The Synthesis and Transformations of Ethyl (Z)-2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate, a New Reagent in the Synthesis of Heterocyclic Compounds

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Received March 13, 1995

Dedicated to Professor Dr. Richard Neidlein, Ruprecht-Karls-Universität Heidelberg, on the occasion of his 65th birthday

Ethyl (Z)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**5**), a new reagent in the synthesis of heteroaryl substituted β-amino-α,β- -dehydro--amino acid derivatives and some fused heterocyclic systems, was prepared from ethyl *N*-2,2-bis(ethoxycarbonyl)vinylglycinate (**3**) and *N,N*-dimethylformamide dimethyl acetal (**4**). The substitution of the dimethylamino group in the compound **5** with heterocyclic amines produced ethyl 2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-heteroarylaminopropenoates **7a-f** and, in some instances, [2,2-bis-(ethoxycarbonyl)vinyl]aminoazolo- or -azinopyrimidine derivatives **8g-k.**

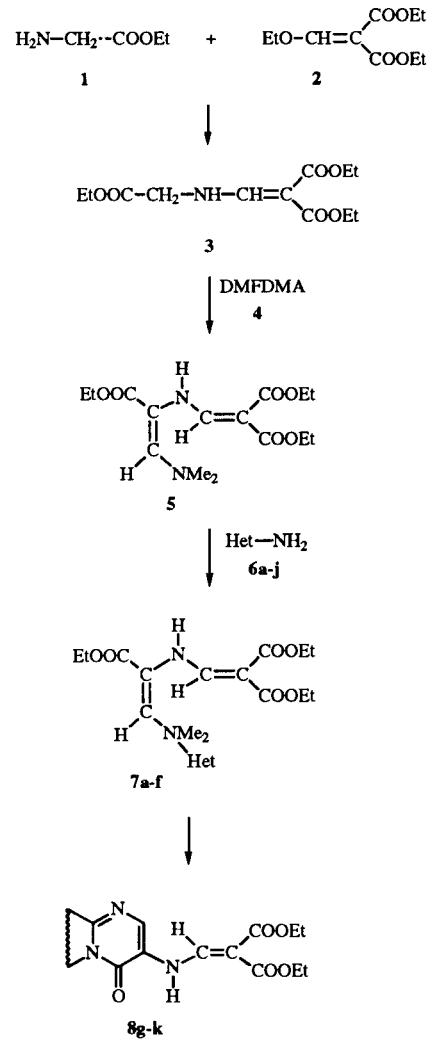
J. Heterocyclic Chem., **32**, 921 (1995).

Recently, a systematic studies of methyl (Z)-2-benzoylamino-3-dimethylaminopropenoate as a versatile reagent in the synthesis of heterocyclic α-amino acids and their derivatives, and heterocyclic systems has been carried out in our laboratory. Many pyranones and fused pyranones, pyridines and pyrimidines have become easily accessible, especially those with the amino function in 3 position in a newly formed heterocyclic system, in which the amino acid structural element is incorporated [1].

In order to extend these studies, we prepared ethyl (Z)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**5**) as a new reagent for the preparation of substitutes β-heteroarylamino-α,β-dehydro-α-amino acid derivatives and some fused pyrimidine derivatives. The starting compound was *N*-2,2-bis(ethoxycarbonyl)vinylglycinate (**3**), prepared from ethyl glycinate (**1**) [2] and diethyl ethoxy-methylenemalonate (**2**) [3] according to the procedure described in the literature [4]. This was then treated with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (**4**) in 50-100% excess in different solvents. The yields are dependent on the solvent and temperature at which the reaction was carried out. In toluene by heating at boiling point for 10 hours, xylene by heating at boiling point for six hours, and DMF by heating at 80-85° for five hours the yields were 54, 28, and 72%, respectively. In this reaction, the active methylene group of the compound **3** was transformed into *N,N*-dimethylaminomethylene group to give the compound **5** (Scheme 1).

