Pyrrolidine-2,3-dione, 1-Allylpyrrolidine-2,3-dione and 1-Ethoxypyrrolidine-2,3-dione

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Authentic pyrrolidine-2,3-dione has been prepared by two different routes. It is shown that the material previously reported is actually a hydrolysis product, 4-amino-2-oxobutyric acid. 1-Allyl- and 1-ethoxypyrrolidine-2,3-dione have been prepared as *N*-protected pyrrolidine-2,3-diones potentially useful in synthesis.

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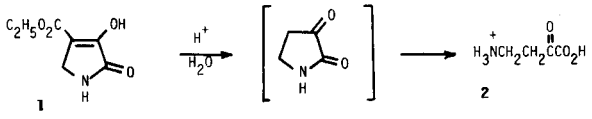
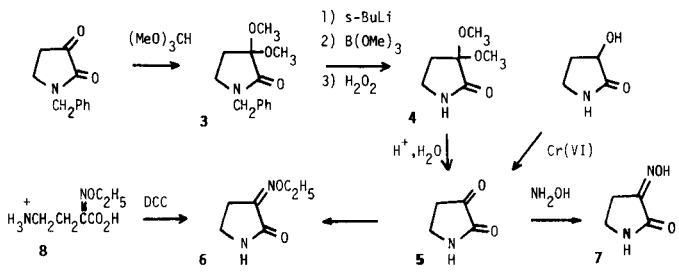
The only literature report of pyrrolidine-2,3-dione is by von Dobeneck, Uhl and Forster who prepared the material by hydrolytic decarboxylation of 4-carboethoxypyrrolidine-2,3-dione [1]. Curiously, the substance was reported to have been isolated as a hydrochloride hydrate. Repetition of the preparation, which involves Dieckmann-type condensation of ethyl β-alanate with diethyl oxalate, followed by acidic hydrolysis, gave the material previously described. Its physical properties and spectra were much more consistent with formulating the substance as the hydrolysis product, 4-amino-2-oxo-butyric acid.



We then embarked on an effort to obtain the authentic pyrrolidine-2,3-dione. The usual preparation of pyrrolidine-2,3-diones is based on condensation of a β-alanine ester with an oxalate ester as in the purported synthesis of pyrrolidine-2,3-dione. A number of *N*-substituted pyrrolidine-2,3-diones have been prepared in this way [2]. One approach to the unsubstituted compounds was to prepare a derivative which could subsequently be dealkylated. The *N*-benzyl compound is reasonably accessible [3] and our initial approach involved debenzylation. This dione was ketalized and then debenzylated by Evans' method [4] involving lithiation of the benzyl methylene group and reaction with methyl borate, followed by oxidation with hydrogen peroxide. The dimethyl ketal of pyrrolidine-2,3-dione **4** was obtained in 41% yield. Treatment of this ketal with concentrated hydrochloric acid in tetrahydrofuran gave a colorless glass having spectral properties consistent with those expected for pyrrolidine-2,3-dione. The compound was of limited stability and was derivatized as the *N*-ethoxyimine **6** and oxime **7**. A second route to the compound became available when a convenient preparation of 3-hydroxypyrrolidin-2-one was published [5]. Oxidation of this compound with Jones reagent gave the crystalline pyrrolidine-2,3-dione in 20-30% yield.

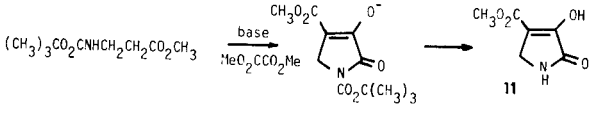


Verification of identity of the material obtained as described by von Dobeneck, *et. al.* was obtained by preparation of **8**, the *O*-ethyloxime of **2**. This material was cyclized with cyclohexylcarbodiimide to give the same compound as obtained by reaction of authentic pyrrolidine-2,3-dione with *N*-ethoxyamine.

