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LETTERS TO THE EDITOR

Synthesis of 3-(4-Isopropoxyphenyl)-4-methylpentanoic Acid Amides

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Amides are of particular interest due to the application in synthesis of different classes of compounds with wide range of biological activity [1–4].

In this work, a series of new amides **IV**–**XV** was synthesized via acylation of different amines with 3-(4-isopropoxyphenyl)-4-methylpentanoyl chloride **A**. 3-(4-Isopropoxyphenyl)-4-methylpentanoic acid **III** was prepared via alkaline hydrolysis of 3-(4-isopropoxyphenyl)-4-methylpentanenitrile **II** [5].

Amides of 3-(4-isopropoxyphenyl)-4-methyl-pentanoic acid **IV** and **VI** were converted into the corresponding dihydrooxalates **XVI** and **XVII** (Scheme 1).

Composition and structure of the obtained compounds were confirmed by elemental analysis as well as IR and ^{1}H NMR spectroscopy data.

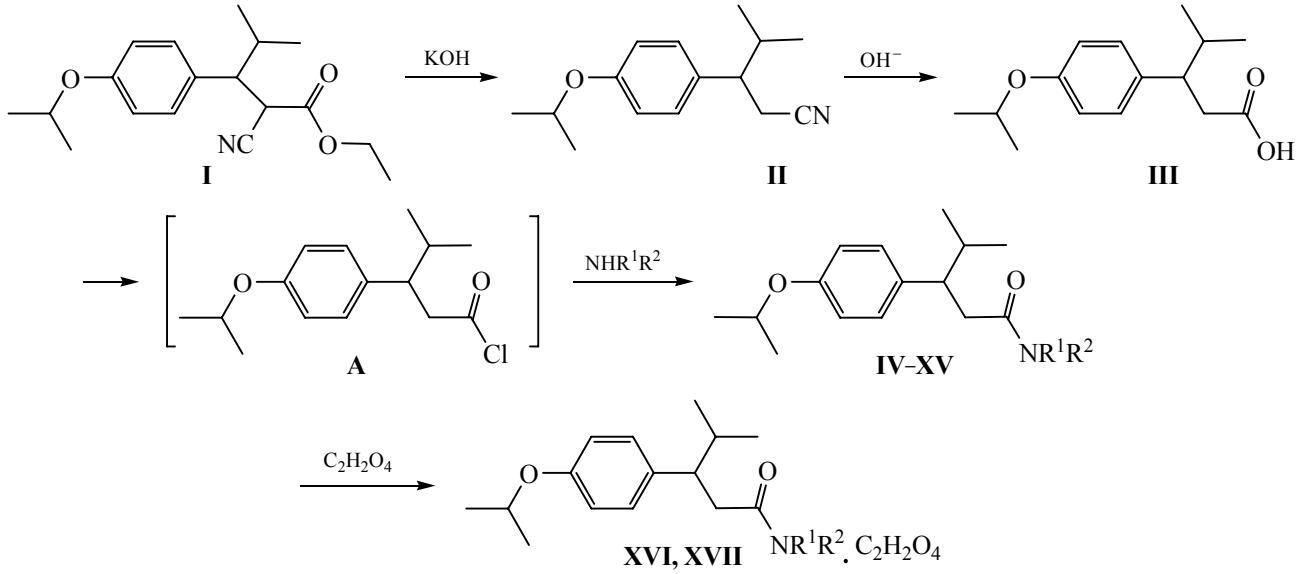
The antibacterial activity of compounds **IV**–**XVII** towards Gram-positive (*Staphylococcus aureus* 209p. 1) and Gram-negative strains (*Sh. Flexneri* 6858, *E. coli* 0-55) was studied as described in [6] using bacterial load of 20 million microbial bodies per 1 mL of medium. The studies showed that amides **IV** and **VI** had a moderate inhibiting effect on growth of the microorganisms over the area with diameter of 14–16 mm. Their oxalates **XVI** and **XVII** exhibited somewhat higher activity (d = 18–23 mm). Activity of other amides was lower (d = 10–13 mm). It should be noted that the studied substances possessed lower activity as compared with furazolidone (d = 24–25 mm) used as a positive reference.

