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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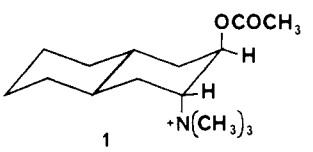
Reduction of 3-quinolinol (**6**) in methanol using Raney Ni gave a mixture of N-methyl-*trans*-decahydro-3(a)-quinolinol (**7**) and N-methyl-*trans*-decahydro-3(e)-quinolinol (**8**). The two alcohols were separated and acetylated with ketene. Quaternization with MeI gave the acetylcholine analogs 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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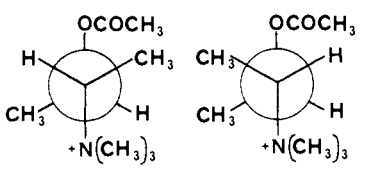
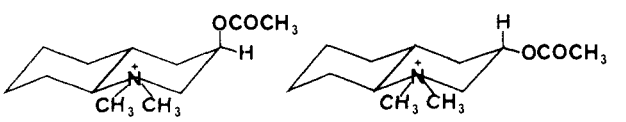


2 3

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

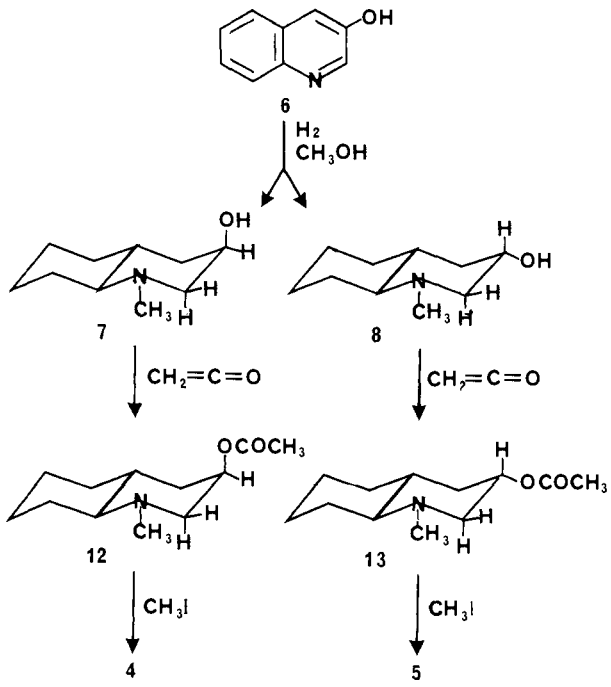
The conversion of 3-aminoquinoline to 3-quinolinol (**6**) was performed by a modification of the method of

(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).

Mills and Watson[3] utilizing the decomposition of the diazonium salt. Catalytic reduction of 3-quinolinol (**6**) in MeOH using Raney Ni (Scheme I) gave a mixture of

SCHEME I



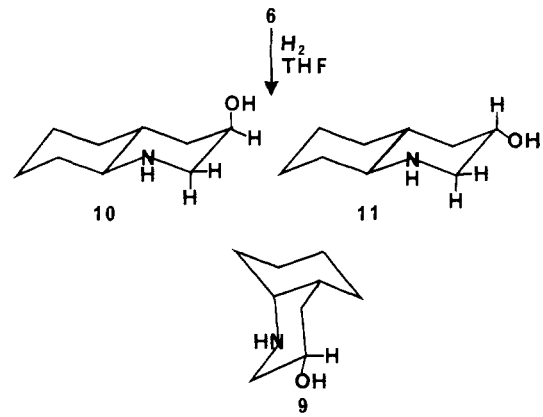
1-methyl-*trans*-decahydro-3(a)-quinolinol (**7**) and 1-methyl-*trans*-decahydro-3(e)-quinolinol (**8**) with some 1-methyl-*trans*-decahydroquinoline. The predominance of a *trans* ring juncture in reductions with Ni catalysts is well documented[4] and the observed N-alkylation by alcoholic solvents is known.[4c] The ratio of equatorial alcohol **8** to axial alcohol **7** was 5:1 when the reduction was performed at 190–200°.

