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Synthesis and structure of N-(4-bromophenyl)-N-carboxyethyl-β-alanine derivatives

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New N-(4-bromophenyl)-N-carboxyethyl-β-alanine derivatives and products of their cyclization were obtained and characterized by IR, mass, NMR spectra and elemental analysis. Data obtained in the studies are presented in the Experimental section, and the most significant cases are discussed.

Key words: N,N-disubstituted-β-alanine, amides, cyclization, heterocycles, isomerism, NMR spectroscopy

INTRODUCTION

Attention is being focused on β-amino acids as potential substances for organic synthesis, bioorganic chemistry, medicinal chemistry, and chemistry of natural compounds. In nature, β-amino acids are found in a free form. Their fragments are parts of peptides, coenzymes, alkaloids and antibiotics. Synthetic β-alanine derivatives are growth-stimulators of live organizms – plants and isolated animal cells, intermediate products in the production of fungicides, drugs, polymer stabilizers. N-substituted amino acids are excellent synthons for the synthesis of 2-pyrrolidinone, imidazole, pyrrole, pyrazine, thiazole, azetidine, pyrimidine, quinoline, diazepine and other heterocyclic systems exhibiting valuable practical properties [1–12].

The title compounds as uniform disubstituted amines possess a variety of fragments with different structural features predetermining their importance and specific spectroscopic problems. Separate structural fragments of these compounds have been widely investigated [13–21]. Some of the synthesized compounds have in their molecules amide [13–16, 22–29] and azomethine [13–16, 29–31] fragments which cause the formation of isomers, whereas others contain different 5-membered heterocycles [32–42]. In spite of the identical substitution of amine, each of the side chains has a different spatial location. This fact was estimated from the optimized molecular models [43]. It should be noted that the molecules of the study compounds are in a dynamic equilibrium in solutions.

The goal of the present work was synthesis of N-(4-bromophenyl)-N-carboxyethyl-β-alanine derivatives, products of their cyclization, and validation of their structure. The structure elucidation was mainly focused on the analysis of NMR spectra. The assignment of NMR resonances was made on the basis of chemical shift theory, multiplicities, intensity and by comparison with similar spectral characteristics of structurally related compounds.

RESULTS AND DISCUSSION

One of the convenient methods of synthesis of N-aryl-β-alanines is interaction of aromatic amines with acrylic acid.

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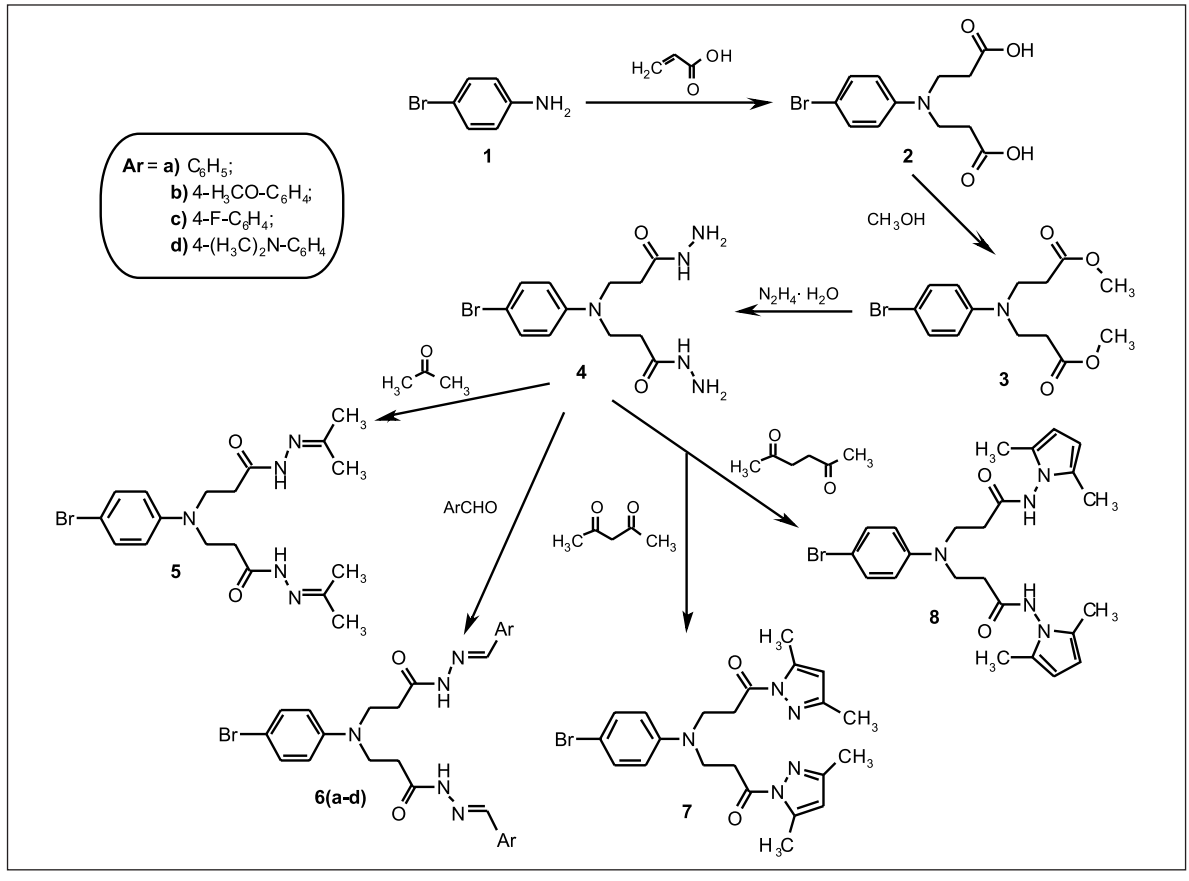
In the presence of excess acrylic acid, such reactions often gave N-aryl-N-carboxyethyl-β-alanines. For the formation of N-aryl-N-carboxyethyl-β-alanine **2**, an excess of acrylic acid was used in the reaction with 4-bromoaniline **1**. The reaction was carried out for 48 hours. Dimethyl ester **3** was synthesized by esterification of acid **2** with an excess of methanol in the presence of a catalytic amount of sulphuric acid. Dihydrazide **4** was synthesized by hydrazinolysis of dimethyl ester **3** in 2-propanol under reflux for 1 hour.