Ethyl 2-cyano-3-(4-isopropoxyphenyl)-4-methyl-pentanoic acid **I** was prepared according to [5].

3-(4-Isopropoxyphenyl)-4-methylpentanenitrile (II). A solution of 10 g (0.18 mol) of potassium hydroxide in 54 mL of ethylene glycol was added to 28 g (0.09 mol) of cyanoether **I**. The mixture was refluxed during 3 h and cooled. Then, 54 mL of water was added, and the mixture was extracted with diethyl ether. The organic layer was washed with water and dried. After removing the solvent, the residue was distilled. Yield 16 g (75%), bp 148–150°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1585, 1610 (C=C$_{Ar}$), 2245 (CN). ^{1}H NMR spectrum, δ, ppm: 0.77 d (3H, CH$_3$, J 6.6 Hz), 1.00 d (3H, CH$_3$, J 6.6 Hz), 1.33 d (6H, CH$_3$, J 6.0 Hz), 1.90–2.05 m (1H, CH), 2.59 q (1H, CHCH$_2$, J 7.0 Hz), 2.71 d (CH$_2$, J 7.0 Hz), 4.54 septet (1H, OCH, J 6.0 Hz), 6.78–6.83 m and 7.07–7.12 m (4H, C$_6$H$_4$). Found, %: C 78.25; H 9.67; N 6.78. C$_{15}$H$_{21}$NO. Calculated, %: C 77.88; H 9.15; N 6.05.

3-(4-Isopropoxyphenyl)-4-methylpentanoic acid (III). A mixture of 40.2 g (0.72 mol) of potassium hydroxide, 140 mL of ethylene glycol, and 41.4 g (0.18 mol) of nitrile **II** was refluxed during 6 h, cooled, diluted with 140 mL of water, and extracted with diethyl ether. The aqueous layer was acidified with 80 mL of conc. HCl and extracted with benzene (3 ×

Scheme 1.



R^1 = H, R^2 = $(CH_2)_2N(CH_3)_2$ (**IV**, **XVI**), $(CH_2)_3OCH_3$ (**V**), $(CH_2)_3NEt_2$ (**VI**, **XVII**), 4-CH_3OPh (**VII**), thiazol-2-yl (**VIII**), furan-2-yl-methyl (**IX**), naphthalene-1-yl (**X**); NR^1R^2 = piperidyl (**XI**), morpholyl (**XII**), *N*,*N*-dipropyl (**XIII**), *N*,*N*-diethyl (**XIV**), pyrrolidinyl (**XV**).

150 mL). The combined benzene extracts were washed with water and dried. After removing benzene, the residue was distilled in vacuum. Yield 36 g (80%), bp 170–172°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3400–3200 (OH), 1715 (C=O). ^1H NMR spectrum, δ, ppm: 0.75 d (3H, CH_3, *J* 6.6 Hz), 0.92 d (3H, CH_3, *J* 6.6 Hz), 1.30 d (6H, CH_3, *J* 6.0 Hz), 1.73–1.87 m (1H, $CH_3\underline{CH}CH_3$), 2.41 d.d (1H, CH_2, *J* 15.2, 9.4 Hz), 2.60 d.d (1H, CH_2, *J* 15.2, *J* 5.6 Hz), 2.77 d.d (1H, $\underline{CH}CH_2$, *J* 9.4, 7.0 Hz), 4.49 septet (1H, OCH, *J* 6.0 Hz), 6.69–6.74 m and 6.97–7.03 m (4H, C_6H_4), 11.52 br. s (1H, COOH). Found, %: C 72.58; H 9.37. $C_{15}H_{22}O_3$. Calculated, %: C 71.97; H 8.86.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl chloride (A). A mixture of 0.1 mol of acid **III**, 0.11 mol of $SOCl_2$, and 50 mL of anhydrous benzene was refluxed during 2 h, and then concentrated. The resulting acid chloride was used without purification.

