Some pyrrolidone derivatives

K. Bailey[1] and A. H. Rees
Department of Chemistry, Trent University, Peterborough, Ontario

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4-Cyano-3-hydroxy-2-oxo-3-pyrrolines are strongly acidic and form salts rather than enamines with strongly basic amines. We have revised the structures proposed for some of their derivatives and report the first synthesis of the parent compound **1** (R = H) and other new related pyrrolines.

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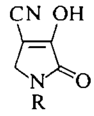
Pyrrolin-2-ones **1** have been obtained by the base-catalyzed condensation of ethyl oxalate with β-cyanoethylamines **2** (1, 2).



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RNHCH$_2$CH$_2$CN

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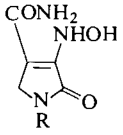

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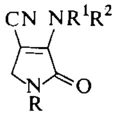
However, the parent compound **1** (R = H) was not known. In the attempt to synthesize **1** (R = COOEt) from **2** (R = COOEt), hydrolysis and decarboxylation took place during work up, so we were able to obtain the parent **1** (R = H) directly.

We now report some reactions of compounds **1**. Our conclusions differ in part from those of other workers (4). When we prepared oximes of **1** (R = PhCH$_2$, H, or Me), the products analyzed as hydrates. The infrared (i.r.) spectra showed no nitrile bands and had increased carbonyl absorption as well as NH bands so we assigned to them the 4-carboxamido-3-hydroxylamino-2-oxo-3-pyrroline structures **3** (R = PhCH$_2$, H, or Me respectively). The spectra showed no saturated carbonyl bands indicating conjugation of the double bands in contrast to the ester-oxime **9** (see below).



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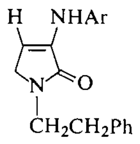

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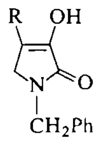

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The mass spectra showed the appropriate molecular ion peaks. Also present was *m/e* 44 (CONH$_2^+$ and CO$_2^+$) which was the base peak in the spectrum of **3** (R = H).

It was reported (4) that **1** (R = Me or *n*-Bu) formed products **4**, as hydrates with various amines. However, we regard these as salts of the strong acid **1** with strongly basic amines, by analogy with the products we obtained from **1** (R = PhCH$_2$) with piperidine and dimethylamine. Our products gave no ions in the mass spectra above *m/e* 214. The cracking pattern for the piperidine salt was identical to that of the starting acid, down to *m/e* 85 (piperidine) and the peak at *m/e* 214 from the dimethylamine salt was shown by high resolution to correspond with the correct formula $C_{12}H_{10}N_2O_2$.[2]

The nuclear magnetic resonance (n.m.r.) spectra of both salts had singlets at 6.18, 5.34, and 2.65 τ which integrated in the ratio 2:2:5 and are ascribed to the C-4, benzylic and aromatic protons respectively. A broad signal integrating for one to two protons at about −0.5 τ disappeared on addition of D$_2$O. The spectra had the correct peaks for the amine moieties. The compounds therefore cannot be enamines **4**, and since triethylamine gave a similar derivative, they must be salts. The ultraviolet (u.v.) spectra are summarized in Table 1 and the light absorption is clearly due to the mesomeric anion. The i.r. spectra of the salts are compared with that of compound **1** (R = PhCH$_2$) and other relevant derivatives in Table 2. In addition, the salts all showed two or three medium to weak bands in the region 2300–3000 cm^{-1}, appropriate for $>\overset{+}{N}H$, whereas the acid **1** (R = PhCH$_2$) has a band at 2610 cm^{-1} and none between 3100–4000 cm^{-1}. Compounds **5** have bands at 3300 (NH), 1670 (C=O), and 1640 (C=C) cm^{-1} (5).

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[1] Present address: Food and Drug Directorate, Tunney's Pasture, Ottawa 3, Canada.

[2] We thank Prof. A. G. Harrison of the Chemistry Department, University of Toronto, Toronto, Ontario, for this determination.

TABLE 1

The u.v. spectra (ethanol) of salts of amines with pyrrolin-2-ones **1***

1	Amine	λ_{max} mμ (ε)	λ_{max} mμ (ε)
R = $PhCH_2$	Piperidine	295 (9870)	231 (9650)
R = $PhCH_2$	Dimethylamine	294 (10050)	233 (9910)
R = $PhCH_2$	Triethylamine	294 (11510)	233 (12420)
R = Me	Piperidine	293 (9250)	232 (7100)

*Compound **1** (R = $PhCH_2$) in 0.01 *N* sodium hydroxide in aqueous ethanol has λ_{max} 293 (8390) and 234 (8730) mμ.

