# 1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylic Acid

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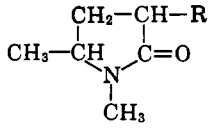
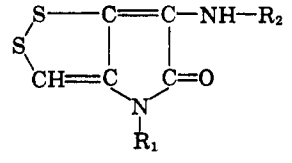
Our general interest in substituted 2-pyrrolidones (I) stemmed from earlier studies on their derivation (*i.e.*, Ia) from the antibiotic Thiolutin (IIa)[1,2] and by synthesis.[3,4] The ability of the pyrrolidine ring to accommodate multiple exocyclic double bonds was investigated further through the preparation of 1,5-dimethyl-2-oxo-3-pyrrolidineglyoxylic acid (Id) and several of its derivatives. Although enol character (positive ferric chloride test) had been previously noted[5] for ethyl 2-oxo-3-pyrrolidineglyoxylate, it remained to be seen whether enol quality carried over to N-substituted variants, such as Id. Discussion of this study, together with pertinent experimental details, are presented in this Note.



I

| R | |
|---|---|
| (a) | —NH—$COCH_3$ |
| (b) | —H |
| (c) | —$COCO_2CH_2CH_3$ |
| (d) | —$COCO_2H$ |
| (e) | —$COCO_2CH_3$ |



II

| $R_1$ | $R_2$ | |
|---|---|---|
| (a) | $CH_3$— | —$COCH_3$ |
| (b) | $CH_3$— | —$COCH_2CH_3$ |
| (c) | $CH_3$— | —$COCH(CH_3)_2$ |
| (d) | H— | —$COCH_3$ |

Reductive methylamination of levulinic acid in methanol solution with palladium-on-charcoal catalyst afforded crystalline 4-N-methylaminovaleric acid,[6] m.p. 160–161°, which when fused gave known[7,8] liquid 1,5-dimethyl-2-pyrrolidone (Ib); $\lambda_{max}^{film}$ 5.94 $\mu$. Reaction of Ib with diethyl oxalate and ethanolic sodium ethoxide furnished crude ethyl 1,5-dimethyl-2-oxo-pyrrolidineglyoxylate (Ic) ($\lambda_{max}^{film}$ 5.88, 6.02 $\mu$, positive ferric chloride test) which was converted without purification[9] to crystalline 1,5-dimethyl-2-oxo-pyrrolidineglyoxylic acid (Id), m.p. 139.5–140.5°. Methanol–sulfuric acid treatment of the free acid afforded its crystalline methyl ester Ie, m.p. 58–59°, which after reaction with acetic anhydride–sulfuric acid gave crystalline methyl ester enol-acetate IIIa, m.p. 92–93°. Pertinent infrared data on IIIa and its precursors are listed and assigned in Table I. Although only enolic forms are evident in all cases, a small amount of the ketonic form could have escaped detection in each of the possible systems: IIIb ⇆ Ie and IIIc ⇆ Id.[10]

## Experimental[11]

**4-N-Methylaminovaleric Acid**[6,12].—To a stirred, chilled (5°) suspension of 5 g. of 5% palladium-on-charcoal in 100 ml. of a 1.67 *M* ethanolic levulinic acid solution was added dropwise 100 ml. of 4.2 *M* ethanolic methylamine solution. Hydrogenation was then conducted in a stainless steel bomb (480-ml. capacity) at 1200 p.s.i. at 66° for 2 hr. After cooling and removing the catalyst by filtration, the solution was evaporated to dryness. Trituration of the residue with ether afforded 14 g. (64%) of crystalline product, m.p. 154–156° (the analytical sample, from ethanol–ether, melted at 160–161°).

*Anal.* Calcd. for $C_6H_{13}NO_2$ (131.17): C, 54.94; H, 9.99; N, 10.68. Found: C, 54.93; N, 10.03; N, 10.23.

