AN UNUSUAL PRODUCT OBTAINED FROM THE REACTION OF ANILINE WITH 1-(2-CHLOROCYCLOPENTYL)-PIPERIDINE

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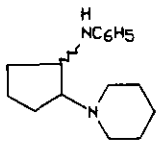
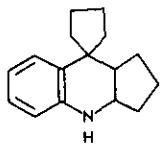
Abstract - Condensation of aniline with 1-(2-chlorocyclopentyl)-piperidine gave the expected 1-(2-anilinocyclopentyl)-piperidine (1) and an unknown compound. The structure of the unknown compound was shown by x-ray analysis to be 3. Mechanism is proposed for the formation of 3.

It was Professor Gilbert Stork who originally inspired me to pursue the chemistry of enamines and aminohalocycloalkanes[1,2]. We were particularly intrigued by the unexpected behavior which this class of compounds displayed; quite often we set out to perform a seemingly simple reaction with these substrates only to find that they underwent some unusual and fascinating transformations[3].

The present case is another illustration of this phenomenon. We set out to prepare 1-(2-anilinocyclopentyl)-piperidine (1) by the condensation of aniline with 1-(2-chlorocyclopentyl)-piperidine at 95°C.



1



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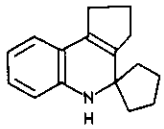

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Examination of the reaction mixture by tlc (silica gel, 10% MeOH-$CHCl_3$) indicated clearly two products, and they were separated by chromatography. The slower running compound was the expected product 1 as shown by analysis and spectral data. The faster running compound displayed M^+ 225. ^1H and ^{13}C nmr indicated two possible structures, 2 and 3. ^{13}C nmr indicated a quaternary carbon at 65.4 ppm and two extra vinyl carbons at 132.5 and 138.3 ppm. ^1H NMR was compatible with the hydrogens present in structures 2 and 3 and showed an NH.

Fortunately, we were able to obtain a good crystal of this unknown compound, and single crystal x-ray analysis showed it to be structure 3[4].

Two possible mechanisms are shown in the Scheme. The molecular species envisioned in these mechanisms are all potentially present in the medium. In Mechanism A, the key intermediate 4 can be formed by standard

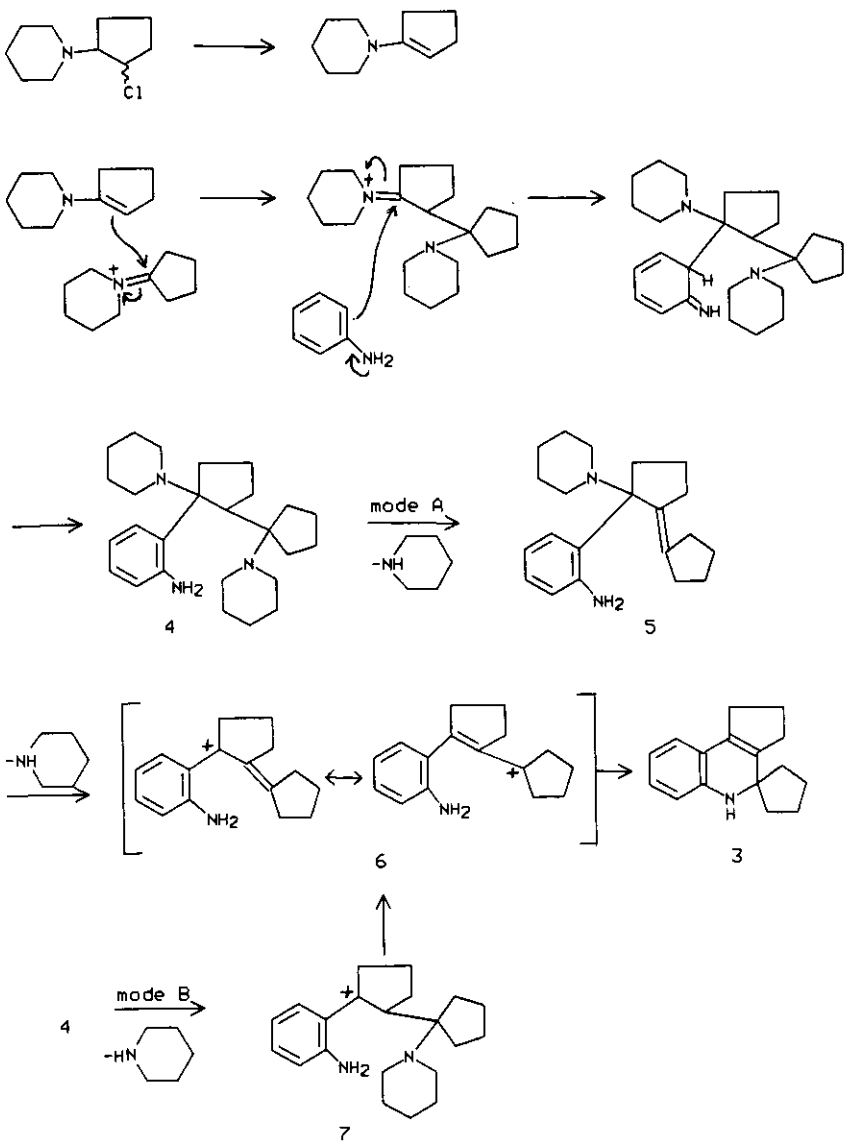
enamine-iminium chemistry as shown in the Scheme. Intermediate 4 can be transformed into the reactive allylic species 6 via two modes.

