

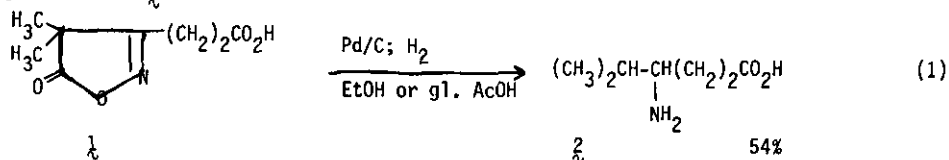
CATALYTIC REDUCTION OF 3-(4,4-DIMETHYL-5-KETO-3-ISOXAZOLE)PROPIONIC ACID AND ITS DERIVATES

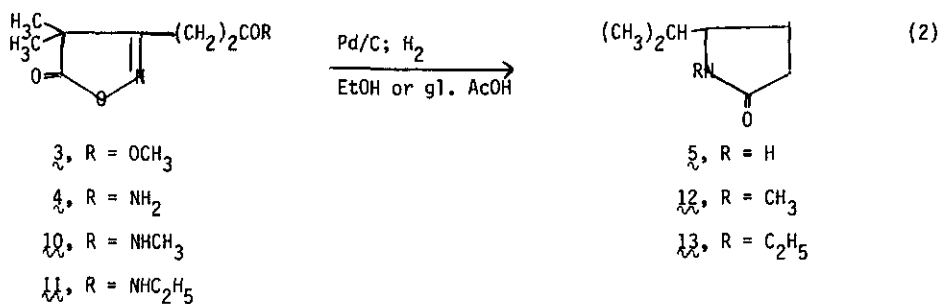
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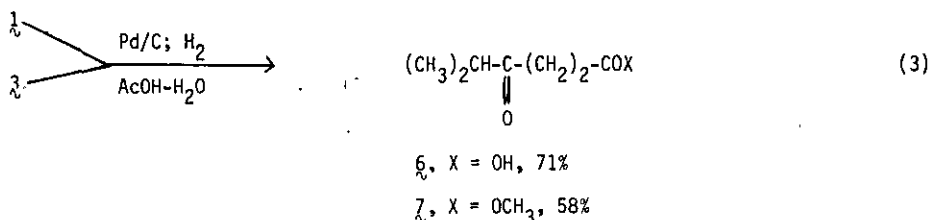
Abstract - Catalytic hydrogenation of 3-(4,4-dimethyl-5-keto-3-isoxazole)propionic acid (**1**) in glacial acetic acid in the presence of 5% palladium on charcoal gives 4-amino-5-methylhexanoic acid (**2**). Reductions of the corresponding ester, methyl 3-(4,4-dimethyl-5-keto-3-isoxazole)propionate (**3**) and amide, 3-(4,4-dimethyl-5-keto-3-isoxazole)propionamide (**4**) afford, however, γ -isopropylbutyrolactam (**5**). Reductions of **1** and **3** in aqueous acetic acid give 4-keto-5-methylhexanoic acid (**6**) and methyl 4-keto-5-methylhexanoate (**7**), respectively. On the other hand amide **4** is converted to 2-hydroxy-5-isopropylidene- Δ^1 -pyrroline (**8**). Compound **8** is also obtained if **4** is reduced in acetic acid containing a small amount of hydrogen chloride.

Syntheses of 3-(4,4-dimethyl-5-keto-3-isoxazole)propionic acid (**1**), its corresponding methyl ester methyl 3-(4,4-dimethyl-5-keto-3-isoxazole)propionate (**3**) and amide 3-(4,4-dimethyl-5-keto-3-isoxazole)propionamide (**4**) from methyl 4,6-dinitro-5,5-dimethylhexanoate have recently been described.^{1,2} We are now reporting on the reductions of these compounds with 5% palladium on charcoal at hydrogen pressures of about one atmosphere. Reactions which were performed in 100% ethanol or glacial acetic acid caused reductive cleavage.³ Compound **1** was converted to 4-amino-5-methylhexanoic acid (**2**) in 54% yield (Eq. 1). On the other hand **3** and **4** gave γ -isopropylbutyrolactam (**5**) in yields of 78% and 72%, respectively² (Eq. 2). Apparently, either the methyl ester and amide of **2** or their imine precursors, which formed during hydrogenation, underwent subsequent ring closure to **5**.