**1,5-Dimethyl-2-pyrrolidone (Ib)**.[7]—Heat was gradually applied to a distilling flask containing 25 g. (0.19 mole) of the amino acid until the contents melted (160°) and evolution of water vapor was complete (1 hr.). The resulting product was then distilled [b.p. 94–95° (17.5–18 mm.)] to afford 18.1 g. (84.5%) of a liquid, $n^{25}D$ 1.4638. Redistillation, after drying over magnesium sulfate, gave 14.5 g. (67.6%) of a colorless liquid, b.p. 95° (18 mm.); $n^{25}D$ 1.4644 [lit. $n^{25}D$ 1.4611; b.p. 84–86° (13 mm.); b.p. 102–104° (27 mm.)[7]; b.p. 215–217° (743 mm.)[8]].

*Anal.* Calcd. for $C_6H_{11}NO$ (113.16): C, 63.68; H, 9.80. Found: C, 63.39; H, 9.93.

**1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylic Acid**.—To a solution of sodium ethoxide (2.02 g. of sodium in 40 ml. of ethanol) was added a mixture of 10 g. (0.0885 mole) of Ib and 13.2 g. (0.0904 mole) of diethyl oxalate. The reaction was kept at 60° (60 mm.) until the distillation of ethanol was virtually complete (3 hr.). The residue was treated with 25 ml. of water, and the resulting alkaline solution was kept at 25°. After 30 min., the solution was acidified with 15 ml. of 6 *N* hydrochloric acid which afforded 7.5 g. of crude acid. The recrystallized sample, from carbon tetrachloride, weighed 3.8 g. (23%) and melted at 139.5–140.5°.

*Anal.* Calcd. for $C_8H_{11}NO_4$ (185.18): C, 51.88; H, 5.99; N, 7.57. Found: C, 51.78; H, 5.92; N, 7.43.

**Methyl 1,5-Dimethyl-2-oxo-3-pyrrolidineglyoxylate**.—To a methanolic solution of 1.85 g. (0.01 mole) of 1,5-dimethyl-2-oxo-3-pyrrolidineglyoxylic acid was added 0.04 ml. of concentrated sulfuric acid. After 16 hr. at 25°, the methanol was removed by vacuum distillation. A solution of most of the residue in 20 ml. of ether was decanted from remaining insoluble sulfuric acid and was neutralized further with sodium bicarbonate. Vacuum distillation of the ether afforded 1.61 g. (80%) of crystalline resi-

(1) W. D. Celmer, F. W. Tanner, Jr., M. Harfenist, T. M. Lees, and I. A. Solomons, *J. Am. Chem. Soc.*, **74**, 6304 (1952).

(2) W. D. Celmer and I. A. Solomons, *ibid.*, **77**, 2861 (1955).

(3) Related antibiotics include aureothricin (IIb), *cf.* ref. 2; isobutyropyrrothine (IIc), *cf.* W. D. Celmer and I. A. Solomons, *Antibiot. Ann.*, 622, (1953–1954), and also D. S. Bhate, R. K. Hulyalkar, and S. K. Menon *Experientia*, **16**, 504 (1960); holomycin (IId), *cf.* L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, and H. Zähner, *Helv. Chim Acta*, **42**, 563 (1959). Total synthesis of the II-type antibiotics has been accomplished by two independent routes: U. Schmidt and F. Geiger, *Angew. Chem. Intern. Ed. Engl.*, **1**, 265 (1962); G. Buchi and G. Lukas, *J. Am. Chem. Soc.*, **85**, 647 (1963).

(4) For a recent report on 4-substituted-2-pyrrolidones, see F. C. Uhle, *J. Org. Chem.*, **27**, 4081 (1962).

(5) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1523 (1937).

(6) This compound (IV) also served as starting material for an alternate synthesis of the previously described (ref. 2) 2-amino-4-N-methylaminovaleric acid (V); W. D. Celmer and I. A. Solomons, unpublished experiments. The following reaction sequence (standard procedures) was employed: IV → N-benzoylation → esterification (Et) → ethoxylation → decarbonylation → nitrosation → reductive acetylation → hydrolysis → V. This route was less satisfactory than the scheme reported previously which involved initial preparation of Ia followed by hydrochloric acid hydrolysis.

