[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXIX. Octa- and Decahydroisoquinolines from 1-Methyl-3-carbethoxy-4-piperidone

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1-Methyl-3-carbethoxy-4-piperidone adds to methyl vinyl ketone to yield the corresponding 3-(γ-ketobutyl) derivative II, which is readily decarbethoxylated and cyclized to 1,2,3,4,6,7,8,9-octahydro-2-methyl-6-oxoisoquinoline (IV). This quinolone is converted by phenyllithium or phenylmagnesium bromide to the 6-phenyl-6-hydroxyoctahydroisoquinoline V, which is readily rearranged by acid to the isomeric 10-hydroxy derivative VI. Both of these carbinols are dehydrated to the hexahydroisoquinoline VII. Hydrogenation converts IV to the *cis*-decahydroisoquinolone VIII. This ketone was converted to the 2-methyl-6-phenyl-6-acetoxyisoquinoline XI, which was found to be devoid of analgesic action.

The Michael addition of 1-methyl-3-carbethoxy-4-piperidone (I) to methyl vinyl ketone proceeds in good yield (76%) when carried out by the procedure, described in a previous paper of this series,[2] for the addition of I to ethyl acrylate. The initial condensation product II could be separated and distilled, or be directly decarbethoxylated and cyclized by the method of Wilds and Close[3] to the octahydroisoquinolone IV. A small yield (3%) of the ketoester III, resulting from the cyclization of II before decarbethoxylation, generally accompanied IV.

The octahydroisoquinolone IV was reported recently by Marchant and Pinder,[4] who obtained it by two different procedures: (a) a Birch reduction of 1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline followed by hydrolysis of the resulting hexahydroisoquinoline, and (b) the interaction of 4-diethylaminobutan-2-one with the keto ester I. Earlier, Georgian[5] had reported the condensation of methyl vinyl ketone with I to form 2-methyl-6-oxo-9-carbomethoxy-10-hydroxydecahydroisoquinoline and the transformation of this product to IV by vigorous treatment with hydrochloric acid, but no details of this work were given.

The reaction of phenyllithium with IV, followed by the decomposition of the resulting lithium salt with water, yielded the 6-phenyl-6-hydroxyoctahydroisoquinoline V in 90% yield. When phenylmagnesium bromide instead of phenyllithium was used with IV, and the magnesium salt decomposed with dilute acid, the isomeric 10-hydroxy compound VI was the product. It was obtained in only 55–60% yield; 25–30% of unchanged IV was recovered. The presence of such an amount of the latter compound with the reaction product was doubtless the result of the enolization of the original unsaturated ketone IV by the Grignard reagent; the formation of the 10-hydroxy derivative VI was due to the action of acid on the initially formed 6-hydroxy derivative V. This acid-catalyzed transformation of V into VI is quite facile and may be accomplished by simply dissolving V in 5% hydrochloric acid. The spectra of the carbinols V and VI were completely devoid of any carbonyl bands showing that none of the organometallic compounds had added 1,4- to the α,β-unsaturated ketone system of IV.

Both carbinols, V and VI, were readily dehydrated in acidic ethanol to a hexahydroisoquinoline to which the structure VII is assigned. This structure seems preferable to VIIa because the product yields a polymeric adduct with maleic anhydride; dienes of the type VIIa, in which both double bonds are in one ring usually give crystalline adducts with maleic anhydride.[6] Also, the formation of the polymeric adducts requires the presence of at least one terminal hydrogen in the diene system.[7] The ultraviolet spectrum of the diene is in agreement with a planar arrangement of the phenylbutadiene chromophore, which is possible in VII but not in VIIa.

The hydrogenation of IV in dilute hydrochloric acid over palladium-on-carbon catalyst gave the decahydroisoquinolone VIII, which was converted by Wolff–Kishner reduction to the known 2-methyl-*cis*-decahydroisoquinoline (IX). There was no evidence of the formation of any of the *trans* isomer. Thus the *cis* ring juncture of VIII is established. Marchant and Pinder[4] hydrogenated IV over Raney nickel at elevated temperature to 2-methyl-6-hydroxydecahydroisoquinoline, which was then oxidized to the corresponding quinolone. This compound was stereochemically homogeneous and was presumed to have the *trans* structure on the basis of an earlier observation by Witkop.

The isoquinolone VIII formed a dibenzylidene derivative. It reacted with phenyllithium to yield the 6-hydroxy-6-phenyldecahydroisoquinoline X, which was converted to the acetate, XI.