We were also interested in other pyrrolidine-2,3-diones with potentially removable *N*-substituents. Two new examples, the *N*-allyl (**9**) and *N*-ethoxy (**10**) derivatives, were prepared. The standard route of synthesis [2] was used, involving addition of either allylamine or ethoxyamine to methyl acrylate followed by base-catalyzed cyclization with dimethyl oxalate. The details of the preparations are given in the Experimental. All of the pyrrolidine-2,3-diones are very prone to self-condensation and we obtained only poor recovery on attempted chromatographic purification. The *N*-benzyl dione is crystalline and, with care, high purity samples can be obtained by recrystallization. Noncrystalline compounds such as **9** and **10** were more troublesome to purify. We found that **9** could be distilled in the presence of a non-volatile acid such as terephthalic acid. Kugelrohr distillation of small amounts gave good recovery under these conditions. In the absence of the acid, attempted distillation led to extensive decomposition of the *N*-allylpyrrolidine-2,3-dione.

We also examined the condensation of several carbamate derivatives of methyl β-alanate with dimethyl oxalate. The methoxycarbonyl, ethoxycarbonyl, *t*-butoxycarbonyl, phenoxycarbonyl and benzyloxycarbonyl derivatives were subjected to conditions which cause condensation between dimethyl oxalate and *N*-alkyl-β-alanate esters

(sodium methoxide in methanol or sodium hydride in tetrahydrofuran. Recovered starting materials were obtained except in the case of the *t*-butoxycarbonyl compound in which condensation occurred *with loss of the t-butoxycarbonyl substituent.* Use of two equivalents of LDA improved the efficiency of this particular reaction. This reaction provides an alternative method for preparation of 4-carboalkoxy derivatives of the unsubstituted pyrrolidine-2,3-dione. We suspect that the carbamates in general fail to



cyclize because of preferentially deprotonation of the carbamate nitrogen which would inhibit enolate formation. The exceptional behavior of the *t*-butoxycarbonyl derivative appears to reflect an enhanced tendency for condensation and cyclization, which is probably followed by deacylation of the presumed intermediate.

EXPERIMENTAL

Unless otherwise stated, infrared spectra are pellets in sodium bromide and nmr spectra are in chloroform-d.

1-Benzyl-3,3-dimethoxypyrrolidin-2-one **3**.

A solution of 1-benzylpyrrolidine-2,3-dione (10.2 g, 0.054 mole), trimethyl orthoformate (29.5 ml, 0.27 mole) and *p*-toluenesulfonic acid (318 mg, 1.85 mmole) was prepared in 150 ml of anhydrous methanol. The solution was heated to reflux for 1 hour and then poured into water. The product was extracted into methylene chloride and the organic layers were washed (aqueous sodium bicarbonate, sodium chloride) and dried (sodium sulfate). The solvent was evaporated to a dark oil which was purified by distillation using a Kugelrohr oven. The ketal **3** was obtained as a colorless oil, bp 180-190°/0.1 mm Hg, which solidified to a solid, mp 50-54° on standing; yield: 9.93 g, 78% IR: 2990, 1695, 1312, 1120, 1100, 1050, 710 cm^{-1} nmr: 90 MHz, δ 2.10 (t, 2H), 3.13 (t, 2H), 3.42 (s, 6H), 4.48 (s, 2H), 7.25 (m, 5H).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.43; H, 7.30; N, 5.92.

3,3-Dimethoxypyrrolidin-2-one **4**.

Ketal **3** (2.0 g, 8.51 mmoles) was dissolved in 30 ml of dry tetrahydrofuran. The mixture was cooled to −78° and *s*-butyllithium (8.28 ml, 1.13*M*) was added dropwise. The red-orange anion was stirred at −78° for 30 minutes and then freshly distilled trimethyl borate (1.12 ml, 10.21 mmoles) was added, giving rise to a clear pale yellow solution. The mixture was stirred at −78° for 30 minutes. The cooling bath was removed, and when the temperature was ≈0°, 10 ml of 30% hydrogen peroxide was slowly added and the mixture was stirred at room temperature for 1 hour. The organic layer was decanted off and evaporated to a pale yellow oil. The product was purified by flash chromatography (1:1 hexanes + ethyl acetate → ethyl acetate) to give **4**, 500 mg, 41%, which appeared as the most polar component of the reaction mixture. Recrystallization from ether-hexanes gave colorless prisms, mp 96.5-97.5°; ir: 3230, 2940, 2810, 1717, 1290, 1110, 1048, 1030 cm^{-1}; nmr: 90 MHz, δ 2.22 (t, 2H), 5.29 (t, 2H), 3.36 (s, 6H), 6.98 (br s, 1H).

Anal. Calcd. for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.70; H, 7.66; N, 9.59.

