$CHCl_3$. The first inch of adsorbent above the origin was removed and extracted with MeOH to give N-methyl-3(e)-phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (**13**) (130 mg). The next 1.252 cm of adsorbent after extraction with MeOH yielded N-methyl-3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**14**) (25 mg). Each of the above compounds was then chromatographed by preparative tlc (Brinkmann silica gel, 2 mm thick, 20 × 20 cm) and developed with 5% MeOH–$CHCl_3$. The equatorial phenyl isomer **13** (110 mg) had ir (tetrachloroethylene) 2.86, 3.27, 3.31, 3.36, 3.42, 3.51, 3.60, 6.25, 6.69, 6.92 μ; nmr ($CDCl_3$), δ 7.40 (multiplet, aromatic protons), 2.72 (four-line multiplet, J_{gem} = 12 cps, J_{ee} = 1.5 cps, equatorial proton at C-2), 2.38 (doublet, J_{gem} = 12 cps), 2.25 (singlet, NCH_3). The axial phenyl isomer **14** (20 mg) had ir (tetrachloroethylene) 2.78, 2.94, 3.28, 3.31, 3.36, 3.42, 3.51, 3.61, 6.07, 6.71, 6.87, 6.92 μ; nmr ($CDCl_3$), δ 7.80 (multiplet, aromatic *o*-protons), 7.30 (multiplet, aromatic *m*- and *p*-protons), 3.28 (four-line multiplet, J_{gem} = 12 cps, J_{ee} = 2 cps, equatorial proton at C-2), 2.31 (doublet, J_{gem} = 12 cps, axial proton at C-2), 2.27 (singlet, NCH_3).

N-Methyl-3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (14).—To 3(a)-phenyl-3(e)-hydroxy-*trans*-decahydroquinoline (**3**) (100 mg) dissolved in MeOH (5 ml, dry) was added 40% H_2CO

solution (0.30 ml) and stirred for 2 hr at 25°. $NaBH_4$ (180 mg) was added portionwise at 10–20°. Stirring was continued for an additional 2 hr. Ice was added and the solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to give a white solid. One recrystallization from petroleum ether (60–70°) gave **14**: mp 120–121°; ir ($CHCl_3$) 2.78, 2.92, 3.27, 3.33, 3.42, 3.51, 3.60, 6.25, 6.71, 6.85, 6.92 μ; nmr ($CDCl_3$) δ 7.78 (multiplet, aromatic *o*-protons), 7.30 (multiplet, aromatic *m*- and *p*-protons), 3.28 (two doublets, J_{gem} = 12 cps, J_{ee} = 2 cps, equatorial proton at C-2), 2.30 (doublet, J_{gem} = 12 cps, axial proton at C-2), 2.26 (singlet, NCH_3). *Anal.* ($C_{16}H_{23}NO$) C, H, N.

3(e)-Phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (4).—N-Methyl-3(e)-phenyl-3(a)-hydroxy-*trans*-decahydroquinoline (**13**) (1.11 g, 4.55 mmoles) was treated with diethyl azodicarboxylate (4.36 g, 25 mmoles) in C_6H_6 (100 ml, Na dry). The solution was refluxed for 20 min and allowed to stand for 18 hr. The C_6H_6 was removed *in vacuo* and 10% H_2SO_4 (40 ml) and MeOH (10 ml) were added. The solution was stirred overnight after which the MeOH was removed *in vacuo*. The aqueous acid solution was extracted with Et_2O which was discarded. The aqueous solution was made basic (K_2CO_3) and extracted (CH_2Cl_2). The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* leaving 1.6 g of a black oil. The oil was chromatographed on silica gel (Brinkmann, 100 g) and eluted with 1%, Et_3N–1% MeOH in C_6H_6. After 600 ml of solvent, the desired demethylated compound was eluted (500 mg) in a partially purified state. It was further purified by chromatography by preparative tlc (Brinkmann silica gel, 2 mm thick, 20 × 40 cm) developed with 10% MeOH–$CHCl_3$. The adsorbent from just above the origin to a colored band was removed and extracted with 2% Et_3N–10% MeOH in C_6H_6 to give 260 mg (25%) of white solid. It was recrystallized from C_6H_6–petroleum ether (60–70°) to give 200 mg (19%) of **13**: mp 133–134°; ir ($CHCl_3$) 2.91, 3.04, 3.27, 3.34, 3.42, 3.51, 6.25, 6.37, 6.71, 6.92 μ; nmr ($CDCl_3$) δ 7.40 (multiplet, aromatic protons), 2.89 (singlet, CH_2 protons at C-2), 2.70 (singlet, OH and NH). *Anal.* ($C_{15}H_{21}NO$) C, H, N.

