

The Structure of β -Heteroaryl- α,β -dehydro- α -amino Acid Derivatives, Intermediates in the Synthesis of Fused Pyran-2-ones. Substituted Methyl (*Z*)-2-Benzoylamino-3-(5-oxopyrazolinyl-4)propenoates

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Dedicated to Professor Erich Ziegler, Karl-Franzens
Universität, Graz, Austria, on the occasion of his 80th birthday.

It was shown by some chemical transformations that β -heteroaryl- α,β -dehydro- α -amino acid derivatives **3** and **7**, obtained from pyrazolone derivatives **1** or **6** and **2**, exist in *Z*-forms. The structure of **7** was confirmed by X-ray analysis.

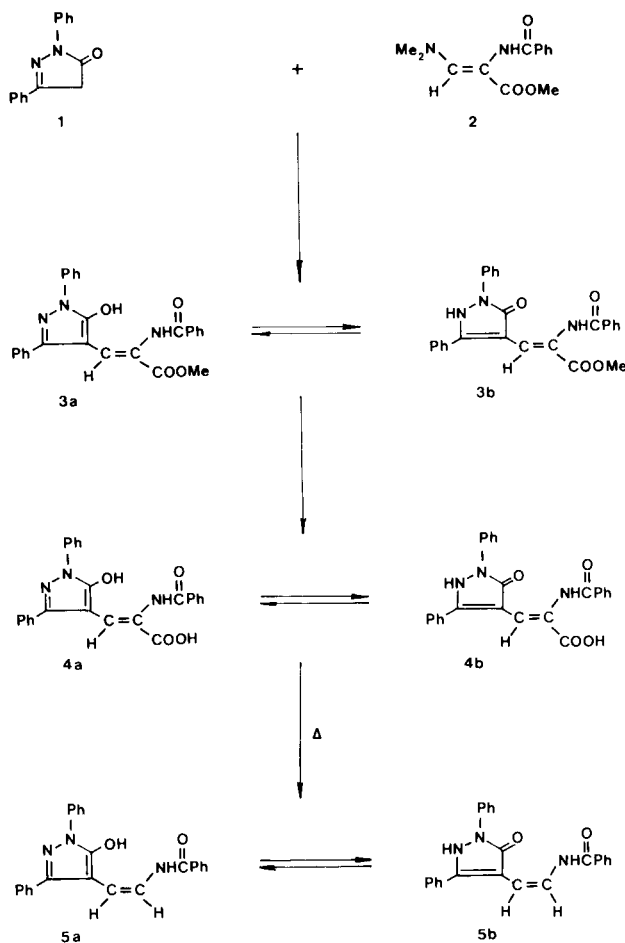
J. Heterocyclic Chem., **28**, 1961 (1991).

Recently, methyl (*Z*)-2-benzoylamino-3-dimethylamino-propenoate [1,2] has been introduced as a reagent for the preparation of methyl 2-benzoylamino-3-(3-indolyl)propenoate [1], methyl 2-benzoylamino-3-heteroarylaminopropenoates [2-4], which cyclize under more drastic conditions into benzoylamino substituted azolo- and azinopyrimidines with a bridgehead nitrogen atom [4], and methyl 3-aryl-amino-2-benzoylamino-propenoates as intermediates in the synthesis of arylaminoalanines [5]. It has been also shown that the compound **2** reacts with aliphatic compounds containing an active methylene group, such as 1,3-diketones and β -keto esters, to afford substituted 3-benzoylamino-2*H*-pyran-2-ones [6], while with cyclic aromatic or heteroaromatic compounds with an active or potentially active methylene group, such as resorcinol, barbiturates and pyrazolones, the corresponding 2*H*-1-benzopyranones, pyranopyrazoles and pyranopyrimidines [7], and with cyclic 1,3-diketones, α - and β -naphthol, and 4,7-dihydroxy-2*H*-1-benzopyran-2-one, the corresponding tetrahydro-2*H*-1-benzopyran-2-one, isomeric naphthopyran-2-ones and pyranobenzopyran-2,5-dione derivatives are formed [8]. In some instances, the corresponding methyl α -heteroaryl- α,β -dehydro- α -amino esters (methyl 2-benzoylamino-3-heteroarylpropenoates) have been isolated as intermediates in the formation of fused pyranones. One such example is methyl 2-benzoylamino-3-(5-hydroxy-1,3-diphenylpyrazolyl-4)propenoate [7] or its tautomeric form found in the pyrazolone series, and another one is methyl 2-benzoylamino-3-(4,6-dihydroxy-2-methylpyrimidinyl-5)propenoate or its tautomeric form found in the pyrimidine series [8]. Since these intermediates represent a new class of α,β -dehydro- α -amino acid derivatives, it seems worthwhile to determine their structures.

