[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF NEW HAMPSHIRE]

Molecular Rearrangements. VII. The Allylic Rearrangement of α-Hydroxybenzhydryltetrahydropyridines[1]

GLORIA G. LYLE, EDWARD F. PERLOWSKI,[2] AND ROBERT E. LYLE

Received December 15, 1955

The allylic rearrangement of two compounds in which the point of unsaturation is located in a heterocyclic ring has been studied. The rearrangement of 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol produced 3-benzhydrylidene-1-methyl-1,2,3,6-tetrahydropyridine, and 1-methyl-1,2,3,6-tetrahydro-4-pyridyldiphenylcarbinol yielded 4-benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine. The ultraviolet absorption spectra of the starting materials and products are discussed.

The use of the allylic rearrangement for the formation of benzhydrylidene compounds has been investigated by Braude and Coles[3] who produced 2-benzhydrylidene cyclohexanol and 3-benzhydrylidene cyclohexene from 1-cyclohexenyldiphenylcarbinol. A study was initiated in this laboratory to investigate this rearrangement with compounds in the piperidine series and to produce substances which might have interesting pharmacological activity or which would be precursors to such products.[4,5]

The preparation of the 1-methyltetrahydro-3(or 4)-pyridyldiphenylcarbinols was accomplished by the action of phenyllithium on the corresponding tetrahydropyridyl ester. Arecoline (methyl 1-methyl-1,2,5,6-tetrahydronicotinate) reacted readily with phenyllithium to give 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (I), while methyl 1-methyl-1,2,3,6-tetrahydroisonicotinate, easily obtained from the reduction of methyl isonicotinate methiodide,[6] yielded the 4-derivative, 1-methyl-1,2,3,6-tetrahydro-4-pyridyldiphenylcarbinol (IV), on treatment with the same reagent.

The ultraviolet absorption spectra of the unsaturated carbinols, I and IV, are indicative primarily of the diphenylmethane system of the molecules.[7] Their spectra are almost identical with that of 1-cyclohexenyldiphenylcarbinol[3] and with that of 1-methyl-4-piperidyldiphenylcarbinol (VII) except that, in the latter case, the maximum at 264 mμ is missing (Table I).

TABLE I

ULTRAVIOLET LIGHT ABSORPTION PROPERTIES[a]

Compound	λ_{max}	ϵ_{max}
1-Methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (I)	247 253 259 265	255 341 417 323
1-Methyl-1,2,3,6-tetrahydro-4-pyridyldiphenylcarbinol (IV)	253 259 264	344 411 312
1-Cyclohexenyldiphenylcarbinol	253 259 264	365 430 324
1-Methyl-4-piperidyldiphenylcarbinol (VII)	253 259	363 414
3-Benzhydrylidene-1-methyl-1,2,3.6-tetrahydropyridine (II)	207 237 281	29,400 15,900 20,700
4-Benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine (V)	207 338	29,200 19,000
1,1-Diphenyl-2-(1'-piperidyl)-ethylene (VIII)	308[b]	16,100[b]

[a] The spectra were determined in 95% ethanol using a Beckman model DU quartz spectrophotometer equipped with a photomultiplier attachment. [b] Ref. 14.

Upon reaction with hydrochloric acid in acetone, the carbinols (I and IV) did not give the expected allylic rearrangement products, 3-benzhydrylidene-1-methyl-4-piperidinol, or 4-benzhydrylidene-1-methyl-3-piperidinol, but yielded, instead, compounds having a butadiene system, the products of dehydration of the carbinols. Thus from I, 3-benzhydrylidene-1-methyl-1,2,3,6-tetrahydropyridine (II) was obtained while IV yielded 4-benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine (V). Neither I nor IV was as easily rearranged as was 1-cyclohexenyldiphenylcarbinol[3] but instead required a more acidic medium and reflux temperature. A quantitative yield of II was obtained from I unless a shorter reaction time than four hours was used, in which case a mixture of starting material and II was isolated. With IV, however, regardless of reaction conditions, a large amount of intractable oil was obtained in addition to V. V yielded neither a methiodide nor a hydrochloride, whereas II easily formed crystalline derivatives.

The reduction of both II and V to the saturated compounds, 3-benzhydryl-1-methylpiperidine (III)

(1) This investigation was supported in part by a research grant, H-1713, from the National Heart Institute of the National Institutes of Health, Public Health Service.

(2) Abstracted in part from the thesis presented to the Graduate School of the University of New Hampshire by E. F. Perlowski in partial fulfillment of the degree of Master of Science.

(3) Braude and Coles, *J. Chem. Soc.*, 2014 (1950).

(4) Sperber, Villani, Sherlock, and Papa, *J. Am. Chem. Soc.*, **73**, 5010 (1951).