The assignment of the axial and equatorial nature of the alcohol groups was made on the basis of their nmr spectra. The spectrum of **8** showed a multiplet at δ 3.70 ($W_{1/2}$ = 21 cps) which shifted to 4.93 on acetylation. The spectrum of **7** exhibited a multiplet at δ 3.72 ($W_{1/2}$ = 7 cps) which shifted to 4.84 on acetylation. The shift on acetylation is consistent with the assignment of these multiplets to the C-3 protons and the peak widths at half-height define the axial and equatorial nature of the respective protons.[5]

The second point of stereochemistry, the *trans* ring juncture, was thought to be verified in the early stages of this work by a broad multiplet at δ 2.8–2.9 ($W_{1/2}$ = 19 cps) which integrated for one proton. In the 60-MHz spectra it appeared as a doublet with further splitting. This multiplet was assigned to the axial methine proton at C-10. This assignment was studied using spin decoupling on the axial alcohol **7**. In the 100-MHz spectrum the multiplet at δ 2.88–2.95 was resolved to a six-line multiplet. Irradiation of the δ 3.72 multiplet collapsed the six line at 2.88–2.95 to a four-line multiplet. This indicated that the proton represented by this chemical shift was coupled with the proton at C-3 and a more logical assignment for this multiplet was the equatorial C-2 proton. This equatorial C-2 proton was geminally coupled with the axial C-2 proton with an observed coupling constant of 12 cps to give the basic doublet pattern. It was further coupled with the equatorial C-3 and C-4 protons, each with an observed coupling constant of 2–3 cps to give the observed pair of triplets. The coupling with the C-4 proton is an example of the "W" effect.[5] The axial C-2 proton was observed at δ 2.00 as a four-line multiplet (J_{gem} = 12 cps, J_{ae} = 3 cps). When the δ 3.72 band was irradiated, the pair of doublets collapsed to a doublet (J_{gem} = 12 cps).

The *trans* ring juncture was proved by the catalytic reduction of 3-quinolinol (**6**) in THF using Raney Ni (Scheme II) which gave *cis*-decahydro-3(e)-quinolinol (**9**), *trans*-decahydro-3(a)-quinolinol (**10**), and *trans*-decahydro-3(e)-quinolinol (**11**). The C-3 proton of **10** appeared at δ 3.86 ($W_{1/2}$ = 7 cps) in the nmr spectrum which is consistent with an equatorial proton and thus an axial alcohol. The C-3 protons of **9** and **11** were split into broad septets at δ 3.85 and 3.65, respectively, which allowed the hydroxyl groups to be assigned the equatorial configuration.

SCHEME II



Isomer **9** was designated as having the *cis* ring juncture on the basis of a multiplet at δ 2.82 ($W_{1/2}$ = 9 cps) which was assigned to the methine protons at C-10. Booth and Bostock[6] found that *cis*-decahydroquinoline exhibited a multiplet at δ 2.65 ($W_{1/2}$ = 8 cps) which they assigned to the C-10 methine proton. The axial C-10 methine proton of *trans*-decahydroquinoline was hidden in the envelope of the other aliphatic protons. This axial C-10 proton was also hidden in **10** and **11**, thus supporting the assignment of *trans* ring juncture to these compounds. Methylation of **10** by the procedure of Minato and Nagaski[7] gave **7**. The equatorial alcohol **11** gave the same methiodide as did **8**.

Acetylation of the pure alcohols **7** and **8** (Ac_2O–pyridine) produced a reasonable yield with the equatorial alcohol **8** but a poor yield with the axial alcohol **7**. Acetylation with ketene gave quantitative yields of 1-methyl-3(a)-acetoxy-*trans*-decahydroquinoline (**12**) and 1-methyl-3(e)-acetoxy-*trans*-decahydroquinoline (**13**).

Quaternization with MeI yielded the desired 1-methyl-3(e)-acetoxy-*trans*-decahydroquinoline methiodide

(3) N. Mills and N. Watson, *J. Chem. Soc.*, 741 (1910).

(4) (a) B. Witkop, *J. Am. Chem. Soc.*, **71**, 2559 (1949); (b) L. Palfrey and S. Sabetay, *Bull. Soc. Chim. France*, **5**, 1923 (1938); (c) R. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965.

(5) N. Bhacca and D. Williams, "Application of NMR Spectroscopy in Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964.

(6) H. Booth and A. Bostock, *Chem. Commun.*, 177 (1967).

