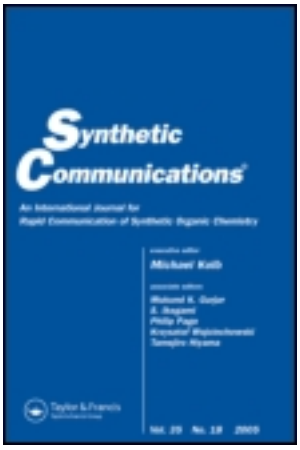


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile One-Pot Synthesis of 1,2,3,4-Tetrahydroquinoline-3-carboxylic Acids and Their Heterocyclic Analogs

Sergey V. Ryabukhin [a b], Andrey S. Plaskon [a b], Dmitriy M. Volochnyuk [a c], Sergey E. Pipko [a] & Andrey A. Tolmachev [b]

[a] Enamine Ltd., Kyiv, Ukraine

[b] National Taras Shevchenko University, Kyiv, Ukraine

[c] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Version of record first published: 28 Aug 2008.

To cite this article: Sergey V. Ryabukhin , Andrey S. Plaskon , Dmitriy M. Volochnyuk , Sergey E. Pipko & Andrey A. Tolmachev (2008): Facile One-Pot Synthesis of 1,2,3,4-Tetrahydroquinoline-3-carboxylic Acids and Their Heterocyclic Analogs, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:17, 3032-3043

To link to this article: http://dx.doi.org/10.1080/00397910802044272

Synthetic Communications®, 38: 3032–3043, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802044272

Taylor & Francis
Taylor & Francis Group

Facile One-Pot Synthesis of 1,2,3,4-Tetrahydroquinoline-3-carboxylic Acids and Their Heterocyclic Analogs

Sergey V. Ryabukhin,[1,2] Andrey S. Plaskon,[1,2] Dmitriy M. Volochnyuk,[1,3] Sergey E. Pipko,[1] and Andrey A. Tolmachev[2]
[1]Enamine Ltd., Kyiv, Ukraine
[2]National Taras Shevchenko University, Kyiv, Ukraine
[3]Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv, Ukraine

Abstract: A facile one-pot method for the synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids and their heterocyclic analogs based on the *tert*-amino effect. A set of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids was readily prepared starting from various *ortho*-dialkylaminoaldehydes and Meldrum's acid using Me_3SiCl in dimethylformamide (DMF) solution.

Keywords: Chlorotrimethylsilane, Meldrum's acid, *ortho*-dialkylaminoaldehydes, 1,2,3,4-tetrahydroquinoline-3-carboxylic acids, *tert*-amino effect

Nipecotic acids **1** (Fig. 1) are widely used as anticonvulsant,[1] antinociceptive,[2] antiepileptic,[3a] anti-inflammatory,[2c] neuroprotective,[3a] neuroregulatoric,[2c,3b] anti-allodynic,[2d] and immunosuppressant[3c] agents. Therefore, the development of effective methods for the synthesis of nipecotic acids remains an interesting challenge. Only a few examples of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **2** (Fig. 1), which are benzo analogs of nipecotic acid, have been described in the literature,[4] and the heteroaromatic analogs are unknown.

Herein we report a facile method for the synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **2** from *ortho*-dialkylaminoaldehydes **3** and Meldrum's acid **4** that employs the *tert*-amino effect.[5,6] Previously it

Received December 11, 2007.
Address correspondence to Sergey V. Ryabukhin, Enamine Ltd., 23 A. Matrosova St., 01103 Kyiv, Ukraine. E-mail: Ryabukhin@mail.enamine.net

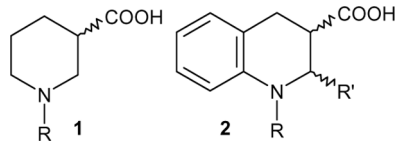
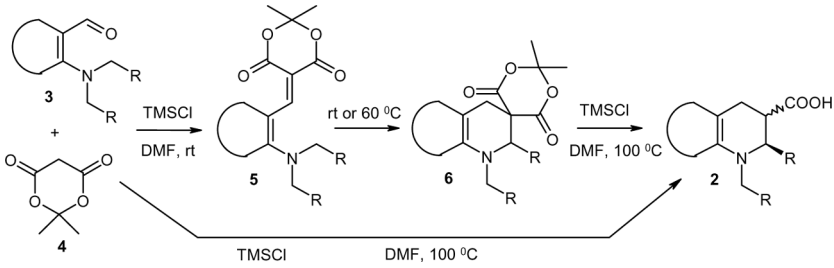