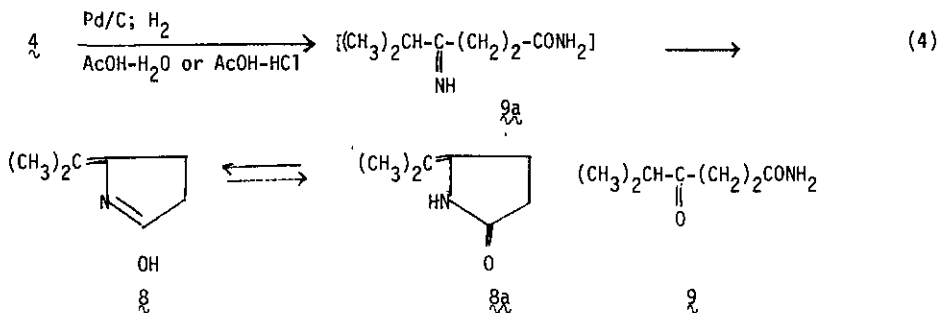




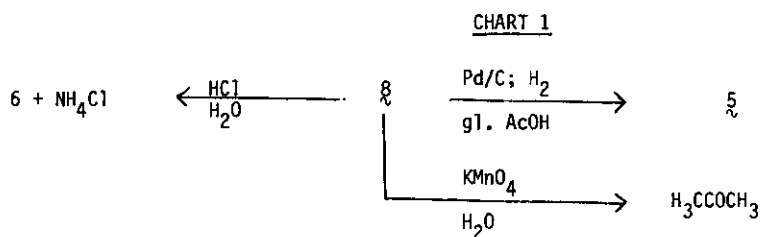
The course of these reactions was affected when reductions were carried out in acetic acid containing 7% water by volume. Compounds $\underline{1}$ and $\underline{3}$ were converted into 5-methyl-4-ketohexanoic acid ($\underline{6}$) and its methyl ester $\underline{7}$ in yields of 71% and 58% respectively (Eq. 3). Apparently, water deactivated the catalyst so that reduction, after ring cleavage and decarboxylation, proceeded only to the imine analogs of $\underline{6}$ and $\underline{7}$ which underwent hydrolysis to $\underline{6}$ and $\underline{7}$.



Reduction of amide $\underline{4}$ in acetic acid containing water did not give the expected product, 5-methyl-4-oxohexanamide ($\underline{9}$), but led instead to 5-isopropylidene-2-hydroxy- Δ^1 -pyrroline ($\underline{8}$) in 67% yield. Evidence has been obtained that the imino compound $\underline{9a}$ and not $\underline{9}$ is very likely the precursor in the formation of $\underline{8}$, for reduction of $\underline{4}$ in glacial acetic acid containing hydrogen chloride also afforded $\underline{8}$ in 55% yield (Eq. 4). In control tests, it was established that amide $\underline{4}$ was not affected by solutions of hydrogen chloride in glacial acetic acid.



As shown in Chart 1, the presence of the five membered ring in **8** was established by its reduction with hydrogen in the presence of palladium on charcoal in glacial acetic acid to lactam **5**. Oxidation of **8** with hot aqueous potassium permanganate gave acetone, indicating the presence of the isopropyl group. Hydrolysis of **8** with concd. hydrochloric acid gave **6** (68% yield) and ammonium chloride.



The spectral data of **8** are in agreement with the assigned structure; however, the presence of the tautomeric structure **8a** is not ruled out. The conjugated system in **8** was clearly indicated in its UV spectrum at 235 nm ($\log \epsilon$ 3.92); the ir spectrum showed absorptions at 3175 (OH or NH), 3030 (CH), 1680 (C=N or C=O) and 1265 cm^{-1} (C-O). The presence of 11 protons, in the ratio of 6:4:1 was indicated in the nmr spectrum [$\delta(\text{CDCl}_3)$ 1.60 (d, 6, CH_3), 2.20 (t, 4, CH_2), 9.36 (s, 1, OH or NH)].

