carboxylic acid (VII), decomposing sharply at 178–179° (reported[10] m.p. 168° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 222 mμ (ε 7297), 254 (6014); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.91 μ (w), 3.07 (m), 6.02 (s); pK_a' 5.75 (reported pK_a 5.80[9]).

Methyl 2-methylpyrrole-3-carboxylate (VIII). To an ethereal solution of 2-methylpyrrole-3-carboxylic acid (VII) was added a large excess of ethereal diazomethane at room temperature, over a period of 5 min. After standing at room temperature for 3 hr., the solution was evaporated to a residue, which was dissolved in fresh ether, and washed once with 1*N* sodium hydroxide. The ether phase was evaporated to a crystalline residue, which was sublimed at 40°/0.1 mm. to yield 95% of methyl 2-methylpyrrole-3-carboxylate (VIII), m.p. 67–68°; ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 223 mμ (ε 7398); 255 (6341); infrared absorption: $\lambda_{max}^{CHCl_3}$ 2.92 μ (m), 3.07 (w), 5.88 sh (m), 5.93 (s).

Pyrrole-2,3-dicarboxylic acid (X). A mixture of 7.0 g. (0.022 mole) of 1,2,3-tricarbethoxy-4-methoxy-Δ^3-pyrroline (IX) and 30 g. (0.066 mole) of barium hydroxide octahydrate in 100 ml. of water was boiled for 4 hr. The acidic fraction was isolated as above, and the combined ether extracts were evaporated to a solid residue which was sublimed at 180°/0.1 mm.; yield, 170 mg. (5%) of pyrrole-2,3-dicarboxylic acid (X), m.p. 220° dec., sintering at 150° (reported[8] m.p. 225° dec.); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 241 mμ (ε 2,450), 276 (4,200).

Dimethyl pyrrole-2,3-dicarboxylate (XI). An ethereal solution of pyrrole-2,3-dicarboxylic acid (X) was treated with a large excess of ethereal diazomethane, and the neutral fraction was isolated as above, yielding, after sublimation at 50°/0.1 mm., 36 mg. of dimethyl pyrrole-2,3-dicarboxylate (XI), m.p. 69–71° (reported[11] m.p. 72–73°); ultraviolet absorption: $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ε 2580), 278 (4422); infrared absorption: $\lambda_{max}^{CHCl_3}$ 3.00 μ (m), 5.84 (s), 5.94 (s).

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Synthesis of Angularly Substituted Octa- and Decahydroquinolines[1]

C. F. KOELSCH AND D. L. OSTERCAMP[2]

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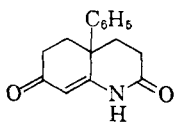
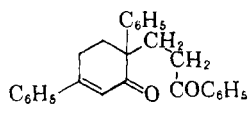
4a-Phenyl-Δ^8-octahydro-2,7-quinolinedione (I) and its *N*-methyl derivative have been reduced with hydrogen and palladium, hydrogen and nickel, and with lithium aluminum hydride. The ultimate reduction product is 4a-phenyldecahydroquinoline or its *N*-methyl derivative, but selection of an appropriate reducing agent enables one to obtain various intermediates in good yield.

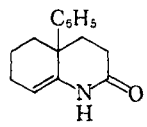
Some time ago it was found that 4a-phenyl-Δ^8-octahydro-2,7-quinoline-dione could be obtained in quantity from readily available materials.[3] The presence of a quaternary carbon in I made it desirable to convert the substance into basic derivatives, for these might have interesting pharmacological properties. Results of experiments in this direction are now reported.



I



II

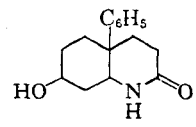


III

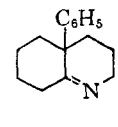
With Grignard reagents, I formed insoluble complexes whose hydrolysis gave back I unchanged. The *N*-methyl derivative of I reacted with phenylmagnesium bromide at both carbonyl groups, but the product lost nitrogen when it was treated with water, and only II was isolated. The structure of this substance was established by synthesis through base-catalyzed reaction of phenylacetone with two equivalents of acrylophenone.

