

4-(3-Dialkylamino-2,5-dioxopyrrolidin-1-yl)benzoic Acid Esters

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Abstract—Reactions of alkyl 4-aminobenzoates with maleic anhydride give the corresponding alkyl 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoates, and the latter are converted into 4-(3-dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrol-1-yl)benzoates by treatment with secondary amines.

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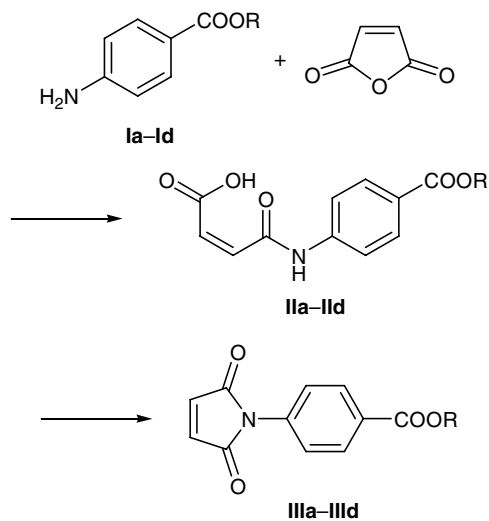
N-Aryl-3-dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrroles exhibit soporific, antispasmodic, and antiarrhythmic activity [1–3], while substituted 4-aminobenzoic acids and their esters are used as anesthetics [4]. Therefore, we thought it to be reasonable to synthesize 4-aminobenzoic acid ester derivatives containing a 3-dialkylamino-2,5-dioxopyrrolidine fragment. Esters **Ia–Id** reacted with maleic anhydride to form unsaturated amido acids **IIa–IIId**, and their cyclization by the action of acetic anhydride in DMF or by heating in DMF–toluene in the presence of *p*-toluenesulfonic acid with simultaneous removal of water as azeotrope (**IIIb**) gave alkyl 4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoates **IIIa–IIIId** (Scheme 1).

Amides **IIa–IIId** are light yellow powders, while imides **IIIa–IIIId** are light yellow to light brown crys-

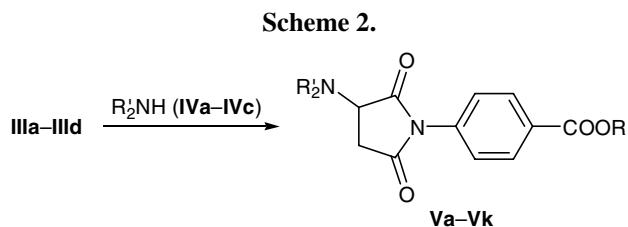
talline substances. Their structure and purity were confirmed by the data of elemental analysis, TLC, and IR and ¹H NMR spectra. In the IR spectra of **IIIa–IIIId**, stretching vibrations of the =C–H bonds appeared as a weak absorption band at 3100–3085 cm⁻¹, and the carbonyl groups gave rise to several strong bands in the region 1700–1635 cm⁻¹ and a weak overtone at 3465–3445 cm⁻¹. The ¹H NMR spectra of **IIIa–IIIId** contained singlets at δ 7.24–7.10 ppm due to protons in the dihydropyrrole ring.

By treatment of imides **IIIa–IIIId** with an equimolar amount of diethylamine (**IVa**), piperidine (**IVb**), or morpholine (**IVc**) in dioxane at 45–90°C we obtained alkyl 4-(3-dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrol-1-yl)benzoates **Va–Vk** (Scheme 2). Compounds **Va–Vk** are colorless to light brown crystalline or amorphous powders. The IR spectra of **Va–Vk** contained absorption bands due to stretching vibrations of the carbonyl groups in the same regions as in the spectra of initial imides **IIIa–IIIId**, and an additional medium-intensity band was present at 1750–1730 cm⁻¹. In the ¹H NMR spectra of esters **Va–Vk**, methylene protons of the succinimide fragment characteristically appeared as a doublet of doublets at δ 2.75–2.86 ppm (³*J*_{HH} = 4, 12 Hz) and a quartet at δ 2.96–3.00 ppm (³*J*_{HH} = 8 Hz). Proton on the carbon atom neighboring to the amino group resonated as a quartet at δ 4.02–4.30 ppm (³*J*_{HH} = 8 Hz). The observed pattern suggests that esters **Va–Vk** are mixtures of stereoisomers. This is also confirmed by nonequivalence of the CH₂ groups linked to the nitrogen atom in the piperidine ring of **Vb**, **Vg**, and **Vj** and in the morpholine ring of **Ve**, **Vh**, and **Vk**; the corresponding protons gave rise to two multiplets in the regions δ 2.46–2.55 and 2.80–2.96 ppm, respectively.

