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1-(2-QUINOXALYL)-, 1-[3,5-DI-(TRIFLUOROMETHYL)PHENYL]-, 1-(2-CARBOXYPHENYL)-, AND 1-ETHOXYCARBONYL-4-OXO-4,5,6,7-TETRAHYDROINDAZOLES

I. Strakova, A. Strakovs, and M. Petrova

The corresponding 1-(2-quinoxalyl)-, 1-[3,5-di(trifluoromethyl)phenyl]-, and 1-ethoxycarbonyl-3-methyl-4-oxo-4,5,6,7-tetrahydroindazoles have been obtained from reactions of 2-acetyl-1,3-cyclohexanedione, its 5,5-dimethyl and 5-(2-furyl) derivatives, with 2-hydrazinoquinoxaline, 3,5-di(trifluoromethyl)phenylhydrazine, and ethoxycarbonylhydrazine. On interaction with ethoxycarbonylhydrazine the intermediate 2-[1-(β-ethoxycarbonyl)hydrazino]ethylidene-1,3-cyclohexanediones were also isolated. From the potassium salt of 2-formyldimedone and 2-carboxyphenylhydrazine hydrochloride, 2-(2-carboxyphenyl)hydrazinomethylene-5,5-dimethyl-1,3-cyclohexanedione was obtained, the cyclization of which in ethanol in the presence of HCl led to 1-(2-carboxyphenyl)- and 1-(2-ethoxycarbonylphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazole.

Keywords: 1-(2-carboxyphenyl)-, 1-[3,5-di(trifluoromethyl)phenyl]-, 1-(2-quinoxalyl)-, and 1-(ethoxycarbonyl)-4-oxo-4,5,6,7-tetrahydroindazoles.

Derivatives of indazole hydrogenated in the carbocyclic part attract attention for several reasons, the principal of which their biological activity [1-6]. Consequently, developing our studies on the modification of indazoles, particularly on the synthesis of indazoles with a heterocyclic [7-9] or a substituted phenyl group [6,10,11] at nitrogen, we have carried out the reactions of 2-acetyl-1,3-cyclohexanedione (**1a**), its 5,5-dimethyl (**1b**) and 5-(2-furyl) (**1c**) derivatives with 2-hydrazinoquinoxaline (**2**), 3,5-di(trifluoromethyl)phenylhydrazine (**3**), and ethoxycarbonylhydrazine (**4**).

Refluxing equimolar quantities of acetyl derivatives **1** with hydrazine **3** in ethanol for 2 h leads directly to the indazole **6** in 85-90% yield. Isolation of the intermediate 2-(1-hydrazinoethylidene) product was unsuccessful. The formation of 1-(2-quinoxalyl)indazoles **5** requires more rigid reaction conditions, *viz.* refluxing in ethanol in the presence of catalytic amounts of acid for 5 h, but also in this case isolation of the intermediate products of the first condensation was unsuccessful. Indazoles **7** from acetyl derivatives **1** and ethoxycarbonylhydrazine **4** may be obtained only on extended refluxing (20 h) in ethanol in the presence of *p*-toluenesulfonic acid. Refluxing the same reactants for 5 min gives 2-[1-(β-ethoxycarbonylhydrazino)-ethylidene]-1,3-cyclohexanediones **8**, which are cyclized into indazoles **7** on refluxing for 20 h in ethanol in the presence of acid.

Riga Technical University, Riga LV-1658, Latvia; e-mail: marina@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 494-498, April, 2002. Original article submitted December 9, 1999.