In mode A, loss of the outer piperidine first leads to structure 5, which is a vinylogous aminal. Then, loss of the inner piperidine leads to the highly reactive species 6. Species 6 may also be produced from the vinylogous aminal 4 by the loss of the inner piperidine first leading to species 7 which is converted to 6. Species 6 undergoes intermolecular ring closure to product 3.

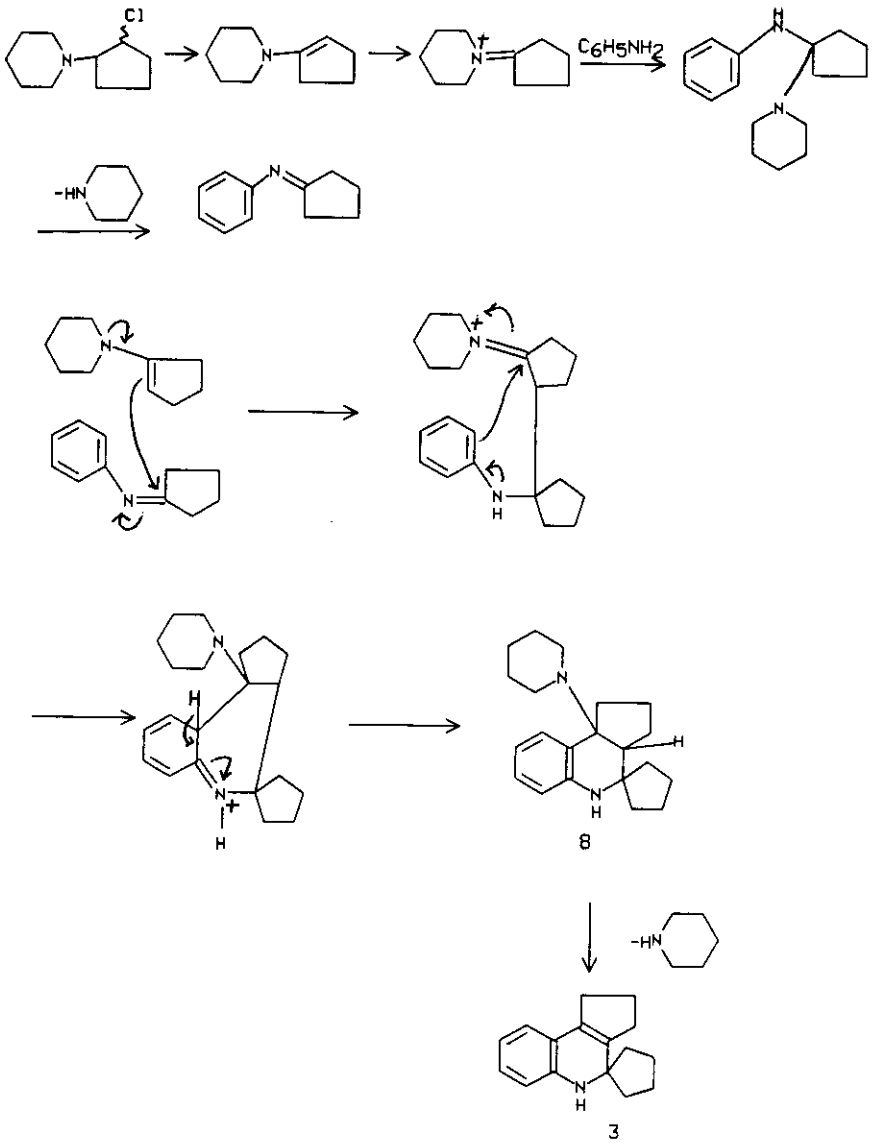
In mechanism B, the key intermediate 8 is formed as shown. Intermediate 8 is a vinylogous aminal and undergoes the loss of piperidine to give product 3[5].