Analysis of ^{1}H NMR spectra of the starting compounds **2–4** shows characteristic triplets of the CH_2CO group in the intervals 2.24–2.54 ppm and 3.47–3.56 ppm for CH_2N. The resonances of *p*-substituted benzene were found at ~6.63 ppm for 2,6-hydrogens and ~7.27 ppm for 3,5-hydrogens. The hydrogen of the COOH group of compound **2** was observed (averaged with H_2O) as a broad singlet at 7.75 ppm, a signal of the CH_3 group of $COOCH_3$ fragment of compound **3** was noted at 3.60 ppm, protons of the NH_2 group – at 4.20 ppm, and a proton of the CONH group of compound **4** – at 9.05 ppm, confirming the structure of primary compounds. Data of ^{13}C NMR studies also certified their structure: the CO group carbons were found to be resonated at 173.89 ppm (**2**), 171.88 ppm. (**3**), 170.52 ppm (**4**).

Condensation of dihydrazyde **4** with acetone gave hydrazone **5** in good yield (75%). The NMR spectra of compound **5** were complicated due to the presence of an amide fragment in both side chains and the magnetic non-equivalence of each of the methyl groups in the azomethine fragment. The amide fragment in compound **5** and in compounds **6**(**a–d**), **8** (Scheme 1), **12**, **13** (Scheme 2) caused formation of rotamers because of the restricted rotation around the CO-NH bond and was able to take part in the intermolecular and intramolecular interactions. Consequently, formation of some stable structures was observed in NMR spectra. For this reason, a double set of resonances was observed in ^{13}C NMR spectra of all carbon atoms. ^{1}H NMR spectra of compound **5** showed the presence of three states of molecules. Due to the presence of a lone pair of a nitrogen atom in the azomethine fragment, CH_3-*cis* was observed at ~17.0 ppm and CH_3-*trans* at ~25.0 ppm in ^{13}C NMR spectra. The notation *cis* was used for the CH_3 group of the azomethine fragment when it was located "*trans*" with respect to the lone pair of a nitrogen atom, and on the contrary – "*trans*".

Condensation of compound **4** with aromatic aldehydes gave the corresponding hydrazones **6**(**a–d**). The difference between compounds **6**(**a–d**) and **5** is due to the mode of substitution in the azomethine fragment. The presence of particular substitution patterns in the benzene ring as a mono substituent of azomethine fragment caused formation of geometrical isomers. Taking into account the two isomerism centers existing in each side chain, 10 isomers of compounds **6**(**a–d**) can be formed. NMR did not provide conclusive infor-



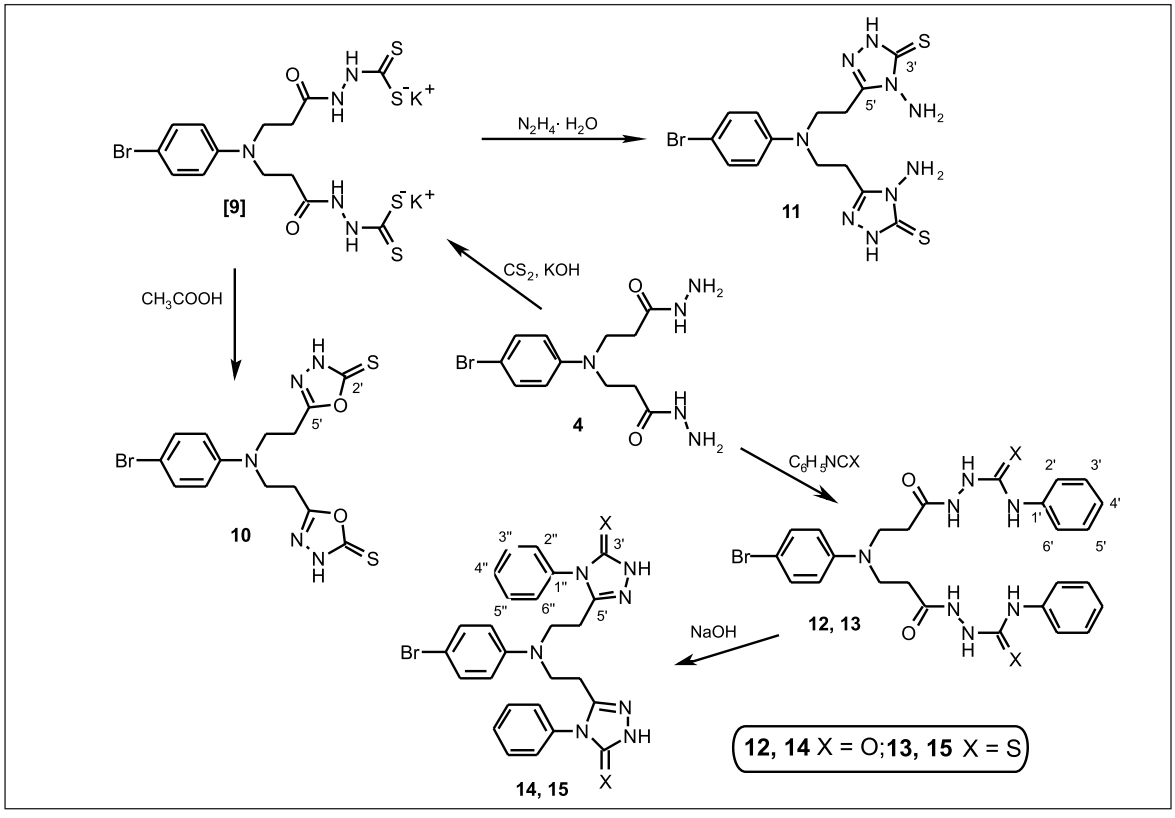
Scheme 1. Synthesis of hydrazones, pyrrole and pyrazole derivatives from dihydrazide of N-(4-bromophenyl)-N-carboxyethyl-β-alanine