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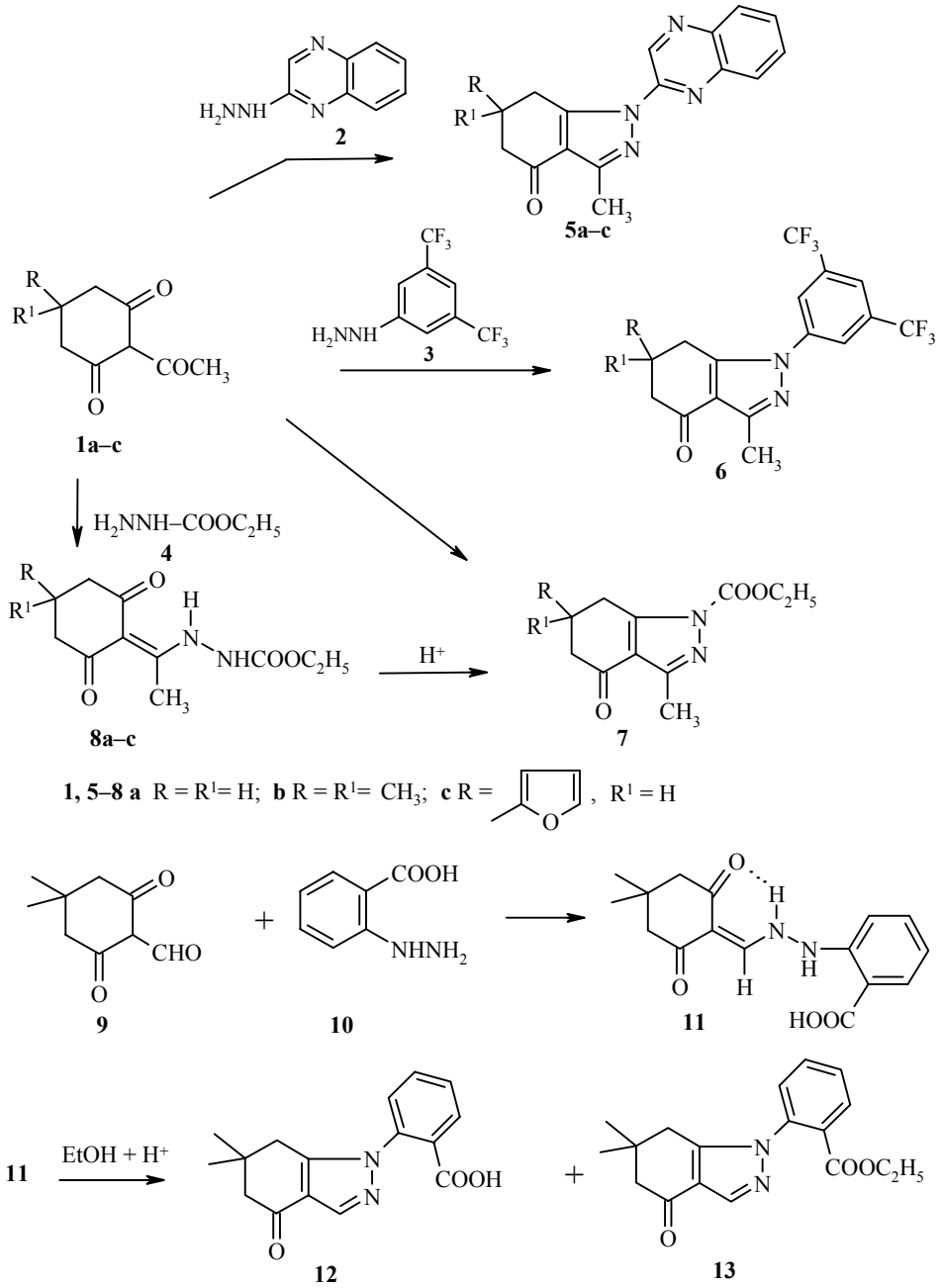

2-(2-Carboxyphenyl)hydrazinomethylene-5,5-dimethyl-1,3-cyclohexanedione (**11**) was obtained from the potassium salt of 2-formyldimedone (**9**) and 2-hydrazinobenzoic acid hydrochloride (**10**). Refluxing compound **11** in ethanol in the presence of HCl leads to a mixture of 1-(2-carboxyphenyl)- (**12**) and 1-(2-ethoxycarbonylphenyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles (**13**), which is readily separated by dissolving acid **12** in alkali.