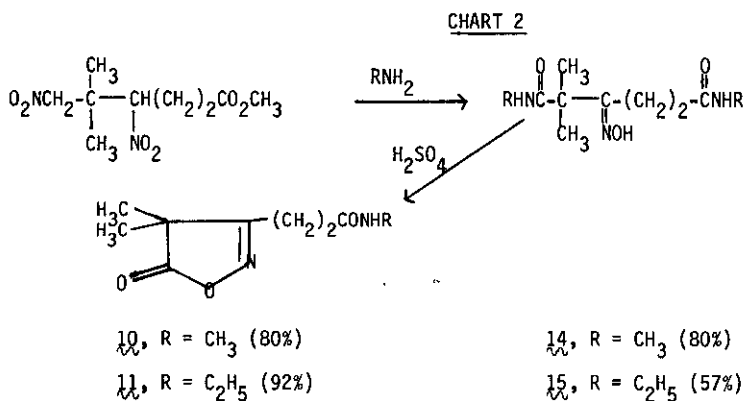
Since the transformation of amide **4** to lactam **5** involved the loss of carbon dioxide and ammonia (Eq. 2), it was of interest to determine which of the two nitrogens in **4** was retained in **5**. Reductions of 3-(4,4-dimethyl-5-keto-3-isoxazole)-N-methylpropionamide (**10**) and 3-(4,4-dimethyl-5-keto-3-isoxazole)-N-ethylpropionamide (**11**) in glacial acetic acid gave N-methyl- γ -isopropylbutyrolactam (**12**) and N-ethyl- γ -isopropylbutyrolactam (**13**) in yields of 70% and 61%, respectively (Eq. 2). These results show that reductions of **10** and **11**, and by analogy, probably also of **4**, proceed with retention of the amide nitrogen and the loss of the ring nitrogen.

Lactams **12** and **13** were found to be unstable at ambient temperatures, as evidenced by their discoloration within a few hours after distillation.

Reduction of **11** in acetic acid containing hydrogen chloride also afforded **13** in 53% yield. This is in contrast to our observations with compound **4** the reduction of which, under similar reaction conditions did not proceed beyond the conjugated double bond structure **8**. Since in the case of **11** such a conjugated system cannot form, its reduction leads to the saturated lactam **13** even in the presence of hydrogen chloride.

The reduction of 11 in the presence of water gave an inseparable mixture. Treatment of this mixture with hydrogen chloride gave keto-acid 6 and ethylammonium chloride. It seems most likely that these products arose from hydrolysis of 4-keto-5-methyl-N-ethylhexanamide.

Compounds 10 and 11 were prepared in yields of 80% and 92% respectively, on treating N,N'-2,2-tetramethyl-3-oximinoadipamide (14) and N,N'-diethyl-2,2-dimethyl-3-oximinoadipamide² (15) with concd. sulfuric acid. Compounds 14 and 15 were prepared by reacting methyl 4,6-dinitro-5,5-dimethylhexanoate¹ with methylamine and ethylamine, respectively² (Chart 2).



EXPERIMENTAL

Apparatus, Reagents, and General Procedure for Hydrogenations.--

All hydrogenations were carried out in a 250 ml filtering flask attached to an inverted U-tube, one end of which was immersed in a mercury well. The apparatus was evacuated to approximately 0.2 atm and hydrogen was introduced to 1.0 atm. This procedure was repeated several times to flush air from the system. Starting with a hydrogen pressure of 1.0 atm, the mixture was agitated with a magnetic stirrer, and the course of the reaction was followed by the rise of mercury in the U-tube. Hydrogen was added to keep the pressure between 0.75 and 1.0 atm. In all reactions 0.5 g of Englehard's "5% Palladium on Carbon" was employed. The reactions were generally complete in about two hours.

γ-Isopropylbutyrolactam (5).--

2-Hydroxy-5-isopropylidene-Δ¹-pyrroline (8) (1.25 g, 0.01 mol) was hydrogenated in 40 ml of glacial acetic acid for 30 min. The reaction mixture was filtered and the solvent removed in vacuo. The residue was dissolved in pentane, the solution decolorized with activated carbon and filtered. Evaporating the solvent and subliming the resulting solid at 100^o (8 mm) afforded 0.54 g (43%) of γ-isopropylbutyrolactam (5): mp 71.5-73.5^o (lit.² mp 72-73^o).

5-Methyl-4-ketohexanoic Acid (6).--

(a) From 3-(4,4-dimethyl-5-keto-3-isoxazole)propionic Acid (1). Hydrogenation of 1.85 g (0.01 mol) 1 in 40 ml glacial acetic acid and 3.3 ml of water was followed by filtration and evaporation of the solvent in vacuo. The residual oil was dissolved in 30 ml of water, the solution extracted with 8 x 25 ml portions of chloroform and the combined extracts dried (MgSO₄). The solvent was removed in vacuo and the oil was dissolved in a 1:9 mixture of ether-pentane. Cooling in dry ice gave 1.04 g (72%) of 5-methyl-4-ketohexanoic acid (6): mp 41-43° (lit.⁴ mp 41-42°); ir (nujol) 2860 (broad, acid OH), 1754 (ketone C=O), and 1724 cm⁻¹ (acid C=O); nmr (CCl₄) δ 1.10 [d,6,(CH₃)₂], 2.62 [m,5,(CH₃)₂CH and (CH₂)₂] and 11.62 (s,1,OH).