mation about separate conformations, but gave a time-averaged spectral view of the structures present in the solution. A detailed analysis of NMR spectral data of **6**(**a–d**) revealed the formation of rotamers. In ^{13}C NMR spectra, fragments of CO, N = CH, CH_2CO, CH_2N were observed as a double set of resonances with a descending value of chemical shift difference. The corresponding (averaged from **6**(**a–d**)) chemical shift differences – 5.66 ppm, 3.54 ppm, 1.63 ppm and 0.25 ppm – indicated the existence of the isomerism centre. CH_2CO fragments of compounds **6** were observed as two multiplets; two resonances were attributed to the NH group in compounds **6a**, **6c**, **6b** and three in **6d**. Protons of the N = CH group were observed as two doubled lines in the ^1H NMR spectra of all **6**(**a–d**) compounds. The intensity ratio of signals was 0.6 : 0.4 in each case. Consequently, the latter was determined by the same process – hindered rotation of the amide fragment. The molecules of compound **6c** possess a benzene ring substituted by fluorine. All possible (C-F) spin–spin coupling constants ($^1J_{C\text{-}F}$ = 247.7 Hz, $^2J_{C\text{-}F}$ = 22.0 Hz, $^3J_{C\text{-}F}$ = 8.5 Hz, $^4J_{C\text{-}F}$ = 2.0 Hz) were detected in the ^{13}C spectrum of this compound.

Our interest was to investigate the products of reaction of dihydrazides **4** and diketones. Condensation of dihydrazide **4** with 2,4-pentanedione in 2-propanol in the presence of a catalytic amount of hydrochloric acid gave pyrazole **7**. The use of 2,5-hexanedione in this reaction with a catalytic amount of acetic acid gave the pyrrole compound **8**. These reactions were carried out under reflux for 5–6 hours. Resonances at 111.18 ppm, 143.14 ppm and 151.48 ppm in the ^{13}C NMR spectrum were attributed to C-4', C-5', C-3' atoms, respectively, and confirmed the formation of a pyrazole ring in compound **7**. Protons of the CH and CH_3 groups resonated in the expected region of the ^1H NMR spectrum and indicated the presence of a pyrazole ring. A characteristic spin–spin coupling (^4J = 0.9 Hz) between CH and CH_3 (CH = CCH_3) was observed. NOE (^1H) and $^1H/^{13}C$ 2D (HETCOR) NMR techniques assisted in the necessary detailed studies of the assignment of resonances in this case. The double intensity resonances at 10.90 ppm, 102.91 ppm and 126.63 ppm in the ^{13}C NMR spectrum suggest the existence of a pyrrole ring in compound **8**. The latter was assigned to both CH_3 groups, C-3', C-4' and C-2', C-5' carbon atoms. Compound **8** had the mentioned above amide fragment, but the pyrrole ring made more sterical hindrance for the rotation of the amide fragment than in the above cases.

Compound **10** was prepared from the reaction of dihydrazide **4** and carbon disulfide in the presence of potassium hydroxide by treating the resulting potassium dithiocarbazate **9** with acetic acid to pH 6. The presence of a broad singlet at 13.60 ppm of the NH proton in ^1H NMR spectrum and the two resonances at 162.24 ppm and 177.63 ppm, attributed to carbon atoms of the N=C and N-CS groups in ^{13}C NMR spectra, confirmed formation of the 5-membered oxadiazole ring in compound **10**.

4-Amino-1,2,4-triazole derivative **11** was prepared by heating dithiocarbazate **9** with hydrazine in water solution under reflux, and then the reaction mixture was acidified



Scheme 2. Synthesis of oxadiazole and triazole derivatives

with acetic acid to pH 6. The characteristic resonances at 13.50 ppm (NH) in the ^{1}H NMR spectrum and at 150.14 ppm (C-5') and 165.99 ppm (C-3') proved the formation of a 1,2,4-triazole ring. The presence of NH_2 group attached to N-4' atom was confirmed by resonance at 5.61 ppm in ^{1}H NMR spectrum.

To synthesize compounds containing two 1,2,4-triazole rings, reactions of dihydrazide **4** with phenyliso- and phenylisothiocianates were investigated. N-phenylhydrazinecarboxamide **12** and N-phenylhydrazinecarbothioamide **13** were synthesized in methanol solution under reflux. Characteristic resonances observed at 170.56 ppm (-CH_2CONH-) and at 155.31 ppm (-NHCONH-) in the ^{13}C NMR spectrum and resonances at 8.05 ppm (-CONHNHCO-), 8.74 ppm (-CONHPh), 9.77 ppm (-CONHNHCO-) in the ^{1}H NMR spectrum confirmed the presence of compound **12**. Resonances at 8.05 ppm and at 9.77 ppm were observed as doublets with a spin–spin coupling J = 1.4 Hz. Molecules of compound **13** possess the -CONHNHCSNHPh fragment. The ^{13}C NMR spectrum of this compound showed resonances at 170.54 ppm and at 181.00 ppm, attributed to CO and CS, respectively. The ^{1}H NMR spectrum of compound **13** showed resonances at 9.59 ppm and 10.00 ppm, attributed to protons of NH groups; their intensity ratio was 0.6 : 0.4.

Triazoles **14**, **15** were obtained by refluxing compounds **12**, **13** in aqueous 2% NaOH for 3 hours with the subsequent acidification of the reaction mixture with acetic acid. The sharp singlet at 11.76 ppm, assigned to the proton of the NH group in the ^{1}H NMR spectrum, and resonances at 144.86 ppm, 154.27 ppm were assigned to C-5', C-3' carbon atoms in the ^{13}C NMR spectrum, proving the formation of a 5-membered heterocycle in compound **14**. The extremely broad singlet at ~7.53 ppm the ^{1}H NMR spectrum may be ascribed to the proton of the NH group (averaged with H_2O). The resonances at 149.78 ppm (C-5') and at 167.27 ppm (C-3') in the ^{13}C NMR spectrum proved the formation of thioanalogue 5-membered heterocycle in compound **15**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova (300 MHz, 75 MHz) spectrometer operating in the Fourier transform mode, using DMSO-d_6 as solvent and TMS as the internal reference (chemical shifts in δ, ppm). IR spectra (ν, cm^{-1}) were recorded on a Perkin–Elmer Spectrum BX FT–IR spectrometer using KBr tablets. Mass spectra were obtained with a Waters ZQ 2000 spectrometer using the atmospheric pressure chemical ionization (APCI) mode and operating at 20 V. Elemental analyses were performed on a CE-440 elemental analyser. Melting points were determined on an automatic APA1 melting point apparatus and are uncorrected.

The synthesis of **2, 4, 6** compounds was described in the conference thesis [44], but data on this compounds were not presented.