The structures of the compounds synthesized were confirmed by the data of IR and ^{1}H NMR spectra. In the IR spectra the keto group of indazoles **5-7, 12**, and **13** is characterized by an intense maximum at 1662-1682, and the ester group of indazoles **7** by a band at 1747-1752 cm^{-1}. The IR spectra of 2-hydrazinoethylidene-1,3-cyclohexanediones **8** remind the spectra of arylhydrazones of 2-acetyl-1,3-cyclohexanediones [12] with a low intensity maximum at 1628-1633 and a broad intense absorption band at 1560-1590 cm^{-1}. In the ^{1}H NMR

spectra of the hydrazinoethylidene derivatives **8** a signal for the proton of the NH group was present in contrast to that of the indazoles **5-7**. The spectrum of the hydrazinomethylene derivative **11** was characterized by the presence of signals for the protons of the *trans*-fixed =CH–NH– fragment and of signals for the protons of the NH and COOH groups.

EXPERIMENTAL

The IR spectra were taken on a Specord IR 75 spectrometer for suspensions of substances in nujol (1500-1800 cm^{-1}) and hexachlorobutadiene (2000-3600 cm^{-1}). The frequencies of the stretching vibrations of the C–H bonds at 2800-3050 cm^{-1} are not given. The ^1H NMR spectra were taken on a Bruker WH 90/DS (90 MHz) spectrometer in $CDCl_3$ and DMSO-d_6 (internal standard TMS).

3-Methyl-1-(2-quinoxalyl)- (5a), 3,6,6-Trimethyl-1-(2-quinoxalyl)- (5b), and 6-(2-Furyl)-3-methyl-1-(2-quinoxalyl)- (5c) 4-Oxo-4,5,6,7-tetrahydroindazoles. 2-Hydrazinoquinoxaline **2** (about 5 mmol) and the corresponding 2-acetyl-1,3-cyclohexanedione **1** in abs. ethanol (40 ml) were refluxed for 2 h, *p*-toluenesulfonic acid (0.02 g) was added and the mixture refluxed for a further 3 h. The reaction mixture was cooled, the solid was filtered off, and recrystallized. Before crystallization compound **5a** was maintained in a flask with a fractionating column in an oil bath at 200-220°C (bath temperature) for 1 h.

5a. Yield 56%; mp 182-184°C (acetic acid). IR spectrum, cm^{-1}: 1670 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 2.12 (2H, m, $C_{(6)}H_2$); 2.48 (3H, s, $C_{(3)}$–CH_3); 2.50 (2H, m, $C_{(5)}H_2$); 3.52 (2H, t, $^3J = 6$, $C_{(7)}H_2$); 7.98 (4H, br m, C_6H_4); 9.45 (1H, s, $CH_{quinoxaline}$). Found, %: C 69.22; H 5.01; N 20.20. $C_{16}H_{14}N_4O$. Calculated, %: C 69.05; H 5.07; N 20.13.

5b. Yield 92%; mp 200-202°C (DMF). IR spectrum, cm^{-1}: 1667 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.12 (6H, s, $2CH_3$); 2.41 (2H, s, $C_{(5)}H_2$); 2.56 (3H, s, $C_{(3)}$–CH_3); 3.41 (2H, s, $C_{(7)}H_2$); 7.68-8.25 (4H, m, C_6H_4); 9.61 (1H, s, $CH_{quinoxaline}$). Found, %: C 70.66; H 5.81; N 18.18. $C_{18}H_{18}N_4O$. Calculated, %: C 70.57; H 5.92; N 18.29.

5c. Yield 88%; mp 189-191°C (DMF). IR spectrum, cm^{-1}: 1677 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.45 (3H, s, $C_{(3)}$–CH_3); 2.76 (1H, m, $C_{(6)}H$); 3.5-4.11 (4H, m, $C_{(5)}H_2$, $C_{(7)}H_2$); 6.20 (1H, m, C_4H_3O); 7.56 (1H, m, C_4H_3O); 7.89 (4H, br. m, C_6H_4); 9.42 (1H, s, $CH_{quinoxaline}$). Found, %: C 69.82; H 4.60; N 16.11. $C_{20}H_{16}N_4O_2$. Calculated, %: C 69.75; H 4.68; N 16.27.

