Amidrazones. 14. The Formation of 1,1-Disubstituted Hydrazines from the Base-promoted Hydrolysis of 1,1-Disubstituted-3-Amino-4,5-dihydro-1*H*-pyrazolium Halides: Mechanistic Considerations [1]

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Three mechanistic pathways are considered for the hydroxide-promoted conversion of 1,1-disubstituted-3-amino-4,5-dihydro-1*H*-pyrazolium halides **1** to 1,1-disubstituted hydrazines, ammonia and sodium 3-hydroxypropanoate. Evidence presented in this paper supports a hydrolysis mechanism *c* that is initiated by hydroxide ion addition to the 3-position of **1** to form a tetrahedral intermediate **7**.

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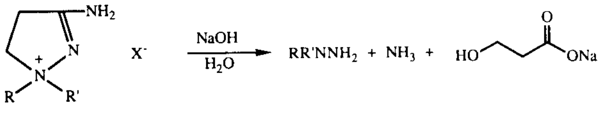
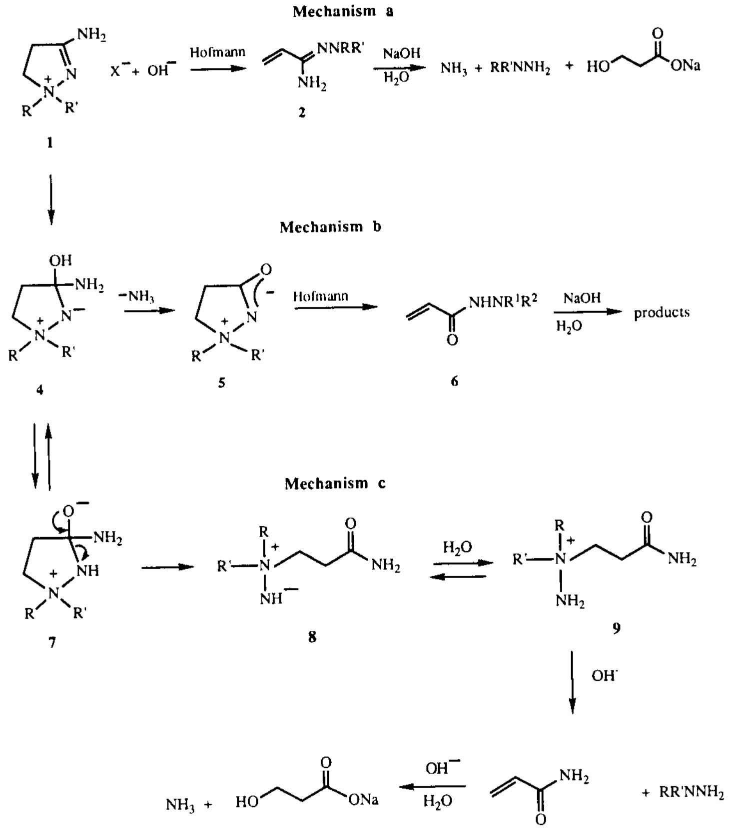
We have reported that the hydroxide-promoted hydrolysis of 1,1-disubstituted-3-amino-4,5-dihydro-1*H*-pyrazolium salts **1** is a synthetically attractive method for the preparation of 1-alkyl-1-phenylhydrazines [2] and 1-alkyl-1-methylhydrazines[1]. Ammonia and sodium 3-hydroxypropanoate are also formed in the hydrolysis reaction.



1, R = Alkyl, R' = Me or Ph

Scheme 1
Hydrolysis Mechanisms



In this paper we report the results of experiments that were designed to probe the mechanistic aspects of the hydroxide-promoted hydrolysis of **1**.

We initially considered that the hydroxide ion initiates a Hofmann ring-opening reaction (mechanism *a*) to give an intermediate acrylamide *N,N*-disubstituted hydrazone **2**. Alkaline hydrolysis of **2** would account for the formation of ammonia, the hydrazine and sodium 3-hydroxypropanoate, which is the reported product from Michael addition of hydroxide ion to acrylate ion [3]. We have found that amidrazones **2** are obtained by alkoxide-promoted Hofmann ring opening reactions on **1** [2]. However, as previously reported [2], mechanism *a* does not seem plausible since acrylamide methylphenylhydrazone (**2**, R = Me, R′ = Ph), which is the 1-methyl-1-phenylhydrazine precursor in mechanism *a*, was recovered unchanged when subjected to reaction conditions (refluxing 1 *N* sodium hydroxide) that give 1-methyl-1-phenylhydrazine in 87% yield from **1** (R = Ph, R′ = Me).