TABLE 2

The i.r. bands (cm^{-1}, nujol) of salts of amines and **1** (R = $PhCH_2$) and some related derivatives

Compound	C≡N	C=O	C=C
1 (R = $PhCH_2$)	2200	1695	1665
Salt of **1** (R = $PhCH_2$) with piperidine	2170	1690	1625
Dimethylamine	2160	1690	1610
Triethylamine	2170	1695	1610
Aniline	2170	1690	1618
1 (R = $PhCH_2$), OH replaced by NH_2	2200	1695	1665
OCH_2Ph	2200	1690	1635
NHNHPh	2180	1680	1660
N=NPh	2200	1675	1580
NHPh	2170	1695	1650

TABLE 3

The pK_a values* of pyrrolidones **1** and **6**

Pyrrolidone	R	pK_a
1	H	4.4
	Me	4.3
	NMe_2	4.25
	$CH_2CH_2CN_2$	4.45
	$PhCH_2$	4.4
6	CN	4.4
	$CONH_2$	5.4
	COOEt	5.7 ±0.1†

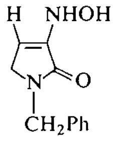
*Potentiometric titrations using 30 ml of 0.015 *M* solution of dione in 50% aqueous ethanol against 0.03 *N* solution of NaOH in 33% ethanol/water. A Beckmann 72 p*H* meter and glass electrode were used.

†Five determinations at varying concentrations of ethanol (10 → 50%) in water.

Enamines were obtained from aromatic amines by Nair and Malik (4) in the presence of acetic acid. We obtained the enamine **4** (R = $PhCH_2$, R^1 = H, R^2 = Ph) from **1** (R = $PhCH_2$) and aniline in alcoholic acetic acid. The anilinium salt which seemed to be the only product in the absence of acetic acid had no bands between 3600 and 3100 cm^{-1} whereas the "anil" had a band at 3300 cm^{-1}. We repeated the preparation (4) of a compound claimed to be **4** (R = Me, R^1R^2 = $[CH_2]_5$). Its spectra had ν_{max} 2706 weak (w), 2500 w, 2450 w, 2160, 1695, 1630, and 1595 cm^{-1}, λ_{max} (EtOH) 232 and 293 mμ (ε 7100 and 9250 respectively). From these data and our analysis, we consider this compound to be a salt.

The pK_a values of a number of pyrrolidones **1** are given in Table 3. The values are close to those of carboxylic acids. The effect of varying the group in position 4 of the pyrrolidone **6** is also shown. Our figure for the ester **6** (R = COOEt) is the average of our values, compare Southwick *et al.*, 4.25 (6). This ester gave enamines with amines, rather than salts, supporting our expectation that it would have a higher pK_a value than **1** (R = $PhCH_2$) since a 4-cyano group would enhance the acidity by its greater inductive effect.

We observed the easy hydrolysis of nitrile to amide, above, after we found that the alleged oxime (4) of **1** (R = Me) was a salt. When the amide **6** (R = $CONH_2$) was treated with hydroxylamine hydrochloride and aqueous sodium acetate, the oximeamide **3** (R = $PhCH_2$) was not formed. The only isolable product was 1-benzyl-3-hydroxylamino-2-oxo-3-pyrroline **7**, (ν_{max} 1680 (C=O), 1050 (C=C), 800, ($>C=CH$—)) identical with a sample prepared according to Southwick *et al.* (6). The nitrile hydrolysis may follow the same course as that outlined recently by Stephenson *et al.* (7).



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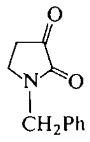

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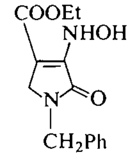

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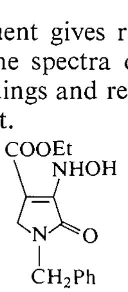
Several investigators (4–6, 8) have reported on the keto–enol tautomerism of pyrrolidine-2,3-diones. The presence of a 4-substituent is stated to result in complete enolization as estimated from n.m.r. and i.r. spectra. Absence of a

4-substituent gives rise to the keto-form exclusively. The spectra of our compounds confirm these findings and reveal some additional points of interest.