Pyrrolidine-2,3-dione **5**. A. By Hydrolysis of **4**.

Ketal **4** (15 mg, 0.1 mmole) was dissolved in tetrahydrofuran-concentrated hydrochloric acid (9:1) and stirred for 30 minutes at room temperature. The solvent was evaporated under vacuum (0.1 mm Hg) to give a colorless glass (15 mg), which rapidly turned yellow on standing; nmr: 90 MHz δ 2.81 (t, 2H), 3.80 (t, 2H), 8.76 (br s, 1H); nmr (dimethyl sulfoxide-d_6): 90 MHz, 2.61 (t), 3.46 (t), 8.20 (br s). The nmr spectrum of this material was identical with the pure compound prepared by method B. The *N*-ethoxyimines derived from the two samples were also identical.

B. By Oxidation of 3-Hydroxypyrrolidin-2-one.

Chromic acid solution was prepared by a standard procedure [6]. 3-Hydroxypyrrolidin-2-one [5] (450 mg) was dissolved in 80 ml of acetone. Over about 5 minutes, chromic acid solution was added to the acetone solution maintained at 20-25° in a water bath. The addition was stopped when a brown tinge remained in the supernatant solution after a few minutes. The total reaction time was about 15 minutes. The excess unreacted chromic acid was removed by adding a little 2-propanol. The solution was filtered and stirred with 5 g of solid sodium bicarbonate for about 5 minutes, filtered and carefully evaporated to dryness. The residue was immediately triturated with 150 ml of ethyl acetate and this solution was dried over sodium sulfate. Careful evaporation left a solid, 100-150 mg, which was recrystallized from chloroform-ether, mp 101-103°. The *N*-ethoxyimine prepared from this material was identical to that prepared from method A.

3-(*N*-Ethoxyimino)pyrrolidin-2-one **6**.

Ketal **4** (15 mg), 0.1 mmole, was dissolved in 9:1 tetrahydrofuran:concentrated hydrochloric acid, 1 ml, and the solution was stirred 30 minutes at room temperature. The solvents were evaporated under vacuum (0.1 mm Hg). The glassy solid remaining was dissolved in dimethyl sulfoxide (0.5 ml), and ethoxyamine (3 drops) was added. The mixture was stirred for 24 hours at room temperature. The dimethyl sulfoxide was removed under vacuum in a Kugelrohr oven, and the crude solid which remained was purified by flash chromatography (ethyl acetate). The product was obtained as a solid and recrystallized from ethyl acetate-hexane, mp 134-136°, 12 mg, 82%; ir: 3280, 2970, 1720, 1680, 1300, 1030 cm^{-1}; nmr: 90 MHz, δ 1.30 (t, 3H), 2.83 (t, 2H), 3.48 (t, 2H), 4.29 (q, 2H), 8.25 (br s, 1H).

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.70. Found: C, 50.76; H, 7.10; N, 19.65.

Conversion of 4-Amino-2-oxobutanoic Acid Hydrochloride ot 3-(*N*-Ethoxyimino)pyrrolidin-2-one.

A dimethylformamide solution (1 ml) of **2** (50 mg, 0.33 mmole) was stirred overnight with excess ethoxyamine (4 drops). The solvent was removed under vacuum in a Kugelrohr oven. Fresh dimethylformamide (1 ml) was added to the residue, followed by dicyclohexylcarbodiimide (67 mg, 0.33 mmole). The mixture was stirred overnight at room temperature and the solvent was then removed under vacuum in a Kugelrohr oven. The crude material was purified by flash chromatography to give a sample of **6**, (42.6 mg, 92%) identical to that produced from **5** by tlc and nmr.

3-(*N*-Hydroxyimino)pyrrolidin-2-one **7**.

A sample of **5** prepared by oxidation (80 mg) was allowed to react with hydroxylamine hydrochloride (80 mg) and sodium acetate (60 mg) overnight in water (1 ml). Refrigeration and recrystallization from water gave the oxime, mp 215° dec.

Anal. Calcd. for $C_4H_5N_2O_2$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.95; H, 5.31; N, 24.49.

We were unable to directly compare this material with that which was described by von Dobeneck, mp 205°. In our hands, their procedure gave the oxime of 4-carboethoxypyrrolidine-2,3-dione, mp 186°.