Experiments utilizing 3-amino-4,5-dihydro-1,4-dimethyl-1-phenyl-1*H*-pyrazolium iodide (**11**) provided results that were also incompatible with mechanism *a*. Hydrolysis of **11** in refluxing 1 *N* sodium hydroxide gave 1-methyl-1-phenylhydrazine in 87% yield. However, **11**, which possesses a sterically hindered 4-position, was recovered unchanged when subjected to Hofmann conditions (refluxing methanolic sodium methoxide). Clearly two different pathways are available for the attack of base on **1**. The more strongly basic alkoxide ion is capable of initiating Hofmann ring openings while aqueous sodium hydroxide initiates a sequence of reactions leading to the formation of the hydrazine, ammonia and sodium 3-hydroxypropanoate.

Proposed mechanisms *b* and *c* proceed *via* a common tetrahedral intermediate **4** which is formed by nucleophilic addition of hydroxide ion to the 3-position of **1**. Product formation *via* mechanism *b* requires collapse of **4** by elimination of ammonia to give the cyclic aminimide **5**. Hofmann ring opening of **5** would give a *N,N*-disubstituted acrylhydrazide **6**. Although base-promoted Hofmann ring opening reactions have not been reported on **5**, Wadsworth [4] reported that thermolysis of the 1,1,4-trimethyl and 1,1,5-trimethyl-substituted **5** compounds affords the corresponding Hofmann-type products.

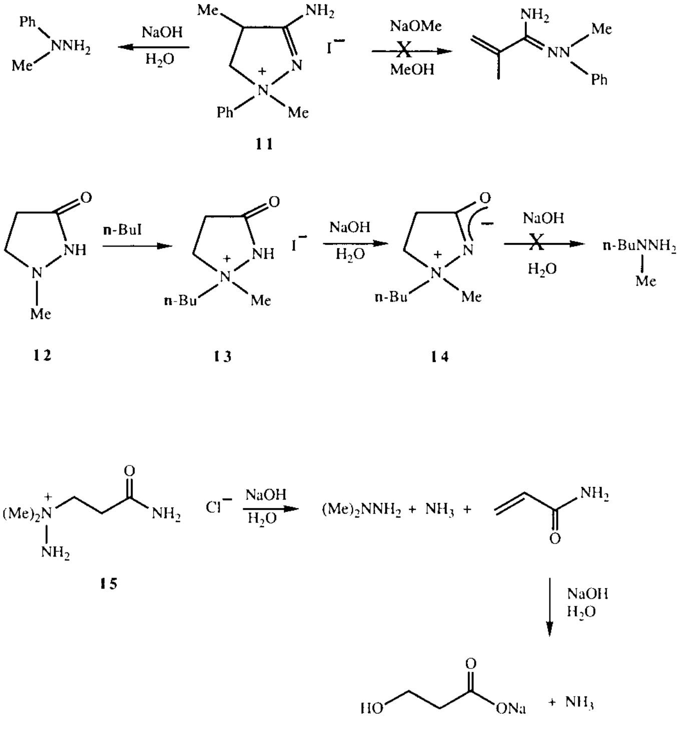
In order to study proposed mechanism *b*, we prepared 1-butyl-1-methyl-3-oxopyrazolidinium iodide (**13**) by alkylation of 1-methyl-3-pyrazolidinone (**12**) with 1-iodobutane. Salt **13** is the conjugate acid of the ylide intermediate **14** leading to 1-butyl-1-methylhydrazine *via* mechanism *b*.

Treatment of **13** with refluxing 6 *N* sodium hydroxide resulted in deprotonation to give the proposed *b* mechanism intermediate, 1-butyl-1-methyl-3-oxo-pyrazolidinium hydroxide inner salt (**14**) and no detectable ring-opened products. Under identical reaction conditions, 1-butyl-1-methyl-3-amino-4,5-dihydro-1*H*-pyrazolium iodide (**1**, R = Me, R′ = *n*-Bu) gave 1-butyl-1-methylhydrazine in 67% yield [1]. These results negate mechanism *b* as a plausible pathway for the hydrolysis of **1**.

