The Stevens Rearrangement of 1-*p*-Methoxybenzyl-1,2,5,6-tetrahydropyridinium Salts

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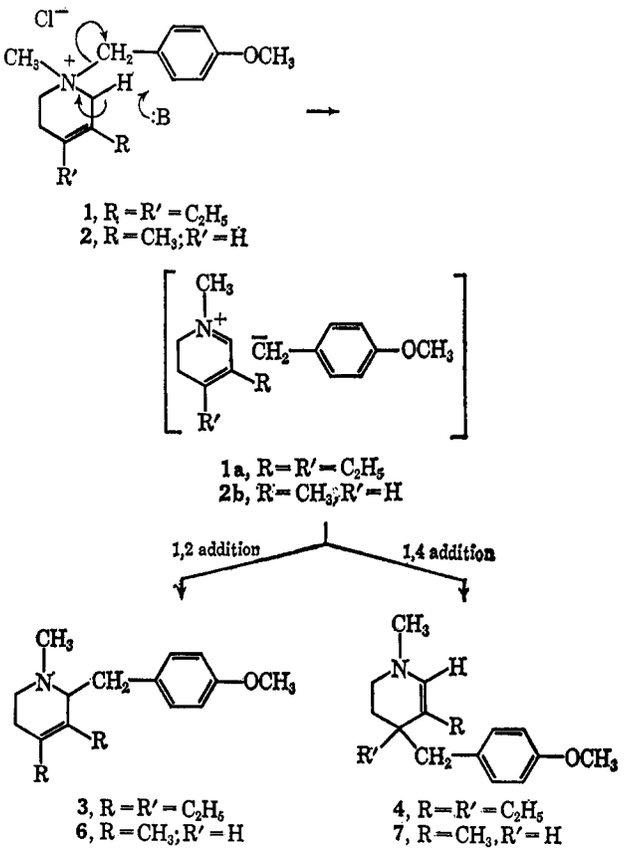
The phenyllithium-induced (Stevens) rearrangement of 1-*p*-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride gives the mechanistically predictable products 1-methyl-2-*p*-methoxybenzyl-3,4-diethyl-1,2,5,6-tetrahydropyridine, 1-methyl-3,4-diethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine, and 1-methyl-2-(2-methyl-5-methoxyphenyl)-3,4-diethyl-1,2,5,6-tetrahydropyridine. Similarly, the Stevens rearrangement of 1,3-dimethyl-1-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridinium chloride led to two products, 1,3-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine and 1,3-dimethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine. The ratios and types of products were influenced by the *p*-benzylic substituent and the size of the substituents of the heterocyclic ring. A pmr method for the assignment of a 2,3 double bond, owing to its rearrangement to the immonium (1,2) form in the tetrahydropyridine ring when in acidic solution, was found to be as reliable as, and experimentally simpler than, the alternative, infrared spectral technique.

The Stevens rearrangement of 1-*p*-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (**1**) gives a mixture of four compounds in the ratio of 2:2:12:5.[2] Since this tetrahydropyridinium compound has been used as an intermediate to medicinally useful 6,7-benzomorphans, we thought it was of interest to determine the nature of the products.[3] The rearrangement of 1,3-dimethyl-1-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridinium chloride (**2**) was examined in order to see if the change from a hindered to an unhindered C-4 heterocyclic ring position would influence the ratio of products obtained.

Separation and purification of three of the four compounds (**3**, **4**, and **5**) obtained on rearrangement of **1**, was achieved by repeated fractional distillation, followed by recrystallization of their salts. The main product (**3**) was found to be identical with the known 1-methyl-2-*p*-methoxybenzyl-3,4-diethyl-1,2,5,6-tetrahydropyridine by mixed glpc and by comparison of their spectra. It was presumably formed by the 1,2-rearrangement path[4] noted in Scheme I.

Compound **4**, which had the highest boiling point, and the longest retention time on glpc was found to be a product of 1,4 rearrangement (Scheme I), namely 1-methyl-3,4-diethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine. The mass spectrum of **4** indicated that it was isomeric with the 1,2-rearrangement product ($M^+ = 273$), and the fragmentation patterns were similar. The pmr spectrum of the base and of its salt (trifluoroacetic acid solution of the base) gave the necessary additional information to prove the structure of **4**. The base showed a one-proton triplet at 5.6 ppm ($J = 1$ cps), indicative of an unsaturated proton coupled to a methylene group. This proton was deshielded to 8.34 ppm ($J = 12$ cps) when the spectrum was obtained in trifluoroacetic acid solution. The shift is characteristic[5] of a double-bond rearrangement from its 2,3 position in the tetrahydropyridine base to the immonium (1,2) position in the salt, and establishes the position of the double bond in **4**.