N-(4-bromophenyl)-N-carboxyethyl-β-alanine (2)

A mixture of 4-bromoaniline **1** (86 g, 0.5 mol), 500 ml of water and acrylic acid (144.12 g, 2 mol) was heated at reflux for 36 h. At the end of reaction the mixture was cooled down, the aqueous phase was carefully decanted off and the residue dissolved in 500 ml of 10% sodium hydroxide solution. The solution was filtered off, and the filtrate was acidified with 20% acetic acid to pH 6. The precipitate of N-(4-bromophenyl)-N-carboxyethyl-β-alanine (**2**) was filtered off, washed with water and dried.

Yield (113.11 g, 72%). M. p. 138.5–139.5 °C. ^{1}H NMR (300 MHz, δ, ppm, J, Hz): 2.37 (t, 4H, J = 7.2, CH_2CO); 3.50 (t, 4H, J = 7.2, CH_2N); 6.60 (d, 2H, J = 9.0, $H_{ar\text{-}2,6}$); 7.25 (d, 2H, J = 9.0, $H_{ar\text{-}3,5}$); 7.55 (br. s, 2H, OH). ^{13}C NMR (75 MHz, δ, ppm): 33.76 (CH_2CO); 46.65 (CH_2N); 106.31 (C-4); 113.59 (C-2,6); 131.54 (C-3,5); 146.21 (C-1); 173.89 (CO). IR (KBr, ν, cm^{-1}): 1703 C=O, 3527–3646 OH. MS (ESI, 18 V): m/z 316 $(M)^+$ (40%), 318 $(M+2)^+$ (100%). Calculated for $C_{12}H_{14}BrNO_4$, %: C, 45.59; H, 4.46; N, 4.43. Found, %: C, 45.53; H, 4.34; N, 4.30.

Dimethyl ester of N-(4-bromophenyl)-N-carboxyethyl-β-alanine (3)

The amino acid **2** (19.02 g, 0.06 mol) was dissolved in methanol (100 ml) and H_2SO_4 (5 ml) was added under gentle stirring. The mixture was heated at reflux for 6 h, and the methanol was then evaporated under a reduced pressure. The residue was poured over with 150 ml of aqueous 5% Na_2CO_3 solution and heated to boiling. The mixture was cooled, and the aqueous phase was carefully poured off. The residue was dissolved in 200 ml of diethyl ether, the solution was dried over sodium sulphate and filtered. The solvent was evaporated under a reduced pressure, the product was purified by column chromatography (eluent : acetone : n-hexane 1 : 3) to give **3** as a liquid.

Yield (13.74 g, 67%). This compound was obtained as an oil, R_f = 0.52 (acetone : hexane 1 : 3). ^{1}H NMR (300 MHz, δ, ppm, J, Hz): 2.54 (t, 4H, J = 7.2, CH_2CO); 3.56 (t, 4H, J = 7.2, CH_2N); 3.60 (s, 6H, OCH_3); 6.65 (d, 2H, J = 9.0, $H_{ar\text{-}2,6}$); 7.29 (d, 2H, J = 9.0, $H_{ar\text{-}3,5}$). ^{13}C NMR (75 MHz, δ, ppm): 31.30 (CH_2CO); 46.04 (CH_2N); 51.31 (OCH_3); 107.18 (C-4); 113.99 (C-2,6); 131.61 (C-3,5); 145.82 (C-1); 171.88 (CO). Calcd. for $C_{14}H_{18}BrNO_4$, %: C, 48.85; H, 5.27; N, 4.07. Found, %: C, 48.45; H, 5.51; N, 3.97.

Dihydrazide of N-(4-bromophenyl)-N-carboxyethyl-β-alanine (4)

A mixture of dimethyl ester **3** (13.74 g, 0.04 mol), hydrazine hydrate (12 g, 0.24 mol), and 50 ml of 2-propanol was heated under reflux for 1 h. The mixture was cooled, the precipitate was filtered and then washed with 2-propanol. Compound **4** was crystallized from a mixture of 2-propanol and water (1 : 1).

Yield (28.25 g, 82%). M. p. 165–166 °C. ^{1}H NMR (300 MHz, δ, ppm, J, Hz): 2.24 (t, 4H, J = 7.2, CH_2CO); 3.47 (t, 4H, J = 7.2,

CH_2N); 4.20 (s, 4H, CONH$\underline{NH_2}$); 6.63 (d, 2H, J = 9.2, $H_{ar\text{-}2,6}$); 7.28 (d, 2H, J = 9.2, $H_{ar\text{-}3,5}$); 9.05 (s, 2H, CO$\underline{NH}NH_2$). ^{13}C NMR (75 MHz, δ, ppm): 32.00 ($\underline{CH_2}CO$); 47.57 (CH_2N); 107.37 (C-2,6); 114.53 (C-4); 132.31 (C-3,5); 146.90 (C-1); 170.52 (CO). IR (KBr, ν, cm^{-1}): 1633–1646 C=O, 3227–3274 NH-NH_2. MS, m/z: 344 $(M)^+$ (90%), 346 $(M+2)^+$ (100%). Calcd. for $C_{12}H_{18}BrN_5O_2$, %: C, 41.87; H, 5.27; N, 20.35. Found, %: C, 42.6; H, 5.8; N, 20.1.

3-(4-Bromo{3-[2-(1-methylethylidene)hydrazino]-3-oxopropyl}anilino)-*N*'-(1-methylethylidene)propanohydrazide (5)

A mixture of dihydrazide **4** (1.03 g, 0.003 mol) and 30 ml of acetone was heated under reflux for 3 h. The reaction mixture was cooled, volatile fractions evaporated under reduced pressure. **5** was obtained by crystallization of residue from 2-propanol.