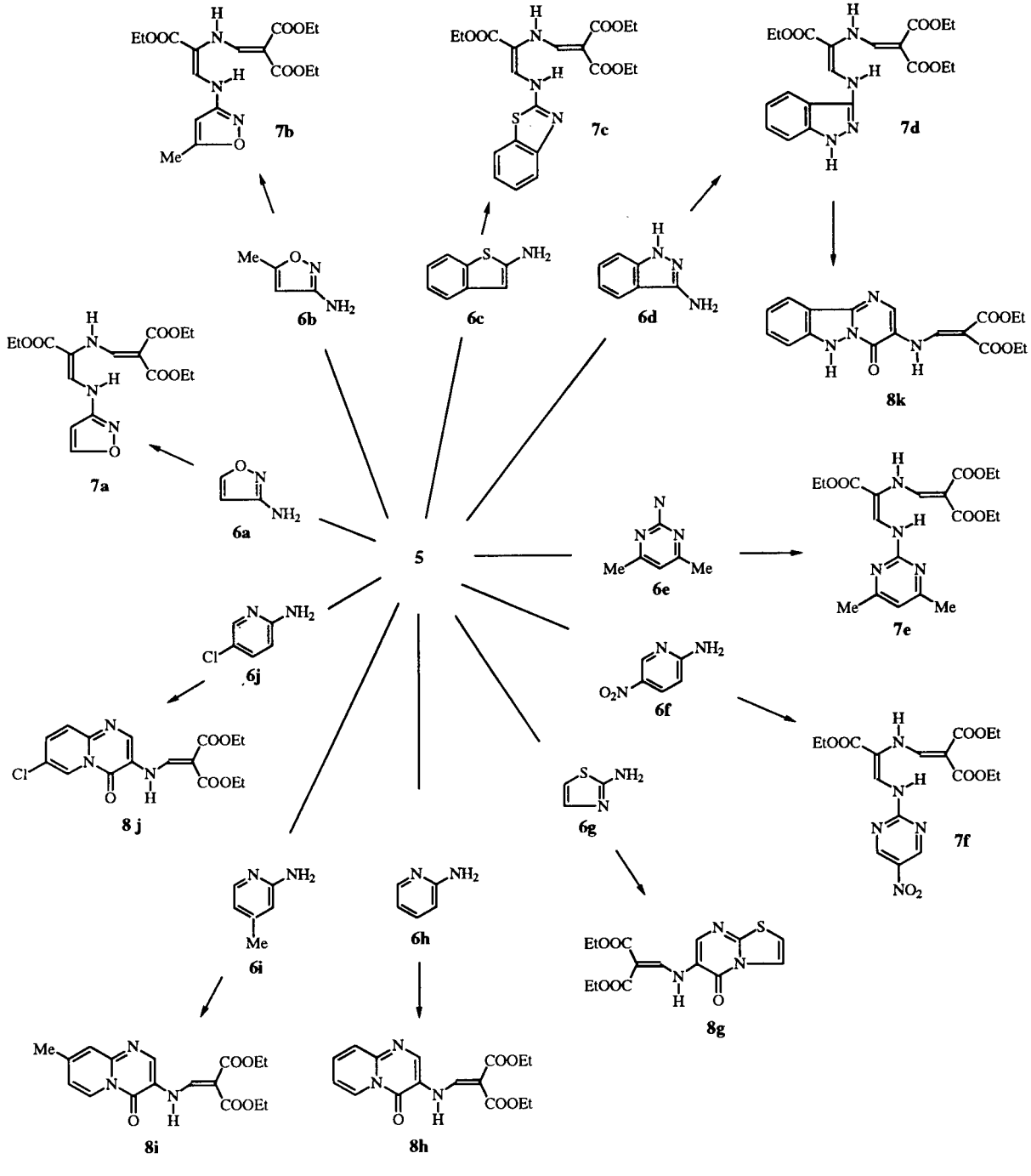
The structure of **5** was supported by elemental analysis, which gives the molecular formula $C_{15}H_{24}N_2O_6 \cdot {}^1/_2H_2O$, mass spectrum, m/z 328 (M+), and ^1H nmr spectrum, which shows two triplets in the ratio 2:1, integrating for nine protons, at δ = 1.20 ppm and 1.26 ppm, two quartets in the ratio 2:1, integrating for six protons, at δ = 4.10

Scheme 1



ppm and 4.18 ppm, corresponding to three ethyl ester groups, a singlet at δ = 3.03 ppm, integrating for six protons, for dimethylamino group, a singlet at δ = 7.33 ppm, integrating for one proton, and two doublets, each integrating for one proton, at δ = 7.37 ppm and 9.55 ppm. The doublet at δ = 9.55 ppm disappears by addition of deuterated water, while the doublet at δ = 7.37 ppm transforms into a singlet. The coupling constant, J_{CHNH} = 14.2 Hz, shows the trans orientation around the single bond. However, on the basis of this information, the decision about the orientation of both substituted amino groups around the double bond can not be reached. In order to solve this problem, an X-ray analysis was carried out, showing that both amino groups are in (Z)-orientation in respect to each other. The details are given in Figures 1 and 2, and Tables 1 and 2. This observation is in agreement with other examples of substituted α-amino-α,β-dehydro-α-amino acid derivatives [5-9].

Scheme 2



In further experiments, the compound **5** was treated with heterocyclic amine in 1:1 molar ratio in boiling acetic acid. A series of 5-membered monocyclic and bicyclic and 6-membered monocyclic heterocyclic amines were selected for this purpose: 3-aminoisoxazole (**6a**), 3-amino-5-methylisoxazole (**6b**), 2-aminobenzothiazole (**6c**), 3-aminoindazole (**6d**), 2-amino-4,6-dimethylpyrimidine (**6e**), 2-amino-5-nitropyridine (**6f**), 2-aminothiazole (**6g**), 2-aminopyridine (**6h**), 2-amino-4-methylpyridine (**6i**), and 2-amino-5-chloropyridine (**6j**). In this reaction, the substitution of the dimethylamino group with heterocyclic amine was taking place to produce ethyl 2-[2,2-bis(ethoxycarbonyl)vinyl]-amino-3-heteroarylaminopropenoates **7a-f**. In some instances, further intramolecular cyclization to the ring nitrogen at α-position was taking place under the reaction conditions to give the corresponding [2,2-bis(ethoxycarbonyl)vinyl]amino azolo- or -azinopyrimidine derivatives **8g-k**. In one example, when the compound **5** reacted with 3-aminoindazole (**6d**) in acetic acid at room temperature, the corresponding propenoate **7d** was isolated as an intermediate, which was cyclized by heating in acetic acid for one hour into fused pyrimidine derivative **8k** (Scheme 2).