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Conformational Aspects of Acetylcholine Receptor Sites. II. The Syntheses of the *dl*-1-Methyl-3-acetoxy-*trans*-decahydroquinoline Methiodides

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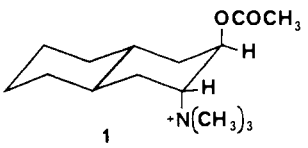
Reduction of 3-quinolinol (**6**) in methanol using Raney Ni gave a mixture of N-methyl-*trans*-decahydro-3(a)-quinolinol (**7**) and N-methyl-*trans*-decahydro-3(e)-quinolinol (**8**). The two alcohols were separated and acetylated with ketene. Quaternization with MeI gave the acetylcholine analogs N-methyl-3(a)-acetoxy-*trans*-decahydroquinoline methiodide (**4**) and N-methyl-3(e)-acetoxy-*trans*-decahydroquinoline methiodide (**5**). Reduction of 3-quinolinol (**6**) in THF using Raney Ni gave a mixture of *trans*-decahydroquinoline, *trans*-decahydro-3(e)-quinolinol (**11**), *trans*-decahydro-3(a)-quinolinol (**10**), and *cis*-decahydro-3(e)-quinolinol (**9**). The stereochemistry was assigned on the basis of the nmr spectra. The results of testing on true acetylcholinesterase and guinea pig ileum are described.

In an effort to study the conformational requirements of the acetylcholine receptor sites, the synthesis and preliminary testing of the isomeric 3-trimethylammonium-2-acetoxy-*trans*-decalin halides and the isomeric α,β-dimethylacetylcholine halides were recently reported.[2] This work indicated that at the muscarinic site a *trans*-diaxial relationship between the quaternary nitrogen and the acetoxyl group was preferred. When hydrolysis rates in the presence of true acetylcholinesterase were measured, the *trans*-diaxial analog **1** was found to be the best substrate, with the *threo* isomer **3** being somewhat slower and the hydrolysis of the *erythro* isomer **2** being negligible. This was suggested to result from hindrance of approach to a very specific enzyme surface. In conformation **3** and in the *trans*-decalin analog **1**, the acetoxyl group and the quaternary nitrogen have a *trans* relationship with the methyl groups skewed, while in conformation **2** the methyl groups are staggered and could hinder approach to, or cause perturbation of, the hydrolase enzyme.



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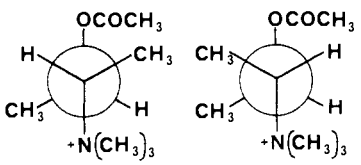
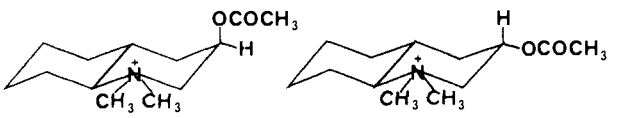


2 3

The four *d,l* pairs of isomeric *trans*-decalin analogs of acetylcholine provided eight of the possible twelve skew forms of acetylcholine in a conformationally rigid state. The synthesis and preliminary testing of the four remaining skew forms of acetylcholine as provided by the two *d,l* pairs of 1-methyl-3(a)-acetoxy-*trans*-decahydroquinoline methiodide (**4**) and 1-methyl-3(e)-acetoxy-*trans*-decahydroquinoline methiodide (**5**) is the subject of this report.



4 5

The conversion of 3-aminoquinoline to 3-quinolinol (**6**) was performed by a modification of the method of

(1) Taken in part from the dissertation presented by G. S. Chappell, Oct 1967, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

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