(7) For a direct synthesis of Ib from levulinic acid employing aqueous methylamine and Raney nickel-catalyzed hydrogenation see R. L. Frank, W. R. Schmitz, and B. Zeidman, *Org. Syn.*, **27**, 28 (1947).

(8) L. Senfter and J. Tafel, *Chem. Ber.*, **27**, 2313 (1894).

(9) Most of the yield loss occurred over the ethoxylation step; no advantage was gained by isolating the intermediate product Ic. For the preparation of the related ethyl 1-methyl-2-oxo-3-pyrrolidineglyoxylate (24%) and its hydrolysis to the free acid (85%), see L. W. Masch and R. Peterson, *Arzneimittel-Forsch.*, **9**, 715 (1959).

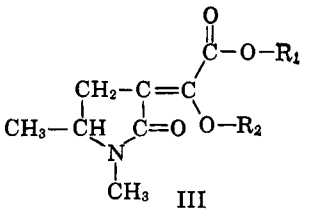
(10) It is assumed that the same principle applies to the ethyl ester Ic which was not extensively studied (*cf.* ref 9).

(11) Melting points are reported as determined on a Kofler hot stage.

(12) Free 4-N-methylaminovaleric acid (zwitterionic form) is recovered despite exposure to excess methylamine (presumably because of greater basicity of the secondary amine); hence portrayal of the methylamine salt of 4-N-methylaminovaleric acid is incorrect (*cf.* ref. 7).

TABLE I

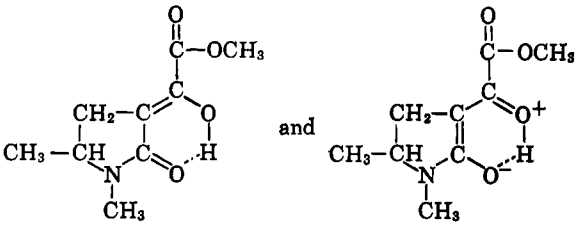
INFRARED SPECTRA AT 2–6 $\mu$[a]



III

| Compound | $R_1$ | $R_2$ | | $\lambda_{max}$ (c 2.5, chloroform) $\mu$ | (cm.$^{-1}$) | Assignments[b] | Ref. |
|---|---|---|---|---|---|---|---|
| IIIa | $CH_3$— | —$COCH_3$ | Shoulder | 6.00–6.03 | (1667–1665) | >C=C< | |
| | | | | 5.93 | (1686) | Lactam C=O | |
| | | | Sharp | 5.78 | (1730) | Conjugated ester C=O | |
| | | | Sharp | 5.65 | (1770) | Enol acetate C=O | |
| | | | | 3.41 | (2933) | C–H | |
| IIIb | $CH_3$— | —H | Shoulder | 6.04–6.07 | (1656–1647) | >C=C< | *c* |
| | | | | 6.01 | (1664) | H-bonded lactam | *d* |
| | | | Sharp | 5.79 | (1727) | Conjugated ester C=O | *e* |
| | | | | 3.43 | (2924) | C–H | |
| | | | Diffuse | 2.8–3.2 | (3571–3125) | Bonded OH | *f* |
| IIIc | H— | —H | | 5.98 | (1672) | Lactam C=O | *g* |
| | | | Sharp | 5.87 | (1704) | Monomeric, conjugated carboxyl C=O | *h, i, j* |
| | | | Doublet | 3.42, 3.48 | (2924, 2874) | Unmasked C–H | *h* |
| | | | Very sharp | 3.00 | (3333) | Unbonded OH | *h, f* |