Scheme 1.



R = Me (**a**), Et (**b**), ClCH₂CH₂ (**c**), C₄H₉ (**d**).



IV, R' = Et (**a**), R₂N = piperidino (**b**), morpholino (**c**); V, R = Me, R' = Et (**a**), R₂N = piperidino (**b**); R = Et, R' = Et (**c**), R₂N = piperidino (**d**), morpholino (**e**); R = ClCH₂CH₂, R' = Et (**f**), R₂N = piperidino (**g**), morpholino (**h**); R = Bu, R' = Et (**i**), R₂N = piperidino (**j**), morpholino (**k**).

EXPERIMENTAL

The IR spectra were recorded from samples prepared as thin films on a Specord 75IR spectrometer. The ¹H NMR spectra were measured on a Bruker DRX-500 spectrometer (500.13 MHz) using DMSO-*d*₆ as solvent and TMS as internal reference. Analytical thin-layer chromatography was performed on Sorbfil PTSKh-P-V plates; eluent ethanol–hexane, 3:1; development with iodine vapor. Elemental analyses were obtained on a Perkin–Elmer 2400 CHN analyzer.

3-[(4-Methoxycarbonylphenyl)carbamoyl]prop-2-enoic acid (IIa). A solution of 7.84 g of maleic anhydride in 15 ml of diethyl ether was added over a period of 10–15 min to a solution of 12.1 g of methyl 4-aminobenzoate in 35 ml of acetone. After 3 h, the precipitate was filtered off, washed with acetone (3 × 4 ml), and dried in air. Yield 18.5 g (93%), light yellow powder, mp 191–193°C, *R*_f 0.11 (ethanol–benzene). IR spectrum, ν , cm⁻¹: 3240, 3150 (NH); 1660 (C=O); 1225 (COC). Found, %: C 57.74; H 4.22; N 31.99. C₁₂H₁₁NO₅. Calculated, %: C 57.91; H 4.44; N 32.10.

Compounds **IIb–IIId** were synthesized in a similar way.

3-[(4-Ethoxycarbonylphenyl)carbamoyl]prop-2-enoic acid (IIb). Yield 91%, mp 194–196°C, *R*_f 0.59. IR spectrum, ν , cm⁻¹: 3280, 3190 (NH); 1680 (C=O); 1230 (COC). Found, %: C 58.98; H 4.91; N 5.18. C₁₃H₁₃NO₅. Calculated, %: C 59.09; H 4.95; N 5.30.

3-[[4-(2-Chloroethoxy)carbonylphenyl]carbamoyl]prop-2-enoic acid (IIc). Yield 93%, mp 182–184°C, *R*_f 0.57. IR spectrum, ν , cm⁻¹: 3270, 3180 (NH); 1670 (C=O); 1230 (COC). Found, %: C 51.97; H 3.89; N 4.61. C₁₃H₁₂ClNO₅. Calculated, %: C 52.45; H 4.06; N 4.70.

3-[(4-Butoxycarbonylphenyl)carbamoyl]prop-2-enoic acid (IIId). Yield 81%, mp 143–145°C (from

acetone), *R*_f 0.77. IR spectrum, ν , cm⁻¹: 3265, 3175 (NH); 1660 (C=O); 1240 (COC). Found, %: C 61.43; H 5.74; N 4.75. C₁₅H₁₇NO₅. Calculated, %: C 61.85; H 5.88; N 4.81.

Methyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (IIIa). A mixture of 14.7 g of amide **IIa**, 1.23 g of anhydrous sodium acetate, 7.7 g of acetic anhydride, and 30 ml of DMF was stirred for 4 h at 45–50°C. The mixture was cooled and diluted with 200 ml of water, and the precipitate was filtered off, washed with water (10 × 5 ml), and dried in air. Yield 12.7 g (93%), light brown fine crystals, mp 161–163°C (from acetone). IR spectrum, ν , cm⁻¹: 3100 (=CH), 3450, 1700, 1680 (C=O), 1245 (COC). ¹H NMR spectrum, δ , ppm: 3.87 s (3H, CH₃), 7.20 s (2H, CH=CH), 7.54 d and 8.07 d (2H each, H_{arom}, ³J_{HH} = 8 Hz). Found, %: C 61.92; H 3.79; N 5.84. C₁₂H₉NO₄. Calculated, %: C 62.34; H 3.92; N 6.06.

Ethyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (IIIb). A mixture of 10.5 g of amide **IIb**, 0.4 g of *p*-toluenesulfonic acid, 20 ml of DMF, and 60 ml of toluene was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated (4 h). The mixture was then evaporated under reduced pressure on heating on a water bath, the residue crystallized on cooling and was ground with 50 ml of water, and the precipitate was filtered off, washed with two portions of water, and dried. Yield 9.1 g (93%), light yellow crystals, mp 114–116°C (from EtOH). IR spectrum, ν , cm⁻¹: 3090 (=CH), 3445, 1700, 1680 (C=O), 1245 (COC). ¹H NMR spectrum, δ , ppm: 1.40 s (3H, CH₃, ³J_{HH} = 8 Hz), 4.35 q (2H, CH₂, ³J_{HH} = 8 Hz), 7.10 s (2H, CH=CH): 7.50 d and 8.07 d (2H each, H_{arom}, ³J_{HH} = 8 Hz). Found, %: C 63.21; H 4.13; N 5.63. C₁₃H₁₁NO₄. Calculated, %: C 63.79; H 4.52; N 5.71.

Compounds **IIIc** and **IIIId** were synthesized in a similar way.

2-Chloroethyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (IIIc). Yield 92%, mp 81–83°C (from EtOH), *R*_f 0.69. IR spectrum, ν , cm⁻¹: 3445, 1670 (C=O), 1225 (COC). ¹H NMR spectrum, δ , ppm: 3.98 t (2H, CH₂Cl, ³J_{HH} = 6 Hz), 4.56 t (2H, CH₂O, ³J_{HH} = 6 Hz), 7.24 s (2H, CH=CH), 7.50 d and 8.10 d (2H each, H_{arom}, ³J_{HH} = 8 Hz). Found, %: C 58.12; H 3.81; N 5.41. C₁₃H₁₀ClNO₄. Calculated, %: C 58.77; H 3.79; N 5.27.

Butyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (IIIId). Yield 89%, mp 46–48°C, *R*_f 0.66. IR spectrum, ν , cm⁻¹: 3085 (CH=CH), 3465, 1695, 1675

(C=O), 1230 (COC). Found, %: C 65.42; H 5.04; N 4.86. C₁₅H₁₅N₂O₄. Calculated, %: C 65.93; H 5.53; N 5.13.

Alkyl 4-(3-dialkylamino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoates Va–Vk (*general procedure*). A solution of 0.015 mol of amine **IVa–IVc** in 5 ml of dioxane was gradually added to a solution of 0.015 mol of imide **IIIa–IIIc** in 5 ml of dioxane, and the mixture was stirred for 2–4 h at 18–20°C and then heated for 1 h at 45–50°C (in the reactions with diethylamine) or at 60–90°C (in the reactions with piperidine and morpholine). The mixture was cooled and diluted with 100–200 ml of water, and the precipitate was filtered off, washed with water (10×5 ml), and dried. Compounds **Vd** and **Ve** separated from the reaction mixture (ester **Vb** separated only partially), while ester **Vi** was isolated by evaporation of the mixture. All compounds **Va–Vk** were purified by recrystallization.