Figure 1. Nipecotic acids **1** and 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **2**.

has been demonstrated that the reaction of *ortho*-dialkylaminoaldehydes **3** with Meldrum's acid **4** leads to spiro products **6**.[7] The use of chlorotrimethylsilane (TMSCl) as a promoter and water scavenger[5c,8] in dimethylformamide (DMF) at 100 °C leads to the formation of the target acids **2** in 21–45% yield (Scheme 1, Table 1). This result is not surprising considering that similar spiro compounds are known to transform into the corresponding acids upon reflux under acidic conditions.[9]

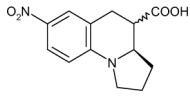
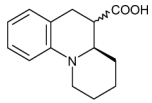
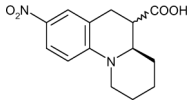
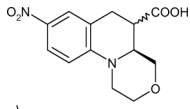
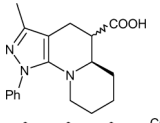
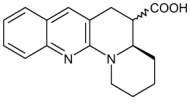
At ambient temperature, the TMSCl-mediated reactions of *ortho*-dialkylaminobenzaldehydes **3a–d** and Meldrum's acid **4** gave spiro products **6** in nearly quantitative yields.

In the case of dialkylaminoaldehydes **3e,f**, benzylidene derivatives **5** and spiro compounds **6** were formed at room temperature and 60 °C respectively. Previously it was reported that Meldrum's acid **4** reacted with *ortho*-dialkylaminoaldehydes **3** to give benzylidene intermediates **5**, which underwent cyclization, leading eventually to compounds **6**.[7] The latter were heated in the presence of HCl generated from TMSCl and H_2O to yield acids **2** in 45–69% yield. On the basis of these results, we have developed a one-pot, two-step procedure for the high-yield synthesis of acids **2** without isolation of intermediate products **6**. First, the reaction mixture was heated for 12 h at 60 °C to generate intermediate spiro compounds **6** and then at 100 °C (6 h for **2a–d**, 10 h for **2e** and 15 h for **2f**) to accomplish the hydrolysis and decarboxylation. The application of this two-step procedure results in a two-fold increase in the yields of compounds **2** compared to the one-step procedure at 100 °C.



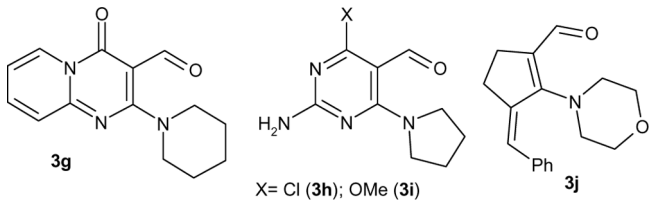
Scheme 1. Synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids from ortho-dialkylaminoaldehydes and Meldrum's acid.

Table 1. Yields[a] and ratio of diastereomers of acids **2a–f** obtained

Aldehyde 3	Acid 2	Yield at 100 °C (%)[a]	Yield at 60 + 100 °C (%)[a]	Ratio of diastereomers *R,R*/*R,S*
3a	 **2a**	38	69	83/17
3b	 **2b**	24	49	78/22
3c	 **2c**	45	67	80/20
3d	 **2d**	28	62	84/16[b]
3e	 **2e**	21	45	81/19
3f	 **2f**	30	53	71/29

[a]Yields refer to pure isolated products.
[b]In this case, ratio for *S,R*/*S,S* is indicated.
*The signals of minor diastereomers in experimental part.

The application of the optimized procedure to compounds **3g–j** (Scheme 2) did not result in the corresponding acids. Aldehyde **3g** undergoes O=C−N bond cleavage of pyrimidine cycle. Compounds **3h** and **3i** did not react, whereas aldehyde **3j** decomposed. Acids **2a–f** are



Scheme 2. Heterocyclic and enaminic *ortho*- dialkylaminoaldehydes.

formed as a 4:1 mixture of two diastereomers that cannot be separated by preparative high performance liquid chromatography (HPLC). Co-crystallization of **2a–f** with 1,4-diazabicyclo[2.2.2]octane (DABCO) also failed to separate the diastereomers.

