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PRODUCTS FROM CONDENSATION OF 1-(3(4)-ACETYLPHENYL)-4-CARBOXY-2-PYRROLIDINONES WITH *o*-PHENYLENE-DIAMINE AND THEIR PROPERTIES

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2-Substituted benzimidazoles were synthesized by the reaction of 1-(3(4)-acetylphenyl)-4-carboxy-2-pyrrolidinones with o-phenylenediamine. Their reactions with sodium hydroxide and hydrazine and some of their chemical characteristics were investigated.

Keywords: 4-(arylamino)-3-(1H-benzimidazol-2-yl)butyric acids, 1-aryl-4-(1H-benzimidazol-2-yl)-2-pyrrolidinones, 1-aryl-4-carboxy-2-pyrrolidinones, hydrazones, o-phenylenediamine, condensation.

Derivatives of benzimidazole have a broad spectrum of biological activity [1-5]. The synthesis and investigation of compounds containing this fragment therefore represent a vital task. One of the most widely used methods for the synthesis of 2-substituted benzimidazoles is the Phillips method [6] – heating carboxylic acids or their derivatives with *o*-phenylenediamines in a 4 M solution of hydrochloric acid.

While continuing investigations into the reactivity of 1-aryl-substituted 4-carboxy-2-pyrrolidinones we realized the condensation of 1-(3(4)-acetylphenyl)-4-carboxy-2-pyrrolidinones **1a**,**b**, synthesized by the method in [7], with *o*-phenylenediamine under the conditions of the Phillips method. The reaction mixture was boiled, and the products in the form of 2-substituted benzimidazoles **2a**,**b** were isolated by making the reaction mixture alkaline to pH 10 with a concentrated solution of ammonia.

It is known that the 2-pyrrolidinone ring is stable to the action of acids but can undergo decyclization in an alkaline medium. We established that when compounds **2a**,**b** were boiled in a 20% solution of sodium hydroxide the 2-pyrrolidinone ring broke down into the corresponding sodium salts of N-substituted γ-amino acids **3a**,**b**). The free γ-amino acids **4a**,**b** were isolated by acidifying the aqueous solutions of the sodium salts to pH 6 with acetic acid.

During comparison of the data from the ^{1}H NMR spectra of compounds **2a**,**b** and **4a**,**b** it is seen that the signals for the protons of the 2-pyrrolidinone ring and for the compounds with an open chain are similar and only differ in their shifts. In the compounds with an open chain **4a**,**b** the signals of the substituted amino group are also observed at 6.14 and 6.82 respectively. In the ^{13}C NMR spectra the line at 173 ppm indicates that compounds **4a**,**b** contain noncyclic bonds, while the chemical shifts of the $CH_2\underline{C}HCH_2$ and $\underline{C}H_2CO$ carbon atoms are fairly close – the difference is only ~0.4 ppm, while the difference in the cyclic compounds **2a**,**b** amounts to ~7 ppm.