Pharmacological Note.—The ester XI has a structure related to the 1-methyl-4-phenyl-4-acyloxypiperidines, which are known to have significant analgesic action. For this reason XI was submitted as its hydrochloride salt to Mr. E. B. Robbins of The Lilly Research Laboratories, Indianapolis, Ind., for pharmacological testing. He has reported that subcutaneous doses of 10–80 mg./kg. produced no analgesia in rats.

Experimental

1,2,3,4,6,7,8,9-Octahydro-2-methyl-6-oxo-isoquinoline (IV).—A flask containing 10.8 g. (0.45 mole) of sodium hydride was flushed with dry nitrogen for 5 minutes and

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(2) S. M. McElvain, W. B. Dickinson and R. J. Athey, THIS JOURNAL, **76**, 5625 (1954).

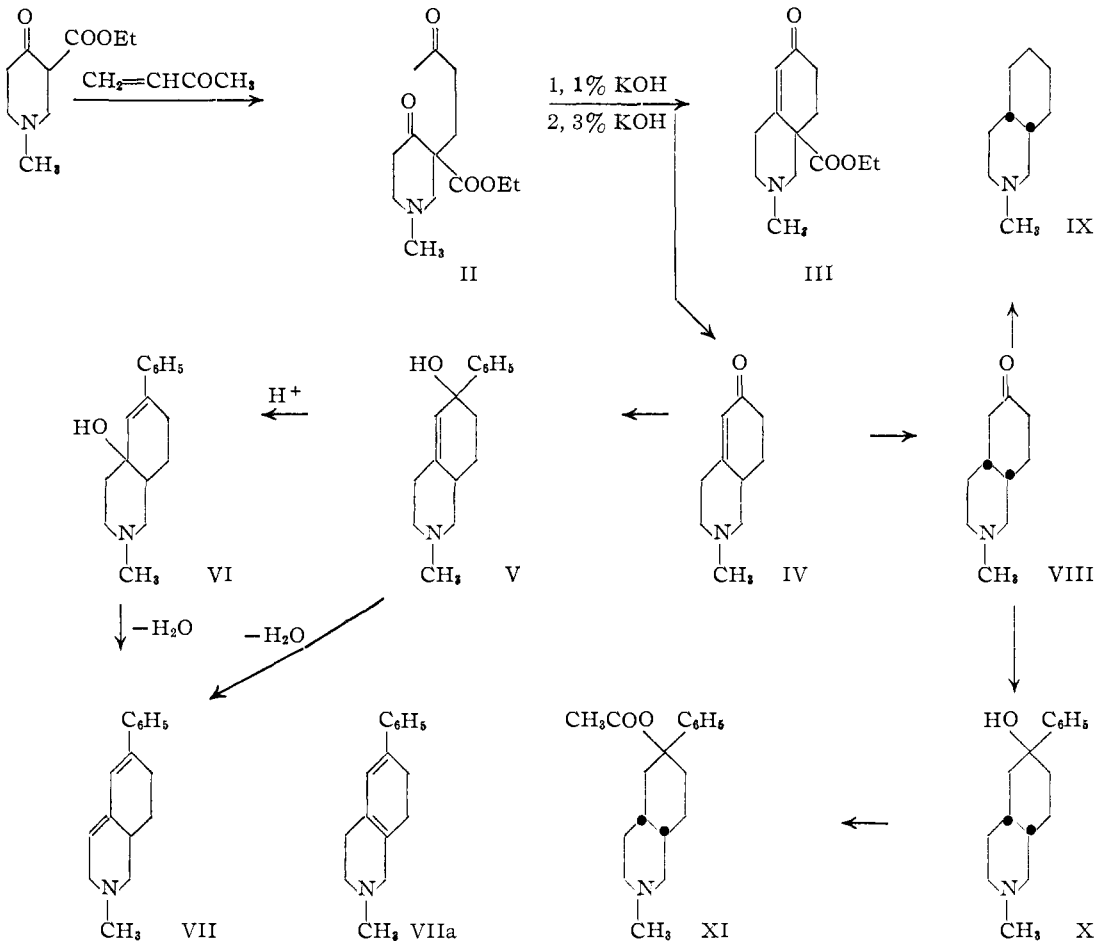
(3) A. L. Wilds and W. J. Close, *ibid.*, **68**, 83 (1946).

(4) A. Marchant and A. R. Pinder, *J. Chem. Soc.*, 327 (1956).