The composition and structure of all the compounds obtained were unambiguously established by NMR spectroscopy (^{1}H and ^{13}C), mass spectrometry, IR spectroscopy, and elemental analysis.

In conclusion, an efficient and facile methodology has been elaborated for the preparative synthesis of 1,2,3,4-tetrahydroquinoline-3-carboxylic acids **3a–d** and their heterocyclic analogs **3e,f**. It is based on the reaction of aryl or heteroaryl 2-(dialkylamino)aldehydes with Meldrum's acid using Me_3SiCl as a promoter, water scavenger, and a source of HCl, which catalyzes the heterocyclizations and transformation of spiro products into acids.

EXPERIMENTAL

All chemicals were obtained from commercially available sources (Aldrich, Fluka, Enamine Ltd.) and used without further purification. DMF was freshly distilled and dried by standard methods; monitoring of water concentration in solvents (the solvent contained less than 0.05%, usually 0.02% of water) was performed using a Mettler Toledo DL31 KF Titrator. All solvents for crystallizations were used without additional purification.

Melting points were measured with a Buchi melting-point apparatus and are uncorrected. ^{1}H NMR (400 MHz and 500 MHz) were recorded on Varian Mercury-400 and Bruker Avance DRX-500 spectrometers with TMS as an internal standard. ^{13}C NMR (125 MHz) were recorded on a Bruker Avance DRX-500 spectrometer with TMS as an internal standard. LC/MS spectra were recorded using chromatography/mass spectrometric system that consisted of a high-performance liquid chromatograph (Agilent 1100 series) equipped with diode-matrix and mass-selective detector (Agilent LC/MSD SL). According to HPLC MS data, all the synthesized compounds have purity greater than 95%. IR spectra were recorded on a Nexus-470 spectrometer for samples in KBr discs. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. A Branson 2510E-MT ultrasonic bath was used.

General Procedure for One-Pot Synthesis of Acids 2

Ortho-dialkylaminoaldehydes **3a–f** (2 mmol) and Meldrum's acid **4** (288 mg, 2.0 mmol for **3a–d**; 317 mg, 2.2 mmol for **3e**; 346 mg, 2.4 mmol

for **3f**) were placed in a 15-mL pressure tube and dissolved in DMF (2–3 mL). Chlorotrimethylsilane (652 mg, 6 mmol) was added dropwise to the solution. The tube was thoroughly sealed and heated on a water bath for 6–15 h. After cooling, the flask was opened (*caution*! excessive pressure inside), and the reaction mixture was poured into water (15 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with small amount of *i*-PrOH. In the case of no precipitation, the product was extracted with CH_2Cl_2 (2×15 mL) after adding triethylamine (607 mg, 6 mmol). The organic layer was separated, dried over Na_2SO_4, and concentrated. Recrystallization from an appropriate solvent yielded target acids **2a–f**.

General Procedure for Two-Stage Synthesis of Acids 2

Ortho-dialkylaminoaldehydes **3a–f** (2 mmol) and Meldrum's acid **4** (288 mg, 2.0 mmol for **3a–d**; 317 mg, 2.2 mmol for **3e**; 346 mg, 2.4 mmol for **3f**) were placed in a 15-mL pressure tube and dissolved in DMF (2–3 mL). Chlorotrimethylsilane (652 mg, 6 mmol) was added dropwise to the solution. The tube was thoroughly sealed and allowed to stand at 60 °C in an ultrasonic bath for 1 day and then heated on a water bath for 6–15 h. After cooling, the flask was opened (*caution*! excessive pressure inside), and the reaction mixture was poured into water (15 mL) and allowed to stand at 20 °C in an ultrasonic bath for 1 h. The precipitate formed was filtered and washed with a small amount of *i*-PrOH. In the case of no precipitation, the product was extracted with CH_2Cl_2 (2×15 mL) after adding triethylamine (607 mg, 6 mmol). The organic layer was separated, dried over Na_2SO_4, and concentrated. Recrystallization from an appropriate solvent yielded target acids **2a–f**.