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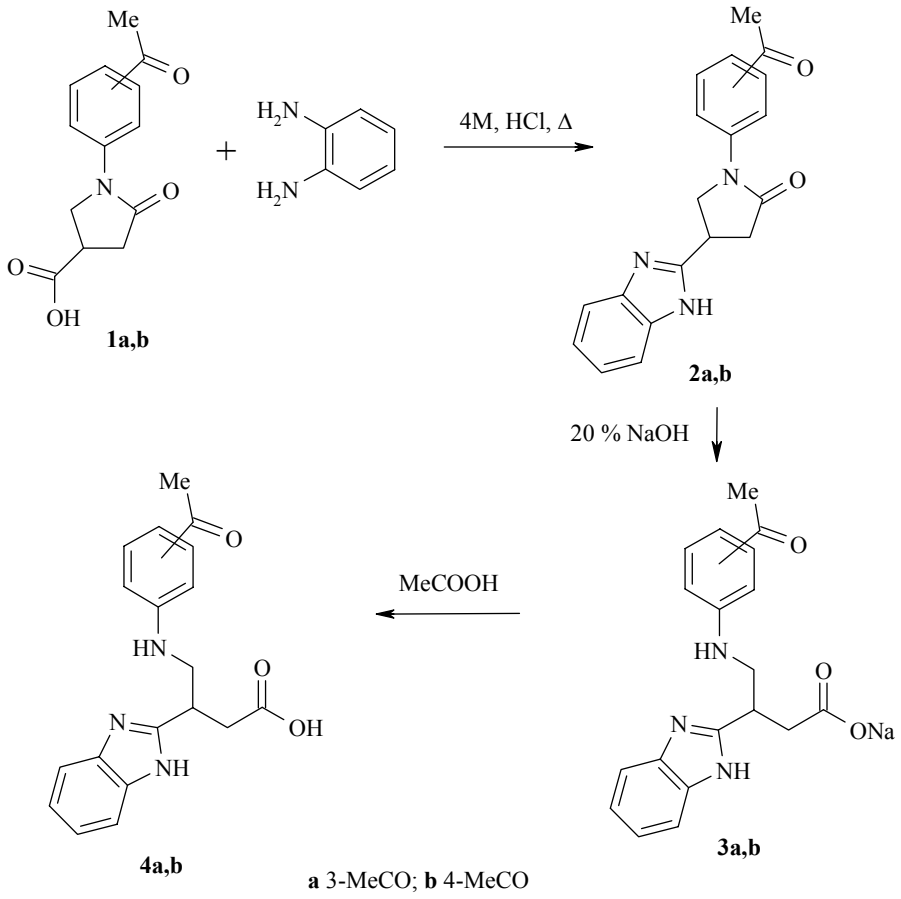
Sheme 1



