SHORT PAPER

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On the stereochemistry of the synthesis of 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea and its *E*-configuration crystal structure†

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The synthesis of 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea leads to only one of the two possible diastereomers, which has been found to be in the *E*-configuration by X-ray analysis.

Keywords: cymoxanil, X-ray analysis, synthesis, stereochemistry

The title compound, commercially known as cymoxanil,[1] is a fungicide with protective and curative action, used to control peronosporales in a range of crops including vines, hops, potatoes and tomatoes. Even though cymoxanil has been used in a large number of applications in the last decade owing to its low toxicity and its high efficacy as a fungicide,[2] very little work has been dedicated to its structure. In fact, cymoxanil may exist as two different disatereomers related to the *Z* and *E* configurations of the oxime group. Here we describe the synthesis and the X-ray structure of the *E* diastereomer, which is the sole stereoisomer formed in the synthesis reported in the experimental section.

Results and discussion

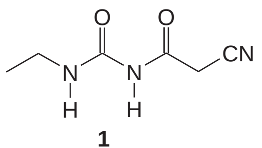
The *N*-ethyl-*N'*-cyanoethylurea **1** was obtained by condensation of ethylurea with cyanoacetic acid in the presence of acetic anhydride. The transformation of **1** into 1-(2-cyano-2-hydroxyiminoacetyl)-3-ethylurea **2** is the crucial point for the formation of the distereomers *E* and *Z*. For this reason all the crystalline white precipitate of the second reaction step was collected by filtration, dried and used directly for the next reaction step. The crude product **2** was then methylated to form compound **3**; in this case too the product precipitated from the reaction medium and was separated by filtration under vacuum. Product **3** was then studied spectroscopically without further purification and the recorded ^{1}H NMR was in agreement with only one diastereomer. This result was also confirmed by the fact that the crude product shows the same melting point as the crystallised one.

Compounds **1**, **2** and **3** show ^{1}H NMR spectra which are in agreement with their structure even if they do not give information on the stereochemistry of compounds **2** and **3**. All compounds show in their ^{1}H NMR spectra two signals that can be attributed to the two N*H* groups, one falling at *ca* δ 7.9 and the other in the range between δ 8.4–10.8: the former was assigned to the N$\underline{H}$ bonded to the ethyl group. In fact, in all compounds the quartet due to the $C\underline{H}_2$-CH_3 protons is split in two (*J* = 5.7 Hz), owing to the coupling with the NH proton. Irradiation at the frequency of the NH signal (δ 7.9) eliminates the splitting of the quartet in the spectra of all compounds. The presence of only one singlet at δ 4.32 in the spectrum of compound **3** suggests that only one diastereomer is present.

However, in the IR spectrum of compound **2** the broad band between 3500 and 2500 cm^{-1} can not be of help for the structure assignement, because it could be due either to an intramolecular (*Z*-configuration) or to an intermolecular (*E*-configuration) hydrogen bonding interaction of the OH group with a carbonyl group.

The formation of only one of the two *E/Z* diastereomers and the *E* configuration of cymoxanil was determined by X-ray analysis.

The structure of 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea was determined by single crystal X-ray diffraction as reported in Table 1, selected bond distances and angles are collected in Table 2 and the perspective view is reported in Fig.1. Supplementary crystallographic data have been



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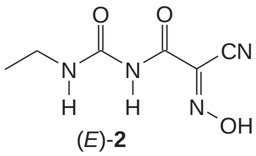
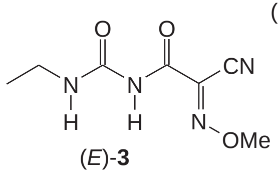


(*E*)-**2**



(*E*)-**3**

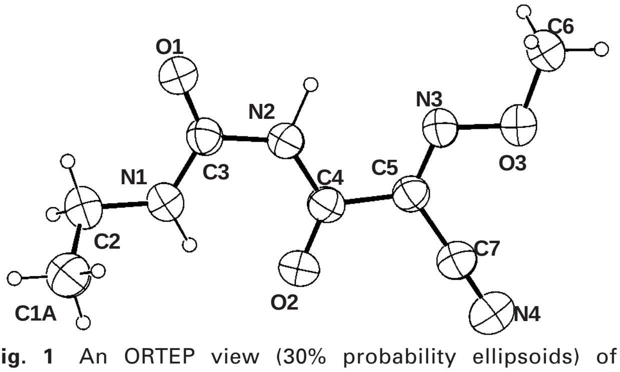


Fig. 1 An ORTEP view (30% probability ellipsoids) of 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea **3**. Disorder affecting C(1) has been omitted for clarity.