(5) V. Georgian, *Chem. and Ind.*, 930 (1954).

(6) M. C. Kloetzel, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 25.

(7) G. B. Bachman and C. G. Goebel, THIS JOURNAL, **64**, 787 (1942).



260 ml. of dry, thiophene-free benzene was added. The dropping funnel was filled with 46.2 g. (0.2 mole) of methyl di-(β-carbethoxyethyl)-amine[8] and 5 ml. was added to the vigorously stirred suspension of sodium hydride in benzene. By means of a pipet, 0.4 ml. of absolute ethanol was added through the condenser to initiate the reaction. Gentle external heating was applied until the evolution of hydrogen became noticeable. The remainder of the diester was added at a rate sufficient to keep the benzene at a steady reflux. After the addition of the diester was complete, the flask was heated gently on a steam-bath one-half hour, at the end of which time no more hydrogen was evolved.

The flask was immersed in ice, the contents cooled to 5°, and treated with 27 g. of glacial acetic acid to neutralize all the sodium hydride used. The mixture became somewhat gelatinous, and efficient stirring was difficult. A seed crystal of sodium acetate trihydrate was introduced into the flask, with subsequent dropwise addition of 24.6 ml. of water. Rapid crystallization of the sodium acetate trihydrate resulted. The solid salt was removed by filtration and washed with two 75-ml. portions of benzene. The washings and filtrate were combined, and the benzene–alcohol azeotrope removed by distillation. When the refractive index of the distillate indicated that pure benzene was distilling (generally 200–250 ml. of distillate was required), the distillation was stopped, the pot residue cooled and treated with 0.14 g. (3 mole %) of sodium hydride. When the sodium hydride had reacted completely, 14 g. (0.2 mole) of methyl vinyl ketone (Pfizer) in 30 ml. of benzene was added dropwise to the solution. The resulting mildly exothermic reaction was complete in 30 minutes. The benzene solution was washed with two 6-ml. portions of water, dried over magnesium sulfate, and the benzene removed by distillation on a steam-bath. The remaining solution, crude **1-methyl-3-carbethoxy-3-(γ-ketobutyl)-4-piperidone** (II), could be used for the next step without further purification. When it was distilled it yielded 39 g. (76%) of II, b.p. 120–121° (0.1 mm.), $n^{25}D$ 1.4226.

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29. Found: C, 61.43; H, 8.53.

The flask containing crude II was swept with nitrogen and 200 ml. of previously boiled water was added. The aqueous suspension was heated to boiling and 2.7 g. of potassium hydroxide in 66 ml. of boiled water was added dropwise, with stirring. The solution was refluxed for 2 hours at the end of which time 7.3 g. of potassium hydroxide in 66 ml. of previously boiled water was added. After refluxing for 6 hours, the basic solution was cooled, saturated with potassium carbonate, and extracted with eight 100-ml. portions of ether. The ether solution was dried over magnesium sulfate and, upon distillation, yielded 14.7 g. of IV, b.p. 80–81° (0.1 mm.), $n^{25}D$ 1.5270, d^{25}_{25} 1.0353; ultraviolet absorption: 232 mμ (log ε 4.15); infrared (liquid film) showed bands at 6.00 and 6.15 μ.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.63; H, 9.26.

The addition of hydrogen chloride gas to an ether solution of IV yielded the hydrochloride. Recrystallization of the hydrochloride from ethyl acetate–isopropyl alcohol afforded an analytical sample, m.p. 197–198°.

Anal. Calcd. for $C_{10}H_{15}ClNO$: Cl, 17.6. Found: Cl, 17.8.

The above distillation yielded, in addition to II, 1.3 g. (3%) of **1,2,3,4,6,7,8,9-octahydro-2-methyl-6-oxo-9-carbethoxyisoquinoline** (III), b.p. 130–135° (0.1 mm.), which crystallized on cooling. Recrystallization from 60–68° petroleum ether afforded an analytical sample, m.p. 88–90°; mol. wt. (Rast) 236; ultraviolet absorption: 232 mμ (log ε 4.13); infrared (potassium bromide pellet) showed bands at 5.82, 6.05 and 6.16 μ.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07. Found: C, 66.17; H, 7.84.

(8) S. M. McElvain and K. Rorig, THIS JOURNAL, **70**, 1820 (1948).