a 3-MeCO; **b** 4-MeCO

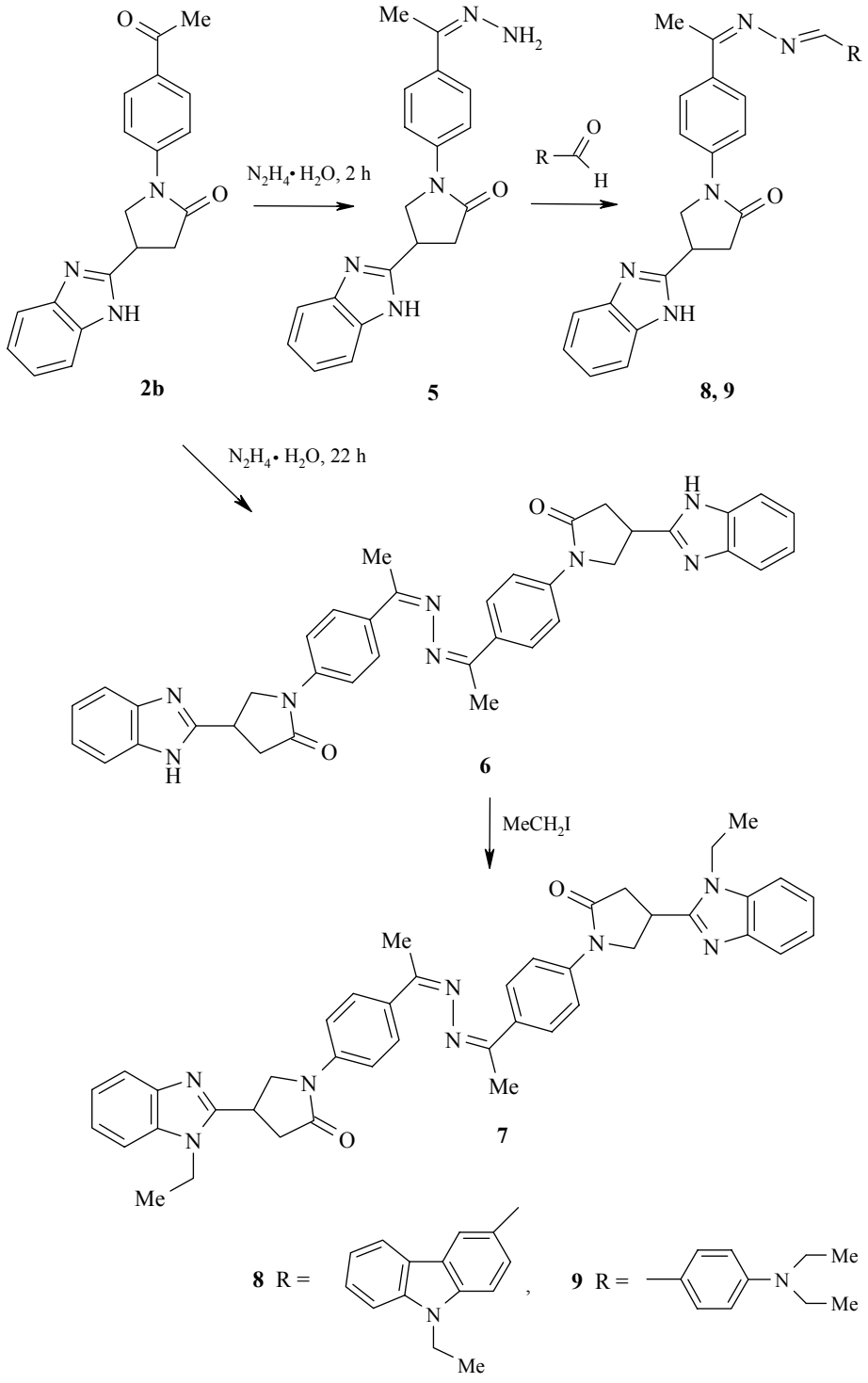
During study of the reaction of compound **2b** with hydrazine hydrate it was established that compound **5** is formed when the reaction is carried out in methanol at the boiling point of the mixture. Increase of the temperature and also increase of the reaction time lead to the formation of a dimeric structure. Thus, by conducting the reaction in boiling dioxane for 22 h, we synthesized a compound of the azine type **6**. In order to increase the solubility and to confirm the structure the compound was alkylated with iodoethane. In addition to the signals of protons characteristic of compound **6**, the ^{1}H NMR spectrum of the alkyl derivative **7** contains signals for the protons of the N–$CH_2C\underline{H}_3$ groups at 1.37 and of the N–$C\underline{H}_2CH_3$ groups in the range of 4.15-4.40 ppm, which overlap with the signals for the protons of the 2-pyrrolidinone ring.

During the condensation of compound **5** with 9-ethyl-3-formyl-carbazole and *para*-diethyl-aminobenzaldehyde the corresponding hydrazones **8** and **9** were obtained. Their structure was confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectra, mass spectrometry, and IR spectra.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity Inova spectrometer (300 and 75 MHz respectively) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on a Perkin–Elmer Spectrum Bx FT IR instrument in tablets with potassium bromide. The mass spectra were obtained on a Waters

Scheme 2



ZQ 2000 spectrometer with electrospray ionization (ESI, 20 V, compounds **2a**,**b** and **4a**,**b**) and chemical ionization at atmospheric pressure (APCI, compounds **5**, **6**, **8**, and **9**). The reaction and the purity of the products were monitored by TLC (on Alugram Sil G/UV-254 plates) with development in UV light (λ = 254 and 366 nm).

1-(3(4)-Acetylphenyl)-4-(1H-benzimidazol-2-yl)-2-pyrrolidinones 2a,b (General Method). A mixture of the respective 2-pyrrolidinone **1a**, **b** (2.47 g, 10 mmol) and *o*-phenylenediamine (2.16 g, 20 mmol) was boiled for 5-6 h in a 4 M solution of hydrochloric acid (20 ml), cooled, and diluted to pH ca 10 with a 24-26% aqueous solution of ammonia. The aqueous layer was decanted, and the obtained resinous mass was inundated with 5% sodium hydroxide solution (20 ml) and heated to boiling. The crystals that separated after the mixture had cooled were filtered off, washed with water, and dried.