Table 1

Fractional Coordinates and Equivalent Temperature Factors (Å^2). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U_{eq}
O(1a)	0.5618(4)	0.1746(3)	-0.1901(2)	0.083(2)
O(2a)	0.4126(3)	0.1404(2)	-0.0421(2)	0.060(1)
O(3a)	0.6638(4)	0.1156(3)	0.2620(2)	0.078(1)
O(4a)	0.4770(3)	0.1742(3)	0.4018(2)	0.069(1)
O(5a)	0.2212(3)	0.3368(3)	0.2335(2)	0.074(1)
O(6a)	0.2374(3)	0.2937(3)	0.3866(2)	0.069(1)
N(1a)	0.4522(3)	0.2666(3)	0.0684(2)	0.051(1)
N(2a)	0.6772(4)	0.3764(3)	-0.0597(3)	0.061(2)
C(1a)	0.5055(5)	0.1894(3)	-0.0981(3)	0.058(2)
C(2a)	0.5319(4)	0.2568(3)	-0.0384(3)	0.050(1)
C(3a)	0.6287(4)	0.3086(3)	-0.0893(3)	0.053(2)
C(4a)	0.6334(5)	0.4128(4)	0.0437(4)	0.068(2)
C(5a)	0.7863(5)	0.4164(4)	-0.1350(4)	0.078(2)
C(6a)	0.3783(5)	0.0719(4)	-0.0971(4)	0.073(2)
C(7a)	0.2879(8)	0.0211(5)	-0.0262(6)	0.103(3)
C(8a)	0.5091(4)	0.2207(3)	0.1391(3)	0.049(1)
C(9a)	0.4428(4)	0.2248(3)	0.2437(3)	0.047(1)
C(10a)	0.5385(5)	0.1664(3)	0.3005(3)	0.056(2)
C(11a)	0.5638(5)	0.1188(4)	0.4638(3)	0.067(2)
C(12a)	0.4782(7)	0.1508(5)	0.5706(4)	0.089(3)
C(13a)	0.2937(5)	0.2886(3)	0.2856(3)	0.052(2)
C(14a)	0.0926(5)	0.3623(4)	0.4291(4)	0.073(2)
C(15a)	0.0459(8)	0.3457(6)	0.5407(5)	0.111(3)
O(1b)	-0.3043(4)	0.3308(3)	0.4697(2)	0.081(2)
O(2b)	-0.3496(3)	0.3640(2)	0.3215(2)	0.060(1)
O(3b)	0.1648(4)	0.3806(3)	0.0230(2)	0.070(1)
O(4b)	0.1330(4)	0.3397(3)	-0.1150(2)	0.084(2)
O(5b)	-0.1181(3)	0.1597(2)	0.0463(2)	0.063(1)
O(6b)	0.0290(3)	0.1882(2)	-0.1054(2)	0.057(1)
N(1b)	-0.1048(3)	0.2319(3)	0.2126(2)	0.050(1)
N(2b)	0.0778(5)	0.1083(3)	0.3444(3)	0.072(2)
C(1b)	-0.2669(5)	0.3134(3)	0.3785(3)	0.057(2)
C(2b)	-0.1338(4)	0.2411(3)	0.3198(3)	0.051(2)
C(3b)	-0.0476(5)	0.1825(3)	0.3728(3)	0.059(2)
C(4b)	0.1604(6)	0.0755(4)	0.2399(4)	0.082(2)
C(5b)	0.1505(7)	0.0629(5)	0.4196(5)	0.096(3)
C(6b)	-0.4877(6)	0.4350(4)	0.3768(4)	0.079(2)
C(7b)	-0.5579(7)	0.4918(5)	0.3054(5)	0.096(3)
C(8b)	-0.0210(4)	0.2788(3)	0.1439(3)	0.047(1)
C(9b)	0.0178(4)	0.2724(3)	0.0391(3)	0.047(1)
C(10b)	0.1124(4)	0.3342(3)	-0.0162(3)	0.053(2)
C(11b)	0.2159(8)	0.4056(6)	-0.1733(4)	0.106(4)
C(12b)	0.177(1)	0.4327(8)	-0.2622(8)	0.154(6)
C(13b)	-0.0311(4)	0.2038(3)	-0.0050(3)	0.048(1)
C(14b)	-0.0076(5)	0.1127(4)	-0.1491(3)	0.063(2)
C(15b)	0.0678(6)	0.1089(5)	-0.2600(3)	0.081(2)
O(7)	0.2273(5)	-0.2206(5)	0.3629(3)	0.121(3)

