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Synthesis and Structure of The N-Nitropyrrolidinones (I)

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In connection with other studies being carried out in these laboratories, the previously unknown N-nitro-2- and 3-pyrrolidinones have been prepared. N-Nitro-2-pyrrolidinone (I) can be obtained by the direct nitration of commercial 2-pyrrolidinone with white fuming nitric acid and acetic anhydride. The isomeric 3-pyrrolidinone is not described in the literature. Although many of its derivatives are known (2-3), the parent compound is too unstable to be isolated. The hydrochloride of 3-pyrrolidinone (II) has now been prepared in four steps from N-(2-cyanoethyl)glycine (III) (6).

Esterification of III with alcoholic hydrogen chloride yields ethyl N-(carbethoxymethyl)- β -alaninate (IV) (7), which can be formylated and cyclized to the 3-pyrrolidinone derivative V. Hydrolysis of V even under mild conditions removes both carbethoxyl and formyl groups, leading directly to II, and direct nitration of II gives N-nitro-3-pyrrolidinone (VI) in good yield.

The assignment of the structure of VI is based on the method of preparation and the absorption spectra of the compounds (Table I). The presence of the carbonyl group gives rise to the strong absorption band at 5.76μ , similar to that in II. The asymmetric and symmetric NO_2 stretching bands resemble those in N-nitropyrrolidine (VII), which has been prepared for comparison, rather than the

corresponding bands in I, and the ultraviolet absorption curves of VI and VII are nearly parallel (Fig. 1) while those of II and VI intersect.

Although I is thermally stable up to 125° , VI begins to decompose at about 80° . Some slow decomposition of VI occurs even at 25° , but the compound may be stored for several days at 0° . In the presence of weak bases, VI is converted to dark polymers with the loss of nitrous acid, a reaction analogous to that of another β -nitramino ketone which has been described earlier (8).

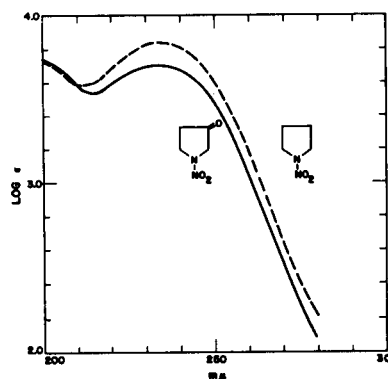
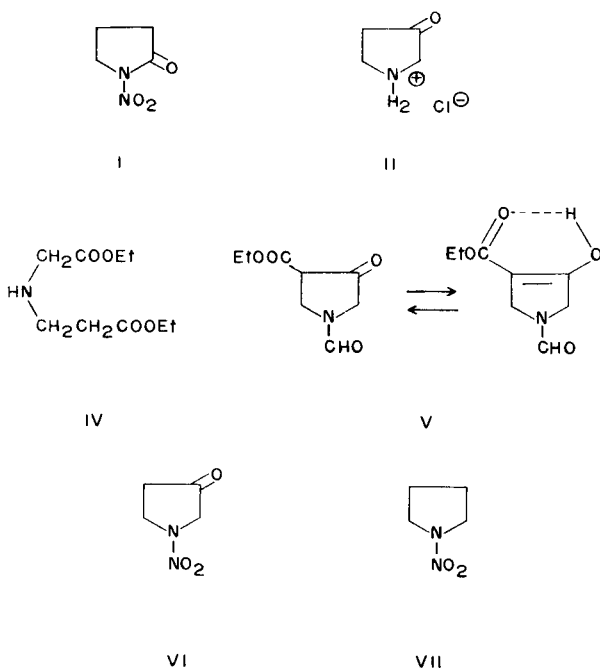


Figure 1. Ultraviolet absorption spectra of N-nitropyrrolidines in hexane.

TABLE I
Absorption Spectra of Pyrrolidines and Intermediates

Compound	λ max, $m\mu$ (a)	ϵ	λ (C=O) (b)	λ (NO_2) (c), μ	
Ethyl N-(carbethoxymethyl)- β -alaninate (IV)	---	-----	5.73	----	----
Ethyl N-(carbethoxymethyl)-N-formyl- β -alaninate	---	-----	5.74, 5.93	----	----
4-Carbethoxy-N-formyl-3-pyrrolidinone (V)	---	-----	5.62, 5.76 5.95	----	----
3-Pyrrolidinone hydrochloride (II)	---	-----	5.71	----	----
N-Nitro-2-pyrrolidinone (I)	233	6,000	5.64	6.43	7.83
N-Nitro-3-pyrrolidinone (VI)	234	5,070	5.76	6.65	7.50
N-Nitropyrrolidine (VII)	235	7,030	----	6.68	7.54

(a) Ultraviolet absorption bands in hexane. (b) Liquids as capillary films and solids in potassium bromide pellets. (c) Asymmetric and symmetric NO_2 stretching bands.



EXPERIMENTAL (9)

N-Nitro-2-pyrrolidinone (I).

Acetic anhydride (10.0 g., 0.098 mole) was cooled to 0° and 5.1 g. (0.073 mole) of white fuming nitric acid (90% HNO₃) was added at below 10°. After addition of the nitric acid, 3.0 g. (0.035 mole) of 2-pyrrolidinone was added to the nitration mixture while the temperature was maintained at 20–30°, followed by 3 drops of acetyl chloride. After being stirred at 35–40° for 1 hour, the mixture was poured over 50 g. of ice and the resulting solution was extracted with 5 x 50 ml. of methylene chloride. The extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from carbon tetrachloride to yield 2.56 g. (56%) of I, m.p. 55.5°.

Anal. Calcd. for C₄H₇N₂O₃: C, 36.92; H, 4.65; N, 21.55. Found: C, 37.17; H, 4.67; N, 21.34.