1-(3-Acetylphenyl)-4-(1H-benzimidazol-2-yl)-2-pyrrolidinone (2a). Yield 38%; mp 103-104°C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 1707, 1678 (CO); 3089, 3051 (NH). ^{1}H NMR spectrum, δ, ppm: 2.59 (3H, s, CH_3CO); 2.98-3.13 (2H, m, CH_2CO); 3.98-4.08 (1H, m, CH_2CHCH_2); 4.26-4.39 (2H, m, CH_2N); 7.15-8.22 (8H, m, H arom.); 12.52 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 26.79 (CH_3); 30.61 ($CH_2\underline{C}HCH_2$); 37.44 ($\underline{C}H_2CO$); 52.04 (CH_2N); 111.06, 118.47, 123.87, 123.94, 129.14, 134.46, 137.18, 139.51 (C_6H_5); 154.84 [C(N)NH]; 172.34 (NCO); 197.65 (CO). Mass spectrum, *m/z* (*I*, %): 320 $[M + H]^+$ (100). Found, %: C 71.62; H 5.72; N 12.95. $C_{19}H_{17}N_30_2$. Calculated, %: C 71.46; H 5.37; N 13.16.

1-(Acetylphenyl)-4-(1H-benzimidazol-2-yl)-2-pyrrolidinone (2b). Yield 40%; mp 222-223°C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 1699, 1682 (CO); 3053, 3007 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.55 (3H, s, CH_3CO); 2.98-3.15 (2H, m, CH_2CO); 3.98-4.09 (1H, m, $CH_2C\underline{H}CH_2$); 4.25-4.38 (2H, m, CH_2N); 7.13-8.01 (8H, m, H arom.); 12.51 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 26.49 (CH_3); 30.48 ($CH_2\underline{H}CH_2$); 37.65 ($\underline{C}H_2CO$); 51.95 (CH_2N); 111.05, 118.39, 121.16, 121.99, 129.18, 132.01, 134.45, 142.73, 143.19 (C_6H_5); 154.77 [C(N)NH]; 172.77 (NCO); 196.63 (CO). Mass spectrum, *m/z* (*I*, %): 320 $[M + H]^+$ (100). Found, %: C 71.37; H 5.30; N 13.02. $C_{19}H_{17}N_30_2$. Calculated, %: C 71.46; H 5.37; N 13.16.

4-[3(4)-Acetylphenylamino]-3-(1H-benzimidazol-2-yl)butyric Acids 4a,b (General Method). A mixture of the respective compound **2a**,**b** (0.32 g, 1 mmol) and 20% sodium hydroxide solution (8 ml) was boiled for 3 h, diluted with water (15 ml), cooled, and filtered. The filtrate was acidified to pH 6 with acetic acid. The crystals of compounds **4a**,**b** that formed were purified by dissolving them in a 5% solution of sodium hydroxide, filtration, and acidification to pH 6 with acetic acid. The crystals that separated were filtered off, washed with water, and dried.

4-(3-Acetylphenylamino)-3-(1H-benzimidazol-2-yl)butyric Acid (4a). Yield 81%; mp 172-173°C. IR spectrum, ν, cm^{-1}: 1681, 1603 (CO); 3372, 3262, 3057 (OH + NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3CO); 2.79-2.96 (2H, m, CH_2CO); 3.34-3.68 (3H, m, $CH_2CHCH_2 + CH_2N$); 6.14 (1H, t, *J* = 5.5, NH); 6.78-7.60 (8H, m, H arom.); 12.28 (1H, bs, COOH). ^{13}C NMR spectrum, δ, ppm: 26.73 (CH_3); 35.43 ($CH_2\underline{C}HCH_2$); 35.80 ($\underline{C}H_2CO$); 46.53 ($\underline{C}H_2NH$); 111.13, 115.86, 116.48, 121.18, 129.17, 137.67, 148.56 (C_6H_5); 155.81 (C=N); 173.10 (COOH); 198.29 (CO). Mass spectrum, *m/z* (*I*, %): 338 $[M + H]^+$ (100). Found, %: C 67.29; H 5.34; N 12.23. $C_{19}H_{19}N_30_3$. Calculated, %: C 67.64; H 5.68; N 12.46-212°C. IR spectrum, ν, cm^{-1}: 1656, 1601 (CO); 3265, 3152, 3057 (OH + NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3CO); 2.76-2.95 (2H, m, CH_2CO); 3.36-3.45 (1H, m, CH_2CHCH_2); 3.51-3.67 (2H, m, CH_2N); 6.82 (1H, t, *J* = 5.8, NH); 6.67-7.73 (8H, m, H arom.); 12.37 (1H, bs, COOH). ^{13}C NMR spectrum, δ, ppm: 25.89 (CH_3); 35.36 ($CH_2\underline{C}HCH_2$; 35.70 ($\underline{C}H_2CO$); 46.04 ($\underline{C}H_2NH$); 110.88, 121.22, 125.03, 130.42, 152.47, 155.54 (C=N); 172.99 (COOH); 195.01 (CO). Mass spectrum, *m/z* (*I*, %): 338 $[M + H]^+$ (100). Found, %:C 67.29; H 5.80; N 12.19. $C_{19}H_{19}N_30_3$. Calculated, %: C 67.64; H 5.68; N 12.46.