SCHEME I



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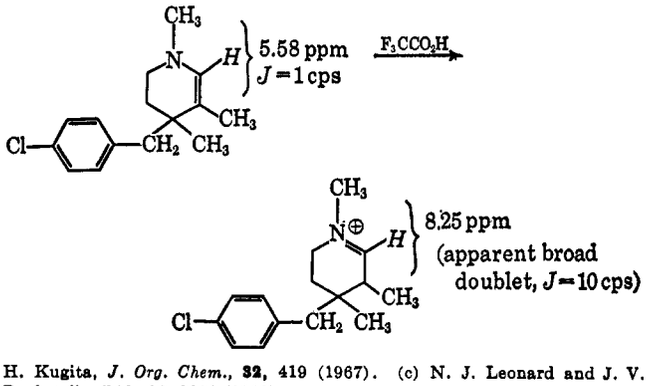
(2) The ratio was determined by the cut-out weights of the glpc pattern.

(3) Only the 1,2-rearrangement product, 1-methyl-2-*p*-methoxybenzyl-3,4-diethyl-1,2,5,6-tetrahydropyridine, was isolated previously: (a) E. M. Fry and E. L. May, *J. Org. Chem.*, **26**, 2592 (1961); (b) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).

(4) For an excellent summary of the presumed mechanism of the Stevens and related rearrangements, see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 229.

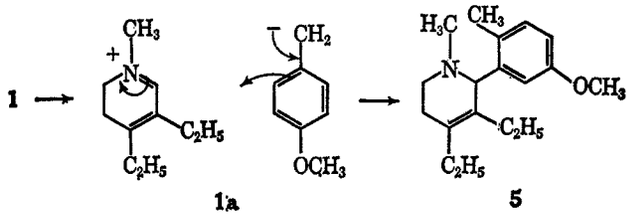
(5) The shift has been demonstrated in the HCl, $HClO_4$, and picrate salts and in a trifluoroacetic acid solution of the base. (a) A similar deshielding effect was noted in the following scheme. (b) R. T. Parfitt, M. Takeda, and



H. Kugita, *J. Org. Chem.*, **32**, 419 (1967). (c) N. J. Leonard and J. V. Paukstelis, *ibid.*, **28**, 3021 (1963).

Compound **5**, which had the lowest boiling point of the four compounds, was found to be 1-methyl-2-(2-methyl-5-methoxyphenyl)-3,4-diethyl-1,2,5,6-tetrahydropyridine. It may have formed through the path noted in Scheme II. The mass spectrum of **5** indicated that it also was isomeric with the main product (M^+ = 273). The fragmentation pattern was, however, quite different. This might be due to the stabilization of the

SCHEME II

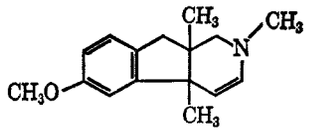


parent ion and fragments by conjugation between the heterocyclic double bond formed at 70 ev and the aromatic ring. The pmr spectra of **5** clearly indicated the presence of a 1,2,4-trisubstituted aromatic ring. A three-proton AA'B pattern was observed,[6] as was an aromatic methyl singlet at 2.2 ppm. The presence of a tetrasubstituted double bond was inferred from the lack of a chemical shift for a proton in the usual unsaturated area of the pmr spectrum. Its position in the molecule (2,3 *vs.* 3,4) was decided by pmr and infrared data. If a 2,3 double bond existed in the base it should migrate to the 1,2 position in the $HClO_4$ salt, with the usual shift[7] in the infrared to 1690 cm^{-1}. No such absorption was noted. In the ultraviolet spectra of the salt and the base, a styrene-type pattern, and an immonium enamine transition from salt to base, might be observed if a 2,3 double bond is present in the molecule. Only the trisubstituted, unconjugated, aromatic absorption was observed[8] in the base, and in the HCl and $HClO_4$ salts. The proton α to the nitrogen in the heterocyclic ring was found to be considerably deshielded by its allylic position to both the double-bond and the aromatic ring, and was observed at 3.82 ppm. The expected deshielding effect of a positive nitrogen atom was noted in the spectrum of the salt, in which the chemical shift of the α proton occurred at 5.1 ppm. Thus the double bond must exist in the 3,4 position in **5**.