Amides (IV–XV) (*general procedure*). Equimolar amount of acid chloride **A** was added to a solution of 0.01 mol of the amine and 0.01 mol of triethylamine in anhydrous benzene upon stirring. The reaction mixture was refluxed during 3 h, cooled, acidified with hydrochloric acid to slightly acidic reaction, and extracted with benzene. The organic layer was washed with water, dried, and concentrated. The residue was distilled in vacuum and recrystallized from ethanol.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(*N*,*N*-dimethylaminoethyl)amide (IV). Yield 63%, bp 183–185°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3296 (NH), 1644 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 d (3H, CH_3, *J* 6.7 Hz), 0.91 d (3H, CH_3, *J* 6.7 Hz), 1.29 d [6H, $(CH_3)_2CHO$, *J* 6.0 Hz], 1.79 octet [1H, $(CH_3)_2\underline{CH}CH$, *J* 6.7 Hz], 1.98–2.18 m (2H, NCH_2), 2.08 s (6H, CH_3NCH_3), 2.28 d.d (1H, CH_2C=O, *J* 13.8, 9.4 Hz), 2.45 d.d (1H, CH_2C=O, *J* 13.8, 5.8 Hz), 2.78 d.d.d (1H, $\underline{CH}CH_2$, *J* 9.4, 6.7, 5.8 Hz), 2.96–3.02 m (2H, $NH\underline{CH_2}$), 4.48 septet (1H, OCH, *J* 6.0 Hz), 6.66–6.71 m and 6.96–7.01 m (4H, C_6H_4), 6.94 br.t (1H, NH, *J* 5.7 Hz). Found, %: C 71.85; H 10.68; N 9.25. $C_{19}H_{32}N_2O_2$. Calculated, %: C 71.21; H 10.06; N 8.74.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(3-methoxypropyl)amide (V). Yield 60%, bp 184–187°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3288 (NH), 1632 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.91 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 1.29 d (6H, $2\underline{CH_3}CHO$, *J* 6.0 Hz), 1.43 quintet (2H, $NCH_2\underline{CH_2}$, *J* 6.5 Hz), 1.78 octet (1H, CHO, *J* 6.7 Hz), 2.28 d.d (1H, CH_2C=O, *J* 13.8, 9.6 Hz), 2.42 d.d (1H, CH_2C=O, *J* 13.8, 5.7 Hz), 2.79 d.d.d (1H, $Ar\underline{CH}$, *J* 9.6, 6.7, 5.7 Hz), 2.85–3.07 m (2H, NCH_2), 3.05–3.12 m (2H, CH_2O), 3.18 s (3H, OCH_3), 4.48 septet (1H, OCH, *J* 6.0 Hz), 6.66–6.71 m and 6.96–7.01 m (4H, C_6H_4), 7.23 br.t (NH, *J* 5.6 Hz). Found, %: C 71.48; H