Data

(3a*R*)-7-Nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-carboxylic Acid **(2a)**

Mp 192–193 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6*—signals of minor diastereomer—see Table 1) $\delta = 1.55$ (m, 1H, CH) and 1.83* (m, 1H, CH), 1.94* (m, 1H, CH) and 2.18(m, 1H, CH), 2.06 (m, 1H, CH), 2.22 (m, 1H, CH), 2.82 (m, 1H, CH), 3.06 (m, 1H, CH), 3.10 (m, 1H, CH) and 3.18* (m, 1H, CH), 3.25 (m, 1H, CH), 3.51 (m, 2H, CH), 6.43* (d, $^3J_{HH} = 9.0$ Hz, Hz, 1H, CH) and 6.47 (d, $^3J_{HH} = 9.0$ Hz, 1H, CH), 7.85* (s, 1H, CH) and 7.91 (s, 1H, CH), 7.87* (d, $^3J_{HH} = 9.0$ Hz, 1H, CH) and 7.94 (d, $^3J_{HH} = 9.0$ Hz, 1H, CH), 12.52 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6*—signals of minor diastereomer—see Table 1) $\delta = 21.5$*

and 23.5, 29.2* and 31.3, 31.1* and 31.7, 42.4, 47.8, 59.0* and 60.3, 109.4* and 109.6, 119.7* and 120.2, 124.57* and 124.61, 124.9* and 125.2, 135.5 and 135.8*, 149.2 and 150.1*, 172.4* and 174.8. IR (KBr): $\nu = 3660-3260$ (br, OH), 3109, 2976, 2931, 1701 (C=O), 1603 (NO_2), 1578, 1518, 1487, 1437, 1396, 1302 (NO_2), 1250, 1203, 1174, 1099, 802, 750 cm^{-1}. APSI MS: $M^+ + 1 = 263$, $M^+ - 1 = 261$. Anal. calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.71; H, 5.27; N, 10.60.

(4a*R*)-2,3,4,4a,5,6-Hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid **(2b)**

Mp 154–155 °C (*i*-PrOH-hexane). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.38$ (m, 2H, CH), 1.47 (m, 1H, CH), 1.61 (m, 1H, CH), 1.70–1.87 (m, 2H, CH), 2.82 (dd, $^2J_{HH} = 17.4$ Hz, $^3J_{HH} = 5.6$ Hz, 1H, CH), 2.92 (m, 1H, CH), 3.07 (m, 2H, CH), 3.71 (m, 1H, CH), 4.11 (d, $^2J_{HH} = 13.7$ Hz, 1H, CH), 6.79 (m, 1H, CH), 6.99–7.15 (m, 3H, CH), 12.78 (br. s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 21.56$* and 21.64, 23.7* and 24.4, 26.0, 29.6, 41.3, 49.4, 57.9, 115.47 and 151.54*, 127.7 and 127.8*, 128.0, 129.1* and 129.4, 130.5, 141.1 and 141.3*, 173.6 and 174.8*. IR (KBr): $\nu = 3660-3300$ (br, OH), 3016, 2951, 2931, 1732 (C=O), 1500, 1435, 1385, 1257, 1209, 1173, 741, 677 cm^{-1}. APSI MS: $M^+ + 1 = 232$, $M^+ - 1 = 230$. Anal. calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.57; H, 7.57; N, 6.15.

(4a*R*)-8-Nitro-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinoline-5-carboxylic Acid **(2c)**

Mp 182–183 °C (EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.28–1.47$ (m, 2H, CH), 1.52–1.75 (m, 3H, CH), 1.81 (m, 1H, CH), 2.67 (m, 1H, CH) and 2.94* (m, 1H, CH), 2.84–2.91 (m, 2H, CH), 2.98 (m, 1H, CH) and 3.10* (m, 1H, CH), 3.57 (m, 1H, CH) and 3.75* (m, 1H, CH), 4.15 (d, $^2J_{HH} = 13.0$ Hz, 1H, CH) and 4.23* (d, $^2J_{HH} = 13.0$ Hz, 1H, CH), 6.88 (d, $^3J_{HH} = 9.3$ Hz, 1H, CH) and 6.94* (d, $^3J_{HH} = 9.3$ Hz, 1H, CH), 7.83–7.91 (m, 2H, CH), 12.66 (s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 24.59$* and 24.62, 24.8 and 25.1*, 25.7 and 26.8*, 28.1 and 32.1*, 44.0, 48.4* and 49.3, 57.9 and 58.3*, 111.1* and 111.3, 121.5 and 122.1*, 124.77 and 124.81*, 124.9* and 125.8, 136.05 and 136.08*, 150.3* and 151.0, 173.4 and 174.4*. IR (KBr): $\nu = 3660–3300$ (br, OH), 2939, 2858, 1709 (C=O), 1603 (NO_2), 1581, 1491, 1439, 1408, 1319 (NO_2), 1198, 1109, 935, 892, 806, 748, 600 cm^{-1}. APSI MS: $M^+ + 1 = 277$, $M^+ - 1 = 275$. Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 61.05; H, 5.71; N, 10.09.