Table 2

Bond Distances (Å) and Bond Angles (°) with e.s.d.'s in parentheses

O(1a)-C(1a)	1.224(5)	O(1b)-C(1b)	1.222(5)
O(2a)-C(1a)	1.329(6)	O(2b)-C(1b)	1.346(6)
O(2a)-C(6a)	1.459(8)	O(2b)-C(6b)	1.453(5)
O(3a)-C(10a)	1.213(5)	O(3b)-C(10b)	1.209(7)
O(4a)-C(10a)	1.339(5)	O(4b)-C(10b)	1.319(5)
O(4a)-C(11a)	1.443(6)	O(4b)-C(11b)	1.446(9)
O(5a)-C(13a)	1.218(6)	O(5b)-C(13b)	1.225(5)
O(6a)-C(13a)	1.329(5)	O(6b)-C(13b)	1.334(4)
O(6a)-C(14a)	1.446(5)	O(6b)-C(14b)	1.455(7)
N(1a)-C(2a)	1.433(4)	N(1b)-C(2b)	1.432(5)
N(1a)-C(8a)	1.322(5)	N(1b)-C(8b)	1.323(5)
N(2a)-C(3a)	1.337(7)	N(2b)-C(3b)	1.335(5)
N(2a)-C(4a)	1.447(7)	N(2b)-C(4b)	1.450(7)
N(2a)-C(5a)	1.460(7)	N(2b)-C(5b)	1.466(9)
C(1a)-C(2a)	1.443(7)	C(1b)-C(2b)	1.447(5)
C(2a)-C(3a)	1.366(6)	C(2b)-C(3b)	1.364(6)
C(6a)-C(7a)	1.409(9)	C(6b)-C(7b)	1.451(9)
C(8a)-C(9a)	1.384(5)	C(8b)-C(9b)	1.383(5)
C(9a)-C(10a)	1.463(6)	C(9b)-C(10b)	1.466(6)
C(9a)-C(13a)	1.450(5)	C(9b)-C(13b)	1.457(7)
C(11a)-C(12a)	1.479(7)	C(11b)-C(12b)	1.40(1)
C(14a)-C(15a)	1.485(8)	C(14b)-C(15b)	1.475(6)
C(1a)-O(2a)-C(6a)	116.2(3)	C(1b)-O(2b)-C(6b)	115.4(3)
C(10a)-O(4a)-C(11a)	117.9(3)	C(10b)-O(4b)-C(11b)	117.5(5)
C(13a)-O(6a)-C(14a)	116.8(4)	C(13b)-O(6b)-C(14b)	116.8(3)
C(2a)-N(1a)-C(8a)	123.2(3)	C(2b)-N(1b)-C(8b)	122.9(4)
C(3a)-N(2a)-C(4a)	125.2(4)	C(3b)-N(2b)-C(4b)	124.7(4)
C(3a)-N(2a)-C(5a)	119.1(4)	C(3b)-N(2b)-C(5b)	119.7(4)
C(4a)-N(2a)-C(5a)	115.7(5)	C(4b)-N(2b)-C(5b)	115.2(4)
O(1a)-C(1a)-O(2a)	121.2(5)	O(1b)-C(1b)-O(2b)	121.2(3)
O(1a)-C(1a)-C(2a)	125.9(5)	O(1b)-C(1b)-C(2b)	126.0(4)
O(2a)-C(1a)-C(2a)	112.8(3)	O(2b)-C(1b)-C(2b)	112.8(3)
N(1a)-C(2a)-C(1a)	118.0(4)	N(1b)-C(2b)-C(1b)	118.9(4)
N(1a)-C(2a)-C(3a)	125.0(4)	N(1b)-C(2b)-C(3b)	124.5(3)
C(1a)-C(2a)-C(3a)	117.0(3)	C(1b)-C(2b)-C(3b)	116.6(4)
N(2a)-C(3a)-C(2a)	133.1(4)	N(2b)-C(3b)-C(2b)	132.5(4)
O(2a)-C(6a)-C(7a)	108.8(5)	O(2b)-C(6b)-C(7b)	109.6(4)
N(1a)-C(8a)-C(9a)	128.0(3)	N(1b)-C(8b)-C(9b)	127.4(4)
C(8a)-C(9a)-C(10a)	114.0(3)	C(8b)-C(9b)-C(10b)	114.1(4)
C(8a)-C(9a)-C(13a)	118.8(4)	C(8b)-C(9b)-C(13b)	118.9(4)
C(10a)-C(9a)-C(13a)	127.1(3)	C(10b)-C(9b)-C(13b)	126.9(3)
O(3a)-C(10a)-O(4a)	121.0(4)	O(3b)-C(10b)-O(4b)	120.8(4)
O(3a)-C(10a)-C(9a)	124.7(4)	O(3b)-C(10b)-C(9b)	124.7(4)
O(4a)-C(10a)-C(9a)	114.2(3)	O(4b)-C(10b)-C(9b)	114.5(5)
O(4a)-C(11a)-C(12a)	106.7(4)	O(4b)-C(11b)-C(12b)	108.4(8)
O(5a)-C(13a)-O(6a)	120.0(3)	O(5b)-C(13b)-O(6b)	120.9(4)
O(5a)-C(13a)-C(9a)	123.5(3)	O(5b)-C(13b)-C(9b)	122.9(3)
O(6a)-C(13a)-C(9a)	116.5(4)	O(6b)-C(13b)-C(9b)	116.1(3)
O(6a)-C(14a)-C(15a)	107.1(4)	O(6b)-C(14b)-C(15b)	107.8(4)