The structure determination of methyl 2-benzoylamino-3-heteroarylpropenoates (β -heteroaryl- α,β -dehydro- α -ami-

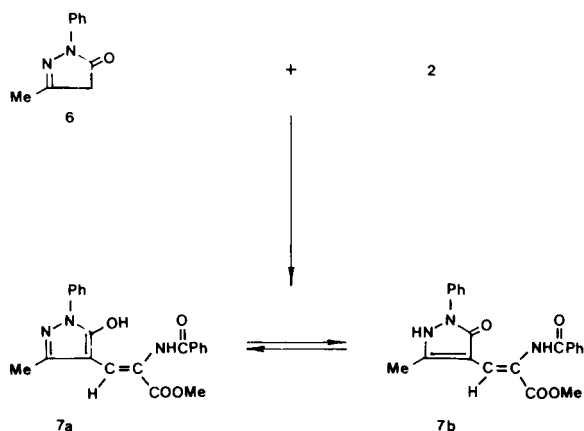
no acid derivatives) is based on the following transformations. The compound **3**, prepared from **1** and **2**, was hydrolysed with sodium hydroxide in aqueous methanol solu-

Scheme 1



tion to afford, after acidification with aqueous hydrochloric acid, the corresponding acids **4a** or its tautomeric form **4b**. When a solid sample of **4** was heated for one week at 50°, the decarboxylation took place to give the compound **5**, which could exist in tautomeric forms **5a** or **5b**. The ¹H nmr spectrum of **5** shows two olefinic protons at $\delta = 5.50$ ppm and $\delta = 6.97$ ppm with a coupling constant $J_{\text{CH}=\text{CH}} = 9.8$ Hz. The magnitude of this coupling constant is characteristic for the *Z*-orientation around the double bond. This also suggests that the orientation of groups in the ester **4** and in the acid **5** is *Z* (Scheme 1).

Scheme 2



Further support was obtained from X-ray analysis of another pyrazole derivative. The compound **7** was prepared from **6** and **2** in ethanol in the presence of catalytic

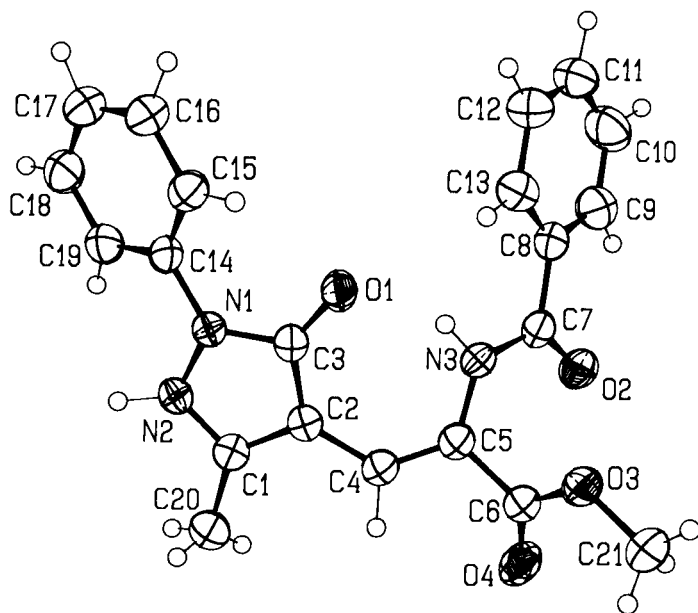


Figure 1. Minimum overlap view of the asymmetric unit (without methanol molecule) of **7b**.

amounts of hydrochloric acid by heating under reflux for two hours (Scheme 2). The X-ray analysis of this ester shows that orientation around the double bond is *Z*- and that the pyrazole part of the molecule exists in "NH" form **7b**, and not in the tautomeric "hydroxy" form **7a** (Figures 1 and 2, Tables 1 and 2).