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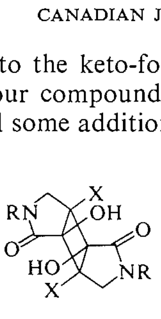

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The i.r. spectrum of **1** (R = H), in which 1,4 interaction is low, indicates that it exists in the enol form, there being extended double bond conjugation. The n.m.r. spectrum of **8** confirms its structure, no enol being observed. However, the oxime **9** of the ester **6** (R = COOEt) had an n.m.r. spectrum showing one exchangeable proton at $-0.4\ \tau$ and a complex ABC pattern for the protons at positions 4 and 5. The i.r. spectrum confirmed the double bond at position 3 to be exocyclic, structure **10** being contraindicated.

The u.v. irradiation of compounds **1** gave mainly dimers **11**. We obtained from **6** (R = COOEt) a solid which we conclude to be **11** (R = $PhCH_2$, X = COOEt). It had i.r. bands at 3320, 1730 (broad), and 1695 cm^{-1} and gave no ferric chloride color. A center of symmetry was indicated by the absence of any permanent dipole.[3]

The n.m.r. spectrum, along with two slowly exchangeable protons at 2.3, ten aromatic protons at 2.68 and two superimposed methyl group triplets at 8.9, had twelve lines in the region 5.0–6.5 τ. These were due to two superimposed methylene group quartets at 5.92 (splitting 7.3 Hz), a pair of doublets at 6.38 and 5.96 (splitting 12 Hz), assigned to ring methylene protons and a pair of doublets at 5.75 and 5.17 τ (splitting 15 Hz) assigned to the four benzylic protons of **11** (R = $PhCH_2$, X = COOEt) on the basis of their chemical shifts and J values which are in line with (negative) geminal coupling constants for methylene protons of each type (10).

Experimental

No attempt was made to optimize yields.

Melting points are uncorrected. The i.r. spectra are in nujol, u.v. spectra in ethanol, and n.m.r. spectra (Jeolco C-60HL) in $CDCl_3$. Mass spectra (A.E.I. M.S.12) were run on the probe at 70 eV, *m/e* (relative intensity) being quoted.

β-*Aminopropionitriles*, **2**

Typically, (9), equimolar quantities of *N,N*-dimethylhydrazine and acrylonitrile were heated 24 h under reflux and fractionated to give β-cyanoethylaminodimethylamine, b.p. 50°/1 mm, yield 80%, characterized as the picrate, m.p. 74° from ethanol.

Anal. Calcd. for $C_{11}H_{14}N_6O_7$: C, 38.6; H, 4.1; N, 24.6. Found: C, 38.6; H, 4.0; N, 24.7.

Preparation of 4-Cyano-3-hydroxy-2-oxo-3-pyrrolines, **1**

A β-aminopropionitrile and diethyl oxalate were reacted according to the literature (2).

Using β-(*N*-carbethoxyamino) propionitrile (3), hydrolysis took place during work up to give the hitherto unknown parent compound 4-cyano-3-hydroxy-2-oxo-3-pyrroline **1** (R = H), yield 41%, recrystallized from water, m.p. 215° (decomp.). Mass spectrum 167 (M^+, 75%), 43, (100%).

Anal. Calcd. for $C_5H_4N_2O_2$: C, 48.4; H, 3.2; N, 22.6. Found: C, 48.6; H, 3.2; N, 22.6.

From **2** (R = NMe_2) we obtained 4-cyano-1-dimethylamino-3-hydroxy-2-oxo-3-pyrroline **1** (R = NMe_2), m.p. 190° (decomp.) yield 1% after recrystallization from benzene. Mass spectrum 167 (M^+, 75%), 43 (100%).

Anal. Calcd. for $C_7H_9N_3O_2$: C, 50.3; H, 5.4; N, 25.1. Found: C, 50.5; H, 5.3; N, 25.0.

1-Benzyl-3-benzyloxy-4-cyano-2-oxo-3-pyrroline

The benzyl ether of **1** (R = $PhCH_2$) was obtained by treating a suspension of the silver salt in benzene (or methanol) with benzyl chloride at reflux overnight, yield 95%. It crystallized as prisms from ethanol, m.p. 210–214°, yield 50%. Mass spectrum 304 (M^+, 8%), 91 (100%).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 75.1; H, 5.2; N, 9.1. Found: C, 75.0; H, 5.3; N, 9.1.