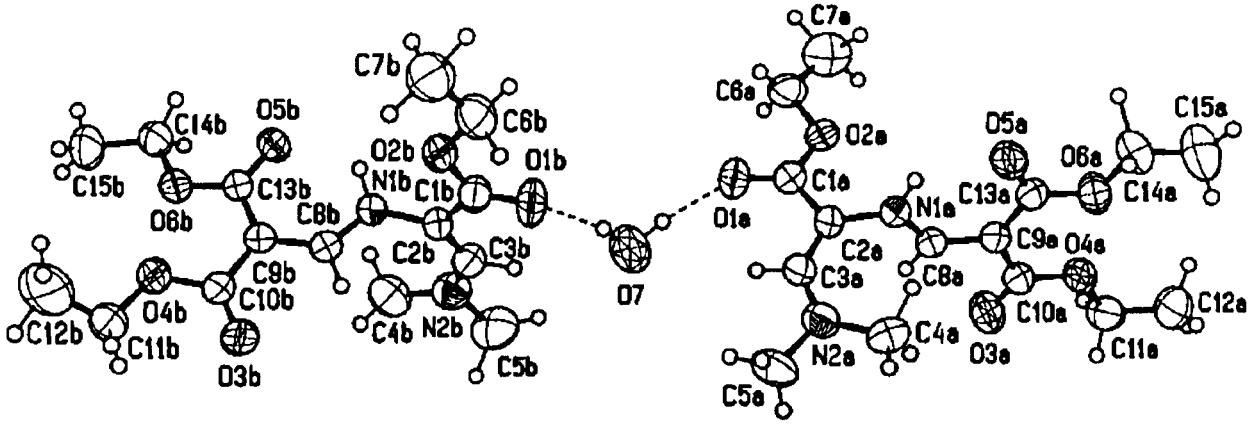


Figure 1. Ortep view of the asymmetric unit of **5**, showing the labeling of the non-hydrogen atoms.

The structure of the compounds **7** was determined by elemental analyses for C, H and N, and by ^{1}H nmr spectra. They exhibit besides the signals for heterocyclic part of the molecule and for three ethyl ester groups, and two pairs of doublets for two CHNH groups. The first pair of doublets appears in the range of δ = 7.81-8.12 ppm (*CH*-NH) and δ = 9.59-9.90 ppm(CH-*NH*) with the coupling constant J_{CHNH} = 13.8-14.4 Hz and corresponds to the CHNH structural element in the vicinity of two ester groups. The other pair of doublets, which appears in the range of δ = 7.81-8.92 ppm (*CH*-NH) and δ = 9.37-11.45 ppm (CH-*NH*) with varying coupling constants, J_{CHNH} = 0-13.8 Hz, corresponds to the CHNH structural element in the vicinity of heterocyclic substituent. On this basis we can conclude, that orientation of both amino substituents around the double bond is (Z), similarly as found in other examples of heteroaryl substituted - β-amino-α,β-dehydro-α-amino acid derivatives [5-9]. The compounds **8** show for the CHNH structural element two doublets at δ = 8.64-8.70 ppm (*CH*NH) and δ = 11.00-11.17 ppm (CH*NH*) with the coupling constant J_{CHNH} = 14.0-14.4 Hz. Both doublets are shifted downfield in respect to the corresponding protons in the compounds **5** and **7** due to the proximity of the heterocyclic ring.

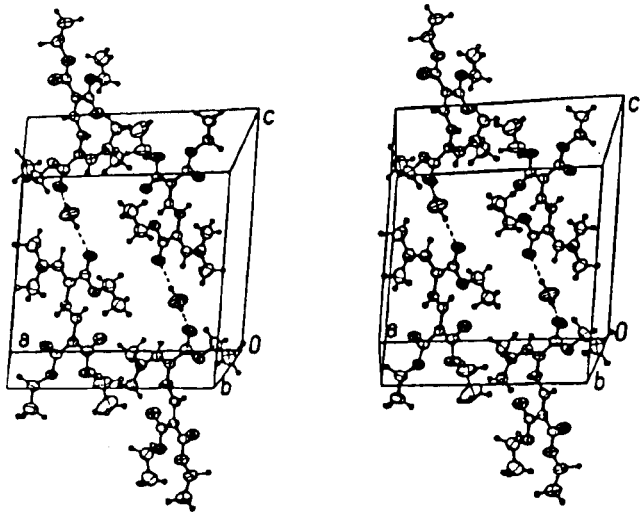


Figure 2. Stereoscopin view of the unit cell of **5**.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian EM 360 L spectrometer, ir spectra on a Perkin-Elmer 1310 instrument, and microanalyses for C, H and N on a Perkin-Elmer Analyser 2400.

The Synthesis of Ethyl (*Z*)-2-[2,2-Bis(ethoxycarbonyl)vinyl]-amino-3-dimethylamino-propenoate (**5**).

The following compounds were prepared according to the procedures described in the literature: ethyl glycinate (**1**) [2], ethyl ethoxymethylenemalonate (**2**) [3], ethyl *N*-[2,2-bis(ethoxycarbonyl)vinyl]glycinate (**3**) [4].

Ethyl (*Z*)-2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**5**).