Product formation by mechanism *c* requires conversion of tetrahedral intermediate **4** to **7** by proton transfer followed by ring opening to give the amido-substituted hydrazinium ylide **8**. Protonation of **8** affords a 1-(2-carbamoyl)-1,1-disubstituted hydrazinium salt **9** which is converted to the 1,1-disubstituted hydrazine and acrylamide by a base-promoted elimination reaction. Conversion of ylide **8** to the products *via* a cyclic Cope-type elimination reaction was considered but rejected since Posvic and Rogers [5] have determined that 1,1,1-trisubstituted hydrazinium salts have p*K*a values greater than 13. The conversion of **7** to **8** has precedence in the work Perrin and Arrhenium [6] who established that the kinetic product from the basic hydrolysis of 2-amino-1-pyrroline is 4-aminobutanamide.

In order to test hydrolysis mechanism *c*, we prepared 1-(2-carbamylethyl)-1,1-dimethylhydrazinium chloride (**15**) [7], which is the proposed intermediate leading to 1,1-dimethylhydrazine. When **15** was hydrolyzed in refluxing 6 *N* sodium hydroxide, it was converted to 1,1-dimethylhydrazine, ammonia and sodium 3-hydroxypropanoate. Under these conditions, 3-amino-1,1-dimethyl-4,5-dihydro-1*H*-pyrazolium iodide (**1** -R = R′ = Me) affords 1,1-dimethylhydrazine in 70% yield [1]. We have also estab-

Scheme 2



lished that hydrolysis of acrylamide in 6 *M* sodium hydroxide affords ammonia and sodium 3-hydroxypropanoate.

We thus conclude that sequence *c* represents a reasonable mechanisn for the base-promoted hydrolysis of **1**.

EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 710B instrument. The ^{1}H nmr spectra were recorded on a Perkin-Elmer 60 MHz instrument employing hexamethyldisiloxane as the internal standard. The ^{13}C nmr spectra were recorded on an IBM-Brucker WP100SY instrument.

3-Amino-4,5-dihydro-1,4-dimethyl-1-phenyl-1*H*-pyrazolium Iodide (**11**).

A solution of 3-amino-4,5-dihydro-4-methyl-1-phenyl-1*H*-pyrazole [8] (15.0 g, 0.087 mole), 15 ml of 1-iodobutane in 150 ml of dry acetonitrile was heated under reflux for 2.5 hours. On cooling, 27 g (65%) of crude **11** crystallized, mp 172-175°. Recrystallization from ethanol afforded colorless crystals, mp 175-177°; ^{1}H nmr (DMSO-d_6): δ 1.2 (d, 3H, 4-CH_3), 3,4-3.9 (m superimposed on a singlet at δ 3.5, 6H, H-4, H-5 and N-CH_3), 7.0-8.0 (m, 7H, NH_2 and ArH); ^{13}C nmr (methanol-d_1): δ 12.6 (4-CH_3), 38.4 (C-4), 58.8 (CH_3N), 72.1 (C-5), 119.5, 129.2, 129.4, 149.9 (aromatic), 170.9 (C-3); ir (potassium bromide): 1615 cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}IN_3$: C, 41.66; H, 5.09; N, 13.25. Found: C, 41.65; H, 5.12; N, 13.07.

Preparation of 1-Methyl-1-phenylhydrazine from **11**.

A solution containing **11** (5.0 g, 0.016 mole) in 50 ml of 6 *N* sodium hydroxide was heated under reflux for 6.5 hours. The cooled reaction mixture was extracted with ether. Evaporation of the dried ether extract gave 1.95 g (89%) of 1-methyl-1-phenylhydrazine which was identified by its ^{1}H nmr and ir spectra [2].

1-Methyl-3-pyrazolidinone (**12**).

A solution containing *N,N*-dimethylacrylamide (49.6 g, 0.50 mole) and methylhydrazine (23.1 g, 0.50 mole) in 50 ml of methanol was kept at room temperature for 48 hours. After removal of the methanol at reduced pressure, distillation afforded 40.3 g (80%) of the product as a colorless liquid, bp 148-153° (18 mm), lit [9], bp 85° (3 mm); ^{1}H nmr (deuteriochloroform): δ 2.58 (t, superimposed on a singlet at 2.61, H-4 and NCH_3, 5H), 3.15 (t, 2H, H-5), 9.7 (bd s, 1H, NH); ir (film): 1675 and 3200 cm^{-1}.