1,2,3,4,6,7,8,9-Octahydro-2-methyl-6-phenyl-6-hydroxyisoquinoline (V).—To 1.38 g. (0.2 mole) of lithium in 50 ml. of ether was added dropwise 10.5 ml. (0.1 mole) of bromobenzene in 50 ml. of ether at such a rate as to cause gentle refluxing of the ether. After the last of the bromobenzene was added, the solution was stirred at room temperature for 30 minutes. To this solution, cooled in an ice-bath, 6.6 g. (0.04 mole) of the octahydroisoquinoline IV in 40 ml. of ether was added dropwise. The solution was allowed to warm to room temperature over a period of one hour. The reaction mixture was cooled and 30 ml. of water was added dropwise, the aqueous layer was separated, saturated with potassium carbonate, and then extracted with seven 50-ml. portions of ether. The combined ether portions after drying over magnesium sulfate were distilled to yield 8.87 g. (91%) of V, b.p. 160–167° (0.1 mm.). Upon cooling, V crystallized; recrystallization from 60–68° petroleum ether afforded an analytical sample, m.p. 137–139°. The infrared spectrum (potassium bromide pellet) showed bands at 3.22, 6.06, 6.25 and 6.72 μ.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.06; H, 8.78.

The yield of V was the same (90%) if phenyllithium solution was added to an ether solution of IV.

1,2,3,4,7,8,9,10-Octahydro-2-methyl-6-phenyl-10-hydroxyisoquinoline (VI).—To 0.07 mole of phenylmagnesium bromide in 50 ml. of ether was added dropwise 6.2 g. (0.04 mole) of IV. A precipitate formed and the mixture was stirred at room temperature for one hour. The solution was cooled and 100 ml. of 5% hydrochloric acid was added, shaken, and the aqueous acid solution separated and washed with three 15-ml. portions of ether, which were discarded. The aqueous solution was then saturated with potassium carbonate and extracted with eight 35-ml. portions of ether. The ether portions were combined, dried over magnesium sulfate and distilled. Two products, 2.13 g. (35%) of IV and 5.51 g. (60%) of VI, b.p. 140–150° (0.1 mm.), were obtained. Upon cooling, VI crystallized; recrystallization from 60–68° petroleum ether afforded an analytical sample, m.p. 119–120°; mol. wt. (Rast) 239; ultraviolet absorption: 244 mμ (log ε 4.16); infrared (potassium bromide pellet) showed bands at 3.15, 6.15, 6.28, 6.38 and 6.69 μ.

Anal. Calcd. for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 79.09; H, 8.54.

Rearrangement of V to VI.—To 25 ml. of 5% hydrochloric acid was added 0.51 g. of V, m.p. 137–139°. After standing for 15 minutes the solution was made alkaline with potassium carbonate. Over a period of two days, 0.46 g. of VI, m.p. 95–115°, crystallized. Recrystallization from 60–68° petroleum ether afforded pure VI, m.p. 118–119°.

1,2,3,7,8,9-Hexahydro-2-methyl-6-phenylisoquinoline (VII).—Hydrogen chloride gas was passed into a solution of 0.67 g. of V in 25 ml. of absolute ethanol for 30 seconds. After the resulting solution had stood at room temperature for 2 hours, the solvent was removed under diminished pressure (water-pump). The remaining solid was dissolved in 20 ml. of water and made basic with potassium carbonate; 0.57 g. of VII, m.p. 93–98° precipitated. Recrystallization from 60–68° petroleum ether afforded an analytical sample, m.p. 112–114°; this recrystallization was difficult as the compound appeared to polymerize on heating; ultraviolet absorption: 284 mμ (log ε 4.46), 242 mμ (log ε 3.73).

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found: C, 84.49; H, 8.60.

When the isomeric carbinol VI was used in the above experiment instead of V a similar yield of VII was obtained.

To 0.8 g. (0.0036 mole) of VII in 4 ml. of benzene was added 0.45 g. (0.004 mole) of maleic anhydride. A brown-black polymer (0.78 g.), which was insoluble in any organic solvents, precipitated over a period of 24 hours.

***cis*-2-Methyl-6-oxo-decahydroisoquinoline (VIII).**—To 9.65 g. (0.058 mole) of the isoquinolone IV in 55 ml. of 5% hydrochloric acid was added 0.3 g. of 10% palladium-on-carbon catalyst. The solution was shaken with hydrogen at 38 pounds pressure until one equivalent of hydrogen per mole of IV had been absorbed (90 minutes). The solution was filtered, saturated with potassium carbonate, and extracted with seven 25-ml. portions of ether. The ether solution was dried over magnesium sulfate and, upon distillation, yielded 6.9 g. (71%) of VIII, b.p. 72–73° (0.1 mm.). The infrared spectrum (liquid film) showed a band at 5.9 μ. The methiodide of VIII after recrystallization from absolute methanol melted at 271–273°.