With hydrogen in presence of palladium-charcoal, I lost the ketonic oxygen, forming III. The *N*-methyl derivative of I behaved similarly, forming the *N*-methyl derivative of III. Both of these substances gave the same hydrolysis product, 2-phenylcyclohexanone-2-propionic acid.

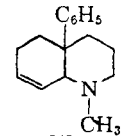
With hydrogen in presence of Raney nickel, I gave a mixture, m.p. 170–205°, in contrast to the previously claimed[3] quantitative formation of IV, erroneously reported to have m.p. 117–119°. The mixture furnished only 48% of IV, m.p. 227–229°, together with 6% of III, and no other pure product could be isolated.



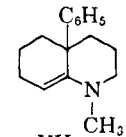
IV



V



VI



VII

With lithium aluminum hydride, I gave V, a deoxidation similar to those discussed by Gaylord.[4] The product (V) was further reduced, using Raney nickel, to known 4a-phenyldecahydroquinoline,

(1) From the Ph.D. Thesis of D. L. Ostercamp, September 1959.

(2) National Science Fellow, 1958–59.

(3) C. F. Koelsch and H. M. Walker, *J. Am. Chem. Soc.*, **72**, 346 (1950).

(4) N. G. Gaylord, Experientia, **10**, 166 (1954). In agreement with structural deductions based on Gaylord's mechanism, the compound showed no NH absorption, and a strong band at 1650 cm.$^{-1}$, corresponding to the 1658 cm.$^{-1}$ C=N band of $\Delta^{1,8a}$-octahydroquinoline assigned by Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

characterized as its *N*-benzoyl and *N*-phenylacetyl derivatives. The latter was reduced again (lithium aluminum hydride) forming *N*-phenethyl-4a-phenyldecahydroquinoline.

When the *N*-methyl derivative of I was reduced with lithium aluminum hydride, the unsaturated amine VI was formed, and not enamine VII. The nature of the product was established by the method of Leonard and Gash[5]; the absorption at 1645 cm.$^{-1}$ of the free base was not shifted in salt formation. Confirmation of this method was obtained by applying it to VII, synthesized both by action of mercuric acetate[6] on 1-methyl-4a-phenyldecahydroquinoline and by reduction of the *N*-methyl derivative of III with lithium aluminum hydride.[7] Here the expected shift in absorption with salt formation was observed; the free base absorbed at 1638 cm.$^{-1}$ (>C=C—N<), the perchlorate at 1671 cm.$^{-1}$ (>C=$\overset{+}{\text{N}}$<).

EXPERIMENTAL

Reaction with phenylmagnesium bromide. A solution of 5 g. of the *N*-methyl derivative of I[8] in 75 ml. of warm benzene was added to ethereal phenylmagnesium bromide prepared from 1.7 g. of magnesium. The mixture was boiled until it became clear (1–2 hr.) and then decomposed with saturated ammonium chloride solution. Removal of solvents left a gum which was dissolved in hot acetic acid containing dilute hydrochloric acid. The solution deposited 1.1 g. of crude product, and 2.2 g. more was obtained by working over the mother liquors. Recrystallization from acetic acid gave 3.0 g. of *1,4-diphenyl-3-oxo-4(β-benzoylethyl)cyclohexene* (II), m.p. 193–195°.

Anal. Calcd. for $C_{27}H_{24}O_2$: C, 85.2; H, 6.36. Found: C, 85.2; H, 6.50.

The same compound was obtained (crude yield 46%) when a suspension of 6 g. of β-chloropropiophenone and 2 g. of phenylacetone in 35 ml. of *tert*-butyl alcohol was treated dropwise with 5*N* methanolic potassium hydroxide to strongly basic reaction and then kept for 12 hr. When less β-chloropropiophenone was used in this synthesis, the product was 1,4-diphenyl-3-oxocyclohexene (yield 37%, m.p. 145–146°) as reported previously.[8]

When 1 g. of II was treated with 1.2 g. of chromic anhydride in acetic acid at 80° it was partly (0.6 g.) recovered and partly converted into an acid, probably *3-(β-benzoylethyl)-2,6-dioxo-3,6-diphenylcaproic acid*, prisms from acetic acid, m.p. 256–259° dec.; absorption at 1715, 1690, and 1675 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{24}O_5$: C, 75.7; H, 5.65. Found: C, 76.2; H, 5.92.