4-(4-Acetylphenylamino)-3-(1H-benzimidazol-2-yl)butyric Acid (4b). Yield 88%; mp 211-212°C. IR spectrum, ν, cm^{-1}: 1656, 1601 (CO); 3265, 3152, 3057 (OH + NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.40 (3H, s, CH_3CO); 2.76-2.95 (2H, m, CH_2CO); 3.36-3.45 (1H, m, $CH_2C\underline{H}CH_2$); 3.51-3.67 (2H, m, CH_2N); 6.82 (1H, t, *J* = 5.8, NH); 6.67-7.73 (8H, m, H arom.); 12.37 (1H, bs, COOH). ^{13}C NMR spectrum, δ, ppm: 25.89 (CH_3); 35.36 ($CH_2\underline{C}HCH_2$; 35.70 ($\underline{C}H_2CO$); 46.04 ($\underline{C}H_2NH$); 110.88, 121.22, 125.03, 130.42, 152.47, 155.54 (C=N); 172.99 (COOH); 195.01 (CO). Mass spectrum, *m/z* (*I*, %): 338 $[M + H]^+$ (100). Found, %: C 67.29; H 5.80; N 12.19. $C_{19}H_{19}N_30_3$. Calculated, %: C 67.64; H 5.68; N 12.46.

4-(1H-Benzimidazol-2-yl)-1-[4-(1-hydrazonoethyl)phenyl]-2-pyrrolidinone (5). A mixture of compound **2b** (2.24 g, 7 mmol), hydrazine monohydrate (1.05 g, 21 mmol), and methanol (10 ml) was boiled for 2 h. The crystals that separated on cooling were filtered off and washed with 2-propanol and ether. Yield 41%; mp >350°C (decomp.) (1,4-dioxane). IR spectrum, ν, cm^{-1}: 1703 (CO); 3387, 3212, 3086, 3052 (NH + NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (3H, s, ($C\underline{H}_3$)C=NNH_2); 2.94-3.10 (2H, m, CH_2CO); 3.93-4.06 (1H, m, $CH_2C\underline{H}CH_2$); 4.20-4.32 (2H, m, CH_2N); 6.35 (2H, s, NH_2); 7.11-7.68 (8H, m, H arom.); 12.49 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 11.24 (CH_3); 30.61 ($CH_2\underline{C}HCH_2$); 37.55 ($\underline{C}H_2CO$); 52.04 (CH_2N); 111.03, 118.46, 118.86, 121.14, 121.97, 124.93, 135.45, 138.12, 141.61; 142.74 (C=N); 154.96 (N=CNH); 171.90 (NCO). Mass spectrum, *m/z* (*I*, %): 334 $[M + H]^+$ (100). Found, %: C 68.07; H 5.59; N 20.78. $C_{19}H_{19}N_sO$. Calculated, %: C 68.45; H 5.74; N 21.01.

