Structure Elucidation of 2-Amino-5-phenyl-2-oxazolin-4-one (Pemoline) and X-Ray Structure of its Hydrolysis Product 5-Phenyl-oxazolidine-2,4-dione

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In this study we compare spectroscopic properties of pemoline (2-amino-5-phenyl-2-oxazolin-4-one) and its acid hydrolysis product 5-phenyl-oxazolidine-2,4-dione. Crystallization of pemoline from aqueous acetic acid gave single crystals of compound **2**, the structure of which was determined by X-ray studies. All four crystallographically independent molecules form dimers linked by N-H···O=C hydrogen bonds.

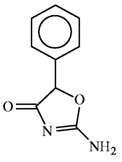
Key words: Pemoline, 2-Amino-5-phenyl-2-oxazolin-4-one, 5-Phenyl-oxazolidine-2,4-dione, Raman Spectra, X-Ray Structure

Pemoline (**1**; phenylisohydantoin, phenylpseudohydantoin, 2-amino-5-phenyl-2-oxazolin-4-one, 2-amino-5-phenyl-1,3-oxazol-4(5H)-one) is known to be a central nervous system stimulant; it has narcotic activity and also enhances effects exerted by other drugs [1, 2]. It is poorly soluble in the majority of organic solvents and in water, but is soluble in acetic and propionic acids.

Magnesium complexes of pemoline have more potent biological activity than pemoline alone, and have been reported to exhibit a protective effect against lethal doses of ionizing radiation [3].

Pemoline has one asymmetric carbon atom at C-5 of the oxazoline ring and it thus occurs in two enantiomeric forms; it has been a subject of chromatographic studies [4]. Acid hydrolysis of pemoline leads to substitution of the amino by a carbonyl group [5]. The ease with which this process occurs can result in false interpretation of the chromatography results (when the mobile phase contains an acid component), or of UV analysis (spectra are recorded in acidic aqueous solutions [6]). The hydrolysis product, 5-phenyloxazolidine-2,4-dione (**2**), can also be obtained by oxidative hydroxylation of substituted barbituric acid [7], hydrolysis of pemoline N-acetyl derivative [8] or direct synthesis from ethyl mandelate and urea [9]. Compound **2** or its derivatives can be used as precursors in the synthesis of substituted penicillins [10].

For our studies pemoline was obtained from ethyl mandelate and thiourea, as described in [5] and compound **2** by subsequent acidic hydrolysis. The purity of both compounds was confirmed by analytical and spectroscopic methods. We attempted to solve the problem of possible pemoline isomers, as discussed in [12], by establishing its crystal structure. Unfortunately, we were not able to obtain single crystals of this compound in any "neutral" (non-acidic) solvent. The acetic acid/water mixture used as a solvent allowed us to obtain (after one year) crystals of moderate quality, the crystal structure of which (see below) showed, however, that the crystallized substance was not pemoline but its hydrolysis product **2**.



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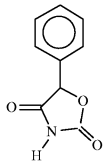

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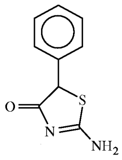

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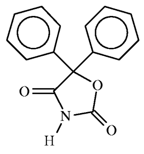

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The published UV spectrum of **1**, which could provide fundamental data characterizing pemoline [6], is

Table 1. Characteristic IR bands and Raman lines for pemoline **1** and compound **2**.

Pemoline **1** [cm^{-1}]		Compound **2** [cm^{-1}]	
IR	Raman	IR	Raman
3265		3295	
3167			
3062	3067	3061	3065
3036	3058	3041	
	3008		
2946	2947	2944	2945
			2933
		1824	1805
1719	1721	1733	
1660	1606		1604
	1590		1588
1564		1530	
1498		1497	
1459		1455	
1450		1382	
1350		1329	
		1298	
1286		1282	
1277			1200
1225	1206	1192	1192
1136		1154	1180
1080		1070	1164
1038		1048	
1023	1027	1027	1030
	1004	1017	1003
972	976	965	
932	934	930	930
		887	
867	867	852	857
763	768	767	
		753	
	730	739	
		727	
699	683	693	699
656	659	638	640
626	628		620
539	538	540	
482	474	491	

Table 2. Selected bond lengths [Å] and angles [°] for compound **2**.