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[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Experimental data for the X-ray diffraction studies on crystalline compound **3**

Formula	*a/Å*	*b/Å*	*c/Å*	*α/°*	*β/°*	*γ/°*	*V/Å³*
$C_7O_3N_4H_{10}$	14.587(2)	15.100(2)	4.544(1)	90	95.60(10)	90	995.1(3)
Z	*Formula weight*	*Space group*	*t/°C*	*λ/Å*	*ρ_{calc}/g cm^{-3}*	*μ/cm^{-1}*	*transmission coefficient*
4	198.2	*P*2$_1$/*n*	23	1.54178	1.322	8.994	0.991–1.000
R [a]	*wR$_2$*	*GOF*	*N-observed* [b]	*N-independent* [c]	*N-refinement* [d]	*Variables*	
0.070	0.182	1.147	977	1896	1660	127	

[a] Calculated on the observed reflections having $I > 2\sigma(I)$.
[b] *N*-observed is the total number of the independent reflections having $I > 2\sigma(I)$.
[c] *N*-independent is the number of independent reflections.
[d] *N*-refinement is the number of reflection used in the refinement having $I > 0$.

Table 2 Selected bond distances (Å) and angles (°) with SDs in parentheses

O(1)–C(3)	1.216(4)	N(1)–C(3)	1.328(4)
O(2)–C(4)	1.219(4)	N(2)–C(3)	1.431(4)
O(3)–N(3)	1.360(4)	N(2)–C(4)	1.364(4)
O(3)–C(6)	1.440(6)	N(3)–C(5)	1.282(4)
N(1)–C(2)	1.466(5)	N(4)–C(7)	1.135(5)
N(3)–O(3)–C(6)	109.6(3)	C(3)–N(2)–C(4)	126.6(3)
C(2)–N(1)–C(3)	121.2(3)	O(3)–N(3)–C(5)	114.2(3)

deposited to the Cambridge crystallographic Data Centre as CIF file (CCDC-207046). The molecule has a nearly planar conformation in agreement with the presence of *sp*^{2} hybridisation of C(3), C(4), C(5) and N(3). The bond distances for C(3)–O(1) and C(4)–O(2) are in agreement with those observed for typical carbonyl groups.

The geometry of the oxime group shows a clear *E*-configuration being the methoxy group and oxyl-ureic moiety in *trans* position. Packing is mainly determined by two mutual intermolecular hydrogen bonds occurring between the N(2)–H and O(4) atoms of centrosymmetric molecules (N(2)–H(2), 1.07 Å; N(2)…O(1)', 2.963(4) Å; N(2)–H(2)…O(1)', 168.8°; ' = –x, –y, 1–z).

Experimental

Melting points are uncorrected and were determined by an electrochemical apparatus. IR spectra were recorded in nujol on a Perkin-Elmer 298 spectrophotometer. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ on a Varian Gemini 200 spectrometer (δ in ppm are relative to $(CH_3)_4Si$). Mass spectra were recorded on a Carlo Erba QMD 1000 spectrometer in EI$^+$ mode. Elemental analyses were performed with a Carlo Erba CHNSO E.A. 1108 elemental analyser. Ethylurea and cyanoacetic acid were purchased from Aldrich and used without further purification.

Synthesis of N-ethyl-N′-cyanoacetylurea **1**: Ethylurea (10 g), cyanoacetic acid (10 g) and acetic anhydride (12 ml) were put in a round flask and heated at 70°C. At the beginning the mixture gave rise to an homogeneous solution, in which a white precipitate, that increased with time, separated out. After 1 h at 70°C, the reaction was cooled to room temperature and the precipitate was separated by filtration under vacuum, washed with water and dried in air; 16 g were obtained (yield 80%), m.p. 165–166°C; 167°C after crystallisation from water (lit. 172–173°C)^3; IR, ν, cm^{-1}: 1560, 1650–1700 (broad), 3120, 3250, 3340, 3375; ^{1}H NMR, δ: 1.20 (3H, t, CH_2–$C\underline{H}_3$, J = 7.3 Hz); 3.35 (2H, qq, $C\underline{H}_2$–CH_3, J = 7.3 and J = 5.7 Hz); 3.54 (2H, s, –CH_2-); 7.98 (1H, bt, CH_3CH_2–N$\underline{H}$); 10.82 (1H, bs, NH). MS: *m/z* 155 (M$^+$, 66.6%), 140 (38.2), 115 (15.1), 85 (81.8). Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.54; H, 5.75; N, 27.14.