10.27; N 4.98. $C_{19}H_{31}NO_3$. Calculated, %: C 70.99; H 9.72; N 4.36.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(3,3-*N*,*N*-diethylaminopropyl)amide (VI). Yield 59%, bp 203–205°C (2 mmHg). IR spectrum, ν, cm^{-1}: 3292 (NH), 1644 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.90 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.95 t (6H, $\underline{CH_3}CH_2NCH_2\underline{CH_3}$, *J* 7.1 Hz), 1.29 d [6H, $(CH_3)_2CHO$, *J* 6.0 Hz], 1.31–1.40 m (2H, $NHCH_2\underline{CH_2}$), 1.78 octet (1H, $\underline{CH}CHAr$, *J* 6.7 Hz), 2.21–2.30 m (3H, $Et_2N\underline{CH_2}$, $CH_2C=O$), 2.35–2.46 m (5H, $CH_3\underline{CH_2}N\underline{CH_2}CH_3$, CH_2CO), 2.80 d.d.d (1H, $Ar\underline{CH}$, *J* 9.2, 6.7, 5.9 Hz), 2.91–2.99 m (2H, $NH\underline{CH_2}$), 4.47 septet (1H, OCH, *J* 6.0 Hz), 6.66–6.71 m and 6.95–7.00 m (4H, C_6H_4), 7.25 br.t (*J* 5.7 Hz). Found, %: C 73.25; H 11.00; N 8.15. $C_{22}H_{38}N_2O_2$. Calculated, %: C 72.88; H 10.56; N 7.73.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(4-methoxyphenyl)amide (VII). Yield 61%, bp 228–232°C (1 mmHg). IR spectrum, ν, cm^{-1}: 3265 (NH), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.79 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.95 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 1.29 d [6H, $(CH_3)_2CHO$, *J* 6.0 Hz], 1.79–1.94 m (1H, $\underline{CH}CHAr$), 2.51 d.d (1H, $CH_2C=O$, *J* 14.3, 9.0 Hz), 2.65 d.d (1H, $CH_2C=O$, *J* 14.3, 6.0 Hz), 2.90–2.99 m (1H, $\underline{CH}Ar$), 3.72 s (3H, OCH_3), 4.48 septet (1H, OCH, *J* 6.00 Hz); 6.68–6.74 m, 7.02–7.08 m and 7.31–7.37 m (8H, C_6H_4), 9.26 s (1H, NH). Found, %: C 74.95; H 8.84; N 4.35. $C_{22}H_{29}NO_3$. Calculated, %: C 74.33; H 8.22; N 3.94.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-thiazol-2-ylamide (VIII). Yield 58%, mp 118–120°C. IR spectrum, ν, cm^{-1}: 3269 (NH), 1695 (C=O). ^1H NMR spectrum, δ, ppm: 0.77 d (3H, $\underline{CH_3}CHCH$, *J* 6.6 Hz), 0.93 d (3H, $\underline{CH_3}CHCH$, *J* 6.6 Hz), 1.28 d [6H, $(\underline{CH_3})_2CHO$, *J* 6.0 Hz], 1.76–1.92 m (1H, $\underline{CH}CHAr$), 2.67–2.28 m (2H, $CH_2C=O$), 2.91–3.00 m (1H, $\underline{CH}Ar$), 4.47 septet (1H, OCH, *J* 6.0 Hz), 6.66–6.72 m and 7.01–7.06 m (4H, C_6H_4), 6.85 d (1H, SCH, *J* 3.5 Hz), 7.28 d (1H, CHN, *J* 3.5 Hz), 11.77 s (1H, NH). Found, %: C 65.74; H 8.00; N 9.05. $C_{18}H_{24}N_2O_2S$. Calculated, %: C 65.03; H 7.28; N 8.43.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(fur-2-ylmethyl)amide (IX). Yield 62%, mp 102–104°C. IR spectrum, ν, cm^{-1}: 3253 (NH), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d ($\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.91 d ($\underline{CH_3}CHCH$, *J* 6.7 Hz), 1.31 d [6H, $(\underline{CH_3})_2CHO$, *J* 6.0 Hz], 1.79 octet (1H, $\underline{CH}CHAr$, *J* 6.7 Hz), 2.37 d.d (1H, $CH_2C=O$, *J* 14.0, 9.4 Hz), 2.48 d.d (1H, $CH_2C=O$, *J* 14.0, 5.8 Hz), 2.83 d.d.d (1H, $CH\underline{CH}Ar$, *J* 9.4, 6.7, 5.8 Hz), 4.11 d.d (1H, NCH_2, *J* 15.7, 5.6 Hz), 4.14 d.d (1H, NCH_2, *J* 15.7, 5.6 Hz), 4.49 septet (1H, OCH, *J* 6.0 Hz), 6.79 br.d (1H, H^3_{Fur}, *J* 3.2 Hz), 6.19 d.d (1H, H^4_{Fur}, *J* 3.2, 1.9 Hz), 6.67–6.72 m and 6.97–7.02 m (4H, C_6H_4), 7.29 d.d (1H, H^5_{Fur}, *J* 1.9, 0.8 Hz), 7.79 br.t (NH, *J* 5.6 Hz). Found, %: C 73.42; H 8.75; N 4.86. $C_{20}H_{27}NO_3$. Calculated, %: C 72.92; H 8.26; N 4.25.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-naphth-1-ylamide (X). Yield 56%, mp 138–140°C. IR spectrum, ν, cm^{-1}: 3241 (NH), 1652 (C=O). ^1H NMR spectrum, δ, ppm: 0.83 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 1.02 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz), 1.30 d [6H, $OCH(CH_3)_2$, *J* 6.0 Hz], 1.91 octet [1H, $(CH_3)_2\underline{CH}$, *J* 6.7 Hz], 2.75–2.81 m and 2.88–2.98 m (3H, $CHCH_2C=O$), 4.50 septet (1H, OCH, *J* 6.0 Hz), 6.74–6.79 m and 7.11–7.16 m (4H, phenyl), 7.29–7.52 m (5H, naphthyl), 7.59 br.d (1H, naphthyl, *J* 8.1 Hz), 7.76 br.d (1H, naphthyl), 9.38 br. s (1H, NH). Found, %: C 80.47; H 8.25; N 4.25. $C_{25}H_{29}NO_2$. Calculated, %: C 79.96; H 7.78; N 3.73.