1-[3,5-Di(trifluoromethyl)phenyl]-3-methyl-4-oxo-4,5,6,7-tetrahydroindazole (6a). A solution of compound **1a** (5 mmol) and hydrazine **3** (5 mmol) in abs. ethanol (20 ml) was refluxed for 2 h. Water (10 ml) was added to the hot reaction mixture, which was then cooled. The solid was filtered off, and recrystallized from 60% ethanol. Yield 89%; mp 112-113°C. IR spectrum, cm^{-1}: 1682 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 2.21 (2H, m, $C_{(6)}H_2$); 2.50 (2H, m, $C_{(5)}H_2$); 2.52 (3H, s, $C_{(3)}$–CH_3); 3.03 (2H, t, $^3J = 6.5$, $C_{(7)}H_2$); 7.82 (1H, m, $^4J < 1.5$, C_6H_3); 8.01 (2H, m, $^4J < 1.5$, C_6H_3). Found, %: C 52.90; H 3.30; N 7.60. $C_{16}H_{12}F_6N_2O$. Calculated, %: C 53.04; H 3.34; N 7.73.

3,6,6-Trimethyl- (6b) and 6-(2-Furyl)-3-methyl- (6c) [1-(3,5-Di(trifluoromethyl)phenyl]-4-oxo-4,5,6,7-tetrahydroindazoles were obtained analogously to compound **6a** from equimolar amounts of hydrazine **3** and compounds **1b,c**. **6b.** Yield 54%; mp 128-130°C (ethanol). IR spectrum, ν, cm^{-1}: 1676 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 (6H, s, $2CH_3$); 2.41 (2H, s, $C_{(5)}H_2$); 2.54 (3H, s, $C_{(3)}$–CH_3); 2.83 (2H, s, $C_{(7)}H_2$); 7.89 (1H, m, C_6H_3); 8.01 (2H, m, C_6H_3). Found, %: C 55.19; H 4.02; N 7.11. $C_{18}H_{16}F_6N_2O$. Calculated, %: C 55.39; H 4.13; N 7.18.

6c. Yield 86%; mp 101-102°C (60% ethanol). IR spectrum, ν, cm^{-1}: 1677 (C=O). ^1H NMR spectrum, ($CDCl_3$), δ, ppm, *J* (Hz): 2.53 (3H, s, $C_{(3)}$–CH_3); 2.86 (2H, m, ($C_{(5)}H_2$); 3.25 (2H, m, $C_{(7)}H_2$); 3.67 (1H, m, $C_{(6)}H$); 6.09 (1H, m, C_4H_3O); 6.32 (1H, m, C_4H_3O); 7.32 (1H, m, C_4H_3O); 7.89 (1H, m, $^4J < 1.5$, C_6H_3); 8.01 (2H, m, $^4J = 1.5$, C_6H_3). Found, %: C 55.90; H 3.13; N 6.39. $C_{20}H_{14}F_6N_2O_2$. Calculated, %: C 56.08; H 3.29; N 6.54.

3-Methyl- (7a), 3,6,6-Trimethyl- (7b), and 6-(2-Furyl)-3-methyl- (7c) 1-Ethoxycarbonyl-4-oxo-4,5,6,7-tetrahydroindazoles. A. A solution of compound **1a-c** (5 mmol), hydrazine **4** (5 mmol), and *p*-toluenesulfonic acid (0.05 g) in abs. ethanol (20 ml) was refluxed for 20 h. The reaction mixture was cooled, the solid filtered off, and recrystallized from ethanol.

B. A solution of the hydrazinoethylidene derivative **8** (5 mmol) and *p*-toluenesulfonic acid (0.05 g) in abs. ethanol (20 ml) was refluxed for 20 h. The reaction mixture was cooled, the solid was filtered off, and recrystallized from ethanol.

The yield of products obtained by method A is indicated below.

7a. Yield of product was 83%; mp 123-125°C. IR spectrum, ν, cm^{-1}: 1752, 1664 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.42 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.16 (2H, m, $C_{(6)}H_2$); 2.47 (2H, t, ^3J = 7, $C_{(5)}H_2$); 2.49 (3H, s, $C_{(3)}$–CH_3); 3.21 (2H, t, ^3J = 7, $C_{(7)}H_2$); 4.49 (2H, q, ^4J = 7, $CH_3\underline{CH_2}$). Found, %: C 58.48; H 6.47; N 12.78. $C_{11}H_{14}N_2O_3$. Calculated, %: C 59.45; H 6.35; N 12.60.