To a solution of ethyl *N*-[2,2-bis(ethoxycarbonyl)vinyl]glycinate (**3**) (10.93 g, 0.040 mole) in *N,N*-dimethylformamide (DMF) (80 ml) *N,N*-dimethylformamide dimethyl acetal (DMFDMA) (**4**) (9.52 g, 0.080 mole) was added and the mixture was heated for 5 hours at 80°. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and ethyl acetate/cyclohexane, 1:2, as solvent). After the reaction was completed, the volatile components were evaporated *in vacuo*. The oily residue was dissolved in chloroform and the solution was extracted with water (3 times, 10 ml each time) to remove the remaining DMF and DMFDMA. The organic phase was dried over anhydrous sodium sulphate and evaporated *in vacuo*. The oily residue crystallized in 24 hours and it was recrystallized from diisopropyl ether to give **5** in 72% yield, mp 38-41°. When toluene or xylene were used as solvents, the yields are 54% and 28%, respectively; ^{1}H nmr (DMSO-d_6): 1.20, 1.26 (2t, CH_2CH_3 3), 3.03 (s, NMe_2), 4.10, 4.18 (2q, CH_2CH_3 x 3), 7.33 (s, *CH*NMe_2), 7.37 (d, *CH*NH), 9.55 (d, CHN*H*), J_{CH2CH3} = 7.2 Hz, J_{CHNH} = 14.2 Hz.

Anal. Calcd. for $C_{15}H_{24}N_2O_6 \cdot {}^1/_2H_2O$: C, 53.40; H, 7.47; N, 8.30. Found: C, 53.33; H, 7.44; N, 8.35.

The Reaction between Heterocyclic Amines **6a-j** and Ethyl (Z)-2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**5**). The Synthesis of Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-heteroarylaminopropenoates **7** and [2,2-Bis(ethoxycarbonyl)vinyl]aminoazolo- and -azinopyrimidines **8**.

General Procedure.

To a solution of heterocyclic amine **6** (0.0015 mole) in acetic acid (6 ml) the compound **5** (0.0015 mole) was added and the mixture was heated under reflux for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1 and 25:1 as solvent). After the reaction was completed, acetic acid was evaporated *in vacuo* and the solid residue recrystallized from an appropriate solvent to give **7** or **8**.

The following compounds were prepared in this manner:

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(isoxazolyl-3)aminopropenoate (**7a**).

This compound was prepared from **6a**, 2.5 hours of reflux, in 51% yield, mp 152-154 (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.20, 1.30 (2t, CH_2CH_3 x 3), 4.10, 4.23 (2q, CH_2CH_3 x 3), 6.45 (d, H_4), 7.84 (d, C*H*NH), 7.86 (br s, C*H*NHHet), 8.75 (d, H_5), 9.59 (d, CHN*H*), 9.79 (br s, CHN*H*Het), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.2 Hz, $J_{H4,H5}$ = 1,6 Hz.).

Anal. Calcd. for $C_{16}H_{21}N_3O_7$: C, 52.31; H, 5.76; N, 11.44. Found: C, 51.99; H, 5.52; N, 11.59.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(5-methylisoxazolyl-3)amino-propenoate (**7b**).

This compound was prepared from **6b**, 2 hours of reflux, in 52% yield, mp 183-185 (from ethanol); ^{1}H nmr (DMSO-d_6): δ 1.19, 1.28 (2t, CH_2CH_3 x 3), 2.40 (s, 5-Me), 4.07, 4.19 (2q, CH_2CH_3 3), 6.13 (s, H_4), 7.81 (br s, C*H*NHHet), 7.84 (d, C*H*NH), 9.56 (d, CHN*H*), 9.58 (br s, CHN*H*Het), J_{CHCH} = 7.0 Hz, J_{CHNH} = 14.4 Hz.

Anal. Calcd. for $C_{17}H_{23}N_3O_7$: C, 53.54; H, 6.08; N, 11.02. Found: C, 53.11; H, 6.04; N, 11.13.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(4,6-dimethylpyrimidinyl-2)aminopropenoate (**7e**).

This compound was prepared from **6e**, 4 hours of reflux, in 43% yield, mp 132-134 (from a mixture of methanol and water); ^{1}H nmr (deuteriochloroform): δ 1.26-1.38 (m, CH_2CH_3 x 3), 2.40 (s, Het-CH_3 x 2), 4.20, 4.33 (2q, CH_2CH_3 x 3), 6.70 (s, H_5), 7.75 (d, CHN*H*Het), 8.12 (d, C*H*NH), 8.67 (d, C*H*NHHet), 9.90 (d, CHN*H*), J_{CHCH} = 7.0 Hz, J_{CHNH} = 13.8 Hz, $J_{CHNHHet}$ = 12,4 Hz.

Anal. Calcd. for $C_{19}H_{26}N_4O_6$: C, 56.15; H, 6.45; N, 13.78. Found: C, 55.78; H, 6.43; N, 13.84.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(5-nitropyridinyl-2)aminopropenoate (**7f**).

This compound was prepared from **6f**, 2 hours of reflux, in 43% yield, mp 203-205 (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.14, 1.26, 1.36 (3t, CH_2CH_3 x 3), 4.13, 4.20, 4.33 (3q, CH_2CH_3 x 3), 7.31 (d, H_3), 8.00 (d, C*H*NH), 8.42 (dd, H_4), 8.82 (d, C*H*NHHet), 9.23 (d, H_6), 9.87 (d, CHN*H*), 10.18 (d, CHN*H*Het), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.0 Hz, $J_{CHNHHet}$ = 12.0 Hz, $J_{H3,H4}$ = 9.0 Hz, $J_{H4,H6}$ = 2.2 Hz.