(7) H. Minato and T. Nagaski, *J. Chem. Soc., C*, 1866 (1966).

(**4**) and 1-methyl-3(e)-acetoxy-*trans*-decahydroquinoline methiodide (**5**).

Biological Results.—Compounds **4** and **5** were subjected to hydrolysis studies in the presence of true acetylcholinesterase isolated from the electric organ of the eel (*Electrophorus electricus*).[8] In preliminary studies it was found that the equatorial acetate, which possesses the quaternary nitrogen and the acetate function in a staggered conformation, served as a substrate. The axial acetate, in which the quaternary nitrogen and the acetate are skewed, acted as an inhibitor to the hydrolyase enzyme. As controls, 3(a)-dimethylamino-2(a)-acetoxy-*trans*-decalin methiodide (**1**) and 3(e)-dimethylamino-2(a)-acetoxy-*trans*-decalin methiodide were assayed concurrently. The *trans*-diaxial **1** served as a substrate, as previously reported, and the skewed decalin analog proved to be an inhibitor of the true acetylcholinesterase.

The four compounds discussed above were submitted to nicotinic assay. None of these compounds proved to be agonists but all four blocked the action of carbamoylcholine.

In an assay of muscarinic action **4** proved to be a partial agonist having a relative potency on a molar basis of 0.02 as compared to acetylcholine when the concentration was 50 μg/ml and 0.015 at a concentration of 75 μg/ml. Compound **5** had no agonist properties at concentrations from 20 to 400 μg/ml but blocked acetylcholine-induced contraction 60% at 50 μg/ml, 75% at 100 μg/ml, and 90% at 200 μg/ml. Compound **4** at concentrations of 100 μg and above also blocked response to acetylcholine.[9]

The above results add support to the earlier report[2] that a staggered conformation of the substrate is required at the very specific true acetylcholine esterase receptor site. The muscarinic results can also be interpreted as supporting the earlier work; however, until **4** and **5** are resolved and the homologs of **4** and **5**, with a methyl group in the axial and equatorial conformation at the 2 position, are prepared, no definitive statement can be made. In the previous report one of the skew decalin analogs of acetylcholine had muscarinic activity which was approximately one-tenth that of the diaxial decalin analog **1**. Compound **4** causes the contraction of the guinea pig ileum in a proportional manner. Further studies will be undertaken with the resolved materials in order to determine if **5** is binding tenaciously to the exact receptor site, thus inhibiting acetycholine.

The nicotinic assay will be attempted on the remaining decalin analogs since from the present data no conclusions are warranted.

Experimental Section[10]

3-Quinolinol (6).—3-Aminoquinoline (14.4 g, 0.1 mole) was dissolved in H_2SO_4 (8.0 ml, 0.3 mole) diluted with 50 ml of H_2O and the solution was cooled to 0°. $NaNO_2$ (8.7 g, 0.13 mole) dissolved in 25 ml of H_2O was added below the surface of the acid solution with stirring at such a rate (15 min) to maintain the temperature below 5°. The temperature was maintained at 0–5° and the solution was stirred for 1 hr. The diazonium solution was added dropwise with stirring to H_2SO_4 (10 ml) diluted with 50 ml of H_2O and heated to 75–80°. The stirring was continued until H_2 evolution ceased. The solution was reduced in volume *in vacuo* with the formation of red crystals. The crystals were filtered, redissolved (hot H_2O), and neutralized with $NaHCO_3$. The light brown precipitate was filtered and dried in a desiccator over P_2O_5; yield 12.47 g (86%), mp 198–201°.

N-Methyldecahydro-3-quinolinol.—3-Quinolinol (**6**) (3 g, 0.02 mole) was dissolved in MeOH (120 ml) and hydrogenated over Raney Ni (W-2,[11] 1.5 g). The H_2 pressure was raised to 215 kg/cm² and the reaction vessel was heated to 190–200° during which time the pressure increased to 281 kg/cm². These conditions were maintained for 11 hr. After cooling, the solution was filtered through Celite and the solvent was removed *in vacuo* leaving 3.1 g of a slightly colored viscous oil: nmr (CCl_4), δ 3.70 (CH at C-3), 2.85 (equatorial H at C-2), 2.19 (NCH_3).