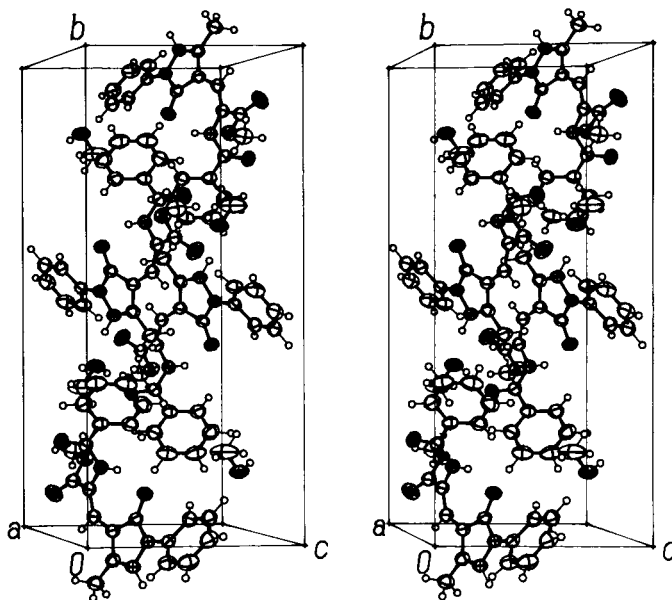


Figure 2. Stereoview of the unit cell of **7b**.

Table 1
Final Fractional Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors, U_{eq} ($\text{\AA}^2 \times 10^4$)

	x	y	z	U_{eq}
O(1)	4127(2)	6034.0(5)	2057(1)	664(7)
O(2)	2491(1)	7061.0(5)	5420(1)	580(7)
O(3)	-398(1)	6605.5(5)	3398(1)	555(7)
O(4)	-78(2)	5901.8(6)	4983(2)	768(9)
N(1)	5096(1)	5114.8(5)	2264(1)	461(7)
N(2)	4876(2)	4610.8(5)	2885(1)	469(7)
N(3)	2625(2)	6518.7(6)	3604(1)	485(7)
C(1)	3761(2)	4687.3(7)	3425(2)	447(8)
C(2)	3312(2)	5255.6(6)	3281(2)	432(8)
C(3)	4152(2)	5531.3(6)	2493(2)	455(8)
C(4)	2155(2)	5503.0(7)	3783(2)	466(8)
C(5)	1814(2)	6054.9(7)	3900(2)	457(8)
C(6)	375(2)	6177.5(7)	4199(2)	493(8)
C(7)	2940(2)	6993.9(7)	4403(2)	450(8)
C(8)	3898(2)	7438.1(7)	4022(2)	474(8)
C(9)	4559(2)	7862.8(8)	5012(2)	628(11)
C(10)	5494(3)	8272.1(9)	4729(3)	745(13)
C(11)	5773(2)	8264.0(9)	3473(3)	753(13)
C(12)	5115(3)	7848.9(9)	2479(3)	743(12)
C(13)	4176(2)	7437.7(8)	2743(2)	599(10)
C(14)	6349(2)	5179.4(6)	1767(2)	425(7)
C(15)	6308(2)	5607.0(7)	797(2)	514(9)

C(16)	7554(2)	5681.7(8)	368(2)	612(10)
C(17)	8803(2)	5326.7(9)	849(2)	685(11)
C(18)	8808(2)	4890.6(8)	1772(3)	680(12)
C(19)	7599(2)	4818.2(7)	2263(2)	546(9)
C(20)	3205(3)	4193.4(8)	4048(3)	619(11)
C(21)	-1895(2)	6717(1)	3467(3)	657(12)
O(5)	4270(2)	6462.1(6)	7735(2)	715(8)
C(22)	5020(4)	6889(1)	8690(5)	1073(21)