7b. Yield 52%; mp 109-111°C. IR spectrum, ν, cm^{-1}: 1747, 1677 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.09 (6H, s, $2CH_3$); 1.47 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.34 (2H, s, $C_{(5)}H_2$); 2.47 (3H, s, $C_{(3)}$–CH_3); 3.09 (2H, s, $C_{(7)}H_2$); 4.49 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$). Found, %: C 62.19; H 7.11; N 11.11. $C_{13}H_{18}N_2O_3$. Calculated, %: C 62.38; H 7.25; N 11.19.

7c. Yield 61%; mp 127-128°C. IR spectrum, ν, cm^{-1}: 1747, 1677 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.45 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.49 (3H, s, $C_{(3)}$–CH_3); 2.78 (4H, m, $C_{(5)}H_2$, $C_{(7)}H_2$); 3.61 (1H, m, $C_{(6)}H$); 4.54 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$); 6.09 (1H, d, ^3J = 6, C_4H_3O); 6.29 (1H, d d, ^3J = 6, ^3J = 2, C_4H_3O); 7.34 (1H, d, ^3J = 2, C_4H_3O. Found, %: C 61.53; H 5.61; N 10.43. $C_{15}H_{16}N_2O_4$. Calculated, %: C 62.49; H 5.59; N 9.72.

5,5-H- (8a), 5,5-Dimethyl- (8b), and 5-(2-Furyl)- (8c) 2-[1-(β-Ethoxycarbonyl)hydrazine]-ethylidene-1,3-cyclohexanediones. A solution of hydrazine **4** (5 mmol) in abs. ethanol (5 ml) heated to 70-75°C was poured into a solution of acetyl derivative **1** (5 mmol) in abs. ethanol (15 ml) heated to the same temperature, and the reaction mixture was refluxed for 5 min. The mixture was cooled, the solid was filtered off, and recrystallized from ethanol, without extended refluxing.

8a. Yield 61%; mp 118-119°C. IR spectrum, ν, cm^{-1}: 1752, 1628 (C=O); 3200-3240 (N–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.23 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 1.91 (2H, m, $C_{(5)}H_2$); 2.49 (4H, m, $C_{(4)}H_2$, $C_{(6)}H_2$); 2.61 (3H, s, $C_{(2')}$–CH_3); 4.24 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$); 8.21 (1H, br s, NH–CO); 14.80 (1H, br. s, NH–$C_{(2')}$). Found, %: C 55.17; H 6.80; N 11.51. $C_{11}H_{16}N_2O_4$. Calculated, %: C 54.99; H 6.71; N 11.66.

8b. Yield 63%; mp 93-94°C. IR spectrum, ν, cm^{-1}: 1742, 1632 (C=O); 3180-3200 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 0.99 6H, s, $2CH_3$); 1.27 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.33 (4H, br. s, $C_{(4)}H_2$, $C_{(6)}H_2$); 2.57 (3H, s, $C_{(2)}$–CH_3); 4.27 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$); 8.22 (1H, br s, NH-CO); 16.63 (1H, br. s, NH–$C_{(2')}$). Found, %: C 58.38; H 7.52; N 10.30. $C_{13}H_{20}N_2O_4$. Calculated, %: C 58.19; H 7.51; N 10.44.

8c. Yield 80%; mp 149-150°C. IR spectrum, ν, cm^{-1}: 1724, 1641 (C=O); 3290-3310, 3130 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.24 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.02 (3H, s, $C_{(2')}CH_3$); 2.23 (4H, m, $C_{(4)}H_2$, $C_{(6)}H_2$); 3.38 (1H, m, $C_{(5)}H$); 4.19 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$); 6.05 (1H, m, C_4H_3O); 6.27 (1H, m, C_4H_3O); 7.33 (1H, m, C_4H_3O); 7.94 (1H, br. s, NH–CO); 14.72 (1H, br. s, NH–$C_{(2')}$). Found, %: C 58.65; H 5.80; N 9.11. $C_{15}H_{18}N_2O_5$. Calculated, %: C 58.81; H 5.92; N 9.14.