3-Benzyloxy-4-cyano-2-oxo-3-pyrroline

The benzyl ether of **1** (R = H) was prepared as above. It has m.p. 169°, crystallized from benzene, yield 7%. Mass spectrum 214 (M^+, 6%), 91 (100%).

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.3; H, 4.7; N, 13.1. Found: C, 67.6; H, 4.5; N, 13.2.

3-Amino-1-benzyl-4-cyano-2-oxo-3-pyrroline

The pyrroline **1** (R = $PhCH_2$), on treatment with urea (4), gave the amine, yield 90%, m.p. 189–191° crystallized from benzene/light petroleum. Mass spectrum 213 (M^+, 42%), 91 (100%).

Anal. Calcd. for $C_{12}H_{11}N_3O$: C, 67.6; H, 5.2; N, 19.7. Found: C, 67.6; H, 5.3; N, 19.9.

1-Benzyl-4-carboxamido-3-hydroxylamino-2-oxo-3-pyrroline (3, R = $PhCH_2$)

A mixture of the pyrroline **1** (R = $PhCH_2$) (5 g), hydroxylamine hydrochloride (6 g), sodium acetate (6 g) and water (40 ml) was kept at 96° for 3 h then cooled to 0°. The amide **3** (R = $PhCH_2$) was collected (4.5 g, 79%), m.p. 202° (decomp.). It was soluble in dilute alkali and could be precipitated unchanged by careful addition of dilute acid. It was sparingly soluble in all common organic solvents and an analytical sample was obtained

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[3] We thank Prof. I. D. Chapman and Mr. A. R. Stevenson of this department for this result, using a General Radio Co. 1610 Capacitance assembly with 716-C bridge.

TABLE 4

Salts of **1** with amines, and their analyses

1	Melting point°	C		H		N	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
R = $PhCH_2$							
Piperidine	134–137*	68.2	68.1	7.1	7.1	14.0	14.3
Dimethylamine	149–151*	64.8	65.0	6.6	6.6	16.2	16.3
Triethylamine	95–105†‡	68.5	68.3	8.0	8.0	13.3	13.2
Aniline	185–189†‡	70.3	70.1	5.6	5.4	13.7	13.6
R = Me							
Piperidine	138–143†§	59.2	59.2	7.7	7.7	18.8	19.0
Hydroxylamine	137–142†‖	42.1	42.4	5.3	5.4	24.5	24.2

*From benzene/light petroleum plus a little ethanol.
†With decomposition.
‡From benzene/light petroleum.
§From benzene/light petroleum, lit. m.p. 146–151° (4).
‖From ethanol, lit. m.p. 147–150° (4).

by thorough washing and drying. Mass spectrum 247 (M^+, 39%), 91 (100%). The i.r. bands 3400, 3100, 1685, 1630, 1605, 1570, 1260, and 950 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.3; H, 5.3; N, 17.0. Found: C, 58.3; H, 5.3; N, 17.4.

4-Carboxamido-3-hydroxylamino-1-methyl-2-oxo-3-pyrroline (3, R = Me)

This was obtained as above, yield 14%, prisms decomposed 230°. Mass spectrum 171 (M^+, 100%).

Anal. Calcd. for $C_6H_9N_3O_3$: C, 42.1; H, 5.3; N, 24.5. Found: C, 42.2; H, 5.2; N, 24.0.

4-Carboxamido-3-hydroxylamino-2-oxo-3-pyrroline (3, R = H)

This compound was obtained by the above method, decomposed 210°. Mass spectrum 157 (M^+, 14%), 44 (100%). The latter peak was a doublet of CO_2 and $CONH_2^+$. Found 44.0132. Required 44.0136.

Anal. Calcd. for $C_5H_7N_3O_3$: C, 38.2; H, 4.5; N, 26.7. Found: C, 38.0; H, 5.1; N, 26.6.

1-Benzyl-4-carbethoxy-3-hydroxylimino-2-oxo-pyrrolidine (9)

1-Benzyl-4-carbethoxy-3-hydroxy-2-oxo-3-pyrroline (2 g), by the method described above, gave the oxime which was recrystallized from chloroform/light petroleum, needles (0.8 g), m.p. 87.5–90°. Mass spectrum 276 (M^+, 20%), 259 (M-17, 9%), 91 (100%).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: N, 10.15. Found: N, 10.2.