Table 2

Bond Distances (Å) and Angles (°) for Nonhydrogen Atoms with e.s.d. s in Parentheses

C(1)-C(2)	1.384(2)	C(7)-O(2)	1.236(2)
C(1)-N(2)	1.334(3)	C(7)-C(8)	1.499(2)
C(1)-C(20)	1.486(3)	C(8)-C(9)	1.393(3)
C(2)-C(3)	1.437(3)	C(8)-C(13)	1.392(3)
C(2)-C(4)	1.453(3)	C(9)-C(10)	1.385(3)
C(3)-N(1)	1.381(2)	C(10)-C(11)	1.371(4)
C(3)-O(1)	1.250(2)	C(11)-C(12)	1.379(3)
N(1)-N(2)	1.379(2)	C(12)-C(13)	1.382(3)
N(1)-C(14)	1.421(2)	C(14)-C(15)	1.387(2)
C(4)-C(5)	1.342(2)	C(14)-C(19)	1.387(2)
C(5)-N(3)	1.407(2)	C(15)-C(16)	1.377(3)
C(5)-C(6)	1.494(3)	C(16)-C(17)	1.377(3)
C(6)-O(3)	1.333(2)	C(17)-C(18)	1.376(3)
C(6)-O(4)	1.198(3)	C(18)-C(19)	1.382(3)
O(3)-C(21)	1.442(3)		
N(3)-C(7)	1.343(2)	C(22)-O(5)	1.398(8)
C(2)-C(1)-C(20)	130.8(2)	C(5)-N(3)-C(7)	122.3(2)
N(2)-C(1)-C(2)	109.5(1)	O(2)-C(7)-N(3)	122.1(2)
N(2)-C(1)-C(20)	119.7(2)	O(2)-C(7)-C(8)	121.2(1)
C(1)-C(2)-C(3)	106.6(2)	N(3)-C(7)-C(8)	116.6(2)
C(1)-C(2)-C(4)	125.3(2)	C(7)-C(8)-C(9)	117.9(2)
C(3)-C(2)-C(4)	128.0(1)	C(7)-C(8)-C(13)	123.0(1)
O(1)-C(3)-N(1)	122.8(2)	C(9)-C(8)-C(13)	119.1(2)
N(1)-C(3)-C(2)	105.7(1)	C(8)-C(9)-C(10)	120.1(2)
O(1)-C(3)-C(2)	131.6(2)	C(9)-C(10)-C(11)	120.4(2)
N(2)-N(1)-C(3)	109.1(1)	C(10)-C(11)-C(12)	120.1(2)
C(3)-N(1)-C(14)	128.8(1)	C(11)-C(12)-C(13)	120.4(2)
N(2)-N(1)-C(14)	120.9(1)	C(8)-C(13)-C(12)	120.1(2)
N(1)-N(2)-C(1)	108.9(1)	N(1)-C(14)-C(15)	119.4(1)
C(2)-C(4)-C(5)	129.6(2)	N(1)-C(14)-C(19)	119.8(2)
N(3)-C(5)-C(4)	124.2(2)	C(15)-C(14)-C(19)	120.9(2)
N(3)-C(5)-C(6)	118.3(1)	C(14)-C(15)-C(16)	118.9(2)
C(4)-C(5)-C(6)	117.1(2)	C(15)-C(16)-C(17)	121.0(2)
O(3)-C(6)-C(5)	111.2(2)	C(16)-C(17)-C(18)	119.6(2)
O(4)-C(6)-C(5)	124.4(1)	C(17)-C(18)-C(19)	120.8(2)
O(3)-C(6)-O(4)	124.2(2)	C(14)-C(19)-C(18)	118.8(2)
C(6)-O(3)-C(21)	116.2(2)		
Hydrogen bonds			
O(5)-H(5)	0.88(3)	O(2) ••• H(5)	1.87(3)
N(2)-H(2)	0.84(2)	O(5) ••• H(2) ^I	1.93(2)
O(5) ••• O(2)	2.744(2)	O(5) - H(5) ••• O(2)	169(3)
N(2) ••• O(5) ^I	2.762(2)	N(2) - H(2) ••• O(5) ^I	171(2)

Symmetry code: I 1-x, 1-y, 1-z

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, ¹H nmr

spectra were obtained on a JEOL JNM 90 Q FT spectrometers, ir spectra on a Perkin-Elmer 1310 instrument and elemental analyses for C, H, and N on a Perkin-Elmer Analyser 240 C.

