The Thermolysis of Heterocyclic Aminimines

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Aminimines derived from six heterocyclic tertiary amines were thermolyzed in *t*-butyl alcohol at *ca.* 80°. *N*-Methylindoline gave a good yield of the ring-opened product, and a double elimination on 1,4,4-trimethylpiperidine gave 3,3-dimethyl-1,4-pentadiene. The aminimine derived from quinuclidine was stable to elimination under these conditions. Simple elimination products were not obtained from *N*-methylpyrrolidine, *N*-methylpiperidine, or *N*-methyltetrahydroisoquinoline.

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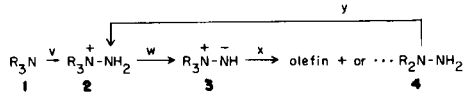
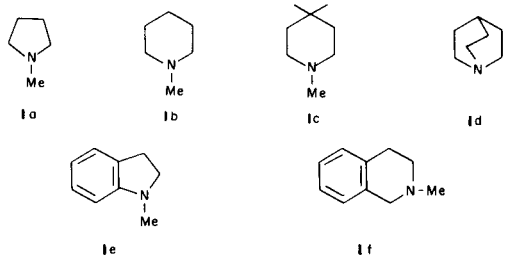
Several quaternary hydrazinium salts **2** have been reported to undergo elimination when heated with strong base (1). Presumably, an aminimine intermediate **3** is formed initially (2) and then fragments by a cyclic mechanism analogous to that of the Cope elimination (3). This reaction has potential uses in synthesis and degradation and is attractive because: (a) strong oxidizing agents are not required in the preparation of the substrates in contrast with the amine oxide, sulfoxide, and selenoxide routes; and (b) the decomposition temperature is lower than that usually required for the Hofmann or Cope eliminations.

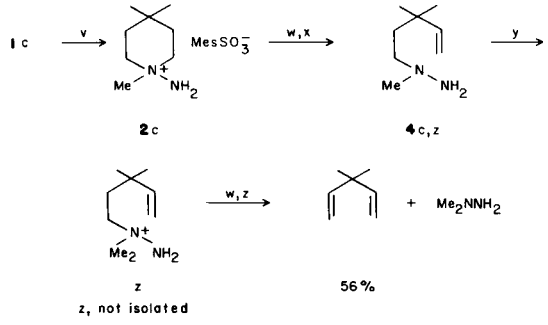


v, $MesSO_2ONH_2$ (MSH); w, KO-t-Bu/HO-t-Bu; x, reflux 12 hours; y, MeI

The amines that have been subjected to this degradation hitherto have had the nitrogen atoms in acyclic structures. Since so many naturally occurring amines are heterocyclic, and present special problems to degradation, it was of interest to us to examine the scope and limitations of the aminimine thermolysis in regard to such structures. This paper reports the application of standardized reaction conditions, not necessarily optimum, to six heterocyclic tertiary amines. The candidate amines, **1a-f**, were selected not primarily to furnish additional examples of elimination, but to challenge the technique with structures likely to present difficulties. The amines were converted to hydrazinium salts **2** by reaction with *O*-mesitylenesulfonyl hydroxylamine (MSH) (4).



A feature to be desired in any procedure intended for degradation of heterocyles is the capability for repetitive application, in order to strip the heteroatom completely from the molecule. Since 1,1-disubstituted hydrazines usually alkylate upon the more substituted nitrogen atom (5), it should be possible to methylate the ring-opened product from an aminimine elimination, thus reconverting it to a hydrazinium salt, and to repeat the elimination. This possibility has now been demonstrated by a "one-pot" double elimination on 1,4,4-trimethylpiperidine **1c**.



