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Esters of 4-(3-Dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenylacetic acids

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Abstract— Reaction of equivalent amounts of alkyl 4-aminophenylacetates with maleic anhydride gave rise to the corresponding alkyl 4-*N*-maleimidophenylacetates which with diethylamine, piperidine, and morpholine afforded esters of 4-(3-dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenylacetic acids as stereoisomer mixtures.

A number of *N*-aryl-2-(4-alkylpiperazino)- and 2-(benzimidazol-2-yl)succinimides are known to possess soporific, anticonvulsive, antiarrhythmic, and other types of activity [1–3]. At the same time a series of substituted derivatives of phenylacetic acid and its esters, in particular, with pyrrole and pyrazole rings as *para*-substituents show antiphlogistic, analgesic, antirheumatic, and anticonvulsive activity [4–6]. Therefore it looks promising to prepare phenylacetic acids esters having a 2-dialkylamino-succinimide ring as a substituent and to study their properties.

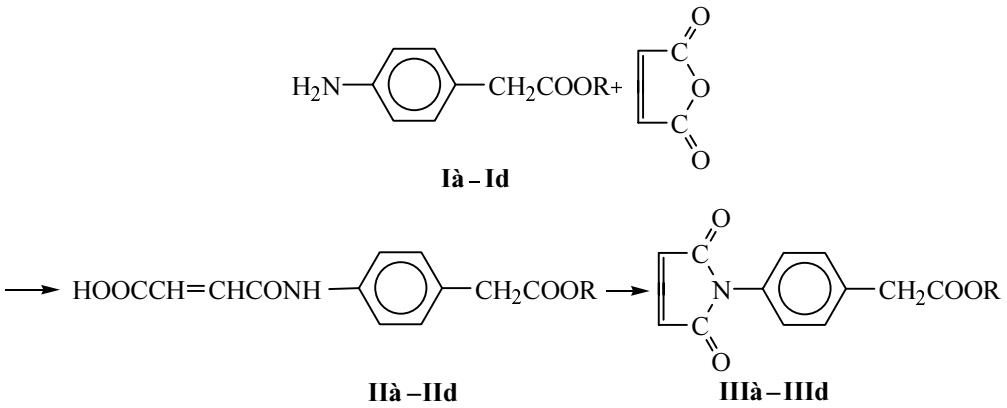
The reaction of alkyl *p*-aminophenylacetates **Ia–Id** with maleic anhydride afforded the corresponding maleamic acids **IIa–IId** whose cyclization effected by acetanhydride in DMF resulted in alkyl 4-*N*-maleimido-phenylacetates **IIIa–IIId**.

Maleamides **IIa–IId** are yellow powders, and maleimides are crystals of light-yellow (**IIIb** and **IIIc**) or light-brown (**IIIa** and **IIId**) color. The composition and the homogeneity of the substances were confirmed by elemental analysis and TLC, and the structure was proved by IR and ^{1}H NMR spectra. In the IR spectra of maleimides **IIIa–IIId** the stretching vibrations of the CH=CH bond give rise to a weak but characteristic absorption band in the region 3095–3070 cm^{-1}, and the stretching vibrations of the C=O group appear as several strong bands in the region 1700–1645 cm^{-1} and a weak overtone at 3455–3445 cm^{-1}. In the ^{1}H NMR spectra of maleimides **IIIa–IIId** the protons of the maleimide ring give a singlet at 7.15 ppm.

The treatment of maleimides **IIIa–IIId** with equivalent amounts of diethylamine (**IVa**), piperidine (**IVb**), and morpholine (**IVc**) in dioxane at 45–90°C afforded the corresponding esters of 4-(3-dialkylamino-2,3,4,5-tetra-hydro-1*H*-pyrrolyl)phenylacetic acids **Va–Vj**.

Compounds **Va–Vj** are crystalline or amorphous powders of color varying from colorless to light-brown. In their IR spectra the bands of the stretching vibrations of the C=O groups appear in the same region as in the spectra of maleimides **IIIa–IIId**, and additional medium

Scheme.



R = Me (**a**), Et (**b**), CH_2CH_2Cl (**c**), C_4H_9 (**d**).