Hydrogenation using palladium. A suspension of 0.5 g. of I in 30 ml. of alcohol absorbed 2 equivalents of hydrogen when it was shaken with 10% palladium on charcoal for 20 hr. The resulting 4a-phenyl-Δ^5-octahydro-2-quinolone (III) formed needles from ethyl acetate (0.31 g.) m.p. 211–214° (reported[9] m.p. 208–210°); $\lambda_{max}^{C_2H_5OH}$ 231 mμ, ε 10,300.

Anal. Calcd. for $C_{15}H_{17}NO$: C, 79.3; H, 7.56; N, 6.17. Found: C, 79.0; H, 7.34; N, 6.21.

The *N*-methyl derivative of I (6 g.) in 180 ml. of alcohol similarly absorbed 2 equivalents of hydrogen during 2 days. The resulting *1-methyl-4a-phenyl-Δ^5-octahydro-2-quinolone* formed needles (4.7 g.) from dilute methanol, m.p. 112–114°; $\lambda_{max}^{C_2H_5OH}$ 233, ε 10,200.

Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.6; H, 7.94; N, 5.81. Found: C, 79.8; H, 8.13; N, 5.95.

Acid hydrolysis[9] gave 71% of 2-phenylcyclohexanone-2-propionic acid, m.p. 110–112° (reported[9] m.p. 113–115°).

Hydrogenation with nickel. Hydrogenation of I according to the published directions gave a nearly quantitative yield of a mixture m.p. 170–205°. When 12.1 g. of this mixture was extracted with three successive portions (100, 75, 75 ml.) of boiling ethyl propionate, there was left 5.6 g. of nearly pure *4a-phenyl-7-hydroxydecahydro-2-quinolone*, m.p. 224–227°. Crystallization from nitromethane gave plates, m.p. 227–229°; the infrared spectrum was consistent with structure IV.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.4; H, 7.80; N, 5.71. Found: C, 73.5; H, 7.58; N, 5.77.

When the crude reduction product (6 g.) was boiled for 10 min. with 60 ml. of acetic anhydride containing 0.2 g. of sulfuric acid, *7-acetoxy-1-acetyl-4a-phenyldecahydro-2-quinolone* (3.8 g.) was obtained. Crystallization from 100° ligroin and then methanol gave prisms m.p. 151–152°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04; N, 4.25. Found: C, 69.6; H, 7.11; N, 4.51.

Boiling the acetyl derivative with 1.5*N* alcoholic potassium hydroxide for 5 min. gave back 43% of IV.

Oxidation of pure IV (3.5 g.) to *4a-phenyldecahydro-2,7-quinolinedione* was accomplished by use of chromium trioxide (1.4 g.) in 1.5 ml. of water and 20 ml. of acetic acid. An excess of chromate was removed by dilution with water and addition of lead acetate, and the organic product was extracted with chloroform. Crystallization from ethyl acetate gave colorless plates (2 g.) which showed a proper infrared spectrum but which could not be obtained in a sharp-melting form; m.p. 184–213°.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.04; N, 5.76. Found: C, 73.8; H, 7.08; N, 5.93.

Reduction with lithium aluminum hydride. A mixture of 10 g. of I and 9 g. of lithium aluminum hydride in 300 ml. of ether was boiled for 21 hr. and then decomposed with 10% sodium hydroxide. Fractional distillation gave 7.4 g. of nearly pure *4a-phenyl-Δ^{8a}-octahydroquinoline* (V), b.p. 182–184° at 26 mm. For analysis this was converted to its *picrate*, yellow plates from alcohol, m.p. 96–99°.