(4a*S*)-8-Nitro-1,2,4,4a,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinoline-5-carboxylic Acid **(2d)**

Mp 229–230 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.57 (m, 1H, CH), 2.81–2.92 (m, 1H, CH), 2.98 (m, 1H, CH), 3.14 (t, $^2J_{HH}$ = 12.8 Hz, 1H, CH), 3.26 (t, $^2J_{HH}$ = 10.8 Hz, 1H, CH), 3.42* (m, 1H, CH), and 3.74 (m, 1H, CH), 3.45–3.59 (m, 2H, CH), 3.88 (m, 1H, CH), 3.94–4.07 (m, 1H, CH), 6.94 (d, $^3J_{HH}$ = 9.2 Hz, 1H, CH) and 6.97* (d, $^3J_{HH}$ = 9.2 Hz, 1H, CH), 7.83–7.98 (m, 2H, CH), 12.80 (br. s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 27.9* and 29.4, 38.5* and 39.5, 46.7 and 48.2*, 55.9* and 56.6, 66.1* and 66.3, 68.1* and 70.2, 111.3 and 112.1*, 122.5 and 122.7*, 124.2* and 124.7, 124.8 and 125.3*, 137.1 and 137.2*, 150.8 and 150.9*, 173.0* and 174.0. IR (KBr): ν = 3660–3150 (br, OH), 2966, 2922, 1716 (C=O), 1605 (NO_2), 1585, 1508, 1491, 1435, 1408, 1321 (NO_2), 1255, 1101, 1055, 947, 750 cm^{-1}. APSI MS: M^++1 = 279, M^+−1 = 277. Anal. calcd. for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.28; H, 4.96; N, 10.02.

(5a*R*)-3-Methyl-1-phenyl-1,4,5,5a,6,7,8,9-octahydropyrazolo[4,3-*c*]quinolizine-5-carboxylic Acid **(2e)**

Mp 200–201 °C (*i*-PrOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.21 (m, 1H, CH), 1.31 (m, 1H, CH), 1.42–1.56 (m, 2H, CH), 1.63 (m, 1H, CH), 1.78 (m, 1H, CH), 2.05 (s, 3H, CH_3), 2.07–2.16 (m, 1H, CH), 2.56–2.67 (m, 2H, CH), 2.82 (m, 1H, CH), 3.33 (d, $^2J_{HH}$ = 13.2 Hz, 1H, CH), 3.43 (m, 1H, CH), 7.24 (m, 1H, CH), 7.39 (m, 4H, CH), 12.24 (br. s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 12.6, 20.3 and 20.4*, 24.8 and 25.0*, 27.1, 33.6, 48.0, 48.2, 61.7, 103.9 and 104.0*, 126.4, 128.2, 128.7, 139.5, 142.5 and 142.6*, 153.9 and 154.1*, 174.0 and 174.7*. IR (KBr): ν = 3660–3100 (br, OH), 3064, 2929, 1709 (C=O), 1597, 1527, 1502, 1441, 1271, 1203, 1120, 1070, 1014, 916, 775, 758, 690 cm^{-1}. APSI MS: M^+ + 1 = 312, M^+ − 1 = 310. Anal. calcd. for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.60; H, 6.63; N, 13.41.

(4a*R*)-2,3,4,4a,5,6-Hexahydro-1*H*-benzo[*g*]pyrido[1,2-*a*]-1,8-naphthyridine-5-carboxylic Acid **(2f)**

Mp 220–221 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.33 (m, 1H, CH), 1.41 (m, 1H, CH), 1.59–1.68 (m, 2H, CH), 2.39–2.48 (m, 2H, CH), 2.92 (m, 1H, CH), 3.00 (m, 1H, CH), 3.25 (m, 1H, CH), 3.33 (m, 1H, CH), 3.72 (m, 1H, CH), 4.22 (m, 1H, CH), 7.50 (m, 3H, CH), 7.61