It is of interest that this compound (**5**) is analgesically active (subcutaneous administration, mouse hot-plate assay). The ED_{50} (mg/kg) was found to be about 20 compared with an ED_{50} of 7.5 for codeine.[9]

The fourth compound formed in the rearrangement of **1** could not be purified by the usual procedures, and its structure remains uncertain.

(6) An almost identical aromatic AA'B pattern was observed in the pmr spectrum of the following. See ref 5.



(7) N. J. Leonard and F. P. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(8) The trisubstituted aromatic moiety in the compound noted in ref 6 displayed a similar ultraviolet absorption: λ_{max} 284 mμ (ϵ_{max} 4000).

(9) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

The phenyllithium-induced rearrangement of 1,3-dimethyl-1-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridinium chloride (**2**) gave a two-component mixture in a 1:1 ratio.[2] These compounds could not be separated by the usual chromatographic techniques nor by fractional distillation. Extensive fractional recrystallization of the picrate derivatives from acetone–water proved to be the only satisfactory method of isolation. Compound **6**, which had the lower retention time on glpc, was found to be the "normal" (1,2) rearrangement product, 1,3-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine (Scheme I). The pmr spectrum of **6** was almost identical, above 3.2 ppm, with the known compound, 1,3,4-trimethyl-2-*p*-chlorobenzyl-1,2,5,6-tetrahydropyridine;[10] a three-proton doublet at 1.62 ppm (J = 1.5 cps) indicated that a methyl group was on a double bond and was coupled to the unsaturated proton, which occurred at 5.5 ppm. The mass spectrum of **6** was consistent with the structure. Apparently, the substituents on the heterocyclic ring do not have much effect on the yield of the 1,2-rearrangement product, which was 57% of the total product from **1**, and 50% from **2**. The *p*-methoxyl substituent on the aromatic ring does effect the course of this rearrangement. Its effect can be seen by comparison with the rearrangement of 1-*p*-chlorobenzyl-1,3,4-trimethyl-1,2,5,6-tetrahydropyridinium chloride, where the amount of the comparable 1,2-rearrangement product formed was only 20% of the total product.[10] It is likely that the *p*-chlorobenzyl anion formed is relatively more stable than the *p*-methoxybenzyl anion, and this stability might enable it to undergo more diverse reaction paths. The 1,4-rearrangement product, however, is affected by the heterocyclic rings substituents. The yield of this product from **1**, which had the bulkier substituents, was 24%, compared with the 50% yield from **2**, where little hindrance to this rearrangement could be expected. The structural proof for this compound is given below. The intermediate case in which the heterocyclic ring was substituted at both the 3 and 4 positions with methyl groups gave a 40% yield of the comparable product.[10]

The final compound **7**, isomeric with **6**, was found to be the product of the 1,4 rearrangement (Scheme I), 1,3-dimethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine. The structure of **7** was indicated by the pmr spectra of the base and of its salts. It was apparent from the spectrum of the base that the methyl group was, as in **6**, situated on a double bond and that it was coupled to an unsaturated proton. The position of the double bond in the molecule was, however, clearly different from that in **6**, as the unsaturated proton was observed to shift from 5.65 in the base (in $CDCl_3$) to 8.3 ppm in trifluoroacetic acid. The shift was even more dramatic in the spectrum of the picrate derivative of **7**, in which the chemical shift of the unsaturated proton occurred at 8.95 ppm (broad doublet, J = 6 cps). This is consistent with the double-bond rearrangement from its 2,3 position in the base to the 1,2 (immonium) position in the salts.[5] The position of the *p*-methoxybenzyl group in relation to the double bond was indicated by the mass spectrum. An $M^+ - 2$ peak at m/e 229 occurred in equal abundance with the M^+ peak. This would be likely to occur in **7**, where a

(10) A. E. Jacobson, *J. Org. Chem.*, **31**, 1569 (1966).

loss of two protons (a heterocyclic C-4 hydrogen atom and a benzylic hydrogen atom) would lead to a stable conjugated structure.

Thus, we have observed that the type and amount of product formed from the Stevens rearrangement is dependent on the substituents in both the aromatic and heterocyclic rings. A *p*-methoxybenzyl group and larger alkyl groups in the 3 and 4 positions of the heterocyclic ring tend to favor the 1,2-rearrangement product, which is the desired product from the medicinal viewpoint.

Experimental Section[11]

1-*p*-Methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (1) was prepared according to the procedure of Ager and May.[3b]

The Stevens rearrangement of 1-*p*-methoxybenzyl-1-methyl-3,4-diethyl-1,2,5,6-tetrahydropyridinium chloride (1) was carried out according to the procedure of Fry and May.[3a,12] The mixture thus obtained was fractionally distilled at 0.1 mm. The individual fractions, enriched in one or two of the components of the mixture, were redistilled until no further enrichment in a desired component could be achieved. They were then converted to their derivatives and recrystallized until purity was achieved.