Separation of 3(a)- and 3(e)-N-Methyl-*trans*-decahydroquinolinol (7 and 8).—The mixture of isomers (2.16 g) was chromatographed on Woelm alumina (200 g, neutral, activity IV). Fractions of 8 ml were collected and analyzed by gas chromatography: solvent 1 (C_6H_6), fractions 1–187; 2 (2% Et_2O–C_6H_6), 187–261; 3 (10% Et_2O–C_6H_6), 261–350; 4 (50% Et_2O–C_6H_6), 350–498; 5 (EtOAc), 400 ml. Fractions 155–310 contained 350 mg of the axial alcohol **7**. Fractions 310–405 contained a mixture of axial (**7**) and equatorial (**8**) alcohol. Fractions 405–498 and the 400-ml fraction contained 1.32 g of the equatorial alcohol **8**.

The axial alcohol **7** was recrystallized from cyclohexane: mp 77–78°; ir (CCl_4), 2.82, 3.42, 3.50, 3.58 μ; nmr (C_6H_6), δ 3.72 ($W_{1/2}$ = 7 cps, equatorial H at C-3), 2.68 (six-line multiplet, J_{gem} = 12 cps, equatorial H at C-2), 1.98 (singlet, NCH_3). *Anal.* ($C_{10}H_{19}NO$) C, H, N.

Equatorial alcohol **8** had ir (CCl_4) 3.0 (very broad), 3.41, 3.49, 3.60 μ; nmr (CCl_4), δ 3.70 ($W_{1/2}$ = 21 cps, axial H at C-3), 2.90 ($W_{1/2}$ = 19 cps, equatorial H at C-2), 2.18 (singlet, NCH_3); methiodide: mp 275–276°; ir (KBr), 3.0, 3.41, 3.49, 6.75, 6.90 μ. *Anal.* ($C_{11}H_{22}INO$) C, H, N.

N-Methyl-3(e)-acetoxy-*trans*-decahydroquinoline (13).—N-Methyl-3(e)-*trans*-decahydroquinolinol (**8**) (340 mg, 2 mmoles) was dissolved in dry C_6H_6 and ketene was passed through the solution until acetylation was complete (glpc). N_2 was bubbled through the solution and the C_6H_6 was removed *in vacuo* leaving **3** as a brown oil (400 mg, 95%): ir (CCl_4), 3.41, 3.49, 3.60, 5.76, 8.04 μ; nmr (CCl_4), δ 4.93 (septet, J_{aa} = 9.5 cps, J_{ea} = 4.5 cps axial H at C-3), 2.90 (poorly resolved four-line multiplets, equatorial H at C-2), 2.17 (singlet, NCH_3), 1.92 (singlet, CH_3COO). The oil was not further purified.

N-Methyl-3(e)-acetoxy-*trans*-decahydroquinoline Methiodide (5).—N-Methyl-3(e)-acetoxy-*trans*-decahydroquinoline (**13**) (400 mg, 1.9 mmoles) was dissolved in 5 ml of dry C_6H_6 and treated with MeI (2 ml) in C_6H_6. After standing for 2 hr the solid was filtered, washed with EtOAc, and recrystallized from EtOAc–MeOH to give **5** (535 mg, 80%): mp 253–254°; ir (KBr), 3.41, 3.49, 5.73, 8.13 μ; nmr ($CDCl_3$), δ 5.1 (broad, axial H C-3), 4.0 (broad, protons C-9 and C-2), 3.66 and 3.25 (singlets, NCH_3), 2.07 (singlet, CH_3COO). *Anal.* ($C_{13}H_{24}INO_2$) C, H, N.

N-Methyl-3(a)-acetoxy-*trans*-decahydroquinoline (12).—N-Methyl-3(a)-*trans*-decahydroquinolinol (**7**) (530 mg, 3.1 mmoles) was acetylated with ketene using the same procedure as for the equatorial alcohol **8** to give a brown oil (610 mg, 93%): ir (CCl_4), 3.41, 3.50, 3.59, 5.77, 8.02, 8.09 μ; nmr (CCl_4), δ 4.84 ($W_{1/2}$ 7 cps, equatorial H at C-3), 2.95 (multiplet, equatorial H at C-2), 2.13 (singlet, NCH_3), 2.00 (singlet, CH_3COO). The oil was not further purified.