SCHEME

Mechanism A:



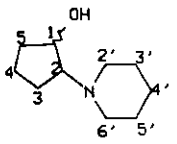
Mechanism B:



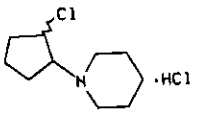
EXPERIMENTAL

Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, IR spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, and NMR spectra on a Varian Model XL-100 spectrometer. NMR peaks are recorded in parts per million downfield from tetramethylsilane.

2-piperidinocyclopentanol and 1-(2-chlorocyclopentyl)-piperidine hydrochloride are reported in the literature[6].

NMR ($CDCl_3$) 

H_1 at 4.3 δ H_2, H_2', H_6' at 2.5, OH at 3.07; H_3', H_5', H_4', H_3, H_4, H_5 at 1.3-2.0.

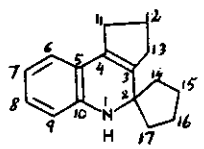
NMR (D_2O) 

H_1, H_2, H_2'e, H_6'e at 3.5-3.9 δ; H_2'a, H_6'a at 3.1 δ; H_3, H_4, H_5, H_3', H_4', H_5' at 1.5-1.9.

1-(2-anilinocyclopentyl)-piperidine (1) and 1,2,3,5-tetrahydrospiro[cyclopentane-1,4-[4H]cyclopenta[c]quinoline] (3)

A mixture of trans-1-(2-chlorocyclopentyl)piperidine (57.14 g, 0.304 mol) and aniline (56.69 g, 0.609 mol) was heated on the steam bath for 20.5 h and then kept at room temperature for 5 days. It was then poured into a mixture containing 78 ml of concentrated HCl, 600 ml of H_2O and 250 ml of ether and shaken until only a trace of solid remained. The ether layer was discarded, the acid layer was cooled and basified with 40% aq. NaOH. The product was extracted with ether, the organic solution was washed with H_2O, then saturated NaCl solution, dried ($MgSO_4$) and evaporated. The resulting oil (55 g) was distilled at 0.05 mm from an oil-jacketed flask: forerun, 42.9 g; product, 12.04 g, bp 160-170°C. Chromatography on 1200 g of silica gel with 2% MeOH-$CHCl_3$ gave 6.27 g of compound 3. Further elution with 10% MeOH-$CHCl_3$ gave 3.52 g of compound 1.

