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REACTIONS OF ACETYLENIC AMINES. VII.
A NOVEL SYNTHESIS OF HOMOMORPHOLINES

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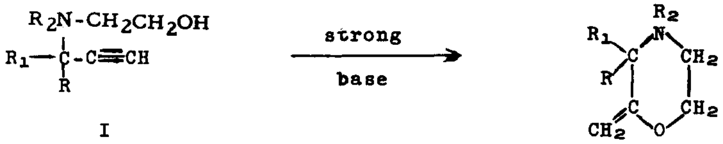
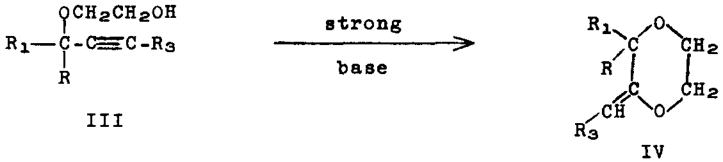
It was shown recently[1] that N-hydroxyethyl derivatives of α,α-disubstituted propargylamines (I) cyclize to the methylenemorpholines (II) when heated with strong base.

It has also been reported[2] that, under similar conditions, the hydroxyethyl derivatives of the γ-substituted propargyl alcohols (III) cyclize to substituted 1,4-dioxanes (IV).



I

II



III

IV

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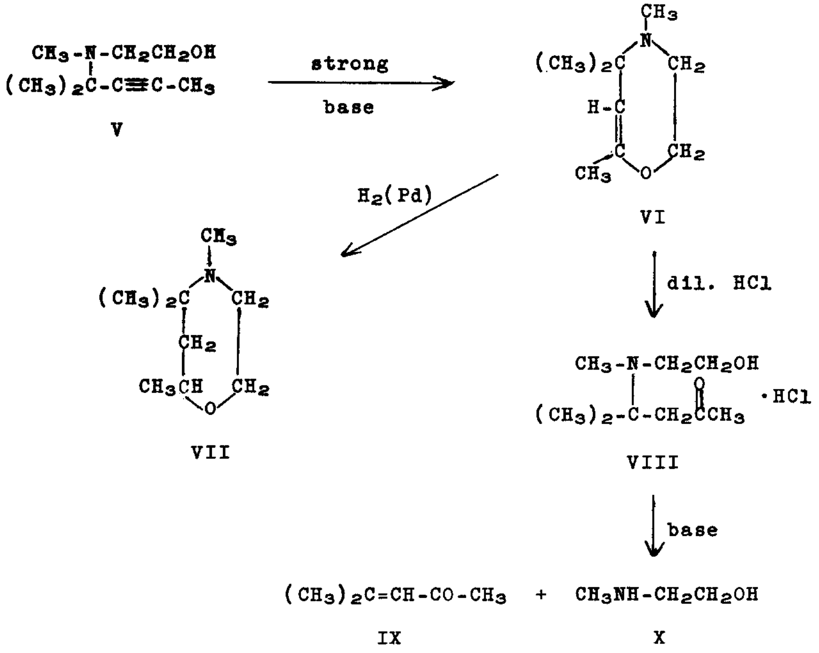
[1] N. R. Easton, D. R. Cassady and R. D. Dillard, J. Org. Chem., 28, 448 (1963).

[2] W. J. Croxall and N. D. Dawson, U.S. Patent 3,021,341.

In contrast to these results, we wish to report our recent findings on the cyclization of N-(β-hydroxyethyl)-N,2-dimethyl-3-pentynyl-2-amine (V). When compound[3] V, b.p. 77°/4 mm., n_D^{25} 1.4713, was treated with potassium hydroxide in boiling xylene, the expected product, 2-ethylidene-3,3,4-trimethylmorpholine, was not produced, although a product, b.p. 71°/15 mm., n_D^{25} 1.4681, was obtained in 55% yield. The n.m.r. spectrum of this material showed unsplit signals at 77 c.p.s. (6H), 104 c.p.s. (3H), 143 c.p.s. (3H), and at 266 c.p.s. (1H). Triplets centered at 184 c.p.s. (2H) and 238 c.p.s. (2H) were also seen.



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[3] All compounds reported herein gave satisfactory carbon and hydrogen analyses.

Since the signals at 266 c.p.s. and 104 c.p.s. were unsplit, the morpholine structure was impossible. However, these data are consistent with the structure VI (4,5,5,7-tetramethyl-2,3,4,5-tetrahydro-1,4-oxazepine), with the signal at 266 c.p.s. being assigned to the proton at position 6 and signal at 104 c.p.s. to the methyl group at position 7.

Convincing chemical evidence of the correctness of the structure VI was also obtained. This material was dissolved in dilute hydrochloric acid and the solution was concentrated to dryness at reduced pressure. The I.R. spectrum (mull) of the remaining solid (VIII), m.p. 98-100°, showed absorption bands at 3.22 μ and at 5.79 μ indicating both a hydroxyl and a carbonyl group. The n.m.r. spectrum (D_2O) showed, in addition to multiple signals, unsplit signals at 87 c.p.s. (6H), 137 c.p.s. (3H), 172 c.p.s. (3H), and 195 c.p.s. (2H). The unsplit signal at 195 c.p.s. shows that this is not an ethyl ketone or a cyclic derivative thereof, and therefore again makes the morpholine structure impossible. However, these data are consistent with the structure VIII and this assignment is further supported by the formation of mesityl oxide (IX) and N-methyl-β-hydroxyethylamine (X) when VIII is treated with base. These experiments confirm the structure assigned to VI since VIII would be the logical product from hydrolysis.

Hydrogenation of VI using palladium-on-carbon as the catalyst showed the absorption of one mole of hydrogen and gave the homomorpholine VII, b.p. 66°/12 mm.; n_D^{25} 1.4489. The I.R. and n.m.r. spectra were consistent with this structure.

The 60 mc. n.m.r. spectra were obtained on a Varian Associate Model HR60 in deuterochloroform with tetramethylsilane as an internal standard or in D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard.

Acknowledgment.--The n.m.r. spectra were obtained by Mr. John Klemm. The authors also wish to thank Messrs. Paul Landis and Donald Woolf, Jr., for their assistance in interpreting the n.m.r. and infrared data.