Yield (0.96 g, 75%). M. p. 186–188 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 1.81, 1.82, 1.83 (3 s, 6H, *cis*, N = C$\underline{CH_3}$); 1.90 (s, 6H, *trans*, N = C$\underline{CH_3}$); 2.42–2.51 (m, 0.4(4H), CH_2CO); 2.69–2.75 (m, 0.6(4H), CH_2CO); 3.51–3.58 (m, 4H, CH_2N); 6.66–7.31 (m, 4H, H_{ar}); 10.00, 10.10 (2 s, (0.4 / 0.6) (2H), NH). ^{13}C NMR (75 MHz, δ, ppm): 17.04, 18.49 (*cis*, CH_3); 24.93, 25.12 (*trans*, CH_3); 30.50, 30.72, 31.74, 31.91 ($\underline{CH_2}CO$); 46.12, 46.23, 47.65, 46.74 (CH_2N); 106.47, 106.56, 106.75 (C-4); 113.66, 113.80, 114.09 (C-2,6); 131.55 (C-3,5); 146.29 (C-1); 150.47, 154.86, 154.90 ($\underline{C}CH_3$); 166.84, 166.88, 172.70 (CONH). IR (KBr, ν, cm^{-1}): 1593 N=C, 1663 CO, 3179 NH. MS, m/z: 424.3 $(M1)^+$(50%), 426.3 $(M+2)^+$ (60%). Calcd. for $C_{18}H_{26}BrN_5O_2$, %: C, 50.95; H, 6.18; N, 16.50. Found, %: C, 50.45; H, 6.17; N, 16.53.

General procedure for synthesis hydrazones 6(a–d)

A mixture of dihydrazide **4** (1.03 g, 0.003 mol) and 0.01 mol of the corresponding aromatic aldehyde in 40 ml of 1,4-dioxane was heated under reflux for 3 h. The reaction mixture was cooled down, the precipitate filtered, then washed with 2-propanol and crystallyzed from the appropriate solvent.

3-[4-Bromo(3-oxo-3-{2-phenylmethylidenehydrazino}propyl)anilino]-*N*'-(phenylmethylidene)propanohydrazide (6a)

Yield (1.45 g, 93%). M. p. 235–237 °C (from 1,4-dioxane). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.47–2.52 (m, 0.4(4H), CH_2CO); 2.85–2.92 (m, 0.6(4H), CH_2CO); 3.59–3.68 (m, 4H, CH_2N); 6.72–7.69 (m, 14H, H_{ar}); 7.97, 7.98 (2 s, 0.6(2H), N=CH); 8.12, 8.14 (2 s, 0.4(2H), N=CH); 11.38, 11.43 (2 s, (0.6 / 0.4)(2H), NH). ^{13}C NMR (75 MHz, δ, ppm): 29.92, 30.07, 32.07, 32.25 ($\underline{CH_2}CO$); 46.42, 46.64 (CH_2N); 106.66, 106.79 (C-4); 113.71, 113.88 (C-2,6); 126.66, 126.99 (C-2',6'); 128.73 (C-3',5'); 129.69, 129.93 (C-4'); 131.66 (C-3,5); 134.12, 134.23 (C-1'); 143.09 (N = CH); 146.14, 146.20 (C-1); 146.28 (N=CH); 167.01, 172.83 (CONH). IR (KBr, ν, cm^{-1}): 1592 N=C, 1667 CO, 3180 NH. Calcd. for $C_{26}H_{26}BrN_5O_2$, %: C, 60.00; H, 5.04; N, 13.46. Found, %: C, 60.27; H, 4.63; N, 13.16.

3-[4-Bromo(3-{2-[(4-methoxyphenyl)methylidene]hydrazino}-3-oxopropyl)anilino]-*N*'-[(4-methoxyphenyl)methylidene]propanohydrazide (6b)

Yield (1.51 g, 87%). M. p. 190–192 °C (from 2-propanol). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.41–2.48 (m, 0.4(4H), CH_2CO); 2.83–2.89 (m, 0.6(4H), CH_2CO); 3.53–3.67 (m, 4H, CH_2N); 3.76, 3.77, 3.79 (3 s, 6H, OCH_3); 6.70–7.62 (m, 12H, H_{ar}); 7.91, 7.92 (2 s, 0.6(2H), N=CH); 8.06, 8.07 (2 s, 0.4(2H), N=CH); 11.25, 11.29 (2 s, (0.6 / 0.4)(2H), NH). ^{13}C NMR (75 MHz, δ, ppm): 29.90, 30.06 ($\underline{CH_2}CO$); 46.48, 46.60 (CH_2N); 55.22 (CH_3O); 106.62, 106.74 (C-4); 113.62, 113.85 (C-2,6); 114.19 (C-3',5'); 126.73 (C-1'); 128.20; 128.57 (C-2',6'); 131.67 (C-3,5); 142.92, 146.02 (N=CH); 146.25 (C-1); 160.46 (C-4') 166.71, 172.58 (CONH). IR (KBr, ν, cm^{-1}): 1604 N=C, 1674 CO, 3173 NH. MS, m/z 602 $(M+Na)^+$ (33%), 604 $(M+2+Na)^+$ (20%). Calcd. for $C_{28}H_{30}BrN_5O_4$, %: C, 57.94; H, 5.21; N, 12.06. Found, %: C, 58.32; H, 5.28; N, 12.11.

3-[4-Bromo(3-{2-[(4-fluorophenyl)methylidene]hydrazino}-3-oxopropyl)anilino]-*N*'-[(4-fluorophenyl)methylidene]propanohydrazide (6c)

Yield (1.32 g, 79%). M. p. 210–212 °C (from 1,4-dioxane). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.46–2.50 (m, 0.4(4H), CH_2CO); 2.84–2.94 (m, 0.6(4H), CH_2CO); 3.59–3.67 (m, 4H, CH_2N); 6.70–7.50 (m, 12H, H_{ar}); 7.95; 7.96 (2 s, 0.6(2H), N=CH); 8.12, 8.14 (2 s, 0.4(2H), N=CH); 11.38. 11.43 (2 s, (0.6 / 0.4) 2H, NH). ^{13}C NMR (75 MHz, δ, ppm): 29.85, 30.01, 31.80, 32.05 ($\underline{CH_2}CO$); 46.40, 46.65 (CH_2N); 106.65, 106.78 (C-4); 113.68, 113.86 (C-2,6); 115.70 (d, J = 22.0 Hz, C-3',5'); 128.75, 129.12 (d, J = 8,5 Hz, C-2',6'); 130.72, 130.83 (d, J = 2 Hz, C-1'); 131.60 (C-3,5); 141.88, 145.01 (CH=N); 146.17 (C-1); 162.78 (d, J = 247.7 Hz, C-4'); 167.02, 172.87 (CONH). IR (KBr, ν, cm^{-1}): 1604 N=C, 1681 CO, 3172 NH. MS, m/z: 578 $(M + Na)^+$ (30%), 580 $(M+2+Na)^+$ (20%). Calcd. for $C_{26}H_{24}BrF_2N_5O_2$, %: C, 56.12; H, 4.35; N, 12.59. Found, %: C, 56.03; H, 4.38; N, 12.37.