The initial attempts at double elimination were carried out on *N*-methylpyrrolidine **1a** and *N*-methylpiperidine **1b**. In neither case was even a trace of diene detected by direct GC of the reaction mixture, under the standard conditions or with several base-solvent combinations. In an attempt to determine the reasons for the failure, single eliminations were performed on **1b** under a variety of conditions, and some indication of the nature of the products was obtained. A substantial amount of unstable ether-extractable base fraction was obtained, showing that the hydrazinium salt had indeed been converted under these conditions. Gas chromatography showed several components. The nmr spectrum of the crude fraction contained, besides the other expected features, what seemed to be small peaks due to vinyl protons, but further upfield, δ 3.5-4, than expected for the simple elimination product *N*-methyl-*N*-(4-pentenyl)hydrazine. This is the region where the vinyl protons of enamines appear, and it seemed likely that under the strongly basic conditions of the reaction, the double bond in the initial product had migrated

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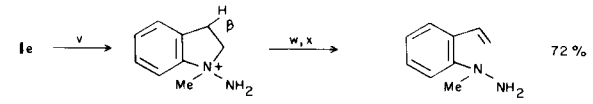
down the carbon chain, giving, in part, *N*-methyl-*N*-(1-pentenyl)hydrazine. Although this explanation is conjectural, it served as the basis for the choice of **1c**, in which the quaternary carbon atom blocks double bond migration, as the substrate for the successful double elimination.

As was anticipated for a *syn* cyclic mechanism (1), the aminimine derived from quinuclidine **1d**, did not eliminate (52% recovery). This not only supports the cyclic mechanism, but indicates that, at least with saturated heterocycles, a Hofmann-like E2 elimination is not likely under mild conditions.

N-methylindoline **1e** gave a surprisingly good yield of the ring-opened hydrazine **4e**. In this case, as with **1a**, a cyclic transition state for intramolecular elimination would be rather strained, and since the β-hydrogen atom in **2e** is benzylic, the possibility of an E2 elimination cannot be ruled out.



2e **4e**

When the degradation sequence was applied to *N*-methyltetrahydroisoquinoline **1f**, no simple ring-opened product could be isolated. A substantial basic fraction was obtained upon work-up, indicating that the aminimine had been converted. However, short-path vacuum distillation of this material gave only a few percent of material boiling in the expected range, leaving a large amount of oily residue, apparently polymeric. The nmr spectra of both distillate and residue showed vinyl protons, but integrating only 20-30% of the expected value. Similar results were also observed using potassium *t*-butoxide in dimethylsulfoxide or ether, sodium methoxide in methanol, or lithium diisopropylamide in tetrahydrofuran. The major reaction probably is S_N2 attack at the benzylammonium carbon atom of the aminimine by the highly nucleophilic imine nitrogen atom of a second molecule of imine. Intramolecular displacement, leading to ring-expanded hydrazine, cannot be very important since the product, isomeric with the ring-opened hydrazine, would have been distillable. Displacement by the bases employed may be ruled out, because methyl-proton signals from the bases did not appear in the nmr spectra of the crude product. The Hofmann degradation of **1f** is reported to give a good yield (6). In contrast, in the aminimine degradation, the greater nucleophilicity of the imine nitrogen atom apparently favors displacement.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns Block calibrated to give corrected melting points. Ir spectra were taken on a Beckman Acculab spectrometer. Nmr spectra were taken on a Varian EM-360 instrument in deuteriochloroform with tetramethylsilane as internal standard. Glc analyses were performed with a Hewlett-Packard Model 5750 chromatograph, using electronic integration. The mass spectrum was measured on a Bendix time-of-flight spectrometer, Model 12-107, from photographs of the CRT. Elemental analyses were performed by Microtech Laboratories, Skokie, Illinois.

Preparation of Starting Materials.

Pyrrolidine, piperidine, and tetrahydroisoquinoline were methylated by the Eschweiler-Clarke procedure (7). This method gave poor results with indoline, which was methylated in good yield by use of sodium hydride and methyl iodide in ether. Quinuclidine was liberated from its hydrochloride (Aldrich) by 20% sodium hydroxide and extracted with methylene chloride. The solution was dried with potassium carbonate and used directly for the preparation of the hydrazinium salt. *N*,3,3-Trimethylglutarimide was prepared either from 3,3-dimethylglutaric anhydride and methylamine, or by methylating 3,3-dimethylglutarimide with sodium hydride and methyl iodide in dimethylformamide, m.p. 52°C (lit. (8) m.p. 52-54°). The imide was reduced to 1,4,4-trimethylpiperidine **1c** by the use of sodium bis-(methoxyethoxy)aluminum hydride (Aldrich, Red-Al) in refluxing benzene (6 hours) (9); yield 85%, b.p. 140° (760 mm), (lit (10) b.p. 141-142°).