1-Benzyl-4-carboxamido-3-hydroxy-2-oxo-3-pyrroline (6, R = CONH₂)

The pyrroline **1** (R = $PhCH_2$) was left overnight at room temperature with five parts sulfuric acid and the solution poured onto ice. The product 91% yield, collected, dried, and recrystallized from ethanol, formed plates, m.p. 222–225° (decomp.). Mass spectrum 232 (M^+, 25%), 91 (100%).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2; N, 12.1. Found: C, 62.1; H, 5.2; N, 12.0.

Reaction of 1-Benzyl-4-carboxamido-3-hydroxy-2-oxo-3-pyrroline with Hydroxylamine

The foregoing amide (0.2 g) was treated with hydroxylamine as described above. The product was extracted into ether, dried ($MgSO_4$), and concentrated giving 50 mg **7**, m.p. 213.5–215.5° twice recrystallized from water. Mixed m.p. with Southwick's material (6), having m.p. 213.5–215°, was 212–215°. The i.r. spectra of the two samples were identical. Mass spectrum 204 (M^+, 4%), 91 (100%).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.5; H, 5.9; N, 13.8.

Preparation of Amine Salts of 4-Cyano-3-hydroxy-2-oxo-3-pyrrolines 1 (see Table 4)

The pyrroline **1** (0.2 g), a tenfold excess of amine, and enough benzene or ethanol for solution were left at room temperature or refluxed 2 h, then concentrated. Light petroleum was added to turbidity and the product crystallized as the mixture cooled. Catalytic amounts of *p*-toluenesulfonic acid did not affect the reactions using piperidine in benzene. Yields were nearly quantitative. The hydroxylamine salt of **1** (R = Me) was prepared according to the literature (4). The salts when washed with acid regenerated the pyrrolidones **1**.

1-Benzyl-4-cyano-2-oxo-3-(2′-phenylhydrazino)-3-pyrroline

The pyrroline **1** (R = $PhCH_2$) (1 g) and phenylhydrazine (1 g) in ethanol (50 ml) were refluxed for 6 h and concentrated to 25 ml. Addition of water precipitated the product which was recrystallized from benzene/light petroleum, needles (1.1 g), m.p. 158.5–160°. Mass spectrum 304 (M^+, 36%), 91 (100%); M-2 was also prominent.

Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.0; H, 5.3; N, 18.4. Found: C, 71.1; H, 5.3; N, 18.3.

1-Benzyl-4-cyano-2-oxo-3-phenylazo-3-pyrroline

The above phenylhydrazone (0.3 g) was refluxed in xylene 1 week. Chromatography then gave the azo-compound (50 mg, 16%), yellow needles, m.p. 173–174.5° crystallized from benzene/light petroleum. Mass spectrum 302 (M^+, 52%), 91 (100%).

Anal. Calcd. for $C_{18}H_{14}N_4O$: C, 71.5; H, 4.7; N, 18.5. Found: C, 71.9; H, 4.7; N, 17.9.

3-Anilino-1-benzyl-4-cyano-2-oxo-3-pyrroline

Compound **1** (R = $PhCH_2$) (0.2 g), aniline (0.1 g), ethanol (4 ml), and glacial acetic acid (6 drops) were heated together under reflux for 5 h then cooled to 0°. The deposit was recrystallized several times from ethanol/light petroleum to give the anil **4** (R = $PhCH_2$, R^1 = H, R^2 = Ph), 75 mg m.p. 148–151°, i.r. bands at 3300, 2170, 1695, 1650, 1600, and 1530 cm^{-1}. Mass spectrum 289 (M^+, 4%), 91 (100%).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.7; H, 5.2; N, 14.5. Found: C, 74.5; H, 5.3; N, 14.4.

1-Benzyl-4-carbethoxy-3-hydroxy-2-oxo-3-pyrroline Dimer (11)

The monomer **6** (R = COOEt) (6) (9 g) in ethanol (500 ml) was irradiated using a 100 W medium pressure Hanovia mercury arc tube so that the solution refluxed gently overnight. Concentration gave the dimer, 3.3 g, m.p. 195–215° (decomp.) recrystallized from ethanol. Mass spectrum 522 (M^+, 1%), 91 (100%).

Anal. Calcd. for $C_{28}H_{30}N_2O_8$: C, 64.3; H, 5.8; N, 5.4. Found: C, 64.0; H, 5.5; N, 5.6.

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