The following compounds were prepared according to the procedures described in literature: 3-methyl-1-phenylpyrazol-5-one (**6**) [9], methyl 2-benzoylamino-3-(5-hydroxy-1,3-diphenylpyrazolyl-4)propenoate (**3**) [7], and methyl 2-benzoylamino-3-dimethylaminopropenoate (**2**) [2].

2-Benzoylamino-3-(1,3-diphenyl-5-oxopyrazolinyl-4)propenoic Acid (**4**).

The compound **3** (439 mg, 0.001 mole) was dissolved in a solution of sodium methoxide, prepared from sodium (1 g) and methanol (10 ml). To the clear solution water (1 ml) was added and the mixture was heated under reflux for 20 minutes. The volatile components were evaporated *in vacuo*. Water (5 ml) was added to the solid residue and the resulting solution was acidified with hydrochloric acid (10%) to pH 2. The mixture was left in the refrigerator overnight, the precipitate was collected by filtration and washed with ice cold water to give **4** (371 mg, 87%), mp 149-154° (from a mixture of ethanol and water); ¹H nmr (DMSO-d₆): δ 6.70 (s, CH=C), 7.13-8.30 (m, 1-Ph, 3-Ph, PhCO), (NH, exchanged).

Anal. Calcd. for C₂₅H₁₉N₃O₄: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.77; H, 4.61; N, 10.05.

(Z)-1-Benzoylamino-2-(1,3-diphenyl-5-oxopyrazolinyl-4)ethene (**5**).

A solid sample of **4** (409 mg, 0.001 mole) was left *in vacuo* for one week at 50° to give **5** (328 mg, 90%), mp 176-179° (from ethanol); ¹H nmr (DMSO-d₆): δ 5.50 (d, CH=CH-NH), 6.97 (dd, CH=CH-NH), J_{CH=CH} = 9.8 Hz, J_{CHNH} = 10.0 Hz.

Anal. Calcd. for C₂₄H₁₉N₃O₂: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.69; H, 5.13; N, 10.79.

Methyl (Z)-2-Benzoylamino-3-(3-methyl-1-phenyl-5-oxopyrazolinyl-4)propenoate (**7**).

A mixture of **6** (348 mg, 0.002 mole) and **2** (496 mg, 0.002 mole) in ethanol (10 ml) and hydrochloric acid (37%, 0.1 ml) was heated under reflux for 2 hours. The volatile components were evaporated *in vacuo* and the solid residue was purified by column chromatography (silicagel and chloroform/methanol, 1:1, as solvent) to give, after evaporation of the solvent, the compound **7b** (405 mg, 51%), mp 126-127° (from ethyl acetate); ¹H nmr (deuteriochloroform): δ 2.11 (s, 3-Me), 3.71 (s, MeO), 6.52 (s, CH=C), 6.94-8.16 (m, 1-Ph, PhCO), (NH exchanged).

Anal. Calcd. for C₂₁H₁₉N₃O₄: C, 66.83; H, 5.07; N, 11.14. Found: C, 67.03; H, 5.27; N, 11.08.

The crystals for X-ray analysis were obtained by recrystallization of **7** from methanol. In this case the compound forms a solvate with methanol.

X-ray Structure Determination.

C₂₁H₁₉N₃O₄·CH₃OH, M = 409.44, monoclinic, P2₁/n, a = 9.304(1), b = 23.352(1), c = 10.045(1) Å, β = 109.56(1), V = 2056.5(4) Å³, Z = 4, D_x = 1.322, D_m = 1.31(1) Mg m⁻³, MoKα radiation λ = 0.71069 Å, μ = 0.081 mm⁻¹, F(000) = 864, T = 294(1) K.