O-Mesitylenesulfonyl hydroxylamine (MSH) was prepared by the method of Tamura (4), however it was found to have short storage life, even at 0°. In fact, explosion of a 100 g. batch of the dried material has been reported (11). We have found that if the crude product, filtered from the hydrolysis of the last intermediate and washed with cold water, is air-dried for only a few minutes, and then stored in that condition at 0°, the usable lifetime is greatly extended. The nmr spectra of several batches prepared in this fashion consistently showed an excess of 2-3 protons in the neighborhood of the broad NH_2 absorption. This is undoubtedly due to water, exchanging with the NH_2 protons, since the excess proton count disappeared when the samples were thoroughly dried. It appears, therefore, that the undried material is a monohydrate which is more stable than anhydrous MSH. Before use in preparation of the hydrazinium salts, small samples of the hydrate were dried for a few hours in a cold vacuum dessicator.

The hydrazinium salts were prepared from equivalent amounts of the tertiary amine and MSH in methylene chloride at 0° (4). After 10-15 minutes, they were precipitated by the addition of ether, and, except for **2e**, were recrystallized from methanol-ether.

1-Amino-1-methylpyrrolidinium Mesitylenesulfonate (**2a**).

The yield of this compound was 88%, m.p. 184-185°; ir (Nujol): 3240, 3120 (-NH_2), 1610 (C=C) cm^{-1}; nmr: δ 6.8 (s, 2H, ArH), 6.2 (s, 2H, NH_2), 3.4 (s, 3H, NCH_3), 4.2-3.0 (br, 4H), 2.6 (s, 6H, *o*-ArCH_3), 2.2 (s, 3H, *p*-ArCH_3), 2.2-1.8 (br, 4H).

Anal. Calcd. for $C_{14}H_{24}N_2O_3S$: C, 55.97; H, 8.05; N, 9.32. Found: C, 55.63; H, 7.98; N, 9.13.

1-Amino-1-methylpiperidinium Mesitylenesulfonate (**2b**).

This was obtained in 85% yield, m.p. 171° (lit. (4) m.p. 172°).

1-Amino-1,4,4-trimethylpiperidinium Mesitylenesulfonate (**2c**).

This compound was obtained in 80% yield, m.p. 183-185°; ir: 3200, 3120, 1620 cm^{-1}; nmr: δ 6.8 (2H), 4.9 (br, 2H, NH_2), 3.45 (br + central singlet, 7H, NCH_3 + 2x NCH_2), 2.6 (s, 6H, o-CH_3), 2.2 (3H, p-CH_3), 2-1 (~4H), 0.95 (s, 6H, gem CH_3).

Anal. Calcd. for $C_{17}H_{30}N_2O_3S$: C, 59.61; H, 8.82; N, 8.17. Found: C, 59.34; H, 8.61; N, 8.03.

1-Aminoquinuclidinium Mesitylenesulfonate (**2d**).

This compound had m.p. 218-219°, yield 91%; ir: 3240, 3120, 1620 cm^{-1}; nmr: δ 6.9 (2H), 6.2 (s, 2H, NH_2), 4.0-3.5 (m, 6H), 2.7 (s, 6H, o-CH_3), 2.25 (s, 3H, p-CH_3), 2.1-1.6 (m, 7H).

Anal. Calcd. for $C_{16}H_{26}N_2O_3S$: C, 58.86; H, 8.02; N, 8.58. Found: C, 58.86; H, 8.03; N, 8.36.

1-Amino-1-methylindolinium Mesitylenesulfonate (**2e**).

It was found advisable to prepare this compound using no more than 1 g. of *N*-methylindoline, **1e**, per run, otherwise the exothermicity of the reaction caused darkening and considerable reduction in yield. This salt was recrystallized from ethanol-ether, yield 76%, m.p. 109°; ir: 3180, 3070, 1595 cm^{-1}; nmr: δ 7.4 (m, 4H), 7.0 (s, 2H), 6.8 (s, 2H), 4.7 (br, 2H), 3.9 (s, 3H, NCH_3), 3.4 (br, 2H), 2.6 (s, 6H), 2.25 (s, 3H).

Anal. Calcd. for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.03. Found: C, 61.97; H, 6.95; N, 8.04.