3-[4-Bromo(3-{2-[(4-dimethylaminophenyl)methylidene]hydrazino}-3-oxopropyl)anilino]-*N*'-[(4-dimethylaminophenyl)methylidene]propanohydrazide (6d)

Yield (1.34 g, 74%). M. p. 211–213 °C (from 1,4-dioxane). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.39–2.51 (m, 0.4(4H), CH_2CO); 2.82–2.89 (m, 0.6(4H), CH_2CO); 2.92, 2.93, 2.95 (3 s, 12H, $N(CH_3)_2$); 3.52–3.66 (m, 4H, CH_2N); 6.63–7.48 (m, 12H, H_{ar}); 7.84, 7.85 (2 s, 0.6(2H), N=CH); 7.98 (2 s, 0.4(2H), N=CH); 11.10 (s, 0.6(2H), NH); 11.12, 11.13 (2 s, 0.4(2H), NH). ^{13}C NMR (75 MHz, δ, ppm): 30.00, 30.15, 32.07, 32.24 ($\underline{CH_2}CO$); 39.78 ($N(CH_3)_2$); 46.39, 46.54, 46.74 (CH_2N); 106.70 (C-4); 111.72 (C-3',5'); 113.67, 113.84 (C-4); 121.56 (C-1'); 127.92, 128.31 (C-2',6'); 131.67 (C-3,5); 143.86, 146.95 (CH=N); 146.30 (C-1); 151.17, 151.39 (C-4'); 166.32, 172.22 (CONH). IR (KBr, ν, cm^{-1}): 1610 N=C, 1667 CO, 3176 NH. MS, m/z: 606 $(M)^+$ (13%), 608 $(M + 2)^+$ (15%). Calcd. for $C_{30}H_{36}BrN_7O_2$, %: C, 59.40; H, 5.98; N, 16.16. Found, %: C, 59.39; H, 6.07; N, 16.04.

3-{4-Bromo[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropyl]anilino}-1-(3,5-dimethyl-1*H*-pyrazol-1-yl)-1-propanone (7)

A mixture of dihydrazide **4** (1.03 g, 0.003 mol), 2,4-pentanedione (1 g, 0.01 mol), 2-propanol (15 ml) and conc. hydrochloric acid (0.5 ml) was heated under reflux for 5 h, then cooled, the precipitate was filtered off, washed with 2-propanol, and **7** was crystallized from 2-propanol.

Yield (1.06 g, 75%). M. p. 109–110 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.15 (s, 6H, CH_3); 2.45 (d, 6H, *J* = 0.9, CH_3); 3.27 (t, 4H, *J* = 7.1, CH_2CO); 3.71 (t, 4H, *J* = 7.1, CH_2N); 6.17 (q, 2H, *J* = 0.9, CH); 6.78 (d, 2H, *J* = 9.1, $H_{ar\text{-}2,6}$); 7.29 (d, 2H, *J* = 9.1, $H_{ar\text{-}3,5}$). ^{13}C NMR (75 MHz, δ, ppm): 13.43 (CH_3(C-5')); 14.05 (CH_3(C-3')); 33.00 (CH_2CO); 46.11 (CH_2N); 107.09 (C-4); 111.18 (C-4'); 114.15 (C-2,6); 131.62 (C-3,5); 143.14 (C-5'); 146.07 (C-1); 151.48 (C-3'); 171.89 (CO). IR (KBr, ν, cm^{-1}): 1724 C=O. MS, m/z: 472 $(M)^+$ (20%), 474 $(M+2)^+$ (30%). Calcd. for $C_{22}H_{26}BrN_5O_2$, %: C, 55.94; H, 5.55; N, 14.83. Found, %: C, 55.55; H, 5.48; N, 14.61.

3-(4-Bromo{3-[(2,5-dimethyl-1H-pyrrol-1-yl)amino]-3-oxopropyl}anilino)-*N*-(2,5-dimethyl-1H-pyrrol-1-yl)propanamide (8)

A mixture of dihydrazide **4** (1.03 g, 0.003 mol), 2,5-hexanedione (1.14 g, 0.01 mol), 2-propanol (20 ml), and acetic acid (1 ml) was heated under reflux for 6 h, then cooled, the precipitate was filtered off, washed with 2-propanol, and **8** was crystallized from 2-propanol.

Yield (1.27 g, 85%). M. p. 220–222 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz: 1.92, 1.93, 1.98 (3 s, 0.1 : 0.8 : 0.1(12H), CH_3); 2.56 (t, 4H, *J* = 6.7, CH_2CO); 3.66 (t, 4H, *J* = 6.7, CH_2N); 5.62 (s, 0.9(4H), CH); 5.69 (s, 0.1(4H), CH); 6.55 (d, 0.2(2H), *J* = 9.0, $H_{ar\text{-}2,6}$); 6.76 (d, 0.8(2H), *J* = 9.0, $H_{ar\text{-}2,6}$); 7.25 (d, 0.2(2H), *J* = 9.0, $H_{ar\text{-}3,5}$); 7.34 (d, 0.8 (2H), *J* = 9.0, $H_{ar\text{-}2,6}$); 10.20, 10.62, 10.66 (3 s, 0.1 : 0.1 : 0.8 (2H), NH). ^{13}C NMR (75 MHz, δ, ppm): 10.90 (CH_3); 31.03 (CH_2CO); 46.41 (CH_2N); 102.91 (C-3',4'); 107.27 (C-4); 114.43 (C-2,6); 126.63 (C-2',5'); 131.71 (C-3,5); 146.05 (C-1); 170.08 (CONH). IR (KBr, ν, cm^{-1}): 1700 O, 3260 NH. MS, m/z: 500 $(M)^+$ (60%), 502 $(M+2)^+$ (100%). Calcd. for $C_{24}H_{30}BrN_5O_2$, %: C, 57.60; H, 6.04; N, 13.99. Found, %: C, 58.07; H, 5.96; N, 13.63.