Synthesis of 1-(2-cyano-2-hydroxyiminoacetyl)-3-ethylurea **2:** *N*-ethyl-*N′*-cyanoacetylurea **1** (33 g), $NaNO_2$ (16.2 g) and CH_3CN (200 ml) were heated in a conical flask at 45°C. At this temperature and under magnetic stirring, 5N HCl (60 ml) was added over 25 min. In time a white precipitate was obtained. After addition of hydrochloric acid, the reaction mixture was cooled to room temperature. The precipitate was filtered off under vacuum, washed with water and dried in air: 32.5 g was obtained (yield 85%); m.p. 195–196°C; 200–201 °C after crystallisation from ethanol (lit. 202-203°C)^3. IR, ν, cm^{-1}: 1500, 1650–1700 broad, 3420, 3450, 3500–2500 broad; ^{1}H NMR, δ: 1.25 (3H, t, $CH_2C\underline{H}_3$, J = 7.3 Hz); 3,45 (2H, qq, $C\underline{H}_2$–CH_3, J = 7.3 and J = 5.7 Hz); 7.92 (1H, bt, CH_3CH_2–N$\underline{H}$); 8.63 (1H, broad, NH). MS: *m/z* 184 (M$^+$, 1.2%), 169 (5.4), 167 (8.5), 97 (7.2), 70 (16.3). Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.42. Found: C, 39.17; H, 4.42; N, 30.25.

Synthesis of 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea **3**: 1-(2-cyano-2-hydroxyiminoacetyl)-3-ethylurea **2** (3.68 g), $NaHCO_3$ (5.24 in 30 ml of H_2O) and $(CH_3)_2SO_4$ (3 g) were put into a three-necked round flask equipped with a thermometer, condenser and dropping funnel. The mixture was then heated at 50-60 °C under magnetic stirring. At this temperature all compounds were in solution; the reaction started and the temperature rose to 60–65°C. At this stage, when the precipitation of a white product was observed, a further amount of dimethylsulphate (4.56 g) was added dropwise at a rate to keep the temperature below 70°C: during this step the amount of the precipitate increased. After the addition was finished, the reaction was kept at 60-65°C for a further 15 min. and then cooled at room temperature. The precipitate was filtered off under vacuum, washed with water and dried in air: 3.53 g was obtained (yield 89%) m.p. 158–160°C; 160–161°C after crystallisation from acetone (lit. 163–165°C)^1. IR, ν, cm^{-1}: 1550, 1700, 3150, 3220, 3340; ^{1}H NMR, δ: 1.22 (3H, t, $CH_2C\underline{H}_3$, J = 7.3 Hz); 3,38 (2H, qq, $C\underline{H}_2$–CH_3, J = 7.3 and J = 5.7 Hz); 4.32 (3H, s, OCH_3); 7.88 (1H, bt, CH_3CH_2–N$\underline{H}$); 8.4 (1H, broad, NH). MS: *m/z* 198 (M$^+$, 1%), 183 (9.0), 167 (26.0), 128 (18.2), 111 (31.0). Anal. Calcd. for $C_7H_{10}N_4O_3$: C, 42.42 H, 5.09; N, 28.27. Found: C, 42.51; H, 5.15; N, 28.38.

Crystal data for 1-(2-cyano-2-methoxyiminoacetyl)-3-ethylurea **(3)** *(CCDC-207046):* $C_7O_3N_4H_{10}$, M_r = 198.2, monoclinic, space group $P2_1/n$, a = 14.587(2), b = 15.100(2), c = 4.544(1) Å, β = 95.60(10)°, V = 995.1(3) Å^3, Z = 4, ρ = 1.322 g cm^{-3}; λ(Cu–Kα) = 1.54178 Å, μ(Cu–Kα) = 8.994 cm^{-1}: colourless prism, crystal dimensions 0.14 x 0.21 x 0.28 mm. The structure was solved by direct methods (SIR97^4) and anisotropically refined for all the non-H atoms, except for the C(1) carbon atom, which was found to be disordered over two positions (called A and B) isotropically refined with site occupation factors of 0.66(2) and 0.34(2), respectively. During the refinement the C-C bond distances involving C(1) were constrained to 1.54(1) Å. The hydrogen atoms were put in geometrically calculated positions and introduced as fixed contributors in the last stage of refinement with U_{iso} assigned to be 1.2 times those of the attached C and N atoms. The structure was refined on F^2 values (SHELX93^5) by using the weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0860P)^2]$ (with $P = (F_o^2 + 2F_c^2)/3$). For 1660 unique reflections having $I > 0$ collected at T = 296(2) K on a Enraf-Nonius CAD4 diffractometer ($3 < 2\theta < 140°$) the final R is 0.070 ($wR2$ = 0.182; S = 1.147).

CCDC-207046 contain the supplementary crystallographic data for compound **3**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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