solution (0.30 ml) and stirred for 2 hr at 25°. NaBH₄ (180 mg was added portionwise at 10–20°. Stirring was continued for an additional 2 hr. Ice was added and the solution was dried (MgSO₄) 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 (CHCl₃), 2.78, 2.92, 3.27, 3.33, 3.42, 3.51, 3.60, 6.25, 6.71, 6.85, 6.92 μ ; mmr (CDCl), 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, $c_{ee} = 12$ cps, $A_{ee} = 12$ cps, $A_{$

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 C₆H₆ (100 ml, Na dry). The solution was refuxed for 20 min and allowed to stand for 18 hr. The C₆H₆ was removed *in vacuo* and 10¹⁷ H₂SO₄ (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 Et₂O which was discarded. The aqueous solution was made basic (K₂CO₃) and extracted (CH₂Cl₂). The CH₂Cl₂ solution was dried (MgSO₄) 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% Et₈N-1%. MeOH in C₆H₆. 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 the (Brinkmann silica gel, 2 nm thick, 20×40 cm) developed with 10% MeOH-CHCl₈. The adsorbent from just above the origin to a colored band was removed and extracted with 2% Et₈N-10% MeOH in C₆H₆ to give 260 mg (25%) of white solid. It was recrystallized from C₆H₆-petroleum ether (60-70°) to give 200 mg (19%) of **13**: mp 133-134°; ir (CHCl₈), 2.91, 3.04, 3.27, 3.34, 3.42, 3.51, 6.25, 6.37, 6.71, 6.92 μ ; mmr (CDCl₃), δ 7.40 (multiplet, aromatic protons). 2.89 (singlet, CH₂protons at C-2), 2.70 (singlet, OH and NH). Anal. (C₁₆H₂₁NO) 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 (**1**), *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



(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). 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.

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*-decahydro-quinoline methiodide (4) and 1-methyl-3(e)-acetoxy-*trans*-decahydroquinoline methiodide (5) is the subject of this report.



The conversion of 3-aminoquinoline to 3-quinolinol (6) was performed by a modification of the method of Mills and Watson³ utilizing the decomposition of the diazonium salt. Catalytic reduction of 3-quinolinol (6) in MeOH using Raney Ni (Scheme I) gave a mixture of



1-methyl-trans-decahydro-3(a)-quinolinol (7) and 1methyl-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 documented⁴ and the observed N-alkylation by alcoholic solvents is known.^{4°} 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 sixline 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

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



Isomer 9 was designated as having the *cis* ring juncture on the basis of a multiplet at $\delta 2.82$ ($W_{1/2} = 9$ cps) which was assigned to the methine protons at C-10. Booth and Bostock⁶ found that *cis*-decahydroquinoline exhibited a multiplet at $\delta 2.65$ ($W_{1/2} = 8$ 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 Nagaski⁷ gave 7. The equatorial alcohol 11 gave the same methiodide as did 8.

Acetylation of the pure alcohols 7 and 8 (Ac₂O-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

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

⁽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.

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

(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 μ g/ml and 0.015 at a concentration of 75 μ g/ml. Compound **5** had no agonist properties at concentrations from 20 to 400 μ g/ml but blocked acetylcholine-induced contraction 60% at 50 μ g/ml, 75% at 100 μ g/ml, and 90% at 200 μ g/ml. Compound **4** at concentrations of 100 μ g and above also blocked response to acetylcholine.⁹

The above results add support to the earlier report² 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 Section¹⁰

3-Quinolinol (6).—3-Aminoquinoline (14.4 g, 0.1 mole) was dissolved in $\rm H_2SO_4$ (8.0 ml, 0.3 mole) diluted with 50 ml of $\rm H_2O$

(9) All assays were performed on gunea 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).

and the solution was cooled to 0° . NaNO₂ (8.7 g, 0.13 mole) dissolved in 25 ml of H₂O 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 $0-5^{\circ}$ and the solution was stirred for 1 hr. The diazonium solution was added dropwise with stirring to H₂SO₄ (10 ml) diluted with 50 ml of H₂O and heated to 75-80°. The stirring was continued until H₂ evolution ceased. The solution was reduced in volume *in vacuo* with the formation of red crystals. The crystals were filtered, redissolved (bot H₂O), and neutralized with NaHCO₅. The light brown precipitate was filtered and dried in a desiccator over P₂O₅; 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 H₂ 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 vacual leaving 3.1 g of a slightly colored viscous oil: nmr (CCl₄), δ 3.70 (CH at C-3), 2.85 (equatorial H at C-2), 2.19 (NCH₃).