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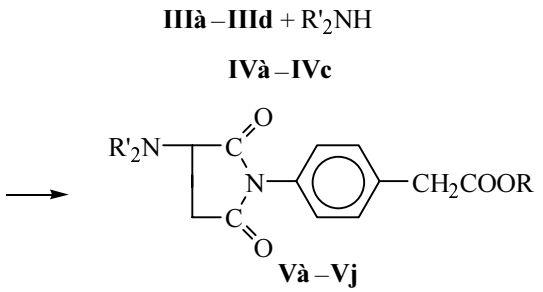

IV, R' = Et (**a**), R'_2 = $(CH_2)_5$ (**b**), $(CH_2)_2O(CH_2)_2$ (**c**); **V**, R = Me, R' = Et (**a**); R = Et, R' = Et (**b**), R'_2 = $(CH_2)_5$ (**c**), $(CH_2)_2O(CH_2)_2$ (**d**); R = CH_2CH_2Cl, R' = Et (**e**), R'_2 = $(CH_2)_5$ (**f**), $(CH_2)_2O(CH_2)_2$ (**g**); R = C_4H_9, R' = Et (**h**), R'_2 = $(CH_2)_5$ (**i**), $(CH_2)_2O(CH_2)_2$ (**j**).

absorption band is seen at 1745–1735 cm^{-1}. In the ^1H NMR spectra of compounds **Va–Vd** and **Vh–Vj** the protons of the CH_2 group of the succinimide ring give rise to two characteristic signals: a doublet of doublets in the region 2.72–2.83 ppm ($^3J_{HH}$ 4 and 12 Hz), and a quartet at 2.95–2.98 ppm ($^3J_{HH}$ 8 Hz). The signal from the proton belonging to the CH group of the succinimide ring appears as a quartet at 3.98–4.25 ppm ($^3J_{HH}$ 8 Hz). The chemical shift of this proton grows in the series of substituents: piperidino > morpholino > diethylamino. The multiplet character of the protons from the succinimide ring indicates that the compounds obtained are mixtures of stereoisomers. It is also revealed by the nonequivalence of the CH_2 groups attached to nitrogen in the piperidine (**Vc** and **Vi**) and morpholine (**Vd** and **Vj**) rings; these signals appear as two multiplets in the 2.47–2.50 and 2.52–2.85 ppm.

EXPERIMENTAL

IR spectra were recorded on a spectrometer IR-75 from thin films. The ^1H NMR spectra were registered on a spectrometer Bruker DRX500 (500.13 MHz) in DMSO-d_6, internal reference TMS. TLC was carried out on Sorbfil PTLC-P-V, eluent ethanol–hexane, 3:1, development in iodine vapor. Elemental analyses were carried out on an analyzer Perkin Elmer 2400 CHN.

3-[(4-Methoxycarbonylmethyl)phenylcarbamoyl]-2-propenoic acid (IIa). To a solution of 5.78 g of methyl 4-aminophenylacetate in 25 ml of ether was gradually added within 10–15 min a solution of 3.43 g of maleic anhydride in 25 ml of ether. In 2 h the separated precipitate was filtered off, washed with ether (3 × 3 ml), and dried in air. Yield 8.9 g (96.7%), yellow powder, mp 161–163°C, R_f 0.48. IR spectrum, ν, cm^{-1}: 3260, 3185 (NHCO), 1700, 1660 (C=O), 1090 (COC). Found, %: C 59.21; H 4.91; N 5.38. $C_{13}H_{13}NO_5$. Calculated, %: C 59.32; H 4.98; N 5.32.

Compounds **IIb–IId** were prepared in the same way.

3-[(4-Ethoxycarbonylmethyl)phenylcarbamoyl]-2-propenoic acid (IIb). Yield 92.4%, mp 153–154°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 3280, 3200 (NHCO), 1700, 1670 (C=O), 1100 (COC). Found, %: C 60.48; H 5.51; N 5.01. $C_{14}H_{15}NO_5$. Calculated, %: C 60.65; H 5.45; N 5.05.