N-Methyl-3(a)-acetoxy-*trans*-decahydroquinoline Methiodide (4).—N-Methyl-3(a)-acetoxy-*trans*-decahydroquinoline (**12**) (610 mg, 2.9 mmoles) was quaternized with MeI in the same manner as **13** to give **4** (750 mg, 73%): mp 219.5–220.5°; ir (KBr), 3.42, 3.50, 5.74, 8.05, 8.15 μ; nmr ($CDCl_3$), δ 5.28 ($W_{1/2}$ 9 cps, equatorial H at C-3), 4.52 (equatorial H C-2), 4.06 (axial H's

(8) H. C. Lawler, *J. Biol. Chem.*, **234**, 799 (1959).

(9) All assays were performed on guinea pig ileum suspended in Tyrodes solution. Method was modified from E. J. Walaszek, R. D. Bũnag, and C. G. Huggins, *J. Pharmacol. Exptl. Therap.*, **138**, 139 (1962).

(10) 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). Gas chromatographic data were obtained using a Beckmann GC-4 gas chromatograph using an 180.3 × 0.3 cm column packed with 3% SE-30 on Chromasorb G (DMCS, acid-washed). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., and on an F and 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.

(11) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1964, p 181.

C-2 and C-9), 3.54 and 3.31 (singlets, NCH_3), 2.16 (singlet, CH_3COO). *Anal.* ($C_{18}H_{24}INO_2$) C, H, N.

Reduction of 3-Quinolinol (6) in THF.—3-Quinolinol (**6**) (10 g) was dissolved in THF (180 ml) and hydrogenated over Raney Ni (*W*-2,[9] 3.0 g) with an initial pressure of 215 kg/cm². It was heated to 150° during which time the pressure rose to 246 kg/cm² and these conditions were maintained for 24 hr. After cooling, the solution was filtered through Celite and the solvent was removed *in vacuo* leaving 10 g of oil. Glpc indicated nearly equal quantities of *trans*-decahydroquinoline, *trans*-decahydro-3(e)-quinolinol (**11**), *trans*-decahydro-3(a)-quinolinol (**10**), and *cis*-decahydro-3(e)-quinolinol (**9**). After standing, the oil solidified. A small amount of EtOAc was added, and the solid was removed by filtration and washed with EtOAc to give 8 g of a white solid, mp 130–136°. Several recrystallizations from MeOH–EtOAc gave 2 g of pure *trans*-decahydro-3(e)-quinolinol (**11**): mp 149–150°; methiodide mp 276°; ir ($CHCl_3$), 2.77, 3.05 broad, 3.35, 3.42, 3.51, 6.92 μ; nmr ($CDCl_3$), δ 3.65 (septet J_{aa} = 11 cps, J_{ae} = 5 cps, axial H at C-3), 3.21 (eight-line multiplet J_{gem} = 11 cps, J_{ae} = 5 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.41 (triplet, $J_{gem,aa}$ = 11 cps, axial H at C-2). *Anal.* ($C_9H_{17}NO$) C, H, N.

The solids, recovered from the purification of *trans*-decahydro-3(e)-quinolinol (**11**) were chromatographed on silica gel (Brinkmann, 100 g) and eluted with MeOH. A small amount of the *trans*-equatorial alcohol **11** was eluted first. It was followed by *cis*-decahydro-3(e)-quinolinol (**9**) and *trans*-decahydro-3(a)-quinolinol (**10**). Recrystallization of *cis*-decahydro-3(e)-quinolinol (**9**) from MeOH–EtOAc gave 300 mg; mp 159–160°; ir ($CHCl_3$), 2.77, 3.0 broad, 3.35, 3.42, 3.51, 6.93 μ; nmr ($CDCl_3$), δ 3.85 (septet, J_{aa} = 9 cps, J_{ae} = 4 cps, axial H at C-3), 3.20 (eight-line multiplet, J_{gem} = 12 cps, J_{ae} = 4 cps, J_{ee} = 1.5 cps, equatorial H at C-2), 2.82 (H at C-10, $W_{1/2}$ = 9 cps), 2.49 (axial H at C-2, four-line multiplet, J_{gem} = 12 cps, J_{aa} = 9 cps). *Anal.* ($C_9H_{17}NO$) C, H, N.