(d, $^3J_{HH} = 7.6$ Hz, 1H, CH), 7.77 (s, 1H, CH), 12.74 (br. s, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 23.7 and 23.8*, 26.3* and 26.6, 27.0, 28.4, 44.1, 49.1, 62.6, 109.8 and 109.9*, 120.2 and 120.5*, 122.7* and 122.8, 123.6 and 123.9*, 125.5 and 125.6*, 128.1 and 128.4*, 128.9* and 129.1, 145.2 and 145.3*, 149.6* and 149.8, 174.1 and 174.9*. IR (KBr): ν = 3650–3200 (br, OH), 3061, 2931, 1707 (C=O), 1587, 1522, 1436, 1261, 1208, 1130, 752, 696 cm^{-1}. APSI MS: $M^+ + 1$ = 283, $M^+ - 1$ = 281. Anal. calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.13; H, 6.59; N, 9.85.

2,2-Dimethyl-5-[(3-methyl-1-phenyl-5-piperidin-1-yl-1*H*-pyrazol-4-yl)methylene]-1,3-dioxane-4,6-dione **(5e)**

Mp 157–158 °C (EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.51 (m, 6H, 3CH_2), 1.75 (s, 6H, 2CH_3), 2.05 (s, 3H, CH_3), 2.99 (m, 4H, 2NCH_2), 7.54 (m, 5H, CH), 8.28 (s, 1H, CH). IR (KBr): ν = 2997, 2983, 2935, 1713 (C=O), 1560, 1512, 1448, 1375, 1360, 1281, 1203, 1101, 974, 930, 825, 789, 775 cm^{-1}. APSI MS: $M^+ + 1$ = 396. Anal. calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.97; H, 6.18; N, 10.71.

2,2-Dimethyl-7′-nitro-1′,2′,3′,3a′-tetrahydro-5′*H*-spiro[1,3-dioxane-5,4′-pyrrolo[1,2-*a*]quinoline]-4,6-dione **(6a)**

Mp 217–218 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.48 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 2.02 (m, 2H, CH), 2.14 (m, 1H, CH), 3.21 (m, 1H, CH), 3.32 (d, $^2J_{HH}$ = 16.7 Hz, 1H, CH), 3.64 (d, $^2J_{HH}$ = 16.7 Hz, 1H, CH), 3.73 (m, 1H, CH), 4.01 (m, 1H, CH), 6.65 (d, $^3J_{HH}$ = 8.5 Hz, 1H, CH), 8.00 (d, $^3J_{HH}$ = 8.5 Hz, 2H, CH), 8.01 (s, 1H, CH). ^{13}C NMR (125 MHz, DMSO-d_6) δ = 23.0, 28.1, 28.3, 29.7, 35.3, 46.3, 48.4, 64.3, 106.2, 110.5, 118.4, 124.91, 124.92, 136.0, 148.9, 164.1, 169.2. IR (KBr): ν = 2968, 2927, 1772 (C=O), 1736 (C=O), 1605 (NO_2), 1520, 1489, 1437, 1396, 1306 (NO_2), 1261, 1173, 1095, 818, 750 cm^{-1}. APSI MS: M^++1 = 347. Anal. calcd. for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.10; H, 5.12; N, 8.17.

2,2-Dimethyl-2′,3′,4′,4a′-tetrahydro-1′*H*,6′*H*-spiro[1,3-dioxane-5,5′-pyrido[1,2-*a*]quinoline]-4,6-dione **(6b)**

Mp 148–149 °C (*i*-PrOH) [150].[7b] ^{1}H NMR (500 MHz, DMSO-d_6) δ = 1.21 (m, 1H, CH), 1.43 (m, 2H, CH), 1.53 (m, 1H, CH), 1.59 (m, 1H, CH), 1.74 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.78 (m, 1H, CH), 2.77

(t, $^2J_{HH} = 12.5$ Hz, 1H, CH), 3.26 (AB-syst, $^2J_{HH} = 16.8$ Hz, 2H, CH_2), 3.41 (d, $^2J_{HH} = 11.5$ Hz, 1H, CH), 4.04 (m, 1H, CH), 6.64 (t, $^3J_{H,H} = 8.3$ Hz, 1H, CH), 6.90 (d, $^3J_{H,H} = 8.3$ Hz, 1H, CH), 6.98 (d, $^3J_{H,H} = 8.3$ Hz, 1H, CH), 7.04 (t, $^3J_{H,H} = 8.3$ Hz, 1H, CH). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 23.8$, 24.1, 27.5, 28.1, 30.1, 32.1, 48.5, 52.1, 61.3, 106.0, 113.6, 118.0, 120.8, 127.3, 129.0, 144.6, 165.3, 168.5. IR (KBr): $\nu = 3068$, 2968, 2951, 1770 (C=O), 1741 (C=O), 1605, 1512, 1462, 1383, 1298, 1271, 1203, 1101, 1028, 964, 933, 746 cm^{-1}. APSI MS: $M^+ + 1 = 316$. Anal. calcd. for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.72; H, 6.57; N, 4.52.