3-(4-Isopropoxyphenyl)-4-methylpentanoylpiperidine (XI). Yield 59%, bp 172–175°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1644 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz], 0.95 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz], 1.30 d [6H, $OCH(CH_3)_2$, *J* 6.0 Hz], 1.12–1.59 m (6H, CH_2), 1.77–1.93 m (1H, $\underline{CH}CHAr$), 2.54 d (2H, $CH_2C=O$, *J* 7.0 Hz), 2.81 q (1H, $\underline{CH}Ar$, *J* 7.0 Hz), 3.21–3.47 m (4H, CH_2NCH_2), 4.49 septet (1H, OCH, *J* 6.0 Hz), 6.68–6.73 m and 6.96–7.01 m (4H, C_6H_4). Found, %: C 76.15; H 10.27; N 5.00. $C_{20}H_{31}NO_2$. Calculated, %: C 75.67; H 9.84; N 4.41.

1-(*N*-Morpholyl)-3-(4-Isopropoxyphenyl)-4-methylpentan-1-one (XII). Yield 63%, bp 188–190°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1644 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d and 0.97 d (6H, $CHCH\underline{CH_3}$, *J* 6.7 Hz), 1.30 d [6H, $(CH_3)_2CO$, *J* 6.0 Hz], 1.78–1.94 m (1H, $\underline{CH}CHAr$), 2.49–2.62 m (2H, $CH_2C=O$), 2.75–2.83 m (1H, $\underline{CH}CH_2$), 3.11–3.53 m (8H, $4CH_2$, morpholine), 4.50 septet (1H, OCH, *J* 6.0 Hz), 6.69–6.74 m and 6.97–7.02 m (4H, C_6H_4). Found, %: C 72.00; H 9.80; N 4.91. $C_{19}H_{29}NO_3$. Calculated, %: C 71.44; H 9.15; N 4.38.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*,*N*-dipropylamide (XIII). Yield 60%, bp 170–173°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1630 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 d (3H, $\underline{CH_3}CHCH$, *J* 6.7 Hz),