5-(2-{4-Bromo[2-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)ethyl]anilino}ethyl)-1,3,4-oxadiazole-2(3*H*)-thione (10)

A solution of dihydrazide **4** (1.72 g, 0.005 mol), potassium hydroxide (1.35 g, 0.02 mol), carbon disulfide (1.52 g, 0.02 mol) and 2-propanol (50 ml) was heated under reflux for 24 h, then volatile fractions evaporated under reduced pressure. The residue was dissolved in water (30 ml), and the solution was acidified with acetic acid to pH 6. The formed residue was filtered off, washed with water and dried.

Yield (1.58 g, 74%). M. p. 175–176 °C (from 2-propanol). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.94 (t, 4H, *J* = 7.0, CH_2CO); 3.68 (t, 4H, *J* = 7.0, CH_2N); 6.70 (d, 2H, *J* = 9.1, $H_{ar\text{-}2,6}$); 7.30 (d, 2H, *J* = 9.1, $H_{ar\text{-}3,5}$); 13.60 (br. s, 2H, NH). ^{13}C NMR (75 MHz, δ, ppm): 23.10 ($\underline{CH_2}C$=); 46.25 (CH_2N); 107.79 (C-4); 114.23 (C-2,6); 131.78 (C-3,5); 145.50 (C-1); 162.24 (C-5'); 177.63 (C-2'). IR (KBr, ν, cm^{-1}): 1156 C=S, 3135 NH. MS, m/z: 428 $(M)^+$ (90%), 430 $(M+2)^+$ (72%). Calcd. for $C_{14}H_{14}BrN_5O_2S_2$, %: C, 39.26; H, 3.29; N, 16.35. Found, %: C, 39.77; H, 3.45; N, 16.30.

4-Amino-5-(2-{[2-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)ethyl]-4-bromoanilino}ethyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (11)

A mixture of dihydrazide **4** (1.72 g, 0.005 mol), potassium hydroxide (1.35 g, 0.02 mol), carbon disulfide (1.52 g, 0.02 mol) and 2-propanol (50 ml) was heated under reflux for 24 h, then volatile fractions were evaporated under a reduced pressure, the residue was dissolved in water (5 ml), and hydrazine hydrate (1.5 g, 0.03 mol) was added. The mixture was heated under reflux for 20 h, diluted with 10 ml of water, cooled and acidified with acetic acid to pH. The formed residue was filtered off, washed with water, 2-propanol, and **11** was crystallized from methanol.

Yield (1.68 g, 74%). M. p. 127–129 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.86–2.91 (m, 4H, CH_2C=); 3.62–3.67 (m, 4H, CH_2N); 5.63 (s, 4H, NH_2); 6.78 (d, 2H, *J* = 9.1, $H_{ar\text{-}2,6}$); 7.29 (d, 2H, *J* = 9.1, $H_{ar\text{-}3,5}$); 13.51 (br. s, 2H, NH). ^{13}C NMR (75 MHz, δ, ppm): 22.43 ($\underline{CH_2}C$=); 46.91 (CH_2N); 107.15 (C-4); 113.94 (C-2,6); 131.70 (C-3,5); 145.81 (C-1); 150.14 (C-5'); 165.99 (C-3'). Calcd. for $C_{14}H_{18}BrN_9S_2$, %: C, 36.84; H, 3.98; N. 27.62. Found, %: C, 36.90; H, 4.05; N, 27.11.

2-[4-({4-[2-(Anilinocarbonyl)hydrazino]-3-oxobutyl}-4-bromoanilino)-2-oxobutyl]-*N*-phenyl-1-hydrazinecarboxamide (12)

A mixture of dihydrazide **4** (3.44 g, 0.01 mol), phenyl isocyanate (3.57 g, 0.03 mol) and 50 ml of methanol was heated under reflux for 2 h. The reaction mixture was cooled, the precipitate filtered off, then washed with methanol, and **12** was crystallized from methanol.

Yield (5.49 g, 94%). M. p. 205–207 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.42 (t, 4H, *J* = 6.8, CH_2CO); 3.56 (t, 4H, *J* = 6.8, CH_2N); 6.61–7.49 (m, 14H, H_{ar}); 8.05 (d, 2H, *J* = 1.4, CONH$\underline{NH}$CO); 8.74 (s, 2H, CONHPh); 9.77 (d, 2H, *J* = 1.4, CO$\underline{NH}$NHCO). ^{13}C NMR (75 MHz, δ, ppm): 31.13 ($\underline{CH_2}CO$); 46.52 (CH_2N); 106.84 (C-4); 113.89; (C-2,5); 118.51 (C-2',6'); 121.94 (C-4'); 128.69 (C-3',5'); 131.72 (C-3,5); 139.60 (C-1'); 146.13 (C-1); 155.31 (NHCONH); 170.56 ($CH_2\underline{CO}$NH). IR (KBr, ν, cm^{-1}): 1620–1655 C=O, 3211–3345 NH. MS, m/z: 604 $(M+Na)^+$ (40%), 606 $(M+2+Na)^+$ (30%). Calcd. for $C_{26}H_{28}BrN_7O_4$, %: C, 53.61; H, 4.85; N, 16.83. Found, %: C, 53.39; H, 4.94; N, 16.84.

2-[4-({4-[2-(Anilinocarbothioyl)hydrazino]-3-oxobutyl}-4-bromoanilino)-2-oxobutyl]-*N*-phenyl-1-hydrazinecarbothioamide (13)

A mixture of dihydrazide **4** (3.44 g, 0.01 mol), phenyl isothiocyanate (4.05 g, 0.03 mol) and 50 ml of methanol was heated

under reflux for 2 h. The reaction mixture was cooled, the precipitate filtered off, then washed with methanol, and **13** was crystallized from methanol.

Yield (5.85 g, 95%). M. p. 163–165 °C. ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.40–2.48 (m, 4H, CH_2CO); 3.55–3.60 (m, 4H, CH_2N); 6.66–7.42 (m, 14H, H_{ar}); 9.36, 9.59, 9.87, 10.00 (4 br. s, 6H, NH). ^{13}C NMR (75 MHz, δ, ppm): 31.12 (CH_2CO); 46.21 (CH_2N); 106.83 (C-4); 113.96 (C-2,6); 125.21 (C-4'); 126.11 (C-2',6'); 128.13 (C-3',5'); 131.70 (C-3,5); 139.09 (C-1'), 146.19 (C-1); 170.54 (CO); 181.00 (CS). IR (KBr, ν, cm^{-1}): 1183 C=S, 1682 C=O, 3063–3246 NH. MS, m/z: 615 $(M)^+$ (15 %), 617 $(M+2)^+$ (20 %). Calcd. for $C_{26}H_{28}BrN_7O_2S_2$, %: C, 50.81; H, 4.59; N, 15.95. Found, %: C, 50.54; H, 4.71; N, 15.61.