2-(2-Carboxyphenyl)hydrazinomethylene-5,5-dimethyl-1,3-cyclohexanedione (11). A solution of 2-hydrazinobenzoic acid hydrochloride (1.89 g, 10 mmol) heated to 60-70°C was poured into a solution of 2-formyldimedone potassium salt (**9**) (2.06 g, 10 mmol) in water (20 ml) at the same temperature. The reaction mixture was cooled, the solid was filtered off, and recrystallized from ethanol. Yield 84%; mp 223-225°C. IR spectrum, ν, cm^{-1}: 1635 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.07 (6H, s, $2CH_3$); 2.34 (2H, s, $C_{(4,6)}H_2$); 2.41 (2H, s, $C_{(4,6)}H_2$); 4.5 (1H, br. s, COOH); 6.94 (2H, m, C_6H_4); 7.48 (1H, m, C_6H_4); 7.98 (1H, dd, ^3J = 8, ^4J = 1.5, C_6H_4); 8.27 (1H, d, ^3J = 9, =CH–); 10.29 (1H, br. s, NH–C_6H_4); 12.34 (1H, d, ^3J = 9, NH–CH=). Found, %: C 63.25; H 5.88; N 9.12. $C_{16}H_{18}N_2O_4$. Calculated, %: C 63.56; H 6.00; N 9.27.

1-(2-Carboxyphenyl)- (12) and 1-(2-Ethoxycarbonylphenyl)- (13) 6,6-Dimethyl-4-oxo-4,5,6,7-tetrahydroindazoles. A solution of compound **11** (3.02 g, 10 mmol) and conc. hydrochloric acid (3 ml) in ethanol (70 ml) was refluxed for 5 h, ethanol was evaporated off to half volume, and water (100 ml) was added to the hot remainder. The oily residue which rapidly hardened was filtered off, and thoroughly ground with 1% aqueous KOH solution. The insoluble solid was filtered off, recrystallized from ethanol, and ester **13** (1.10 g, 36%) was obtained. The filtrate was acidified with conc. HCl, the precipitated solid was filtered off, recrystallized from 50% ethanol, and acid **12** (0.90 g: 31%) was obtained. Refluxing acid **11** for 2 h in ethanol in the presence of catalytic amounts of acid leads exclusively to indazole **12** in 35% yield.

12. Mp 183-185°C. IR spectrum, ν, cm^{-1}: 1703, 1681, 1651 (C=O); 2500-2650 (COOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 (6H, s, $2CH_3$); 2.36 (2H, s, $C_{(5,7)}H_2$); 2.47 (2H, s, $C_{(5,7)}H_2$); 7.32 (1H, m, C_6H_4); 7.62 (2H, m, C_6H_4); 7.89 (1H, s, $C_{(3)}H$); 8.05 (1H, m, C_6H_4); 8.81 (1H, br. s, COOH). Found, %: C 67.80; H 5.60; N 9.73. $C_{16}H_{16}N_2O_3$. Calculated, %: C 67.59; H 5.67; N 9.85.

13. Mp 127-128°C. IR spectrum, ν, cm^{-1}: 1721, 1662 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.05 (6H, s, $2CH_3$); 1.07 (3H, t, ^3J = 7, $\underline{CH_3}CH_2$); 2.36 (2H, s, $C_{(5,7)}H_2$); 2.52 (2H, s, $C_{(5,7)}H_2$); 4.09 (2H, q, ^3J = 7, $CH_3\underline{CH_2}$); 7.32 (1H, m, C_6H_4); 7.56 (2H, m, C_6H_4); 7.96 (1H, m, C_6H_4); 7.98 (1H, s, $C_{(3)}H$). Found, %: C 69.03; H 6.40; N 8.81. $C_{18}H_{20}N_2O_3$. Calculated, %: C 69.21; H 6.45; N 8.97.

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