N-Allyl-β-Alanine Methyl Ester.

Methyl acrylate (129 g, 1.50 moles) was added to a solution of allylamine, (85.7 g, 1.50 moles) in 200 ml of dry methanol. The reaction mixture was allowed to stir at room temperature for 48 hours. Removal of the solvent under reduced pressure afforded an oil which was distilled

(57°/ .8 mm) to give *N*-allyl-β-alanine methyl ester (165 g, 77%); nmr: 90 MHz, δ 2.50, (t, 2H), 2.90 (t, 2H), 3.25 (d, 2H), 3.70 (s, 3H), 5.00-5.35 (m, 2H), 5.65-6.15 (m, 1H).

1-Allyl-4-Carbomethoxypyrrolidine-2,3-dione.

N-Allyl-β-alanine methyl ester (20.0 g, 0.140 mole) and dimethyl oxalate (16.52, 0.140 mole) were added to 200 ml of absolute methanol in which one equivalent of sodium metal (3.22 g, 0.140 mole) had been dissolved. The reaction mixture was allowed to reflux for 1.5 hours, cooled to room temperature and evaporated under reduced pressure. The residue was treated with 100 ml of water and acidified to *p*H 2 with 10% hydrochloric acid. The product was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation afforded 26.9 g of 1-allyl-4-carbomethoxypyrrolidine-2,3-dione. Recrystallization from methanol/-hexane gave 24.6 g of pure white needles mp 98-100°, 89%; nmr : 90 MHz, δ 3.80-4.05 (m, 5H), 4.15 (d, 2H), 5.10-5.35 (m, 2H), 5.60 (d, 2H), 5.60-6.10 (m, 1H); nmr: 360 MHz, δ 3.855 ppm (s, 3H), 3.969 (s, 2H), 4.118 (d, 2H), 5.196-5.261 (m, 2H), 5.737-5.783 (m, 1H).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.58; N, 7.11. Found: C, 54.90; H, 5.66; N, 7.05.

1-Allylpyrrolidine-2,3-dione **9**.

An optimization of the hydrolytic decarboxylation was done by following the progress of the reaction by nmr. 1-Allyl-4-carbomethoxypyrrolidine-2,3-dione (1.00 g, 0.0051 mole) was dissolved in 40 ml of 10% hydrochloric acid and refluxed for 35 minutes. During the reaction, aliquots were removed every five minutes, neutralized, the solvent evaporated, and a 360 MHz nmr recorded. Optimum yields of 1-allylpyrrolidien-2,3-dione were obtained after 25 minutes. This reaction time was adopted for preparative experiments. 1-Allyl-4-carbomethoxypyrrolidine-2,3-dione (8.00 g, 0.040 mole) was dissolved in 300 ml of 10% hydrochloric acid and refluxed for 25 minutes. The solution was cooled, treated with 100 ml of saturated sodium chloride solution and extracted with two 200 ml portions of methylene chloride. Removal of the solvent under reduced pressure afforded 4.01 of an oil shown by nmr to contain a mixture of 1-allylpyrrolidine-2,3-dione (90% by nmr, 3.61 g, 65% yield) and unreacted 1-allyl-4-carbomethoxypyrrolidine-2,3-dione (10% by nmr, 0.40 g, 5.2% recovery). Kugelrohr distillation in the presence of terephthalic acid afforded 1-allylpyrrolidine-2,3-dione (2.90 g, 52%); nmr: 360 MHz, δ 2.740 ppm (t, 2H), 3.665 ppm (t, 2H), 4.145 ppm (d, 2H), 5.280 ppm-5.335 ppm (m, 2H), 5.735 ppm-5.845 ppm (m, 1H).

Methyl 3-(Ethoxyamino)propionate.

A mixture of ethoxyamine (60 g, 0.98 mole) and freshly distilled methyl acrylate (56.4 g, 0.66 mole) was heated without solvent at 80-85° for 2.5 hours. The reaction mixture was stirred overnight at room temperature and then distilled under vacuum through a Vigreux column. Distillation afforded 21.5 g of recovered ethoxyamine, the product (71.1 g, 74%, bp 70°/2.5 mm Hg) and 18.5 g of a higher boiling fraction which was assumed to be mainly the *bis* adduct on the basis of the nmr spectrum: ir (neat film): 3280, 2980, 1735, 1440, 1200, 1180, 1040 cm^{-1}; nmr: 90 MHz, δ 1.12 (t, 3H), 2.51 (t, 2H), 3.17 (t, 2H), 3.79 (q, and s, 5H), 5.70 (br s, 1H).