3-{[4-(2-Chloroethoxy)carbonylmethyl]phenylcarbamoyl}-2-propenoic acid (IIc). Yield 81.2%, mp 134–136°C. R_f 0.55. IR spectrum, ν, cm^{-1}: 3260, 3185 (NHCO), 1690, 1670 (C=O), 1115 (COC). Found, %: C 53.66; H 4.52; N 4.52. $C_{14}H_{14}ClNO_5$. Calculated, %: C 53.95; H 4.53; N 4.49.

3-[(4-Butoxycarbonylmethyl)phenylcarbamoyl]-2-propenoic acid (IIc). Yield 48.0%, mp 118.5–121°C. R_f 0.58. IR spectrum, ν, cm^{-1}: 3280, 3200 (NHCO), 1705, 1675 (C=O), 1090 (COC). Found, %: C 63.07; H 6.63; N 4.63. $C_{16}H_{19}NO_5$. Calculated, %: C 62.95; H 6.27; N 4.59.

Methyl [4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrolyl)-phenyl]acetate (IIIa). A mixture of 7.89 g of maleamide **IIa**, 0.45 g of anhydrous sodium acetate, 4.5 g of acetanhydride, and 25 ml of DMF was stirred for 4 h at 45–50°C. The reaction mixture was cooled to room temperature and mixed with 150 ml of water. The precipitate was filtered off, washed with water (10×5 ml), and dried in air. Yield 5.6 g (76.1%), light-brown crystals, mp 91–92°C (2×MeOH), R_f 0.66. IR spectrum, ν, cm^{-1}: 3455, 1700, 1670 (C=O), 3085 (CH=CH), 1110 (COC). ^1H NMR spectrum, δ, ppm: 3.63 s (3H, CH_3), 3.73 s (2H, CH_2Ar), 7.15 s (2H, CH=CH), 7.28 d and 7.38 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 63.97; H 4.50; N 5.68. $C_{13}H_{11}NO_4$. Calculated, %: C 63.68; H 4.52; N 5.71.

Compounds **IIIb–IIId** were prepared similarly.

Ethyl [4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrolyl)-phenyl]acetate (IIIb). Yield 81%, mp 83–85°C (2×EtOH). R_f 0.68. IR spectrum, ν, cm^{-1}: 3450, 1690, 1670 (C=O), 3095 (CH=CH), 1110 (COC). ^1H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, $^3J_{HH}$ 8 Hz), 3.72 s (2H, CH_2Ar), 4.10 q (2H, CH_2, $^3J_{HH}$ 8 Hz), 7.15 s (2H, CH=CH), 7.28 d and 7.38 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 65.02; H 5.08; N 5.43. $C_{14}H_{13}NO_4$. Calculated, %: C 64.86; H 5.05; N 5.40.

2-Chloroethyl [4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrolyl)phenyl]acetate (IIIc). Yield 99.0%, mp 114–

116°C (2 × EtOH). R_f 0.63. IR spectrum, ν, cm^{-1}: 3450, 1700, 1670, 1650 (C=O), 3070 (CH=CH), 1250 (CH_2–Cl), 1105 (COC). ^{1}H NMR spectrum, δ, ppm: 3.77 s (2H, CH_2Ar), 3.83 t (2H, CH_2Cl, $^3J_{HH}$ 8 Hz), 4.35 t (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.15 s (2H, CH=CH), 7.28 d and 7.38 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 57.41; H 4.15; N 4.81. $C_{14}H_{12}ClNO_4$. Calculated, %: C 57.26; H 4.12; N 4.77.

Butyl [4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrolyl)-phenyl]acetate (IIId). Yield 65.9%, mp 59–61°C (2 × BuOH), R_f 0.73. IR spectrum, ν, cm^{-1}: 3445, 1690, 1660, 1645 (C=O), 3085 (CH=CH), 1095 (COC). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, $^3J_{HH}$ 8 Hz), 1.32 m and 1.56 m (4H, $2CH_2$), 3.72 s (2H, CH_2Ar), 4.05 t (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.15 s (2H, CH=CH), 7.28 d and 7.38 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 67.01; H 6.00; N 4.92. $C_{16}H_{17}NO_4$. Calculated, %: C 66.89; H 5.96; N 4.88.