(b) From 2-Hydroxy-5-isopropylidene-Δ¹-pyrroline (8). A solution of 8 (1.88 g, 0.015 mol) in 20 ml of concd. hydrochloric acid was refluxed for 30 min and after cooling was extracted with 6 x 25 ml portions of chloroform. Drying the combined extracts (MgSO₄) and evaporating the solvent in vacuo gave an oil which was suspended in 10 ml of pentane. Dropwise addition of ether gave a clear solution which upon cooling in dry ice deposited 1.47 g (68%) of 6: mp 41-43°.

Methyl-5-Methyl-4-ketohexanoate (7).--

Methyl 3-(4,4-dimethyl-5-keto-3-isoxazole)propionate (3) (0.88 g, 0.01 mol) was hydrogenated in a mixture of 40 ml glacial acetic acid and 3.3 ml of water. The reaction mixture was filtered and the solvent removed. The residue was dissolved in 75 ml of chloroform and the solution extracted with aqueous sodium carbonate. The aqueous layer was then extracted with 6 x 25 ml portions of chloroform and the combined extracts were dried (MgSO₄). Filtering and distilling gave 0.85 g (54%) of methyl 5-methyl-4-ketohexanoate (7): bp 91-93° (13-14 mm) [lit.⁵ bp 93° (13 mm)]; ir (neat) 1748 (ester C=O), 1724 (ketone C=O), 1212 and 1170 cm⁻¹ (C-O); nmr (CCl₄) δ 1.09 [d,6,(CH₃)₂], 2.55 [m,5,(CH₃)₂CH and (CH₂)₂], 3.61 (s,3,OCH₃). Anal. Calcd. for C₈H₁₄O₃: C, 60.74; H, 8.92 mol. wt. 158. Found: C, 60.66, H, 9.00; mol. wt. 159 (CHCl₃).

2-Hydroxy-5-isopropylidene-Δ¹-pyrroline (8).--

A mixture consisting of 3-(4,4-dimethyl-5-keto-3-isoxazole)propionamide (4) (1.84 g, 0.01 mol) 40 ml of glacial acetic acid and 3 ml of water was hydrogenated and filtered. Removal of solvent in vacuo gave a solid to which were added 60 ml of chloroform and 30 ml of water. The water layer was separated and extracted with 30 ml of chloroform. The combined chloroform extracts were dried (MgSO₄) and evaporated in vacuo to give a solid. Dissolving the solid in 95% ethanol and cooling to -70° afforded 0.83 g (66%) of 2-hydroxy-5-isopropylidene-Δ¹-pyrroline (8):

mp 163-166^o; ir (nujol) 3175 (OH), 1689 (C=N) and 1265 cm⁻¹; nmr (CDCl₃) δ 1.60 [d,6,(CH₃)₂], 2.60 [t,4,(CH₂)₂], 9.36 [s(broad),1,OH]. Anal. Calcd. for C₇H₁₁NO: C, 67.17; H, 8.86; N, 11.19; mol. wt. 125. Found: C, 67.52; H, 9.02; N, 11.19; mol. wt. 129 (CHCl₃).

When **4** was hydrogenated in 40 ml of glacial acetic acid containing 0.2 mol of hydrogen chloride, pyrroline **8** was obtained in 55% yield.

N-Methyl-γ-isopropylbutyrolactam (12).--

The procedure described for preparing **7** was followed except that 1.98 g (0.01 mol) of 3-(4,4-dimethyl-5-keto-3-isoxazole)-N-methylpropionamide (**10**) and 40 ml of acetic acid were employed. The yield of N-methyl-γ-isopropylbutyrolactam (**12**) was 0.99 g (70%): bp 60^o (0.55 mm); ir (neat) 1694 cm⁻¹ (C=O); nmr (CCl₄) δ 0.83 [d,6,(CH₃)₂], 1.6-2.3 [m,5,(CH₃)₂CH and (CH₂)₂], 2.70 (s,3,CH₃N), and 3.42 (m,1,CHN). Anal. Calcd. for C₈H₁₅NO: C, 68.04; H, 10.71; N, 9.92; mol. wt. 141. Found: C, 67.49; H, 10.59; N, 10.04; mol. wt. 144 (CCl₄).