Recrystallization of *trans*-decahydro-3(a)-quinolinol (**10**) from EtOAc gave 200 mg; mp 95–96.5°; ir ($CHCl_3$), 2.92, 3.34, 3.42, 3.51, 6.93 μ; nmr ($CDCl_3$), δ 3.86 ($W_{1/2}$ = 7 cps, equatorial H at C-3), 3.02 (six-line multiplet, J_{gem} = 13 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.73 (four-line multiplet, J_{gem} = 13 cps, J_{ae} = 2 cps, axial H at C-2). *Anal.* ($C_9H_{17}NO$) C, H, N.

N-Methylation of *trans*-Decahydro-3(a)-quinolinol (10).—The amino alcohol **10** (1.3 g, 8.44 mmoles) was stirred with H_2CO (2.4 ml of 40% solution) in dry MeOH (40 ml) at 25° for 2 hr. $NaBH_4$ (1.2 g) was added portionwise at 10–20°. The solution was allowed to stir for 2 hr at 25°. Me_2CO was added dropwise until the excess $NaBH_4$ was decomposed. Ice was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* leaving N-methyl-*trans*-decahydro-3(a)-quinolinol (**7**) as a crystalline solid (1.39 g, 97%): mp 74–78°; nmr (C_6H_6), δ 3.80 ($W_{1/2}$ = 8 cps, equatorial H at C-3), 2.80 (six-line multiplet, J_{gem} = 12 cps, J_{ee} = 2 cps, equatorial H at C-2), 2.07 (singlet, NCH_3).

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Aroylalkylpyrrolidines. Central Nervous System Depressants

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The title compounds were prepared by alkylating 3-substituted pyrrolidines with the ketal of γ-chlorobutyrophenones. Several compounds show CNS depressant activity comparable to chlorpromazine. Hypotensive effects were also observed in many of the compounds.

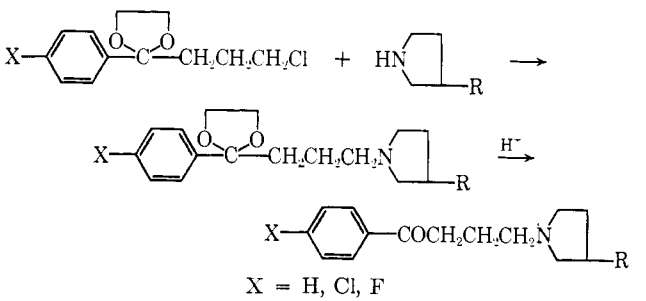
Our continued interest in drugs which affect the CNS has led us to explore in some detail the structural requirements for CNS depressant activity in the group of compounds generally classified as aminobutyrophenones.[1] This paper is the first of several which describe a series of chemical modifications beginning with the aminobutyrophenone I and leading to new structures with potent CNS activities.

I

The work described in this paper deals primarily with variations on the amino portion of the molecule. More specifically, our interest in pyrrolidine chemistry led us to prepare a series of 3-substituted pyrrolidine analogs, most of which are structurally more rigid than the better studied piperidine derivatives. The compounds described herein include a group of 3-aryloxypyrrolidines (Table I), 3-acyloxypyrrolidines (Table II), and 3-anilinopyrrolidines (Table III) which are attached to the 4 position of a butyrophenone moiety.

Chemistry.—Most of the 3-aryloxy- and 3-anilinopyrrolidinylbutyrophenones reported herein (Tables I and III) were prepared by alkylating the appropriate pyrrolidine with a γ-chlorobutyrophenone (protected as the ethylene glycol ketal) followed by removal of the protecting group (Chart I). By the same reaction

CHART I



X = H, Cl, F

sequence 3-hydroxypyrrolidinyl analogs were prepared and converted by standard methods to the acyloxy and carbamoyloxy derivatives described in Table II.

Compounds reported in Table IV were prepared from

(1) (a) P. A. J. Janssen in "Medicinal Chemistry," M. Gordon, Ed., Academic Press, Inc., New York and London, 1967, p 199; (b) P. A. J. Janssen, P. Demoen, B. Hermans, P. Van Daele, K. H. L. Schellekens, C. Vander Eychen, and C. J. E. Nremegeers, *J. Med. Pharm. Chem.*, **1**, 281 (1959).