O(1)-C(2)	1.352(4)	O(1”)-C(5”)	1.452(4)
O(1)-C(5)	1.449(4)	O(2”)-C(2”)	1.201(4)
O(2)-C(2)	1.194(4)	C(2”)-N(3”)	1.370(5)
C(2)-N(3)	1.377(5)	N(3”)-C(4”)	1.372(5)
N(3)-C(4)	1.368(5)	O(4”)-C(4”)	1.193(4)
O(4)-C(4)	1.209(5)	C(4”)-C(5”)	1.529(5)
C(4)-C(5)	1.524(6)	C(5”)-C(11”)	1.494(5)
C(5)-C(11)	1.507(5)	O(1#)-C(2#)	1.339(4)
O(1’)-C(2’)	1.341(4)	O(1#)-C(5#)	1.457(4)
O(1’)-C(5’)	1.459(4)	O(2#)-C(2#)	1.199(4)
O(2’)-C(2’)	1.196(4)	C(2#)-N(3#)	1.372(5)
C(2’)-N(3’)	1.383(5)	N(3#)-C(4#)	1.363(5)
N(3’)-C(4’)	1.364(5)	O(4#)-C(4#)	1.214(4)
O(4’)-C(4’)	1.214(5)	C(4#)-C(5#)	1.509(5)
C(4’)-C(5’)	1.507(5)	C(5#)-C(11#)	1.505(5)
C(5’)-C(11’)	1.510(5)	O(1”)-C(2”)	1.339(4)
C(2)-O(1)-C(5)	109.9(3)	O(1’)-C(5’)-C(4’)	103.4(3)
O(2)-C(2)-O(1)	122.1(4)	O(1’)-C(5’)-C(11’)	109.9(3)
O(2)-C(2)-N(3)	128.9(4)	C(4’)-C(5’)-C(11’)	114.8(3)
O(1)-C(2)-N(3)	109.0(3)	C(2”)-O(1”)-C(5”)	109.9(3)
C(4)-N(3)-C(2)	112.4(3)	O(2”)-C(2”)-O(1”)	122.2(4)
O(4)-C(4)-N(3)	127.9(4)	O(2”)-C(2”)-N(3”)	128.2(4)
O(4)-C(4)-C(5)	127.1(3)	O(1”)-C(2”)-N(3”)	109.6(3)
N(3)-C(4)-C(5)	104.9(3)	C(2”)-N(3”)-C(4”)	112.3(3)
O(1)-C(5)-C(11)	110.4(3)	O(4”)-C(4”)-N(3”)	128.1(4)
O(1)-C(5)-C(4)	103.7(3)	O(4”)-C(4”)-C(5”)	127.4(3)
C(11)-C(5)-C(4)	113.7(4)	N(3”)-C(4”)-C(5”)	104.5(3)
C(2’)-O(1’)-C(5’)	109.9(3)	O(1”)-C(5”)-C(11”)	110.5(3)
O(2’)-C(2’)-O(1’)	122.9(4)	O(1”)-C(5”)-C(4”)	103.5(3)
O(2’)-C(2’)-N(3’)	128.0(3)	C(11”)-C(5”)-C(4”)	113.1(3)
O(1’)-C(2’)-N(3’)	109.0(3)	C(2#)-O(1#)-C(5#)	109.9(3)
C(4’)-N(3’)-C(2’)	111.9(3)	O(2#)-C(2#)-O(1#)	123.0(3)
O(4’)-C(4’)-N(3’)	127.2(4)	O(2#)-C(2#)-N(3#)	127.7(4)
O(4’)-C(4’)-C(5’)	127.1(3)	O(1#)-C(2#)-N(3#)	109.3(3)
N(3’)-C(4’)-C(5’)	105.7(3)	C(4#)-N(3#)-C(2#)	111.9(3)
O(4#)-C(4#)-N(3#)	127.5(4)	O(4#)-C(4#)-C(5#)	126.9(3)
N(3#)-C(4#)-C(5#)	105.6(3)	O(1#)-C(5#)-C(11#)	110.0(3)
O(1#)-C(5#)-C(4#)	103.1(3)	C(11#)-C(5#)-C(4#)	116.3(4)

identical with that of compound **2**. These spectra were however recorded in acidic solutions; thus in both cases they could pertain to the same substance, compound **2**. Unfortunately, precise determination of ε values for both compounds was not successful because of insufficient solubility.