Anal. Calcd. for $C_4H_8N_2O$: C, 47.99; H, 8.05; N, 27.98. Found: C, 47.92; H, 8.16; N, 28.22.

1-Butyl-1-methyl-3-oxopyrazolidinium Iodide (**13**).

A solution containing **12** (4.23 g, 0.042 mole) and 1-iodobutane (8.1 g, 0.046 mole) in 40 ml of dry acetonitrile was heated under reflux for 4 hours. After cooling, 150 ml of ether was added to precipitate 11.3 g (82%) of crude product, mp 110-122°. Recrystallization from ethanol-ether gave colorless, hygroscopic crystals, mp 131-134°; ^{1}H nmr (DMSO-d_6): δ 0.85 (distd t, CH_2CH_3, 3H), 1.2-1.9 (m, $CH_2CH_2CH_2CH_3$, 4H), 2.85 (t, 2H, H-4), 3.4-3.7 (m, superimposed on a singlet at 3.35 N–CH_2– and N–CH_3, 5H), 4.15 (t, 2H, H-5), 8.0 (bd s, 1H, NH, deuterium oxide exchangeable); ir (potassium bromide): 1720 cm^{-1}.

Anal. Calcd. for $C_8H_{17}IN_2O$: C, 33.82; H, 6.03; N, 9.86. Found: C, 33.71; H, 6.19; N, 9.82.

1-Butyl-1-methyl-3-oxopyrazolidinium Hydroxide Inner Salt (**14**).

A solution containing 2.5 g of **13** in 12.5 ml of 6 *N* sodium hydroxide was heated under reflux in a nitrogen atmosphere for 5.5 hours. The cooled reaction mixture was extracted with methylene chloride. Evaporation of the dried methylene chloride solution gave **14** as a yellow, hygroscopic oil; ^{1}H nmr (DMSO-d_6): δ 0.79 (distd t, 3H, -CH_2CH_3), 1.0-1.9 (m, 4H, -$CH_2CH_2CH_3$), 2.41 (m, 2H, H-4), 2.9-3.3 (m, superimposed on a singlet at δ 2.89, N–CH_2 and N–CH_3), 3.55 (m, 2H, H-5). Acidification at the DMSO-d_6 solution with trifluoroacetic acid gave a solution whose ^{1}H nmr spectrum was identical to that of **13**.

Alkaline Hydrolysis of 1-(2-Carbamylethyl)-1,1-dimethylhydrazinium Chloride (**15**).

A solution containing 141.7 g (1.08 moles) of **15** [7] in 350 ml of 6 *N* sodium hydroxide was heated under reflux for 1.5 hours at which time ammonia evolution was no longer evident. The reaction mixture was rapidly distilled while maintaining the original volume by dropwise addition of water. After collection of 400 ml of distillate, the distillate was acidified with concentrated hydrochloric acid and evaporated to dryness *in vacuo*. Recrystallization of the residue from absolute ethanol afforded 56.6 g (54%) of 1,1-dimethylhydrazine hydrochloride, mp 78-80°, lit [2] mp 81-82°; ^{1}H nmr (DMSO-d_6): δ 2.80 (s, 6H), 8.3 (bd s, 3H).

In a separate experiment, the alkaline distillation pot residue was saturated with solid sodium hydroxide. After cooling, crude sodium 3-hydroxypropanoate precipitated. Recrystallization from ethanol gave the salt in 15% yield; ^{1}H nmr (deuterium oxide): 3.7 (t), 2.3 (t) [2].

Alkaline Hydrolysis of Acrylamide.

A reaction mixture containing acrylamide (2.3 g, 0.032 mole) and 200 ml of 1 *N* sodium hydroxide was heated under reflux for 2 hours. The solvent was removed *in vacuo* and the solid residue was extracted with 60 ml of boiling ethanol. The ice-cooled solution deposited sodium 3-hydroxypropanoate which was filtered off, washed with ether and dried at reduced pressure. The yield of the salt (identified by ^{1}H nmr) obtained by this procedure was 2.03 g (57%).

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