Methyl 4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Va). Yield 71%, mp 85–87°C. IR spectrum, ν , cm⁻¹: 3450, 1730, 1660 (C=O), 1230 (COC). Found, %: C 62.79; H 6.58; N 8.96. C₁₆H₂₀N₂O₄. Calculated, %: C 63.15; H 6.62; N 9.20.

Methyl 4-(2,5-dioxo-3-piperidino-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vb). Yield 73%, mp 179–181°C (from dioxane), *R*_f 0.65 (ethanol–benzene, 3:1). IR spectrum, ν , cm⁻¹: 3450, 1740, 1680, 1660 (C=O), 1230 (COC). Found, %: C 64.03; H 5.96; N 8.27. C₁₇H₂₀N₂O₄. Calculated, %: C 64.55; H 6.37; N 8.85.

Ethyl 4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vc). Yield 51%, mp 94.5–95.5°C (from EtOH), *R*_f 0.70. IR spectrum, ν , cm⁻¹: 3450, 1740, 1700 (C=O), 1260 (COC). ¹H NMR spectrum, δ , ppm: 1.03 t (6H, CH₃, ³*J*_{HH} = 8 Hz), 1.33 t (3H, CH₃, ³*J*_{HH} = 8 Hz), 2.63 m (4H, CH₂), 2.75 d.d and 2.96 q (2H, CH₂CO), 4.28 q (1H, CHN), 4.34 q (2H, CH₂O, ³*J*_{HH} = 7 Hz), 7.45 d and 8.07 d (2H each, H_{arom}, ³*J*_{HH} = 8 Hz). Found, %: C 63.91; H 6.68; N 8.59. C₁₇H₂₂N₂O₄. Calculated, %: C 64.14; H 6.96; N 8.80.

Ethyl 4-(2,5-dioxo-3-piperidino-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vd). Yield 49%, mp 147–149°C (from dioxane and EtOH), *R*_f 0.68. IR spectrum, ν , cm⁻¹: 3460, 1745, 1690 (C=O), 1245 (COC). Found, %: C 65.19; H 6.28; N 8.13. C₁₈H₂₂N₂O₄. Calculated, %: C 65.44; H 6.71; N 8.48.

Ethyl 4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Ve). Yield 44%,

mp 166–168°C (from dioxane and EtOH), *R*_f 0.56. IR spectrum, ν , cm⁻¹: 3450, 1750, 1690 (C=O), 1245 (COC). Found, %: C 60.99; H 5.91; N 7.82. C₁₇H₂₀N₂O₅. Calculated, %: C 61.44; H 6.06; N 8.43.

2-Chloroethyl 4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vf). Yield 75%, mp 78–80°C (from EtOH), *R*_f 0.65. IR spectrum, ν , cm⁻¹: 3450, 1735, 1660, 1640 (C=O), 1210 (COC). ¹H NMR spectrum, δ , ppm: 1.03 t (6H, CH₃, ³*J*_{HH} = 8 Hz), 2.25 m (4H, CH₂), 2.78 d.d and 2.97 q (2H, CH₂CO), 3.98 t (2H, CH₂Cl, ³*J*_{HH} = 6 Hz), 4.30 q (1H, CHCO), 4.57 t (2H, CH₂O, ³*J*_{HH} = 6 Hz), 7.48 d and 8.10 d (2H each, H_{arom}, ³*J*_{HH} = 8 Hz). Found, %: C 63.94; H 6.23; N 8.27. C₁₇H₂₁N₂O₄. Calculated, %: C 64.34; H 6.66; N 8.83.