N-(2-Cyanoethyl)glycine (III) (6).

One mole of glycine was suspended in 200 ml. of water and a solution of 1 mole of sodium hydroxide in 200 ml. of water was added with stirring while the temperature was kept below 30°. After the addition was complete, one mole of acrylonitrile was added, also at a temperature below 30°. The mixture was stirred at room temperature overnight. One mole of acetic acid was added, and the mixture was concentrated to 200 ml. under reduced pressure, diluted with 800 ml. of ethanol, and cooled to below 0°. The crystals were filtered and dried to yield 98.8 g. (77%) of III, m.p. 193–195° (lit. (2) m.p. 190–191°).

Ethyl N-(carbethoxymethyl)-β-alaninate (IV) (7).

N-(2-Cyanoethyl)glycine (III) (98.8 g., 0.77 mole) was suspended in 580 ml. of absolute ethanol and the mixture was saturated with dry hydrogen chloride at 10°. After being stirred at room temperature overnight, the solution was refluxed for 1 hour and concentrated to about 400 ml. under reduced pressure. The ammonium chloride formed was filtered off with suction. The filtrate was neutralized with sodium bicarbonate, filtered, and concentrated under reduced pressure to an oil, which was distilled to yield 108 g. (69%) of IV, b.p. 98–99°/1.0 mm. (lit. (3) b.p. 97–100°/1–2 mm.), n_D²⁵, 1.4370.

Ethyl N-(carbethoxymethyl)-N-formyl-β-alaninate.

Ethyl N-(carbethoxymethyl)-β-alaninate (108 g., 0.533 mole) was refluxed with 67.0 g. (1.45 mole) of 98% formic acid for 30 minutes. The excess formic acid was removed by distillation and the residue was distilled to give 112.0 g. (98%) of ester, b.p. 120–121°/0.02 mm., n_D²⁵, 1.4548, d₄²⁵, 1.137.

Anal. Calcd. for C₁₀H₁₇NO₅: C, 51.93; H, 7.41; N, 6.06. Found: C, 51.73; H, 7.51; N, 6.07.

N-Formyl-4-carbethoxy-3-pyrrolidinone (V).

To a solution of 0.135 mole of sodium ethoxide in 300 ml. of benzene

was added 31.2 g. (0.135 mole) of ethyl N-(carbethoxymethyl)-N-formyl-β-alaninate slowly with stirring (3). The mixture was then refluxed for 1 hour, poured into an equal volume of water, and made slightly acid with hydrochloric acid. The layers were separated and the aqueous layer was continuously extracted with benzene overnight. The combined benzene extracts were dried over magnesium sulfate, concentrated, and distilled to yield 15.0 g. (60%) of V, b.p. 120°/0.04 mm., n_D²⁵, 1.4948, d₄²⁵, 1.243. The distillate gave a strong enol test with aqueous ferric chloride.

Anal. Calcd. for C₈H₁₁NO₄: C, 51.90; H, 5.98; N, 7.57. Found: C, 51.60; H, 5.99; N, 7.58.

3-Pyrrolidinone hydrochloride (II).

N-Formyl-4-carbethoxy-3-pyrrolidinone (4.8 g., 0.026 mole) was refluxed with 50 ml. of 18% hydrochloric acid until an aliquot gave a negative ferric chloride test (3). The solution was decolorized with Norite and concentrated under reduced pressure to about 5 ml. Acetone (100 ml.) was added and the mixture was cooled to 0°. The crystallized II was filtered with suction to yield 2.3 g. (73%) of crude product which was recrystallized from ethanol-acetone. The light brown crystals melted at 141–142°.

Anal. Calcd. for C₄H₇ClNO: C, 39.50; H, 6.62; N, 11.52. Found: C, 39.70; H, 6.78; N, 11.73.

N-Nitro-3-pyrrolidinone (VI).

3-Pyrrolidinone hydrochloride (3.04 g., 0.025 mole) was added slowly to a mixture of 5.6 g. (0.089 mole) of 100% nitric acid and 10.8 g. (0.106 mole) of acetic anhydride at 0°. The temperature was raised to 20° and the mixture was stirred at this temperature for 1 hour. The mixture was poured over 50 g. of ice and the resulting mixture was extracted with 5 x 50 ml. of methylene chloride. The extracts were dried over magnesium sulfate and evaporated to dryness under reduced pressure. The residue was crystallized from benzene-hexane to yield 2.28 g. (70%) of VI, m.p. 86–88° (dec.).

Anal. Calcd. for C₄H₇N₂O₃: C, 36.92; H, 4.65. Found: C, 36.99; H, 4.81.

N-Nitropyrrrolidine (VII).

This nitramine has been prepared by the nitration of pyrrolidine (10,11). We have found it easier to make the compound by the nitrolysis of N-formylpyrrolidine, which could be prepared from commercial pyrrolidine. Refluxing the amine with 98% formic acid and fractionating the reaction mixture gave a colorless distillate containing some formic acid. This was removed by washing with a little aqueous sodium hydroxide and water and redistilling. The pure N-formylpyrrolidine boiled at 69–70° (3 mm.), n_D²⁵, 1.4742. Nitration of 4.26 g. of the pure formyl derivative with 30.6 ml. of trifluoroacetic anhydride and 10.3 ml. of 100% nitric acid (caution!) (13) gave an average yield of 3.4 g. (68%) of VII. The crude product after recrystallization from hexane consisted of colorless needles, m.p. 58–59° (lit. m.p. 58–59° (11)).

Absorption Spectra.

Absorption spectra were determined at 25° with a Perkin-Elmer Model 21 (infrared) and a Cary Model 14 (ultraviolet) spectrophotometer.

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