The IR spectra (Table 1) show two carbonyl bands for both compounds at 1719 cm^{-1} and 1660 cm^{-1} for **1** and 1824 and 1733 cm^{-1} for **2**. The vibration occurring at 1719 cm^{-1} for pemoline is of low intensity and can be assigned to the imino group. In the Raman spectra lines at 1721 and 1805 cm^{-1} for **1** and **2**, respectively, represent the carbonyl group. Also, the vibrations at 1606 and 1590 cm^{-1} for **1** and 1604 and 1588 cm^{-1} for **2** can be assigned to carbonyl (amido) units of both molecules. Strong lines at 1027 cm^{-1} for **1** and 1030 cm^{-1} for **2** in the Raman spectra and bands at 1023 cm^{-1} for **1** and 1017 cm^{-1} for **2** in the IR spectra are associated with δ_{CH} vibrations of aromatic rings. In the Raman spectra the most characteristic lines are those of $\nu_{\mathrm{C=Csym}}$ of aromatic rings at 1004 and 1003 cm^{-1} for **1** and **2**, respectively; they are absent in the IR spectra.

The ESI-MS spectrum of **1** reveals a pseudomolecular ion at $m/z = 177\,[\mathbf{1}+\mathrm{H}]^+$, but the most abundant ion is a dimer of the pseudomolecular ion at $m/z = 353\,[2\times\mathbf{1}+\mathrm{H}]^+$. The spectrum also features an ion at $m/z = 106\,[\mathrm{C_6H_5CHO}]^+$ and a very small signal at $m/z = 529\,[3\times\mathbf{1}+\mathrm{H}]^+$. Under the impact

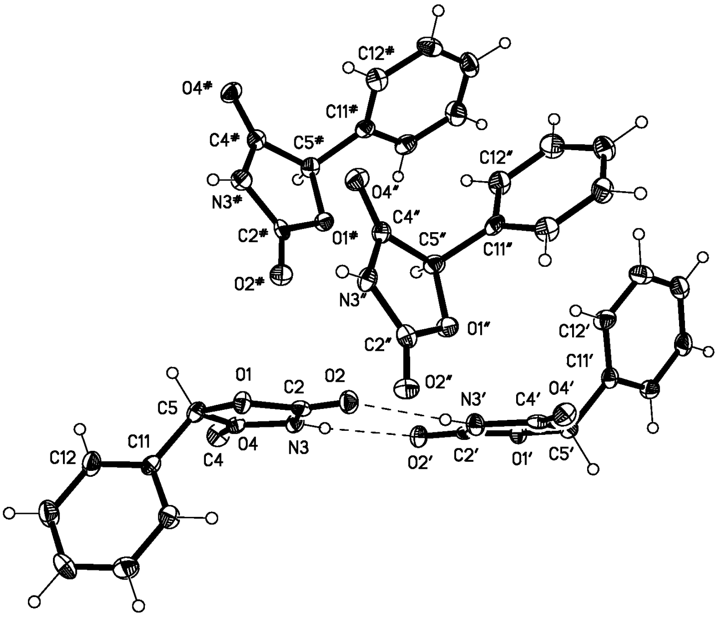

Fig. 1. The four independent molecules of compound **2** in the crystal. Ellipsoids represent 50% probability levels. Dashed lines represent hydrogen bonds.

Table 3. Hydrogen bonds [Å and °] for compound **2**.

D-H...A	d(D-H)	d(H...A)	d(D...A)	⟨(DHA)
N(3)-H(3)...O(2’)	0.83(2)	2.15(3)	2.911(4)	153(4)
N(3’)-H(3’)...O(2)	0.83(2)	2.11(3)	2.877(4)	155(4)
N(3”)-H(3”)...O(2”)#1	0.82(2)	2.21(3)	2.954(4)	150(4)
N(3#)-H(3#)...O(2#)#2	0.83(2)	2.11(3)	2.906(4)	162(4)
N(3)-H(3)...O(1#)#3	0.83(2)	2.53(4)	3.083(4)	125(4)
N(3’)-H(3’)...O(1”)	0.83(2)	2.52(4)	3.020(4)	120(4)
N(3”)-H(3”)...O(1’)#4	0.82(2)	2.43(4)	3.055(4)	133(4)
N(3#)-H(3#)...O(1)#2	0.83(2)	2.51(4)	2.968(4)	116(4)
C(5”)-H(5”)...O(4)#3	1.00	2.54	3.412(5)	145.9
C(5#)-H(5#)...O(4’)#5	1.00	2.56	3.490(5)	155.2
C(5)-H(5)...O(4”)#2	1.00	2.49	3.390(5)	148.9
C(5’)-H(5’)...O(4#)#6	1.00	2.60	3.517(5)	151.7

Symmetry transformations used to generate equivalent atoms: #1 $-x+2,-y+2,-z$; #2 $-x+1,-y+2,-z$; #3 $-x+1,-y+1,-z$; #4 $x,y+1,z$; #5 $x-1,y,z$; #6 $x+1,y-1,z$.