Alkyl [4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetates Va–Vj. To a solution of 0.01 mol of an appropriate maleimide **IIIa–IIId** in 4 ml of dioxane was gradually added a solution of 0.01 mol of secondary amine **IVa–IVc** in 4 ml of dioxane, the mixture was stirred for 2–4 h at room temperature and then heated for 1 h at 45–50°C (with diethylamine) or 1 h at 60–90°C (with piperidine and morpholine). The reaction mixture was cooled to room temperature and mixed with 150–200 ml of water. The separated precipitate was filtered off, washed with water (10×5 ml), and dried in air. Compounds **Va**, **Vb**, and **Vb** precipitated (**Vb** partially) directly from the reaction mixture. The compounds obtained were additionally purified by crystallization.

Methyl [4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Va). Yield 58.2%, mp 124–124.5°C (dioxane and MeOH), R_f 0.58. IR spectrum, ν, cm^{-1}: 3445, 1740, 1690, 1670 (C=O), 1110 (COC). ^{1}H NMR spectrum, δ, ppm: 1.02 t (6H, $2CH_3$, $^3J_{HH}$ 8 Hz), 2.65 m (4H, $2CH_2N$), 2.72 d.d and 2.95 q (2H, CH_2 of ring), 3.63 s (3H, CH_3O), 3.73 C (2H, CH_2Ar), 4.25 q (1H, CH of ring, $^3J_{HH}$ 8 Hz), 7.18 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 64.28; H 7.04; N 8.85. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.14; H 6.97; N 8.80.

Ethyl[4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vb). Yield 81.2%, mp 111.5–112.5°C (dioxane and EtOH), R_f 0.68. IR spectrum, ν, cm^{-1}: 3450, 1745, 1690, 1670 (C=O), 1110 (COC). ^{1}H NMR spectrum, δ, ppm: 1.03 t (6H, $2CH_3$, $^3J_{HH}$ 8 Hz), 1.20 t (3H, CH_3, $^3J_{HH}$ 8 Hz), 2.63 m (4H, $2CH_2N$), 2.72 d.d. and 2.95 q (2H, CH_2 of ring), 3.72 s (2H, CH_2Ar), 4.10 q (2H, CH_2O, $^3J_{HH}$ 8 Hz), 4.25 q (1H, CH of ring, $^3J_{HH}$ 8 Hz), 7.20 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8). Found, %: C 65.01; H 7.33; N 8.48. $C_{18}H_{24}N_2O_4$. Calculated, %: C 65.05; H 7.28; N 8.43.

Ethyl [4-(3-piperidino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vc). Yield 85.8%, mp 102.5–104°C (2 × EtOH). R_f 0.62. IR spectrum, ν, cm^{-1}: 3445, 1735, 1680, 1665 (C=O), 1110 (COC). ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, $^3J_{HH}$ 8 Hz), 1.40 m (2H, CH_2 of piperidine), 1.57 s (4H, $2CH_2$ of piperidine), 2.47 m and 2.78 m (4H, $2CH_2$ of piperidine), 2.75 d.d and 2.97 q (2H, CH_2 of ring), 3.70 s (2H, CH_2Ar), 3.98 q (1H, CH of ring), 4.12 q (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.18 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 66.37; H 7.10; N 8.08. $C_{19}H_{24}N_2O_4$. Calculated, %: C 66.26; H 7.02; N 8.13.

Ethyl [4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vd). Yield 60.7%, mp 142–143°C (dioxane and MεOH), R_f 0.53. IR spectrum, ν, cm^{-1}: 3450, 1740, 1680, 1670 (C=O), 1105 (COC). ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, $^3J_{HH}$ 8 Hz), 2.50 m and 2.85 m (4H, $2CH_2$ of morpholine), 2.82 d.d and 2.98 q (2H, CH_2 of ring), 3.60 s (4H, $2CH_2$ of morpholine), 3.72 s (2H, CH_2Ar), 4.00 q (1H, CH of ring), 4.12 q (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.20 d and 7.38 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 62.49; H 6.35; N 8.14. $C_{18}H_{22}N_2O_5$. Calculated, %: C 62.42; H 6.40; N 8.09.