4-(1H-benzimidazol-2-yl)-1-(4-{1-[(1-{4-[4-(1H-benzimidazol-2-yl)-2-oxopyrrolidin-1-yl]phenyl}-ethylidene)hydrazono]ethyl}phenyl)-2-pyrrolidinone (6). A mixture of compound **2b** (21.8 g, 66 mmol), hexane monohydrate (6.51 g, 130 mmol), and 1,4-dioxane (100 ml) was boiled for 22 h. The crystals that separated on cooling were filtered off and washed with 2-propanol and with ether. Yield 51%; mp >360°C (decomp.) (1:1 mixture of 1,4-dioxane and DMF). IR spectrum, ν, cm^{-1}: 1697 (CO); 3370, 3054 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (6H, s, $2CH_3$); 2.99-3.15 (4H, m, $2CH_2CO$); 3.01-4.12 (2H, m, $2CH_2C\underline{H}CH_2$); 4.24-4.39 (4H, m, $2CH_2N$); 7.17-7.97 (18H, m, 2NH + H arom.). ^{13}C NMR spectrum, δ, ppm: 14.48 (CH_3); 30.46 ($CH_2\underline{C}HCH_2$); 37.52 ($\underline{C}H_2CO$); 51.93 (CH_2N); 114.69, 118.79, 121.76, 125.01, 126.96, 133.29, 140.41 (C_6H_5); 154.76 (N=CNH); 157.26 (C=N); 172.17 ($CH_2\underline{C}O$). Mass spectrum, *m/z* (*I*, %): 635 $[M + H]^+$ (100). Found, %: C 71.47; H 5.59; N 17.78. $C_{38}H_{34}O_2$. Calculated, %: C 71.91; H 5.40; N 17.65.

4-(1-Ethyl-1H-benzimidazol-2-yl)-1-(4-{1-[(1-{4-[4-(1-ethyl-1H-benzimidazol-2-yl)-2-oxopyrrolidin-1-yl]phenyl}ethylidene)hydrazono]ethyl}phenyl)-2-pyrrolidinone (7). A mixture of compound **6** (1.9 g, 3 mmol), iodoethane (50 ml), potassium hydroxide (2.36 g, 42 mmol), potassium carbonate (0.97 g, 7 mmol), and tetrabutylammonium iodide (ca 1 g) was boiled for 10 h. The liquid fractions were distilled under vacuum on a rotary evaporator, and the residue was inundated with water (10 ml) and stirred. The crystals were filtered off, washed with water, and dried. Yield 83%; mp 242-244°C (1,4-dioxane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (6H, t, *J* = 7.2, $2CH_2C\underline{H}_3$; 2.30 (6H, s, $2CH_3C$); 2.94-3.17 (4H, m, $2CH_2CO$); 4.15-4.40 (10H, m, $2CH_2C\underline{H}CH_2$ + $2CH_2N$ + $2C\underline{H}_2CH_3$); 7.16-7.98 (16H, m, H arom.). Found, %: C 72.87; H 5.86; N 16.15. $C_{42}H_{42}N_80_2$. Calculated, %: C 73.02; H 6.13; N 16.22.