Anal. Calcd. for $C_{15}H_{19}N + C_6H_3N_3O_7 + C_2H_5OH$: C, 56.6; H, 5.78; N, 11.47; C_2H_5OH, 9.43. Found: C, 57.0; H, 6.03; N, 10.96; C_2H_5OH (loss in weight at 110° at 2 mm.), 9.26.

The solvent-free picrate had m.p. 188–190°.

Anal. Calcd. for $C_{15}H_{19}N + C_6H_3N_3O_7$: C, 57.0; H, 5.01; N, 12.6. Found: C, 58.0; H, 5.08; N, 12.4.

Regenerated from its picrate, the free base had b.p. 168° at 15 mm., $n_D^{25.1}$ 1.5708.

Anal. Calcd. for $C_{15}H_{19}N$: C, 84.5; H, 8.98; N, 6.57. Found: C, 84.6; H, 9.11; N, 6.76.

Hydrogenation of 4 g. of V in alcohol using Raney nickel and hydrogen at 30 lbs. required 13 days and gave 3.2 g. of 4a-phenyldecahydroquinoline, b.p. 175–178° at 16 mm. that still contained a small amount of V. The *benzoyl derivative* of the decahydro compound, obtained in 95% yield using Schotten-Baumann conditions, formed plates from alcohol, m.p. 156–157°.

Anal. Calcd. for $C_{22}H_{25}NO$: C, 82.7; H, 7.89; N, 4.39. Found: C, 82.9; H, 7.73; N, 4.39.

Regenerated from the benzoyl derivative by hydrolysis with hydrobromic–acetic acid, the decahydro compound gave a picrate m.p. 115–116° (alcohol solvate) and 154–156° (reported[10] 118° and 155–157°).

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With 3.2 g. of phenylacetyl chloride in ether and aqueous sodium bicarbonate, 3.2 g. of the decahydro compound gave 4.4 g. of *4a-phenyl-1-phenylacetyldecahydroquinoline*, plates from ligroin, m.p. 106–107°.

Anal. Calcd. for $C_{23}H_{27}NO$: C, 82.8; H, 8.16; N, 4.2. Found: C, 83.0; H, 8.05; N, 4.4.

Reduction of the phenylacetyl derivative (3.3 g.) was effected with 1.75 g. of lithium aluminum hydride in 30 ml. of ether by boiling 20 hr. *4a-Phenyl-1-phenethyldecahydroquinoline* was isolated by decomposition with 10% sodium hydroxide. The *hydrobromide* formed colorless crystals (3.6 g.) from ethyl acetate–alcohol, m.p. 243–244°.

Anal. Calcd. for $C_{23}H_{29}N$ + HBr: C, 69.0; H, 7.55; N, 3.50. Found: C, 69.3; H, 7.50; N, 3.48.

The *hydrochloride* had m.p. 228–230°.

Anal. Calcd. for $C_{23}H_{29}N$ + HCl: C, 77.6; H, 8.5; N, 3.94. Found: C, 77.9; H, 8.78, N, 3.97.

1-Methyl-4a-phenyl-Δ^8-octahydro-2,7-quinolinedione (10 g.) reduced with 8.7 g. of lithium aluminum hydride (8.7 g.) gave 7.93 g. of crude product. This was purified through its *picrate*, yellow needles (12.3 g.) from alcohol, m.p. 182–184°.

Anal. Calcd. for $C_{16}H_{21}N$ + $C_6H_3NO_7$: C, 57.9; H, 5.3; N, 12.3. Found: C, 58.8; H, 5.43; N, 12.3.

Regenerated from its picrate, *1-methyl-4a-phenyl-Δ^7-octahydroquinoline* (VI, 87% yield) had b.p. 172–173° at 13 mm., n_D^{25} 1.5653 (supercooled); m.p. 57–59°; weak absorption at 1642 cm.$^{-1}$ ($CHCl_3$).

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.5; H, 9.31. Found: C, 84.4; H, 8.91.

The *hydroiodide* formed crystals from water, m.p. 256–258° dec.; weak absorption at 1645 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{21}N$ + HI: C, 54.1; H, 6.24; N, 3.94. Found: C, 54.4; H, 6.19; N, 4.02.