2,2-Dimethyl-8′-nitro-2′,3′,4′,4a′-tetrahydro-1′*H*,6′*H*-spiro[1,3-dioxane-5,5′-pyrido[1,2-*a*]quinoline]-4,6-dione **(6c)**

Mp 209–210 °C (EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.24$ (m, 1H, CH), 1.40 (m, 1H, CH), 1.52 (m, 1H, CH), 1.61 (m, 1H, CH), 1.67 (m, 1H, CH), 1.77 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.81 (m, 1H, CH), 3.06 (t, $^2J_{HH} = 13.2$ Hz, 1H, CH), 3.28 (d, $^2J_{HH} = 16.5$ Hz, 1H, CH), 3.52 (d, $^2J_{HH} = 16.5$ Hz, 1H, CH), 3.74 (d, $^3J_{HH} = 12.0$ Hz, 1H, CH), 4.22 (m, 1H, CH), 7.04 (m, 1H, CH); 7.93 (m, 2H, CH). IR (KBr): $\nu = 3001$, 2972, 2947, 2920, 1767 (C=O), 1736 (C=O), 1605 (NO_2), 1583, 1497, 1396, 1317 (NO_2), 1296, 1259, 1213, 1103, 928, 814, 754 cm^{-1}. APSI MS: $M^+ + 1 = 361$. Anal. calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.16; H, 5.46; N, 7.70.

2,2-Dimethyl-8′-nitro-1′,2′,4′,4a′-tetrahydro-6′*H*-spiro[1,3-dioxane-5,5′-[1,4]oxazino[4,3-*a*]quinoline]-4,6-dione **(6d)**

Mp 220–221 °C (EtOH). ^{1}H NMR (500 MHz, DMSO-d_6) $\delta = 1.74$ (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 3.15–3.24 (m, 2H, CH), 3.36 (d, $^2J_{HH} = 16.4$ Hz, 1H, CH), 3.47 (d, $^2J_{HH} = 13.2$ Hz, 1H, CH), 3.60 (d, $^2J_{HH} = 16.4$ Hz, 1H, CH), 3.78 (d, $^2J_{HH} = 11.2$ Hz, 1H, CH), 3.89 (d, $^2J_{HH} = 11.2$ Hz, 1H, CH), 3.94 (d, $^2J_{HH} = 11.2$ Hz, 1H, CH), 4.08 (d, $^2J_{HH} = 13.2$ Hz, 1H, CH), 7.07 (d, $^3J_{HH} = 8.8$ Hz, 1H, CH), 7.97 (s, 1H, CH), 7.98 (d, $^3Jx_{HH} = 8.8$ Hz, 1H, CH). ^{13}C NMR (125 MHz, DMSO-d_6) $\delta = 28.1$, 29.7, 34.1, 46.1, 47.3, 58.7, 66.2, 66.6, 106.7, 111.8, 120.0, 124.2, 124.9, 137.6, 150.3, 164.1, 168.0. IR (KBr): $\nu = 2968$, 2924, 1769 (C=O), 1738 (C=O), 1604 (NO_2), 1587, 1510, 1437, 1319 (NO_2), 1256, 1104, 1058, 751 cm^{-1}. APSI MS: $M^+ + 1 = 363$. Anal. calcd. for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.51; H, 4.89; N, 7.64.

2,2,3′-Trimethyl-1′-phenyl-1′,4′,6′,7′,8′,9′-hexahydro-5a′*H*-spiro [1,3-dioxane-5,5′-pyrazolo[4,3-*c*]quinolizine]-4,6-dione **(6e)**

Mp 166–167 °C (EtOH). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 1.38$ (m, 3H, CH), 1.46 (m, 1H, CH), 1.60–1.68 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.14 (m, 1H, CH), 3.11 (AB-syst, $^2J_{HH} = 16.1$ Hz, 2H, CH_2), 3.18–3.26 (m, 2H, CH), 3.38 (m, 1H, CH), 7.28 (t, $^3J_{HH} = 7.6$ Hz, 1H, CH), 7.40–7.59 (m, 4H, CH). IR (KBr): $\nu = 3061$, 3001, 2935, 1780 (C=O), 1738 (C=O), 1599, 1502, 1450, 1383, 1323, 1288, 1203, 1113, 1070, 1024, 945, 775, 702 cm^{-1}. APSI MS: $M^+ + 1 = 396$. Anal. calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.95; H, 6.16; N, 10.54.