2-Amino-2-methyl-1,2,3,4-tetrahydroisoquinolinium Mesitylenesulfonate (**2f**).

This compound had m.p. 156-157°, yield 82%; ir: 3240, 3130, 1620 cm^{-1}; nmr: δ 7.4-6.6 (complex multiplet, ~8H, ArH + NH_2), 4.75 (br, 2H), 4.0 (br, 2H), 3.5 (s, 3H, NCH_3), 3.1 (br, 2H), 2.6 (s, 6H), 2.2 (s, 3H).

Anal. Calcd. for $C_{19}H_{26}N_2O_3S$: C, 62.95; H, 7.22; N, 7.72. Found: C, 62.86; H, 7.15; N, 7.68.

Degradation of 1,4,4-Trimethylpiperidine **1c**. Double Elimination.

To a suspension of 0.86 g. (2.5 mmoles) of the hydrazinium salt **2c** in 25 ml. of *t*-butyl alcohol was added 0.34 g. (3 mmoles) of potassium *t*-butoxide. The mixture was stirred and refluxed under nitrogen for 12 hours. After cooling, 0.20 ml. (3 mmoles) of methyl iodide was added, and stirring continued for ½ hour, then 0.28 g. (2.5 mmoles) of potassium *t*-butoxide was added, and stirring and refluxing were continued an additional 12 hours. Because of the similarity of boiling points the product could not be separated from the accompanying *t*-butyl alcohol and dimethylhydrazine by distillation. Analysis by gc (SE-30, 6 feet, 35°) gave a large solvent peak followed closely by two smaller peaks of comparable height. The third peak was identified as 1,1-dimethylhydrazine by spiking. The yield of product was calculated by comparison of the integration of the second peak with that of the solvent assuming that the response factor of the diene would be the same as that of a comparable weight of isobutylene, derived from the *t*-butyl alcohol. A small sample of the second peak was collected and further purified by bulb-to-bulb distillation in the inlet vacuum train of the mass spectrometer. The mass spectrum gives a reasonable identification of the product as being 3,3-dimethyl-1,4-pentadiene, which has also been obtained in 30% yield by double Hofmann degradation of **1c** (9), although the mass spectrum is not reported in the literature (9,12); ms: m/e (%) 96 (20, molecular ion), 95 (50), 94 (25), 92 (30), 80 (60), 79 (30), 78 (40), 68 (40), 67 (100), 66 (40).

Attempted Degradation of Quinuclidine **1d**.

The conditions were the same as in the previously described experiment. Gc of the reaction mixture (SE-30, 6 feet, 160°) showed only two peaks, identified by spiking as *t*-butyl alcohol and quinuclidine (12% yield). Separate injection of the hydrazinium salt (in chloroform) gave no quinuclidine, showing that the deamination had occurred during the refluxing. The reaction mixture was diluted with 30 ml. of methanol, filtered, and ether was added slowly. The solid which separated was found to be starting material, hydrazinium mesitylenesulfonate **2d** (52% recovery), m.p. 217°, nmr identical with that of authentic material.

Degradation of *N*-methylindoline **1e**.

To a suspension of 0.87 g. (2.5 mmoles) of the hydrazinium salt **2e** in 25 ml. of *t*-butyl alcohol was added 0.56 g. (5 mmoles) of potassium *t*-butoxide, and the mixture was stirred and refluxed for 12 hours under a nitrogen atmosphere. After cooling, water was added and the product was extracted with ether. The base was extracted from the ether with 10% hydrochloric acid and liberated with sodium hydroxide. After taking up in ether, drying, and stripping, the product was distilled in a short-path apparatus at 0.1 mm. pressure, bath temperature 70°, yield 72% of 1-methyl-1-(2-ethenylphenyl)-hydrazine; ir: 3280 (br), 2940, 1600, 1570, 1485 (s), 1450 (s), 1340, 1210, 1180, 880, 800, 730 cm^{-1}; nmr: δ 7.1 (m, 4H, ArH), 6.8 (m, 1H) and 5.4 (m, 2H) (vinyl), 3.6 (s, br, 2H, NH_2), 2.8 (singlet with some splitting, 3H, CH_3).

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.92; H, 8.17. Found: C, 72.93; H, 8.21

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