The *perchlorate* formed crystals from alcohol, m.p. 253–255° dec.; weak absorption at 1645 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{16}H_{21}N$ + $HClO_4$: C, 58.6; H, 6.77; N, 4.27. Found: C, 58.8; H, 6.73; N, 4.22.

When VI (5.5 g.) was shaken with Raney nickel in alcohol under hydrogen at 30 lbs., one equivalent of the gas was absorbed and 5.14 g. of 1-methyl-4a-phenyldecahydroquinoline was obtained, b.p. 160–161° at 8 mm., $n_D^{25.5}$ 1.5541; reported[11] 126–128° at 3 mm. Its hydrochloride had m.p. 224–226°, reported,[11] 225–226°. Its perchlorate formed crystals from alcohol m.p. 210–211°.

Anal. Calcd. for $C_{16}H_{23}N$ + $HClO_4$: C, 58.3; H, 7.33; N, 4.25. Found: C, 58.5; H, 7.38; N, 4.11.

Oxidation of 3.1 g. of 1-methyl-4a-phenyldecahydroquinoline was effected by heating it with 16.7 g. of mercuric acetate in 135 ml. of 5% acetic acid for 1 hr. at 95°. Mercurous acetate (99–100% yield) was then removed by filtration, and the remainder of the mercury was precipitated with hydrogen sulfide. The resulting crude enamine (VII), a pale yellow oil, showed strong absorption at 1638 cm.$^{-1}$. Treatment with perchloric acid in alcohol gave 2.3 g. of *1-methyl-4a-phenyl-Δ^8-octahydroquinoline perchlorate*, prisms m.p. 134–136°; strong absorption at 1671 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{21}N$ + $HClO_4$: C, 58.6; H, 6.77; N, 4.27. Found: C, 58.9; H, 6.75; N, 4.21.

The same perchlorate was obtained in 70% yield from the base obtained from 3 g. of 1-methyl-4a-phenyl-Δ^8-octahydro-2-quinolone by treatment with 1.4 g. of lithium aluminum hydride in 100 ml. of ether for 10 hr.

Regenerated from its perchlorate, *1-methyl-4a-phenyl-Δ^8-octahydroquinoline* (VII) formed an oil that darkened on exposure to air; b.p. 125–127° at 3 mm.; n_D^{25} 1.5718.

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.5; H, 9.31. Found: C, 84.7; H, 9.25.

Acknowledgment. The authors thank Mrs. O. Hamerston and Mr. W. C. Kuryla for analytical results.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS]

The Synthesis of *trans*-2,4-Dioxo-3-hydroxydecahydroquinazoline[1]

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The synthesis of *trans*-hexahydrophthalo(benzoylhydroxamic) and 5-norbornene-*endo-trans*-2,3-dicarbo(benzoylhydroxamic) acids, III and IV, is described. Various rearrangements of these hydroxamic acids are discussed.

The synthesis of 3-hydroxy-[2] and 3-benzenesulfonyloxy-5,6-dihydrouracil[3] was extended to a synthesis of 2,4-dioxo-3-hydroxydecahydroquinazoline, V, and to several of its derivatives. Our original intention was to prepare both the *cis* and *trans* isomers of V by unequivocal syntheses from the corresponding *cis* and *trans* methyl hexahydrophthalates.

To avoid isomerization during the synthesis of methyl *cis*-hexahydrophthalate, *cis*-hexahydrophthalic anhydride was refluxed with methanol to afford methyl hydrogen *cis*-hexahydrophthalate[4] which in turn was treated with diazomethane. The *cis* ester so obtained was identical with that made more conveniently by the esterification of the anhydride with methanol in the presence of sulfuric acid.[5] Isomerization of the *cis* ester by sodium ethoxide in methanol at 100° according to the method of Hückel[6] yielded the *trans* ester.

(1) The authors would like to express their appreciation for the support of this work through Grant CY-4661 from the National Cancer Institute of the National Institute of Health, United States Public Health Service.

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