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 (C₈H₆), fractions 1–187; 2 (2% Et₂O-C₆H₆), 187–261; 3 (10% Et₂O-C₆H₆), 261–350; 4 (50% Et₂O-C₆H₆), 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 (CCl₄), 2.82, 3.42, 3.50, 3.58 μ ; mmr (C₆H₆), 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, NCH₂). Anal. (C₁₀H₁₉NO) C, H, N.

Equatorial alcohol 8 had ir (CCl₄) 3.0 (very broad), 3.41, 3.49, 3.60 μ ; nmr (CCl₄), δ 3.70 ($W_{1/2} = 21$ cps, axial H at C-3), 2.90 ($W_{2/2} = 19$ cps, equatorial H at C-2), 2.18 (singlet, NCH₃); methiodide: mp 275–276°; ir (KBr), 3.0, 3.41, 3.49, 6.75, 6.90 μ . Anal. (C₁₁H₂₂INO) 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). N₂ was bubbled through the solution and the C_6H_6 was removed in vacuo leaving **3** as a brown oil (400 mg, 95%): ir (CCl₄), 3.41, 3.49, 3.60, 5.76, 8.04 μ ; nmr (CCl₄), 5.4.93 (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, NCH₃), 1.92 (singlet, CH₃COO). 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 C₆H₆ and treated with MeI (2 ml) in C₆H₆. 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 (CDCl₃), δ 5.1 (broad, axial H C-3), 4.0 (broad, protons C-9 and C-2), 3.66 and 3.25 (singlets, NCH₃), 2.07 (singlet, CH₃COO). Anal. (Cl₃H₂INO₂) 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 (CCl₄), 3.41, 3.50, 3.59, 5.77, 8.02, 8.09 μ ; mmr (CCl₄), δ 4.84 ($W_{1/2}$ 7 cps, equatorial H at C-3), 2.95 (multiplet, equatorial H at C-2), 2.13 (singlet, NCH₃), 2.00 (singlet, CH₃COO). 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 (CDCl₃), 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).

⁽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, Iuc., 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 $\pm 0.4\%$ 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, NCH₃), 2.16 (singlet, CH₃COO). Anal. (C₁₃H₂₄INO₂) 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,*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*-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 (CHCl₃), 2.77, 3.05 broad, 3.35, 3.42, 3.51, 6.92 μ ; nmr (CDCl₃), δ 3.65 (septet $J_{aa} = 11$ cps, $J_{ae} = 5$ cps, axial H at C-3), 3.21 (eight-line multiplet $J_{gem.aa} = 11$ cps, $J_{ae} = 11$ cps, $J_{ae} = 11$ cps, $J_{aa} = 1$

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 (CHCl₃), 2.77, 3.0 broad, 3.35, 3.42, 3.51, 6.93 μ ; nmr (CDCl₃), 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. (C₉H₁₇NO) C, H, N.

Recrystallization of trans-decahydro-3(a)-quinolinol (10) from EtOAc gave 200 mg; mp 95-96.5°; ir (CHCl₃), 2.92, 3.34, 3.42, 3.51, 6.93 μ ; nmr (CDCl₃), δ 3.86 ($W_{3/4} = 7$ 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. (C₉H₁₇NO) 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 H₂CO (2.4 ml of 40% solution) in dry MeOH (40 ml) at 25° for 2 hr. NaBH₄ (1.2 g) was added portionwise at 10-20°. The solution was allowed to stir for 2 hr at 25°. Me₂CO was added dropwise until the excess NaBH₄ was decomposed. Ice was added and the mixture was extracted with CH₂Cl₂. The CH₂Cl₂ solution was dried (MgSO₄) 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 (C₆H₆), 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, NCH₃).

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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.

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



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).