2-Chloroethyl 4-(2,5-dioxo-3-piperidino-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vg). Yield 80%, mp 124–125°C (from EtOH), *R*_f 0.58. IR spectrum, ν , cm⁻¹: 3445, 1735, 1635, 1620 (C=O), 1200 (COC). ¹H NMR spectrum, δ , ppm: 1.38 m (2H, CH₂), 1.50 m (4H, CH₂), 2.46 m and 2.78 m (2H each, CH₂N), 2.80 d.d and 2.97 q (2H, CH₂CO), 3.98 t (2H, CH₂Cl, ³*J*_{HH} = 6 Hz), 4.04 q (1H, CHCO), 4.57 t (2H, CH₂O, ³*J*_{HH} = 6 Hz), 7.47 d and 8.10 d (2H each, H_{arom}, ³*J*_{HH} = 8 Hz). Found, %: C 65.41; H 6.33; N 8.43. C₁₈H₂₁N₂O₄. Calculated, %: C 65.64; H 6.42; N 8.50.

2-Chloroethyl 4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vh). Yield 80%, mp 131–133°C (from EtOH), *R*_f 0.53. IR spectrum, ν , cm⁻¹: 3440, 1730, 1630 (C=O), 1200 (COC). ¹H NMR spectrum, δ , ppm: 2.55 m and 2.97 m (4H, CH₂N), 2.97 m and 3.02 q (2H, CH₂CO), 3.60 t (4H, CH₂OCH₂), 3.98 t (2H, CH₂Cl, ³*J*_{HH} = 6 Hz), 4.06 q (1H, CHCO), 4.57 t (2H, CH₂O, ³*J*_{HH} = 6 Hz), 7.48 d and 8.10 d (2H each, H_{arom}, ³*J*_{HH} = 8 Hz). Found, %: C 61.38; H 5.56; N 8.39. C₁₇H₁₉N₂O₅. Calculated, %: C 61.63; H 5.77; N 8.45.

Butyl 4-(3-diethylamino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vi). Yield 81%, mp 50–52°C, *R*_f 0.67. IR spectrum, ν , cm⁻¹: 3450, 1740, 1650 (C=O), 1210 (COC). Found, %: C 65.58; H 7.44; N 8.04. C₁₉H₂₆N₂O₄. Calculated, %: C 65.89; H 7.51; N 8.09.

Butyl 4-(2,5-dioxo-3-piperidino-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vj). Yield 84%, mp 109–111°C (from diethyl ether), *R*_f 0.71. IR spectrum, ν , cm⁻¹: 3455, 1740, 1670 (C=O), 1225 (COC). ¹H NMR spectrum, δ , ppm: 0.95 t (3H, CH₃CH₂, ³*J*_{HH} = 8 Hz), 1.42 m (4H, CH₂), 1.52 s (4H, CH₂), 1.72 m (2H, OCH₂CH₂), 2.48 m and 2.80 m (4H,

CH₂N), 2.77 m and 2.97 q (2H, CH₂CO), 4.02 q (1H, CHCO), 4.30 t (2H, CH₂O, ³J_{HH} = 6 Hz), 7.43 d and 8.07 d (2H each, H_{arom}, ³J_{HH} = 8 Hz). Found, %: C 66.84; H 6.96; N 7.55. C₂₀H₂₆N₂O₄. Calculated, %: C 67.02; H 7.30; N 7.82.

Butyl 4-(3-morpholino-2,5-dioxo-2,3,4,5-tetrahydro-1H-pyrrol-1-yl)benzoate (Vk). Yield 84%, mp 90–91°C (EtOH), R_f 0.57. IR spectrum, ν, cm⁻¹: 3445, 1740, 1660 (C=O), 1220 (COC). ¹H NMR spectrum, δ, ppm: 0.94 t (3H, CH₃CH₂, ³J_{HH} = 8 Hz), 1.43 m (2H, CH₃CH₂), 1.70 s (2H, CH₃CH₂CH₂), 2.52 m and 2.88 m (4H, CH₂NCH₂), 2.86 m and 3.00 q (2H, CH₂CO), 3.63 t (4H, CH₂OCH₂), 4.05 q (1H, CHCO), 4.30 t (2H, CH₂O, ³J_{HH} = 7 Hz), 7.45 d and

8.08 d (2H each, H_{arom}, ³J_{HH} = 8 Hz). Found, %: C 62.86; H 6.52; N 7.46. C₁₉H₂₄N₂O₅. Calculated, %: C 63.32; H 6.71; N 7.77.

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