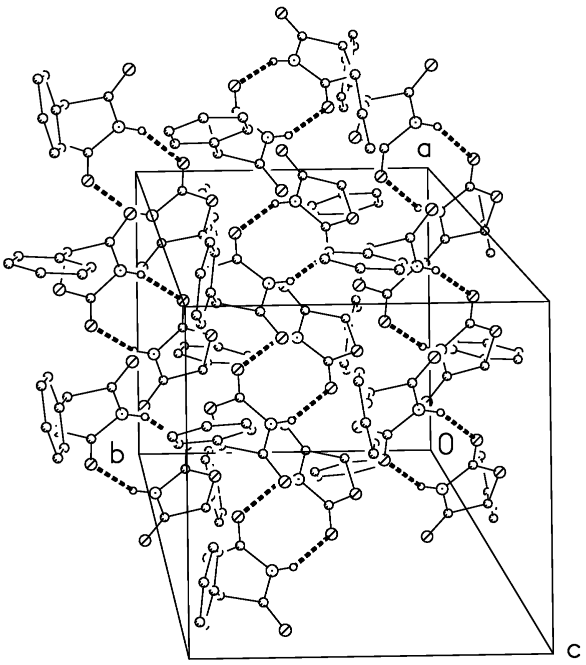

Fig. 2. Packing diagram of compound **2** viewed perpendicular to the *xy* plane in the region $z \approx 0$. Hydrogen bonds are indicated by thick dashed lines. Hydrogen atoms not involved in H bonding are omitted. Hydrogen-bonded pairs may be located as follows: Top centre, molecules 1/2; top left, two molecules 3; under these, two molecules 4.

of increased ms/ms conditions, the ion at $m/z = 353$ becomes fragmented into an ion at $m/z = 177$ (pemoline). In the negative ion mode the mass spectrum of **1** is complicated and the intensities of the peaks are very low. The ESI-MS spectrum of **2** can be recorded only in the negative ion mode. Only one intense peak is observed at $m/z = 176[\text{M-H}]^-$. In the positive ion mode the intensities of the peaks are very low.

The crystal structure of **2** is complex, with four independent molecules in the asymmetric unit (Fig. 1, Table 2). Molecules 2, 3 and 4 are distinguished by adding prime, double prime or hash symbols to the atom names. Despite the moderate crystal quality, atom types could be assigned unambiguously and hydrogen atoms were located in difference syntheses, thus confirming the formula **2**. Bond lengths and angles may be considered normal (*e. g.* C2-N3 1.370 – 1.383(5) and C4-N3 1.363 – 1.372(5); cf. the standard value of 1.376 for O=C-NH-C=O systems [12]). The molecules have a torsional degree of freedom about the C5-C11 bond, and the torsion angles are appreciably different; C12-C11-C5-O1 is 150.9, −94.6, 152.3 and −95.6 for the *R* enantiomers of the four molecules. The crystal packing (Fig. 2) involves pairs of molecules, one *R* and one *S* in each case, linked by N-H···O=C hydrogen bonds (Table 3, first four entries; in each case O2 is the acceptor). Molecules 1 and 2 form such a dimer, whereas molecules 3 and 4 are paired as homo-dimers across inversion centres. The second four entries in Table 2 represent N-H···O1 contacts that might be regarded as weak components of three-centre H bond systems (not shown in Fig. 2). The carbonyl oxygen atoms O4 are not involved in classical H bonding but accept weak H bonds from C5-H5 (last four entries in Table 3; not shown in Fig. 2).

The X-ray structure of **3**, the sulphur analogue of pemoline (with sulphur in position 1 of the heterocyclic ring) has been reported; there are two modifications, both crystallizing in space group $P2_1/c$ with two independent molecules. In one form, the two independent molecules form a dimer *via* two N-H···N hydrogen bonds [13, 14]; in the other [15], these dimers display inversion symmetry. Both modifications additionally form two N-H···O=C hydrogen bonds.

The structure of **4**, the diphenyl derivative of 1,3-oxazolidine-2,4-dione, is similar. This compound does not, however, contain an asymmetric carbon atom and its crystal structure is less complex, with only one independent molecule; a hydrogen bond N-H···O=C is observed [16].