2-Chloroethyl [4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Ve). Yield 59.9%, mp 62–65°C (50% EtOH), R_f 0.53. IR spectrum, ν, cm^{-1}: 3425, 1665 (C=O), 1260 (CH_2Cl), 1105 (COC). Found, %: C 59.01; H 6.23; N 7.69. $C_{18}H_{23}ClN_2O_4$. Calculated, %: C 58.94; H 6.32; N 7.64.

2-Chloroethyl [4-(3-piperidino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vf). Yield 51.6%, mp 67–71°C. R_f 0.59. IR spectrum, ν, cm^{-1}: 1640 (C=O), 1250 (CH_2Cl), 1110 (COC). Found, %: C 60.33; H 6.15; N 7.73. $C_{19}H_{23}ClN_2O_4$. Calculated, %: C 60.24; H 6.12; N 7.39.

2-Chloroethyl [4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vg). Yield 59.1%, mp 79–81°C, R_f 0.46. IR spectrum, ν, cm^{-1}: 1740, 1680, 1640 (C=O), 1245 (CH_2Cl), 1100 (COC). Found, %: C 56.89; H 5.63; N 7.41. $C_{18}H_{21}ClN_2O_5$. Calculated, %: C 56.77; H 5.56; N 7.36.

Butyl [4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vh). Yield 79.2%, mp 67–68°C (ether), R_f 0.67. IR spectrum, ν, cm^{-1}: 3445, 1740, 1685, 1670, 1640 (C=O), 1100 (COC). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3 of butyl, $^3J_{HH}$ 8 Hz), 1.03 s (6H, $2CH_3$, $^3J_{HH}$ 8 Hz), 1.33 m and 1.57 m (4H, $2CH_2$ of butyl), 2.63 m (4H, $2CH_2$, N), 2.72 d.d and 2.95 q (2H, CH_2 of ring), 4.72 s (2H, CH_2Ar), 4.05 t (2H, CH_2O, $^3J_{HH}$ 8 Hz), 4.25 q (1H, CH of ring), 7.18 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 66.78; H 7.90; N 7.72. $C_{20}H_{28}N_2O_4$. Calculated, %: C 66.65; H 7.83; N 7.77.

Butyl [4-(3-piperidine-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (VI). Yield 79.3%, mp 82–84°C (ether), R_f 0.65. IR spectrum, ν, cm^{-1}: 3455, 1745, 1690, 1670 (C=O), 1110 (COC). ^{1}H NMR spectrum, δ, ppm: 0.83 t (3H, CH_3 of butyl, $^3J_{HH}$ 8 Hz), 1.40 m (2H, CH_2 of piperidine), 1.32 m and 1.57 m (4H, $2CH_2$ of butyl), 1.52 s (4H, $2CH_2$ of piperidine), 2.48 m and 2.78 m (4H, $2CH_2$), 2.75 d.d and 2.97 q (2H, CH_2 of ring), 3.70 s (2H, CH_2Ar), 3.98 q (1H, CH of ring), 4.07 t (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.18 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz). Found, %: C 67.69; H 7.48; N 7.48. $C_{21}H_{28}N_2O_4$. Calculated, %: C 67.72; H 7.58; N 7.52.

Butyl [4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolyl)phenyl]acetate (Vj). Yield 81.6%, mp 97–98.5°C (BuOH), R_f 0.54. IR spectrum, ν, cm^{-1}: 3455, 1740, 1685, 1670 (C=O), 1105 (COC). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3 of butyl, $^3J_{HH}$ 8 Hz), 1.32 m and 1.56 m (4H, $2CH_2$ of butyla), 2.52 m and 2.85 m (4H, $2CH_2$ of morpholine), 2.83 d.d and 2.98 q (2H, CH_2 of ring), 3.60 c (4H, $2CH_2$ of morpholine), 3.72 c (2H, CH_2Ar), 4.00 q (1H, CH of ring), 4.07 t (2H, CH_2O, $^3J_{HH}$ 8 Hz), 7.20 d and 7.37 d (4H, H_{arom}, $^3J_{HH}$ 8 Hz) Found, %: C 64.27; H 7.08; N 7.43. $C_{20}H_{26}N_2O_5$. Calculated, %: C 64.16; H 7.00; N 7.48.

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