Anal. Calcd. for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.26. Found: C, 51.50; H, 5.09; N, 13.50.

6-[2,2-Bis(ethoxycarbonyl)vinyl]amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidine (**8g**).

This compound was prepared from **6g**, 3 hours of reflux, in 56% yield, mp 208-210 (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.35, 1.41 (2t, CH_2CH_3 x 2), 6.32, 6.39 (2q, CH_2CH_3 x 2), 7.20 (d, H_3), 8.10 (d, H_2), 8.15 (s, H_7), 8.64 (C*H*NH), 11.00 (d, CHN*H*), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.0 Hz, $J_{H2,H3}$ = 1,6 Hz.

Anal. Calcd. for $C_{14}H_{15}N_3O_5S$: C, 49.85; H, 4.48; N, 12.46. Found: C, 49.49; H, 4.23; N, 12.24.

3-[2,2-Bis(ethoxycarbonyl)vinyl]amino-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**8h**).

This compound was prepared from **6h**, 2 hours of reflux, in 40% yield, mp 165-167 (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.38, 1.45 (2t, CH_2CH_3 x 2), 4.30, 4.39 (2q, CH_2CH_3 x 2), 7.20 (ddd, H_7), 7.73 (dd, H_6, H_9), 8.46 (s, H_2), 8.70 (d, C*H*NH), 9.12 (dd, H_6), 11.17 (d, CHN*H*), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.2 Hz, $J_{H6,H7}$ = 7,0 Hz, $J_{H7,H8}$ = 4,2 Hz, $J_{H6,H8}$ = 1,0 Hz.

Anal. Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.02; H, 5.17; N, 12.75. Found: C, 57.96; H, 5.11; N, 12.69.

3-[2,2-Bis(ethoxycarbonyl)vinyl]amino-8-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**8i**).

This compound was prepared from **6i**, 2 hours of reflux, in 29% yield, mp 186-188 (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.36, 1.41 (2t, CH_2CH_3 x 2), 2.51 (s, 8-Me), 4.31, 4.42 (2q, CH_2CH_3 2), 7.01 (dd, H_7), 7.46 (dd, H_9), 8.39 (s, H_2), 8.67 (d, C*H*NH), 8.95 (d, H_6), 11.10 (d, CHN*H*), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.2 Hz, $J_{H6,H7}$ = 7,2 Hz, $J_{H7,H9}$ = 2,0 Hz.

Anal. Calcd. for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.54; N, 12.17. Found: C, 59.20; H, 5.45; N, 12.56.

3-[2,2-Bis(ethoxycarbonyl)vinyl]amino-7-chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**8j**).

This compound was prepared from **6j**, 2 hours of reflux, in 57% yield, mp 196-198 (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.36, 1.42 (2t, CH_2CH_3 x 2), 4.33, 4.43 (2q, CH_2CH_3 x 2), 7.73 (2d, H_8, H_9), 8.49 (s, H_2), 8.70 (d, C*H*NH), 9.08 (d, H_6), 11.16 (d, CHN*H*), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.2 Hz, $J_{H6,H8}$ = 1,5 Hz.

Anal. Calcd. for $C_{16}H_{16}N_3O_5Cl$: C, 52.54; H, 4.41; N, 11.49. Found: C, 52.51; H, 4.21; N, 11.32.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(benzothiazolyl-2)aminopropenoate (**7c**)

A mixture of **6c** (0.300g, 0.002 mole) and **5** (0.656 g, 0.002 mole) in a mixture of ethanol (5 ml) and concentrated hydrochloric acid (0.2 ml) was heated under reflux for 1 hour. The solvent was evaporated *in vacuo* and the solid residue recrystallized from a mixture of ethanol and ethyl acetate to give **7c** in 21% yield, mp 197-200; ^{1}H nmr (DMSO-d_6): δ 1.20, 1.27, (2t, CH_2CH_3 x 3), 4.20, 4.32 (2q, CH_2CH_3 x 3), 7.28-7.95 (m, Ph), 8.17 (d, C*H*NH), 8.17 (s, C*H*NHHet), 9.84 (d, CHN*H*), 11.45 (br s, CHN*H*Het), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.2 Hz.

Anal. Calcd. for $C_{20}H_{23}N_3O_6S$: C, 55.42; H, 5.34; N, 9.69. Found: C, 55.05; H, 5.18; N, 9.34.

Ethyl 2-[2,2-Bis(ethoxycarbonyl)vinyl]amino-3-(indazolyl-3)aminopropenoate (**7d**).

A mixture of **6d** (0.266 g, 0.002 mole) and **5** (0.656 g, 0.002 mole) in acetic acid was mixed at room temperature for 1 hour. The precipitate was collected by filtration to give **7d** in 42% yield, mp 218-220 (from methanol); ^{1}H nmr (DMSO-d_6): δ 1.19, 1.28, (2t, CH_2CH_3 x 3), 4.13, 4.25 (2q, CH_2CH_3 x 3), 6.91-7.53 (m, Ph), 7.97 (d, C*H*NH), 8.32 (s, C*H*NHHet), 9.73 (d, CHN*H*), 10.00 (d, CHN*H*Het), 12.5 (s, H_1), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.4 Hz, $J_{CHNHHet}$ = 12.0 Hz.