Anal. Calcd. for $C_{11}H_{20}INO$: C, 42.73; H, 6.52. Found: C, 42.68; H, 6.36.

Hydrogen chloride was passed into a solution of 3 g. (0.018 mole) of VIII and 4 g. (0.04 mole) of benzaldehyde in 56 ml. of absolute ethanol for one minute. After standing in the refrigerator for 3 days, 1.3 g. of ***cis*-2-methyl-6-oxo-5,7-dibenzylidene-decahydroisoquinoline hydrochloride** was filtered off. Recrystallization from isopropyl alcohol afforded an analytical sample that crystallized with one mole of alcohol of crystallization, which it lost at 160–170° and then melted at 225°; ultraviolet absorption: 329 mμ (log ε 4.57) and 232 mμ (log ε 4.34).

Anal. Calcd. for $C_{24}H_{24}ClNO$: C, 74.03; H, 7.37. Found: C, 73.94; H, 7.30.

To 12 ml. of hydrazine hydrate was added 2.5 g. of VIII and the solution refluxed for 24 hours. The solution was cooled and 25 ml. of triethylene glycol was added and the reflux condenser replaced with a 10-cm. column equipped with a take-off condenser. The pot temperature was gradually raised to 210° over a period of four hours. Approximately 14 ml. of distillate was collected during this time. This distillate was extracted with ether; distillation yielded 1.5 g. (65%) of ***cis*-2-methyldecahydroisoquinoline**, b.p. 85–86° (14 mm.). The infrared spectrum (liquid film) showed no bands, other than the C–H bands, between 2 and 7 μ. The picrate of this amine, recrystallized from methanol, melted at 209–211° (reported[9] m.p. 210°).

***cis*-2-Methyl-6-phenyl-6-hydroxy-decahydroisoquinoline (X).**—To 1.4 g. (0.2 mole) of small pieces of lithium wire covered with 50 ml. of ether was added a solution of 10.3 ml. (0.1 mole) of bromobenzene in 35 ml. of ether from the dropping funnel at such a rate as to keep the solution refluxing gently. After the addition of the bromobenzene, the solution was stirred at room temperature for 30 minutes. To the solution, cooled in an ice-bath, was added a solution of 6 g. (0.036 mole) of the decahydroisoquinolone VIII in 50 ml. of ether. The reaction mixture was allowed to warm to room temperature over a period of one hour, after which 30 ml. of water was added and the mixture stirred for two hours. The water layer was saturated with potassium carbonate and extracted with eight 80-ml. portions of ether. The combined ether portions were dried over magnesium sulfate. After removal of most of the ether by distillation, 4.9 g. (60%) of X, m.p. 160–161°, crystallized and was filtered. Recrystallization from 60–68° petroleum ether afforded an analytical sample, m.p. 164–165°. Infrared spectrum (potassium bromide pellet) showed bands at 3.19, 6.29 and 6.72 μ.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.46; H, 9.52.

***cis*-2-Methyl-6-phenyl-6-acetoxydecahydroisoquinoline (XI) Hydrochloride.**—A solution of 0.5 g. (0.002 mole) of X and 0.3 g. (0.0037 mole) of fused sodium acetate in 15 ml. of freshly distilled acetic anhydride was heated at 115° and stirred under nitrogen for 12 hours. The solution was cooled, poured into 125 ml. of water, made basic with potassium carbonate, and extracted with five 30-ml. portions of ether. The ether was dried over potassium carbonate and upon addition of a solution of hydrogen chloride in ether a tacky white precipitate formed. The ether was decanted, and the solid hydrochloride dried. This salt was dissolved in 10% methanol–acetone; upon removal of most of the solvent by distillation followed by addition of acetone and cooling, 0.35 g. (54%) of the hydrochloride of XI, m.p. 193–194°, precipitated. Recrystallization from methanol–acetone afforded an analytical sample, m.p. 193–194°. Infrared spectrum (Nujol) showed bands at 5.82, 6.35 and 6.65 μ.

Anal. Calcd. for $C_{18}H_{26}ClNO_2$: C, 66.75; H, 8.09. Found: C, 67.05; H, 8.26.

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(9) B. Witkop, This Journal, **70**, 2617 (1948).