4-(1H-Benzimidazol-2-yl)-1-(4-{1-[(9-ethyl-9H-carbazol-3-ylmethylene)hydrazono]ethyl}phenyl)-2-pyrrolidinone (8). A mixture of compound **6** (3.0 g, 9 mmol), 9-ethyl-3-formyl-carbazole (4.0 g, 18 mmol), and 1,4-dioxane (100 ml) was boiled for 4 h. The crystals that formed on cooling were filtered off, washed with 2-propanol, and dried. Yield 52%; mp 195-197°C (1:1 mixture of 1,4-dioxane and 2-propanol). IR spectrum, ν, cm^{-1}: 1697 (CO); 3051 (N=CH); 3386 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 2.56 (3H, s, CH_3C); 2.99-3.15 (2H, m, CH_2CO); 4.00-4.10 (1H, m, $CH_2C\underline{H}CH_2$); 4.26-4.39 (2H, m, CH_2N); 4.45-4.52 (2H, m, $C\underline{H}_2CH_3$); 7.14-8.73 (16H, m, N=CH + H arom.); 12.53 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 13.70 (CH_3); 14.48 (CH_3); 30.54 ($CH_2\underline{C}HCH_2$); 37.12 (CH_2); 37.61 ($\underline{C}H_2CO$); 51.97 (CH_2N); 109.51, 118.66, 119.46, 120.57, 121.49, 121.60, 125.39, 125.64, 126.24, 127.16, 133.12, 139.94, 139.99, 140.69; 141.11, 154.86 (C_6H_5 + N=CH); 159.27 (C=N); 162.63 (N=CNH); 172.32 (NCO). Mass spectrum, *m/z* (*I*, %): 561 $[M + Na]^+$ (100). Found, %: C 75.27; H 5.69; N 15.84. $C_{34}H_{30}N_6O$. Calculated, %: C 75.81; H 5.61; N 15.60.

4-(1H-Benzimidazol-2-yl)-1-(4-{1-[(4-diethylaminobenzylidene)hydrazono]ethyl}phenyl)-2-pyrrolinone (9). A mixture of compound **6** (1.0 g, 3 mmol), of *para*-diethylaminobenzaldehyde (0.64 g, 3.6 mmol), and 1,4-dioxane (10 ml) was boiled for 5 h. The crystals that formed on cooling were filtered off, washed with 2-propanol and with ether, and dried. Yield 66%; mp 244-245°C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 1672 (CO); 3055, 3012 (N=CH); 3391, 3182, 3146 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (6H, t, *J* = 7.2, $2CH_2C\underline{H}_3$); 2.48 (3H, s, CH_3C); 2.97-3.13 (2H, m, CH_2CO); 3.32-3.43 (4H, m, $2CH_2CH_3$); 3.98-4.09 (1H, m,

$CH_2C\underline{H}CH_2$); 4.25-4.37 (2H, m, CH_2N); 6.71-8.40 (13H, m, N=CH + H arom.); 12.49 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.38 ($2CH_3$); 14.33 (CH_3); 30.54 ($CH_2\underline{C}HCH_2$); 37.61 ($\underline{C}H_2CO$); 43.74 ($2CH_2$); 51.99 (CH_2N); 110.92, 111.02, 118.46, 118.65, 120.75, 121.13, 121.97, 126.98, 130.07, 133.35, 134.50, 140.47, 142.73, 149.43, 152.36, 154.87 (C_6H_5 + N=CH); 159.02 (C=N); 161.66 (N=CNH); 172.27 (NCO). Mass spectrum, *m/z* (*I*, %): 515 $[M + Na]^+$ (100). Found, %: C 72.73; H 6.48; N 16.72. $C_{30}H_{32}N_6O$. Calculated, %: C 73.14; H 6.55; N 17.06.

REFERENCES

1. M. D. Mashkovsky, I. N. Yakhontov, M. E. Kaminka, E. E. Mikhlina, M. D. Nair, K. Nagarajan Satyavan Sharma, Syed Abuzar J. Symoens, G. Cauwenbergh, and I. Zirngibl, *Progress in Drug Research*, **27**, 85 (1983).
2. A. Rao, A. Chimirri, S. Ferro, A. M. Monforte, P. Monforte, and M. Zappala, *ARKIVOC*, v, 147 (2004).
3. D. Yang, D. Fokas, J. Li, L. Yu, and C. M. Baldino, *Synthesis,* 47 (2005).
4. J. V. Starikova, G. V. Dolgushin, L. I. Larina, T. N. Komarova, and V. A. Lopyrev, *ARKIVOC,* xiii, 119 (2003).
5. J. Hazelton, B. Iddon, A. D. Redhouse, and H. Suschitzky, *Tetrahedron,* **51**, 5597 (1995).
6. M. A. Phillips, *J. Chem. Soc.,* 1143 (1931).
7. P. L. Paytash, E. Sparrow, and J. C Gathe, *J. Am. Chem. Soc.*, **72**, 1415 (1950).