5-(2-{4-Bromo[2-(5-oxo-4-phenyl-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)ethyl]anilino}ethyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (14)

The semicarbazide **12** (0.58 g, 0.001 mol) and 20 ml of aqueous 2% sodium hydroxide solution was heated under reflux for 3 h, cooled and acidified with acetic acid to pH 6. The formed residue was filtered off, washed with water and dried.

Yield (0.35 g, 64%). M. p. 201–203 °C (from 2-propanol). ^{1}H NMR (300 MHz, δ, ppm, *J*, Hz): 2.53–2.56 (m, 4H, CH_2C=); 3.23–3.28 (m, 4H, CH_2N); 5.97 (d, 2H, *J* = 9.2, $H_{ar\text{-}2,6}$); 7.03 (d, 2H, *J* = 9.2, $H_{ar\text{-}3,5}$); 7.34–7.55 (m, 10H, H_{ar}); 11.76 (s, 2H, NH). ^{13}C NMR (75 MHz, δ, ppm): 23.39 (CH_2C=); 46.64 (CH_2N); 106.80 (C-4); 113.01 (C-2,6); 127.52 (C-2",6"); 128.73 (C-4"); 129.52 (C-3"5"); 131.49 (C-3,5); 132.73 (C-1"); 144.86 (C-5'); 145.34 (C-1); 154.27 (C-3'). IR (KBr, ν, cm^{-1}): 1698 C=O, 3180 NH. MS, m/z: 546 $(M)^+$ (30%), 548 $(M+2)^+$ (50%). Calcd. for $C_{26}H_{24}BrN_7O_2$, %: C, 57.15; H, 4.43; N, 17.94. Found, %: C, 56.62; H, 4.51; N, 17.16.

5-(2-{4-Bromo[2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)ethyl]anilino}ethyl)-4-phenyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (15)

The thiosemicarbazide **13** (0.61 g, 0.001 mol) and 20 ml of aqueous 2% sodium hydroxide solution was heated under reflux for 3 h, cooled down and acidified with acetic acid to pH 6. The formed residue was filtered off, washed with water and dried.

Yield (0.42 g, 73%). M. p. 262–264 °C (from 2-propanol). ^{1}H NMR (300 MHz, δ, ppm, *J* Hz): 2.52–2.57 (m, 4H, CH_2C=); 3.26–3.31 (m, 4H, CH_2N); 5.90 (d, 2H, *J* = 9.1, $H_{ar\text{-}2,6}$); 7.00 (d, 2H, *J* = 9.1, $H_{ar\text{-}3,5}$); 7.31–7.57 (m, 10H, H_{ar}); 7.79 (br. s, 2H, NH). ^{13}C NMR (75 MHz, δ, ppm): 23.09, 23.51 (CH_2C=); 47.08 (CH_2N); 106.90 (C-4); 113.02 (C-2,6); 128.42 (C-3',5'); 129.21 (C-4'); 129.41 (C-2'6'); 131.52 (C-3,5); 134.14 (C-1'); 145.21 (C-1); 149.78 (C-5'); 167.27 (C-3'). IR (KBr, ν, cm^{-1}): 13370 C=S, 3428 NH. MS, m/z: 578 $(M)^+$ (13%), 580 $(M+2)^+$ (15%). Calcd. for $C_{26}H_{24}BrN_7S_2$, %: C, 53.98; H, 4.18; N, 16.95. Found, %: C, 54.10; H, 4.06; N, 17.10.

CONCLUSIONS

Dihydrazide of N-(4-bromophenyl)-N-carboxyethyl-β-alanine was synthesized, and its condensation with mono- and dicarbonyl compounds was studied. Reactions of dihydrazide with aromatic aldehydes and acetone provide hydrazones, condensation with diketones afford dimethylpyrrole or dimethylpyrazole derivatives. It has been shown that dihydrazide and its derivatives can be used for the synthesis of 1,3,4-oxadiazole, triazole compounds.

The newly synthesized compounds are identically disubstituted amines possessing in their side chains different structural fragments showing a variety of properties. The structure of the synthesized compounds was determined, and the characteristics of each compound were elucidated and discussed.

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N-(4-BROMOFENIL)-N-KARBOKSIETIL-β-ALANINO DARINIŲ SINTEZĖ IR STRUKTŪRA

S a n t r a u k a

Reaguojant 4-bromanilinui su akrilo rūgšties pertekliumi susidaro N-(4-bromofenil)-N-karboksietil-β-alaninas, iš kurio susintetintas atitinkamas dikarboksirūgšties dihidrazidas, ištirta jo kondensacija su karboniliniais junginiais. Nustatyta, kad reaguojant dihidrazidui su aromatiniais aldehidais, acetonu susidaro neciklinės struktūros hidrazonų tipo junginiai, tuo tarpu su dikarboniliniais junginiais – 2,4-pentandionu ir 2,5-heksandionu, gaunamos ciklinės struktūros – pirazolo ir pirolo dariniai. Nustatyta, kad reaguojant N-(4-bromofenil)-N-karboksietil-β-alanino dihidrazidui su anglies disulfidu susidaro ditiokarbazatas, kuris dėl rūgšties poveikio ciklizuojasi į oksadiazolo, o veikiant hidrazinu – į triazolo darinius. Ištyrus N-(4-bromofenil)-N-karboksietil-β-alanino dihidrazido reakcijas su fenilizocianatu ir fenilizotiocianatu nustatyta, kad jų metu susidaro neciklinės struktūros semikarbazidų tipo junginiai, kurie šarminėje terpėje lengvai transformuojasi į triazolo darinius. Visi gautieji junginiai apibūdinti remiantis elementinės analizės, IR, masių ir BMR spektrų duomenimis. Šių junginių struktūros ypatybės išsamiai ištirtos ir aptartos pasitelkus ^{1}H ir ^{13}C BMR spektrinės analizės duomenis.