Anal. Calcd. for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.89; H, 8.93; N, 9.51.

1-Ethoxy-4-carbomethoxypyrrolidin-2,3-dione.

A solution of sodium methoxide in methanol was prepared by the addition of freshly cut sodium (1.56 g, 0.068 mole), to 150 ml of dry methanol under nitrogen. Dimethyl oxalate (8.03 g, 0.068 mole) was added to the methanol solution, followed by methyl 3-ethoxyaminopropionate (10 g, 0.068 mole). The mixture was stirred for 1 hour at room temperature, at which time it had solidified to a white cake. The solid was brought into solution by heating and was refluxed for an additional 5 minutes. Evaporation of the methanol left a white solid, which was dissolved in 100 ml of water. The aqueous solution was made slightly acidic by the addition of concentrated hydrochloric acid. The solution was extracted with methylene chloride. Drying (sodium sulfate) and evaporation of the extracts gave a crude solid, which was recrystallized from chloroform-hexanes to give 9.97 g, 73%, of product as long colorless needles, mp 115-119°. A second recrystallization from chloroform gave colorless prisms, mp 116-118°; nmr: 90 MHz, δ 1.30 (t, 3H), 3.80 (s, 3H), 4.09 (q, 2H), 4.15 (s, 2H), 8.02 (br s, 1H).

Anal. Calcd. for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.77; H, 5.54; N, 6.92.

1-Ethoxypyrrolidin-2,3-dione **10**.

1-Ethoxy-4-carbomethoxypyrrolidine-2,3-dione (2.0 g, 9.95 mmoles) was dissolved in 100 ml of 5% hydrochloric acid and the solution was heated under reflux for 1.5 hours. The aqueous solution was saturated with sodium chloride and extracted with methylene chloride (4 × 30 ml). The extracts were evaporated and gave 9 as a crude yellow oil, 530 mg, 37%. The dione was purified by flash chromatography (85:15 hexanes:-ethyl acetate → ethyl acetate) to give 357 mg, 25%, of product; nmr : 90 MHz, δ 1.30 (t, 3H), 2.80 (t, 2H), 3.87 (t, 2H), 4.18 (q, 2H).

4-Carbomethoxypyrrolidine-2,3-dione from *N*-(*t*-Butoxycarbonyl)-β-alanine Methyl Ester.

A 100 ml three-neck flask containing 30 ml of dry tetrahydrofuran was charged with 0.01 mole (2 equivalents, 6.26 ml of a 1.6*M* solution) of *n*-butyllithium and cooled to 0°. Freshly distilled diisopropylamine (1.0 g, 0.01 mole, 2 equivalents) was added dropwise to the stirred solution. The reaction mixture was cooled to −78°, *N*-(*t*-butoxycarbonyl)-β-alanine methyl ester (1.0 g, 0.005 mole) was added and the solution was stirred at −78° for 30 minutes. Dimethyl oxalate (0.65 g, 0.005 mole) was added as a solution in tetrahydrofuran. The temperature was raised to 0°, and the reaction mixture was stirred at 0° for 1 hour, then refluxed for an additional hour. The solution was cooled, poured into saturated sodium bicarbonate and carefully acidified to *p*H 4 with aqueous acetic acid. Extraction with ethyl acetate and removal of the solvent under reduced pressure afforded 320 mg of a yellow solid identified (nmr, ir, tlc) as 4-carbomethoxypyrrolidine-2,3-dione (42%). The aqueous solution was acidified to *p*H 2 with dilute hydrochloric acid and extracted with ethyl acetate. Removal of the solvent gave an additional 240 mg of a yellow solid also identified (nmr, ir, tlc) as the product, giving a combined yield of 72%. Recrystallization from methanol gave a white solid, mp 220° dec; nmr: 360 MHz, δ 3.845 ppm (s, 2H), 3.665 ppm (s, 3H), 8.786 (s, 1H).

Anal. Calcd. for $C_6H_7NO_4$: C, 45.86; H, 4.46; N, 8.92. Found: C, 45.86; H, 4.51; N, 8.87.

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