1-Methyl-2-*p*-methoxybenzyl-3,4-diethyl-1,2,5,6-tetrahydropyridine (3) distilled at 129–135° (0.15 mm). The physical constants, etc., were identical with those of the known[3] material: ultraviolet (base or HCl salt) λ_{max}^{EtOH} 284 mμ (ε max 1650), 278 mμ (ϵ_{max} 1860); pmr (base) δ 2.3 (singlet, NCH_3), 2.74 (multiplet, benzylic methylene), 6.73 and 7.12 (AA'BB' multiplet, $J_{AB} \sim 8.5$ cps, aromatic protons); pmr (HCl salt) δ 2.75 (doublet, J = 4.5 cps, N^+CH_3). Some of the major peaks in the mass spectrum (*m/e*, relative intensity) were 273 (1, parent ion), 244 (2), 153 (12), 152 (100), 151 (2), 150 (3), 123 (8), 122 (12), and 121 (8); a metastable ion was noted at *m/e* 148 (152 → 150).

1-Methyl-3,4-diethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine (4) distilled at 135–140° (0.15 mm). It was purified by recrystallization of HCl salt from acetone–methanol, conversion to base, followed by conversion to and recrystallization of the methiodide derivative and its reconversion to the free base 4: infrared (liquid film) 1654 (s), 830 (s), 820 (s) cm^{-1} (trisubstituted double bond);[13] pmr (base) δ 2.43 (singlet, NCH_3), 2.63 (quartet, J = 9 cps, benzylic methylene), 5.6 (triplet, J = 1 cps, H on double bond α to N), 6.73 and 7.12 (AA'BB' multiplet, $J_{AB} \sim 9$ cps, aromatic protons); pmr (in trifluoroacetic acid) δ 2.77 (singlet, benzylic methylene), 3.67 (broad singlet, N^+CH_3), 7.0 (singlet, aromatic protons), 8.34 (broad doublet, J = 12 cps, H on double bond α to N^+). Some of the major peaks in the mass spectrum were (*m/e*, relative intensity) 273 (2, parent ion), 244 (1), 153 (6) 152 (100), 150 (3), 123 (6), 122 (11), and 121 (9); metastable ions were noted at *m/e* 148 (152 → 150) and 84.6 (273 → 152).

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95. Found: C, 79.13; H, 9.88.

The methiodide was recrystallized in methanol–ether, mp 163–164°.

Anal. Calcd for $C_{19}H_{30}INO$: C, 54.94; H, 7.28. Found: C, 54.97; H, 7.04.

1-Methyl-2-(2-methyl-5-methoxyphenyl)-3,4-diethyl-1,2,5,6-tetrahydropyridine (5) distilled at 86–89° (0.05 mm). It was purified by conversion to HCl salt in ether–acetone and recrystallization from acetone–methanol–ether: mp 210–212°; infrared (KBr) 1920 (w), 1810 (w), 1750 (w), 850 (s), 820 (m) cm^{-1} (1,2,4-substituted aromatic); ultraviolet (base) λ_{max}^{EtOH} 280 mμ (ϵ_{max} 2200), 288 mμ (ϵ_{max} 2050); (HCl or $HClO_4$ salt) λ_{max}^{EtOH} 284 mμ (ϵ_{max} 2570), 292 mμ (ϵ_{max} 2190); pmr (base) δ 2.2 (singlet, NCH_3), 2.32 (singlet, aromatic methyl), 3.82 (broad singlet, H allylic to double bond and aromatic ring, and α to N), and 6.8 (AA'B multiplet, aromatic protons); pmr (in trifluoroacetic acid) δ 2.5 (singlet, aromatic methyl), 3.12 (doublet, J = 5 cps, N^+CH_3), 5.1 (broad singlet, H allylic to double bond and aromatic ring, and α to N^+), and 7.17 (AA'B multiplet, aromatic protons). Some of the major peaks in the mass spectrum were (*m/e*, relative intensity) 273 (16, parent ion), 244 (57), 242 (3), 153 (9), 152 (100), 122 (7), and 121 (2); a metastable ion was noted at *m/e* 218.1 (273 → 244).

Anal. Calcd for $C_{18}H_{28}ClNO$: C, 69.77; H, 9.11. Found: C, 69.81; H, 9.27.