Anal. Calcd. for $C_{20}H_{24}N_4O_6$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.40; H, 5.61; N, 13.27.

3-[2,2-Bis(ethoxycarbonyl)vinyl]amino-4-oxo-6*H*-pyrimido[1,2-*b*]indazole (**8k**).

A solution of **7d** (0.300 g, 0.00072 mole) in acetic acid (5 ml) was heated under reflux for 1 hour. The precipitate formed during the heating was collected by filtration to give **8k** in 55% yield, mp 330-336° dec (from DMSO); ^{1}H nmr (DMSO-d_6): δ 1.28, 1.33 (2t, CH_2CH_3 x 2), 4.19, 4.30 (2q, CH_2CH_3 x 2), 7.22-8.35 (m, Ph), 8.68 (s, H_2), 8.74 (d, C*H*NH), 10.95 (d, CHN*H*), (H_2 exchanged), J_{CH2CH3} = 7.0 Hz, J_{CHNH} = 14.0 Hz.

Anal. Calcd. for $C_{18}H_{18}N_4O_5$: C, 58.37; H, 4.90; N, 15.13. Found: C, 58.19; H, 4.67; N, 15.42.

X-ray Structure Determination.

$C_{15}H_{24}N_2O_6 \cdot {}^1/_2H_2O$, M_r = 337.4, triclinic, $P\bar{1}$, No.: 2, a = 10.128(1), b = 13.938(2), c = 13.912(2) Å, α = 84.88(2)°, β = 70.67(1)°, γ = 72.32(1)°, V = 1765.5(4) Å^3, Z = 4, D_x = 1.269 Mg/m^3, D_m = 1.26(2) Mg/m^3, MoKα radiation, λ = 0.71069 Å, μ = 0.093 mm^{-1}, T = 293(2) K.

Colorless crystal with dimensions 0.10 0.44 0.82 mm was used for data collection on an Enraf Nonius CAD-4 diffractometer with graphite monochromatized MoKα radiation. Lattice parameters were determined by a least-square treatment of 99 carefully centered θ values in the range 8.1° < θ < 14.3°. Entire sphere to θ_{max} 28° of data was measured with an index range -13 ≤ h ≤ 13, -18 ≤ k 18 and -18 ≤ l ≤ 18 at room temperature (293(2) K) and ω-2θ scans with a scan width 0.9 + 0.3 tgθ, aperture 2.4 + 0.9 tgθ, and maximum scan time 60 seconds. Background was measured at $^1/_4$ of the scan at each limit. Crystal stability was monitored by periodic measuring of three standard reflections (4,6,-1; 3,5,3; -1,-3,-7) every 20000 seconds of scanning time. Orientation control was every 600 reflections. A change of -12.6% intensities of standard reflections was observed and correction applied. Due to the low value of the linear absorption coefficient (0.093 mm^{-1}) no absorption correction was done. 17228 reflections were collected, averaging gave 8479 unique reflections with R_{int} 0.020; 2740 of them were observed (I > 4.0σ(I)).

Structure was solved by direct methods using MULTAN88 [10] system of computer programs. The positions of hydrogen atoms were partially located in an intermediate difference map and partially calculated on the basis of standard geometry. We employed full-matrix least-squares refinement on F magnitudes with anisotropic temperature factors for all non-hydrogen atoms, using the empirical weighting function: w = 6.0$W_f W_s$ where $W_f(|F_o|<6.14) = (|F_o|/6.14)^2$, $W_f(F_o>23.0) = (23.0/|F_o|)$, $W_f(6.14|F_o|23.0) = 1.0$ and $W_s(\sin\theta<0.38) = (\sin\theta/0.38)^{2.4}$, $W_s(\sin\theta>0.53) = (0.53/\sin\theta)^{3.5}$ and $W_s(0.38\leq\sin\theta\leq0.53) = 1$. The parameters of hydrogen atoms were included in F_c calculations with isotropic temperature factors, they were not refined. In the final least-square cycle were 5632 contributing reflections (included were those unobserved reflections for which F_c was greater than F_o) and 424 parameters. The final R and R_w were 0.060 and 0.065, respectively. Goodness of fit was 0.982. Average and maximum shift/error were 0.0013 and 0.0259. The residual density in final difference map was max. 0.324 and min. -0.353 e/Å^3.

The Xtal3.2 [11] system of crystallographic programs was used for the correlation and reduction of data, structure refinement and interpretation. ORTEPII [12] was used to produce molecular graphics. All calculations were performed on VAX 8550 computers at the University Computer Center, Ljubljana.

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 with their e.s.d.'s are listed in Table 1. Bond lengths and bond angles are presented in Table 2.

The asymmetric unit contains two propenoate molecules (with very similar geometry) and one water molecule. Propenoate molecules are through O(1a) and O(1b) connected with water molecule by weak hydrogen bonds of length 2.813(6) and 2.868(6) Å.

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