(5) Plait and Wenner, U. S. Patent 2,546,652, March 27, 1951; *Chem. Abstr.*, **45**, 7154 (1951).

(6) Lyle, Perlowski, Troscianiec, and Lyle, *J. Org. Chem.*, **20**, 1761 (1955).

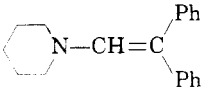
(7) Kumler, Strait, and Alpen, *J. Am. Chem. Soc.*, **72**, 1463 (1950).

and 4-benzhydryl-1-methylpiperidine (VI) respectively, occurred at low pressure over Adams' catalyst. In order to verify the structure of VI and prove that no new ring system had been formed, the hydrogenolysis of 1-methyl-4-piperidyldiphenylcarbinol (VII)[8] was carried out yielding VI.

Further evidence for the structures of II and V was obtained by examination of their ultraviolet absorption spectra. It has been noted by Woodward[9] that the position of the ultraviolet absorption maximum in butadiene derivatives is dependent upon the degree of substitution in the compounds and on the endocyclic or exocyclic nature of the double bonds, an alkyl substituent or an exocyclic double bond causing a bathochromic shift. From this, II and V would be expected to show maxima in the region of 240 mμ indicating a tetrasubstituted butadiene and an exocyclic double bond, provided that the aryl groups did not cause a further increase in wave length as might be anticipated. A maximum at 237 mμ is observed in the case of II and fine structure between 240 and 245 mμ is found in the ultraviolet absorption spectrum of V.

Both II and V show very high maxima in the region of 206–208 mμ which appear to be due to the tertiary nitrogen atom. II shows a broad "phenyl butadiene band"[10] at 281 mμ; however, in V this band is found at 338 mμ.

Apparently the displacement of the maximum from 281 to 338 mμ is due to the increased conjugation because of participation of the nitrogen. Such a bathochromic shift has been observed in vinyl amines, as, for example, 1-ethyl-2-methyl-1,4,5,6-tetrahydropyridine has a maximum at 231 mμ as compared with 1-ethyl-1,2,5,6-tetrahydropyridine (218 mμ) and 1-methylpiperidine (213 mμ).[11] Similar observations have been made in the case of α, β-unsaturated-β-amino esters.[12,13] A compound closely related to V, 1,1-diphenyl-2-(1′-piperidyl)-ethylene (VIII),[14] was found to have a maximum at



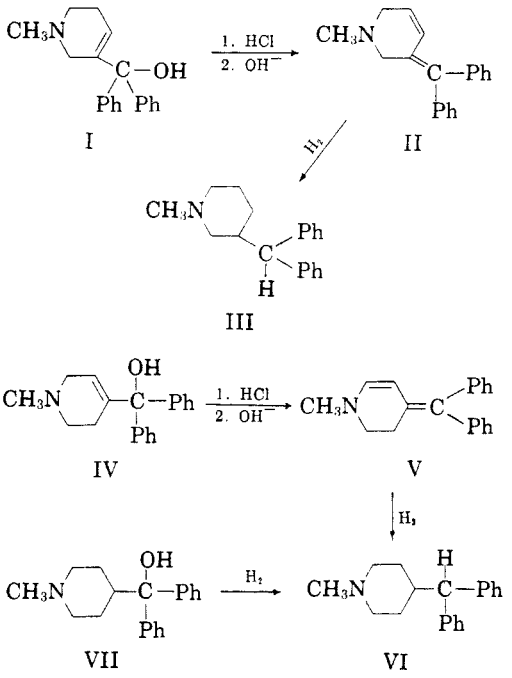
VIII

308 mμ. It would be expected that the addition of the second ethylenic chromophore as well as the exocyclic double bond in IV would cause a further bathochromic displacement of the maximum.

(8) Lyle and Lyle, *J. Am. Chem. Soc.*, **76**, 3536 (1954).
(9) Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).
(10) Braude, Jones, and Stearn, *J. Chem. Soc.*, 1087 (1947).
(11) Leonard and Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).
(12) Glickman and Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).
(13) Albertson, *J. Am. Chem. Soc.*, **74**, 3816 (1952).
(14) Sury and Hoffmann, *Helv. Chim. Acta*, **38**, 728 (1955).

EXPERIMENTAL

FLOW SHEET



1-Methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (I). To an ethereal solution of 0.2 mole of phenyllithium 5.0 g. (0.032 mole) of arecoline in dry ether was added dropwise. The solution was refluxed and stirred for 0.5 hour and was decomposed with water. The product, insoluble in both ether and water, was separated by filtration yielding 6.6 g. (74%) of 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (I), m.p. 181–188°. Recrystallization from ethanol gave an analytical sample, m.p. 187.5–188.5°.

Anal. Calc'd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.32; H, 7.49.