Experimental Section

The proton NMR spectra were recorded with a Bruker spectrometer (500 MHz), chemical shifts are in ppm ($CDCl_3$/TMS). Electronic spectra were recorded on a Genesys 6 (ThermoSpectronic) spectrophotometer in propionic acid-water (1:1, v/v) solutions. IR spectra were recorded with the Nicolet FT-IR Magna 560 spectrometer in KBr pellets. The Raman spectra were measured using the Raman accessory with the Nicolet FT-IR Magna 560 spectrometer (Nd:WVO_4 laser worked in the near infrared range (9600 cm^{-1})). ESI mass spectra were recorded on a LCQ DUO FINNINGAN THERMOQUEST instrument. HRMS and EI mass spectra (70 eV) were measured on a AMD 604 (AMD Intectra) spectrometer.

2-Amino-5-phenyl-2-oxazolin-4-one (1)

The compound was synthesized from racemic ethyl mandelate and thiourea as described in [5]. Yield: ∼ 40%. M. p. 254 – 256 °C (lit. 257 °C [8]). – UV (propionic acid – water): $\lambda_{max} = 251, 256, 262, 268$ nm. – ^1H NMR ($CDCl_3$ dispersion): $\delta = 8.8$ (bs, 2H), 7.33 – 7.50 (m, 5H), 5.80 (s, 1H). – ^1H NMR ($CDCl_3$ + DMSO-d_6): $\delta = 8.64$ (s, 1H), 8.36 (s, 1H), 7.20 – 7.9 (m, 5H), 5.53 (s, 1H). – HR MS: 176.05951 (calcd. for $C_9H_8O_2N_2$ 176.05858). – MS (EI, 70 eV): *m/z* (%) = 176(100) [M^+], 148(9), 147(8), 108(8), 107(82), 105(28), 90(44), 89(38), 79(27), 78(8), 77(35), 71(9), 70(22), 63(11), 51(19), 50(9), 42(20). – $C_9H_8O_2N_2$ (176): calcd. C 61.34, H 4.58, N 15.91; found C 60.91, H 4.68, N 15.41.

5-Phenyl-oxazolidine-2,4-dione (2)

A slurry of 0.1 g of pemoline **1** in 10 ml of 10% aqueous sulfuric acid was boiled for 0.5 h. During this time the solid dissolved. The mixture was cooled and filtered. The white powder was washed with water and dried in air to give 0.09 g (90%) of product.

M. p. 108 – 109 °C (lit. 111 – 112 °C [5]). – UV (propionic acid / water): $\lambda_{max} = 250, 255, 262, 268$ nm. – ^1H NMR (DMSO-d_6): $\delta = 12.15$ (s, 1H), 7.3 – 7.6 (m, 5H), 6.04 (s, 1H). – HR MS: 177.04165 (calcd. for $C_9H_8O_3N$ 177.04259). – MS (EI, 70 eV): *m/z* (%) = 177(100) [M^+], 107(20), 106(50), 105(65), 91(7), 90(90), 89(41), 78(11), 77(35), 63(11), 51(20), 50(10). – $C_9H_8O_3N$ (177): calcd. C 61.01, H 3.98, N 7.90; found C 60.70, H 4.02, N 7.63.

X-ray structure determination of compound 2

Crystal data: Triclinic, space group $P\bar{1}$, $a = 9.666(2)$, $b = 9.985(2)$, $c = 16.899(4)$ Å, $\alpha = 97.785(5)$, $\beta = 106.043(3)$, $\gamma = 90.185(5)^\circ$, $U = 1551.6$ Å^3, $Z = 8$, $D_x = 1.517$ Mg m^{-3}, $F(000) = 736$, $\mu = 0.12$ mm^{-1}, $T = -140$ °C. *Data collection*: A crystal *ca.* $0.3 \times 0.1 \times 0.07$ mm was used to record 12980 intensities (Mo-K_α radiation, $2\theta_{max} = 52.6^\circ$) on a Bruker SMART 1000 CCD diffractometer. *Structure refinement*: The structure was refined anisotropically against F^2 (program SHELXL-97, G. M. Sheldrick, Univ. of Göttingen) to $wR2 = 0.177$, $R1 = 0.087$ for 482 parameters and all 6233 independent reflections; max. $\Delta\rho = 0.32$ eÅ^{-3}, $S = 1.11$. Hydrogen atoms of NH groups were refined freely with distance restraints, other H atoms were included using a riding model.

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC-268342. Copies can be obtained free of charge from CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (Fax: Int.+1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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