[a] A Baird double beam spectrometer, Model AB, was employed. [b] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958. [c] A similar occurrence of shoulder absorption on the long wave-length side of the lactam C=O $\lambda_{max}$ in IIIa (containing unequivocal C=C) is consistent with this ethylenic assignment. [d] This lactam C=O $\lambda_{max}$ occurs at a substantially longer wave length than that exhibited by lactam in IIIa. Factors such as H-bonding or conjugation are well known to shift carbonyl absorption in a bathochromic manner (*i.e.*, to lower frequency). "Ordinary" H-bondings result in slight downward shifts (less than 10 cm.$^{-1}$) whereas resonance stabilized H-bondings, associated with so-called "conjugate chelate" systems, give rise to substantially lower C=O frequencies (60- to 90-cm.$^{-1}$ shifts for affected esters); *cf.* I. M. Hunsberger, R. Ketcham, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **74**, 4839 (1952); L. J. Bellamy and L. Beecher, *J. Chem. Soc.*, 4487 (1954). A $\Delta\nu$ (C=O, lactam) value of 23 cm.$^{-1}$ (expression of Hunsberger, *et al.*) is observed here which, although lower than the standard $\Delta\nu$ (C=O, ester) range of values, may be typical of conjugate chelate lactam systems for which a norm is yet to be established. Resonance stabilization of IIIb would presumably occur between the forms



We are indebted to a referee for calling our attention to lack of precedent for this type of conjugate chelate. [e] The striking similarity of this $\lambda_{max}$ to its counterpart in IIIa, both in position and quality (band width at half maximum intensity), supports formulation IIIb; absorption at a lower wave length expected of form Ie is not detected; *cf.* methyl pyruvate $\lambda_{max}$ 5.72 $\mu$, ref. *b*. [f] This diffuse absorption (significantly also observed in ester film spectra) is consistent with resonance-stabilized formulations; *cf.* ref. *d;* ref. *b*, p. 96. [g] Sparsity of appropriate reference compounds makes any estimate of possible $\Delta\nu$ (C=O, lactam) here extremely tenuous; *cf.* ref. *d* and p. 214 in ref. *b*. [h] The sharp hydroxyl and unmasked C—H absorption define this acid as monomeric. The observed carboxyl C=O $\lambda_{max}$ is definitely in the conjugated region; hence, formulation IIIc is preferred. Monomeric, unconjugated form Id would be expected to manifest carboxyl C=O $\lambda_{max}$ near 5.60 $\mu$ where, in fact, no absorption is observed; *cf.* M. L. Josien, M. Jousset-Dubien, and J. Vizet, *Bull. soc. chim. France*, **5**, 1148 (1957). [i] Comments on the infrared spectrum of pyruvic acid by Bellamy (*cf.* p. 141 in ref. *b*) called to our attention by a referee are misleading since the data cited, single $\lambda_{max}$ 5.73 $\mu$, obviously refer to the dimeric form (commonly observed in film spectra). A number of $\alpha$-keto acids in addition to pyruvic acid can be measured as their monomeric form in carbon tetrachloride or chloroform solution; *cf.* Josien, *et al.*, ref. *h*. We and others (P. A. Leermakers, personal communication) have noted three carbonyl bands exhibited by phenylglyoxylic acid in chloroform solution which are attributed to the presence of both monomeric and dimeric forms. [j] Monomeric enolic qualities (*cf.* ref. *h* and *i*) persist in the solid state judging from an infrared spectrum obtained, on a crystalline suspension in Nujol; $\lambda_{max}$ at 3.00, 5.90, 6.00 $\mu$.

due, m.p. 52–55°. The analytical sample from hexane melted at 58–59°.

*Anal.* Calcd. for $C_9H_{13}NO_4$ (199.20); C, 54.26; H, 6.58. Found: C, 54.28; H, 6.54.

**Methyl $\alpha$-Acetoxy-1,5-dimethyl-2-oxo-$\Delta^{3,\alpha}$-pyrrolidineacetate.**—To a solution of 600 mg. (0.03 mole) of the methyl ester in 15 ml. of acetic anhydride was added 0.01 ml. of concentrated sulfuric acid. After 16 hr. at 25° the solution was vacuum distilled. The residue was triturated with 10 ml. of ether and the decanted solution was evaporated to give 542 mg. (75%) of crystalline residue, m.p. 92–93°.

*Anal.* Calcd. for $C_{11}H_{15}NO_5$ (241.24): C, 54.76; H, 6.27. Found: C, 54.63; H, 6.39.

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