N-Ethyl-γ-isopropylbutyrolactam (13).--

Hydrogenation of 2.12 g (0.01 mol) 3-(4,4-dimethyl-5-keto-3-isoxazole)-N-ethylpropionamide (**11**) in 40 ml glacial acetic acid was followed by filtering and saturating the solution with hydrogen chloride. The precipitated ammonium chloride was removed and the solvent evaporated in vacuo. Distillation gave 0.95 g (61%) of N-ethyl-γ-isopropylbutyrolactam (**13**): bp 117^o (8 mm); ir (neat) 1695 cm⁻¹ (C=O); nmr (CCl₄) δ 0.9 [m,9,CH₃-CH₂N and (CH₃)₂CH], 1.6-2.3 [t,4,(CH₂)₂], 2.81 (m,1,CHN) and 3.52 (m,2,CH₂N). Anal. Calcd. for C₉H₁₇NO: C, 69.93; H, 11.04; N, 9.02; mol. wt. 155. Found: C, 69.27; H, 10.91; N, 9.26; mol. wt. 159 (CHCl₃).

N,N'-2,2-Tetramethyl-3-oximinoadipamide (14).--

Methylamine was added through a gas dispersion tube at room temperature to 25 g (0.1 mol) of methyl 4,6-dinitro-5,5-dimethylhexanoate¹ dissolved in a mixture of 100 ml methanol and 25 ml water. The temperature rose to the boiling point in about 15 min. After the addition of amine was terminated, the reaction mixture was cooled and stirred 1 hr at room temperature. The solution was concentrated in an air stream to give 12.9 g (56%) of crude **14**, mp 175-180^o (CH₃OH). Three additional recrystallizations gave the analytical sample, mp 180-182^o (decomn.); ir (nujol) 3125 (=NOH), 1652 (C=O) and 1582 cm⁻¹ (C=N); nmr (D₂O) δ 1.94 [s,6,(CH₃)₂], 3.08 [t,4,(CH₂)₂], 3.34 (s,3,NCH₃) and 4.88 (m,3,NH and OH). Anal. Calcd. for C₁₀H₁₉N₃O₃: C, 52.38; H, 8.35; N, 18.33; mol. wt. 229. Found: C, 52.47; H, 8.46; N, 18.46; mol. wt. 231 (H₂O).

3-(4,4-Dimethyl-5-keto-3-isoxazole)-N-methylpropionamide (10).--

A mixture of compound 14 (11.45 g, 0.050 mol) and 15 ml of concd. sulfuric acid was cooled in an ice bath for 1 hr and was then allowed to stand at room temperature for 96 h. The reaction mixture was poured over ice and neutralized with aqueous methylamine at 0°. The solution was evaporated (air stream), the residue dried in vacuo and extracted first with 100 ml of 2-propanol and then with 2 x 100 ml portions of acetone. The combined extracts were concentrated to give 5.2 g (52%) of compound 10: mp 102-103° (2-propanol); ir (nujol), 3225 (NH), 1785 (ring C=O), 1667 (amide C=O), 1639 (C=N) and 1570 cm⁻¹ (amide II band); nmr (CDCl₃) δ 1.38 [s,6,(CH₃)₂], 2.74 [m,7,(CH₂)₂ and CH₃N] and 6.50 (s,1,NH). Anal. Calcd. for C₉H₁₄N₂O₃: C, 54.53; H, 7.12; N, 14.13; mol. wt. 198. Found: C, 54.51, H, 7.08; N, 14.39; mol. wt. 204 (CHCl₃).

3-(4,4-Dimethyl-5-keto-3-isoxazole)-N-ethylpropionamide (11).--

A mixture consisting of N,N'-diethyl-2,2-dimethyl-3-oximino adipamide² (15) (58 g, 0.226 mol) and 80 ml of concd. sulfuric was placed in an ice bath, stirred until the solid had dissolved, and was then allowed to stand for 24 hr at ambient temperature. The solution was poured over ice, neutralized at 0° with concd. ammonium hydroxide and evaporated. The remaining solid was extracted first with 300 ml of cold acetone and then by 4 x 100 ml portions of hot acetone. The combined extracts were evaporated (air stream) to give 44 g (92%) of 11: mp 108-110° (2-propanol); ir (nujol) 3268 (NH), 1802 (ring C=O), 1681 (amide C=O), 1650 (C=N) and 1570 cm⁻¹ (amide II band); nmr (CDCl₃) δ 1.15 (t,3,NCH₂-CH₃), 1.37 [s,6,(CH₃)₂], 2.67 [m,4,(CH₂)₂], 3.29 (m,2,CH₂-N) and 7.32 (s,1,NH). Anal. Calcd. for C₁₀H₁₆N₂O₃: C, 56.59; H, 7.60; N, 13.20; mol. wt. 212. Found: C, 56.53; H, 7.46; N, 13.14; mol. wt. 213 (CHCl₃).

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