The methiodide derivative was crystallized in acetone–ether, mp 202–203° dec.

Anal. Calcd for $C_{19}H_{30}INO$: C, 54.94; H, 7.28. Found: C, 54.68; H, 7.42.

The Stevens rearrangement of 1,3-dimethyl-1-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridinium chloride (2) was carried out according to the usual procedure.[3b] The mixture thus obtained was converted to its mixed picrate in acetone and was precipitated by the addition of water. The material was recrystallized many times from acetone–water. Compound **7, 1,3-dimethyl-4-*p*-methoxybenzyl-1,4,5,6-tetrahydropyridine**, separated first as yellow needles: mp 89–90°; pmr (base) δ 1.7 (doublet, J = 1 cps, methyl on double bond), 2.53 (singlet, NCH_3), 5.65 (broad, H on double bond), 6.87 and 7.17 (AA'BB' multiplet, $J_{AB} \sim 9$ cps, aromatic protons); pmr (picrate salt in deuterioacetone-d_6) 1.43 (doublet, J = 7.5 cps, methyl on saturated carbon atom), 3.8 (broad singlet, N^+CH_3), 6.72 and 7.06 (AA'BB' multiplet, $J_{AB} \sim 8.5$ cps), and 8.95 (broad doublet, J = 6 cps, H on double bond α to immonium N). Some of the major peaks in the mass spectrum were (*m/e*, relative intensity) 231 (4, parent ion), 229 (4), 121 (3), 110 (100), 108 (9), 96 (1), 95 (6), 94 (6), and 91 (3); metastable ions were noted at *m/e* 106 (110 → 108), 82 (110 → 95), and 52.4 (231 → 110).

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.71; H, 5.26; N, 12.40.

The picrate of the other isomer could not be isolated completely free of 7 picrate. It was reconverted into the base. A hydrochloride salt of **1,3-dimethyl-2-*p*-methoxybenzyl-1,2,5,6-tetrahydropyridine** (6) was prepared and was recrystallized from acetone (needles): mp 208–210°; pmr (base) δ 1.62 (doublet, J = 1.5 cps, methyl on double bond), 2.39 (singlet, NCH_3), 2.85 (multiplet, benzylic methylene), 5.5 (broad, H on double bond), 6.8 and 7.22 (AA'BB' multiplet, $J_{AB} \sim 9$ cps, aromatic protons). Some of the major peaks in the mass spectrum were (*m/e*, relative intensity) 231 (1, parent ion), 121 (5), 110 (100), 108 (10), 94 (9), and 91 (3); metastable ions were noted at *m/e* 106 (110 → 108), 68.4 (121 → 91), 63.4 (231 → 121), and 52.4 (231 → 110).

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 67.26; H, 8.28. Found: C, 67.38; H, 8.13.

Registry No.—**3**, 10293-64-8; hydrochloride of **3**, 10293-65-9; **4**, 10293-66-0; methiodide of **4**, 10293-67-1; **5**, 10273-68-2, hydrochloride of **5**, 10293-69-3; methiodide of **5**, 10293-70-6; **6**, 10293-71-7; hydrochloride of **6**, 10277-33-5; **7**, 10316-20-8; picrate of **7**, 10305-68-7.

Acknowledgment.—The authors are indebted to Dr. G. W. Milne, National Heart Institute, National Institutes of Health, for the recording of the mass spectra.

(11) Melting points were taken in a capillary (Hershberg apparatus, total immersion thermometers). Microanalyses were by the Analytical Services Section of these institutes. Mass spectra were determined at 70 ev on an Associated Electronics Industries, MS-9, double-focusing mass spectrometer, introducing the compound directly into the inlet. The pmr spectra were determined by Mrs. J. Goodwin on a Varian A-60 spectrometer. All of the spectra were obtained in $CDCl_3$ with tetramethylsilane as the internal standard except where indicated. Chemical shifts are listed as δ values in parts per million (ppm); single values for multiplets represent the approximate center. Assignment was made on the basis of the integrated values obtained for the number of protons. Infrared spectra were obtained on a Perkin-Elmer 237-B grating spectrophotometer. The glpc were run isothermally at 190° on a Warner-Chilcott 1600 series chromatograph. A 1.83-m glass column, 6.3 mm in diameter, was used, silanized, and packed with 5% XE-60 on 80–100 mesh Chromosorb G. It was equipped with a flame ionization detector.

(12) We would like to thank the Regis Chemical Co. for a generous supply of the mixture of products obtained from the rearrangement and for preparing the pure **3** hydrochloride.

(13) Band assignments are comparable with known absorptions: K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962.