Compound 3 was crystallized several times from petroleum ether (bp 30-60°C) to give pale yellow rods, mp 77-78°C. UV (EtOH) max 231 nm (34,810), 276 (2,625), 306 (sh, 1512), 320 (sh, 2796), 340 (3898); Mass spectrum, m/z 225; IR, 3380 (NH), 1650, 1600, 1575, 1500, 1480 (C=C), 1315, 1305, 1040, 745 (C- N/other). NMR ($CDCl_3$) ^1H:

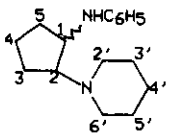


H_{14}, H_{15}, H_{16}, H_{17} at δ 1.4-2.1, H_{11}, H_{13} at 2.4-2.7, NH at 3.7-4.0, Hg at 6.35, H_7 at 6.55, H_6, H_8 at 6.9

^{13}C: C2 at 65.4 ppm, C_3 at 132.5, C_4 at 138.3, C_5 at 120.6, C_6 at 117.2, C_7 at 128.0; C_8 at 123.8, C_9 at 112.5, C_{10} at 143.2, C_{11} at 32.6, C_{12} at 22.9, C_{13} at 31.6; C_{14}, C_{17} at 40.5; C_{15}, C_{16} at 24.2.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.96; H, 8.93; N, 6.29.

Compound 1 was converted to the hydrochloride with 1N ethereal HCl. It was crystallized from MeOH-ether to give colorless needles, mp 207-209°C. UV (EtOH) max 246 nm (15,450), 293 (2,050); mass spectrum, m/z 244; IR 2670, 2520, 2480, 2460, 2400, (NH^+), 1600, 1570, 1500 (NH_2^+/C=C), 755, 695 (other); NMR (D_2O)



H_1 at 4.4 δ, H_2 at 3.85; H_2'e, H_6'e at 3.4; H_2'a, H_6'a at 2.85; H_3', H_4', H_5', H_3, H_4, H_5 at 1.5-2.3.

Anal. Calcd. for $C_{16}H_{22}N_2 \cdot 2\ HCl \cdot 1/3\ MeOH$: C, 59.81; H, 8.40; N, 8.54; Cl, 21.62. Found: C, 60.12; H, 8.73; N, 8.82; Cl, 21.62.

REFERENCES

1. Dedicated to my friend, Professor Gilbert Stork, on the occasion of his 65th birthday.

2. G.Stork, R.Terrell and J.Szmuszkovicz, J. Amer. Chem. Soc., 1954, 76, 2029. G.Stork, A.Brizzolara, H.Landesman, J.Szmuszkovicz and R.Terrell, J. Amer. Chem. Soc., 1963, 85, 207. J.Szmuszkovicz, Enamines, in "Advances in Organic Chemistry," Ed. R.A.Raphael, E.C.Taylor, H.Wynberg, Vol. 4, p. 1, Interscience, New York, 1963.

3. For our discovery of the cyclopropanation reaction, see, J.Szmuszkovicz, E.Cerda, M.F.Grostic and J.F.Zieserl, Jr., Tetrahedron Lett., 1967, 3969; J.Szmuszkovicz, D.J.Duchamp, E.Cerda and C.G.Chidester, Tetrahedron Lett., 1969, 1309. Later several investigators have contributed some beautiful chemistry based on the above reaction. See for example: H.H.Wasserman, M.H.Adickes and O.E.deOchoa, J. Amer. Chem. Soc., 1971, 93, 5586, and the review by N.DeKimpe and N.Schamp, Org. Prep. Proc. Int., 1983, 15, 71.

   For other rearrangements encountered in our work, see J.Szmuszkovicz, "Some Novel Aspects of Heterocyclic Chemistry", Lectures in Heterocyclic Chemistry, Ed. R.N.Castle and T.Kappe, Vol. 6, p. 5-81, Hetero-Corporation, Tampa, Florida, 1982.

4. To be submitted to Acta Crystallographica Section C.

5. We gratefully acknowledge the discussion with Drs. P.A.Aristoff, D.J.Cram, E.J.Jacobsen and E.Vedejs.

6. R.P.Pioch, U.S. Patent 3,772,308 (1973): Chem. Abstr. 1974, 80, 59558t.

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