Allylic rearrangement of 1-methyl-1,2,5,6-tetrahydro-3-pyridyldiphenylcarbinol (I). A solution containing 70 ml. of 80% aqueous acetone, 2 *N* in hydrochloric acid, and 2.0 g. of I was refluxed for 4 hours and evaporated to dryness on a steam-bath under reduced pressure. Water was added and the mixture was made basic with potassium hydroxide solution. The precipitated amine was removed by filtration, giving a quantitative yield of 3-benzhydrylidene-1-methyl-1,2,3,6-tetrahydropyridine (II). After recrystallization from aqueous ethanol, the compound melted at 113–115°.

Anal. Calc'd for $C_{19}H_{19}N$: C, 87.31; H, 7.33. Found: C, 87.27; H, 7.44.

The *hydrochloride* melted at 254–256° (dec.) after recrystallization from an ethanol-acetone solution.

Anal. Calc'd for $C_{19}H_{20}ClN$: C, 76.62; H, 6.77. Found: C, 76.51; H, 7.09.

3-Benzhydryl-1-methylpiperidine (III). A solution of 1.8 g. of 3-benzhydrylidene-1-methyl-1,2,3,6-tetrahydropyridine (II) in 90 ml. of methanol was reduced under 2–3 atm. of hydrogen in the presence of 0.2 g. of Adams' catalyst. After the hydrogen uptake ceased (about 1.5 hour) the catalyst was removed by filtration and the solution was fractionated. The product was obtained as a colorless oil, b.p. 145–146° at 0.5 mm., 0.9 g. (48%), which slowly crystallized to a low-melting solid extremely soluble in organic solvents. It was converted to the hydrochloride, m.p. 233–236°; lit. m.p. 240–242°.[15]

Allylic rearrangement of 1-methyl-1,2,3,6-tetrahydro-4-pyri-

(15) German Patent 803,235, April 2, 1951; *Chem. Abstr.*, **45**, 8562 (1951).

dyldiphenylcarbinol (IV). To an 80% solution of aqueous acetone (175 ml.), 2 *N* in hydrochloric acid, 5 g. (0.018 mole) of IV[8] was added and the solution was heated under reflux for 2.5 hours. The solvents of the resulting clear, yellow-red solution were removed under reduced pressure leaving a semi-solid residue which was dissolved in water, made basic with 6 *N* sodium hydroxide, and extracted with four 50-ml. portions of ether. The ethereal solution was dried over potassium carbonate and distilled. The residue was dissolved in hot methyl alcohol from which there was obtained 1.5 g. (32%) of 4-benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine (V), m.p. 121–123°.

Anal. Calc'd for $C_{19}H_{19}N$: C, 87.31; H, 7.33. Found: C, 87.20; H, 7.36.

An attempt to prepare the methiodide of V from both an ethereal solution and a methyl alcohol solution gave no reaction and V was recovered unchanged. An attempt to prepare the hydrochloride of V from an ethereal solution resulted in an oil which could not be crystallized.

4-Benzhydryl-1-methylpiperidine (VI). (*a*) *From 4-benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine* (V). A solution of 0.6 g. (0.0023 mole) of 4-benzhydrylidene-1-methyl-1,2,3,4-tetrahydropyridine (V) in 75 ml. of methanol was subjected to 3 atm. of pressure of hydrogen at room temperature with 0.2 g. of platinum oxide catalyst. After the pressure of hydrogen ceased to change, about 1.5 hours, the reaction mixture was filtered and the solution was fractionated yielding 0.4 g. (66%) of 4-benzhydryl-1-methylpiperidine (VI), b.p. 186–190° at 6 mm., which crystallized on standing, m.p. 87.5–88.5°.

Anal. Calc'd for $C_{19}H_{23}N$: C, 85.98; H, 8.74. Found: C, 86.28; H, 8.76.

The *hydrochloride* of VI melted at 293.5–295° after recrystallization from acetone; lit. m.p. 287–288°.[14]

(*b*) *From 1-methyl-4-piperidyldiphenylcarbinol* (VII). A solution of 5 g. (0.018 mole) of 1-methyl-4-piperidyldiphenylcarbinol (VII) in 100 ml. of methanol was subjected to 110–180 atm. of pressure of hydrogen at 26–194° with 3 ml. of a Raney Nickel[16] suspension in 95% ethanol as catalyst. The rise in temperature was allowed to proceed over an approximately 4-hour period. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The oily residue was washed with ligroin (b.p. 30–60°) leaving 1.8 g. of the starting material (VII), m.p. 99–122°. Concentration of the ligroin solution yielded 2.8 g. (96%) of 4-benzhydryl-1-methylpiperidine (VI), m.p. 45–75°, which, after recrystallization from ligroin, melted at 89.5–90.5°. A mixture melting point with VI obtained in (*a*) showed no depression.

DURHAM, NEW HAMPSHIRE

(16) Pavlic and Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).