A prismatic crystal with the approximate dimensions 0.44 x 0.46 x 0.65 mm was used for data collection on an ENRAF-

NONIUS CAD-4 diffractometer with graphite monochromatized MoK α radiation. Lattice parameters were determined by a least-squares treatment of 125 carefully centered θ values in the range $10 < \theta < 16^\circ$. A hemisphere of data with an index range $0 \leq h \leq 11$, $-27 \leq k \leq 27$ and $-11 \leq l \leq 11$ was measured at room temperature (294(1) K) to θ max 25° by the $\omega - 2\theta$ scan technique with a minimum and maximum scan rate of 1.04 and 5.55 $^\circ$ /min and a scan width $(0.7 + 0.3 \times \text{tg}\theta)^\circ$ with aperture $(2.4 + 0.9 \times \text{tg}\theta)$ mm, maximum scan time 60 seconds. Background intensities were measured at 1/4 of the scan at each limit. Crystal stability was monitored by periodic measuring of three standard reflections (1,0,-5; 4,7,0; 5,1-1) every 10000 seconds of scanning time; there was no evidence of crystal deterioration. A change of -1.95% intensities of standard reflections was observed and a correction applied. Owing to the low value of the linear absorption coefficient (0.080 mm $^{-1}$) no absorption correction was applied. 7810 reflections were collected, averaging gave 3603 unique reflections with R_{int} 0.024, 2439 of them were observed ($I > 2.5\sigma(I)$).

Structure determined by direct methods using the program MULTAN. The hydrogen atom positions were partially located in an intermediate difference map and partially calculated on the basis of standard geometry and were included in the refinement with isotropic thermal factors. Their positions do not differ significantly from idealised positions. Three blocks matrix least-squares refinement on F magnitudes with anisotropic temperature factors for all nonhydrogen atoms, using the empirical weighting function $w = 8.0 \times W_f \times W_s$ where $W_f (|F_o| < 6.0) = (|F_o|/6.0)^{1.5}$, $W_f (|F_o| > 12.0) = 12.0/|F_o|$, $W_f (6.0 < |F_o| < 12.0) = 1.0$ and $W_s(\sin\theta < 0.42) = (\sin\theta/0.42)^2$, $W_s(0.42 < \sin\theta < 0.95) = 1.0$ to keep $\Sigma w(\Delta F)^2$ uniform over the ranges of $\langle \sin\theta/\lambda \rangle$ and $\langle F_o \rangle$. In the final least-squares cycle were 2974 (m) contributing reflections (Included were those unobserved reflections for which F_c was greater than F_o) and 363 (n) refined parameters, data-to-variable ratio (m/n) 8.2, scale factor 0.999, $S(=[\Sigma w(\Delta F)^2/(m-n)]^{1/2})$ 0.82, average and maximum shift/error 0.025 and 0.371, residual density in final difference map was max. 0.18 and min. -0.22 e/ \AA^3 . The final R and R_w are 0.032 and 0.040, respectively.

Atomic scattering factors for hydrogen atoms were taken from

Stewart, Davidson & Simpson [10] and for other neutral atoms from Cromer & Mann [11] and dispersion corrections from Cromer & Liberman [12]. All calculations were performed on the DEC-10 computer at RCU-Ljubljana using XRAY76 system of crystallographic programs [13].

Minimum-overlap view of the asymmetric unit with atom-numbering scheme is shown in Figure 1, the stereoview of the unit cell in Figure 2. Final atomic coordinates and equivalent isotropic thermal parameters along with their e.s.d.'s are listed in Table 1. Interatomic distances and angles are presented in Table 2.

During the early stage of structure determination an additional molecule of methanol denoted in tables with O(5) and C(22) in asymmetric unit was detected indicated also by density measurements. It links molecules with hydrogen bonds O(5) \cdots O(2) and O(5) \cdots N(2) with values 2.744(2) and 2.762(2) \AA .

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