0.96 d (3H,$\underline{CH_3}CHCH$, *J* 6.7 Hz), 0.74 t (3H, $\underline{CH_3}CH_2$, *J* 7.3 Hz), 0.87 t (3H, $\underline{CH_3}CH_2$, *J* 7.3 Hz), 1.29 d [6H, $(CH_3)_2CO$, *J* 6.0 Hz], 1.21–1.54 m [4H, $2CH_3\underline{CH_2}$)], 1.77–1.93 m (1H, $\underline{CH}CHAr$), 2.43–2.56 m (2H, $CH_2C{=}O$), 2.80–2.88 m (1H, $\underline{CH}Ar$), 2.90–3.21 m (4H, CH_2NCH_2), 4.48 septet (1H, OCH, *J* 6.0 Hz), 6.66–6.71 m and 6.95–7.00 m (4H, C_6H_4). Found, %: C 76.05; H 11.07; N 4.77. $C_{21}H_{35}NO_2$. Calculated, %: C 75.63; H 10.58; N 4.20.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*,*N*-diethylamide (XIV). Yield 63%, bp 160–162°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1640 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz], 0.96 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz], 0.92 t [3H, $(CH_2\underline{CH_3})_2$, *J* 7.0 Hz), 1.05 t [3H, $(CH_2\underline{CH_3})_2$, *J* 7.0 Hz], 1.29 d [6H, $(\underline{CH_3})_2CHO$, *J* 6.0 Hz], 1.86 octet [1H, $(CH_3)_2\underline{CH}CH$), *J* 6.7 Hz], 2.47 d.d (1H, $CH_2C{=}O$, *J* 14.8, 8.3 Hz), 2.53 d.d (1H, $CH_2C{=}O$, *J* 14.8, 5.7 Hz), 2.86 d.d.d (1H, CHAr, *J* 8.3, 6.7, 5.7 Hz), 3.06–3.28 m (4H, $2\underline{CH_2}CH_3$), 4.48 septet (1H, OCH, *J* 6.0 Hz), 6.67–6.72 m and 6.96–7.01 m (4H, C_6H_4). Found, %: C 75.17; H 10.83; N 5.05. $C_{19}H_{31}NO_2$. Calculated, %: C 74.71; H 10.23; N 4.59.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-pyrrolidinylamide (XV). Yield 59%; bp 187–191°C (1 mmHg). IR spectrum, ν, cm^{-1}: 1625 (C=O). ^1H NMR spectrum, δ, ppm: 0.74 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz), 0.95 d [3H, $(\underline{CH_3})_2CHCH$, *J* 6.7 Hz], 1.30 d [6H, $(\underline{CH_3})_2CHO$, *J* 6.0 Hz], 1.62–1.93 m (5H, $CH_{2пуг}$, $\underline{CH}CHAr$), 2.42 d.d (1H, $CH_2C{=}O$, *J* 14.8, 8.5 Hz), 2.52 d.d (1H, $CH_2C{=}O$, *J* 14.8, 5.3 Hz), 2.84 d.d.d (1H, $\underline{CH}Ar$, *J* 8.5, 6.7, 5.3 Hz), 3.12–3.35 m (4H, CH_2NCH_2), 4.49 septet (1H, OCH, *J* 6.0 Hz), 6.67–6.72 m and 6.97–7.02 m (4H, C_6H_4). Found, %: C 75.77; H 10.15; N 5.21. $C_{19}H_{29}NO_2$. Calculated, %: C 75.21; H 9.63; N 4.62.

Synthesis of oxalates (XVI, XVII). A solution of oxalic acid in diethyl ether was added to a solution of the corresponding amide in diethyl ether. The resulting precipitate was filtered off and recrystallized from ethanol.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(*N*,*N*-dimethylaminoethyl)amide, dihydrooxalate salt (XVI). mp 90–92°C.

3-(4-Isopropoxyphenyl)-4-methylpentanoyl *N*-(3,3-*N*,*N*-diethylaminopropyl)amide, dihydrooxalate salt (XVII). mp 133–135°C.

IR spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer. ^1H NMR spectra (DMSO-d_6) were registered with a Varian Mercury-300 spectrometer relative to internal TMS reference.

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