ACKNOWLEDGMENT

The authors acknowledge V. V. Polovinko (“Enamine Ltd.”) and Dr. S. A. Alekseev (Department of Chemistry of Kyiv National Taras Shevchenko University) for spectral measurements and D. A. Dontsova and Dr. A. N. Shivanyuk for helpful discussions.

REFERENCES

1. (a) Andersen, K. E.; Soerensen, J. L.; Lau, J.; Lundt, B. F.; Petersen, H.; Huusfeldt, P. O.; Suzdak, P. D.; Swedberg, M. D. B. Synthesis of novel γ-aminobutyric acid (GABA) uptake inhibitors, 5: Preparation and structure–activity studies of tricyclic analogues of known GABA uptake inhibitors. *J. Med. Chem.* **2001**, *44*, 2152–2163; (b) Andersen, K. E.; Lau, J.; Lundt, B. F.; Petersen, H.; Huusfeldt, P. O.; Suzdak, P. D.; Swedberg, M. D. B. Synthesis of novel GABA uptake inhibitors, part 6: Preparation and evaluation of N-Ω asymmetrically substituted nipecotic acid derivatives. *Bioorg. Med. Chem.* **2001**, *9*, 2773–2785; (c) Andersen, K. E.; Soerensen, J. L.; Huusfeldt, P. O.; Knutsen, L. J. S.; Lau, J.; Lundt, B. F.; Petersen, H.; Suzdak, P. D.; Swedberg, M. D. B. Synthesis of novel GABA uptake inhibitors, 4: Bioisosteric transformation and successive optimization of known GABA uptake inhibitors leading to a series of potent anticonvulsant drug candidates. *J. Med. Chem.* **1999**, *42*, 4281–4291; (d) Knutsen, L. J. S.; Andersen, K. E.; Lau, J.; Lundt, B. F.; Henry, R. F.; Morton, H. E.; Naerum, L.; Petersen, H.; Stephensen, H.; Suzdak, P. D.; Swedberg, M. D. B.; Thomsen, C.; Sorensen, P. O. Synthesis of novel GABA uptake inhibitors, 3: Diaryloxime and diarylvinyl ether derivatives of nipecotic acid and guvacine as anticonvulsant agents. *J. Med. Chem.* **1999**, *42*, 3447–3462.
2. (a) Suzuki, R.; Edwards, M.; Dickenson, A. H. ReN-1869 [(R)-1-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-1-propyl)-3-piperidine carboxylic acid], a novel histamine H1 receptor antagonist, produces potent and

selective antinociceptive effects on dorsal horn neurons after inflammation and neuropathy. *J. Pharmacol. Exp. Ther*. **2004**, *309*, 1230–1238; (b) Olsen, U. B.; Eltorp, C. T.; Ingvardsen, B. K.; Jørgensen, T. K.; Lundbaek, J. A.; Thomsen, C.; Hansen, A. J. ReN 1869, a novel tricyclic antihistamine, is active against neurogenic pain and inflammation. *Eur. J. Pharmacol*. **2002**, *435*, 43–57; (c) Laughlin, T. M.; Tram, K. V.; Wilcox, G. L.; Birnbaum, A. K. Comparison of antiepileptic drugs tiagabine, lamotrigine, and gabapentin in mouse models of acute, prolonged, and chronic nociception. *J. Pharmacol. Exp. Ther*. **2002**, *302*, 1168–1175.

3. (a) Halonen, T.; Nissinen, J.; Jansen, J. A.; Pitkaenen, A. Tiagabine prevents seizures, neuronal damage and memory impairment in experimental status epilepticus. *Eur. J. Pharmacol*. **1996**, *299*, 69–81; (b) Cleton, A.; Altorf, B. A.; Voskuyl, R. A.; Danhof, M. Pharmacokinetic–pharmacodynamic modelling of tiagabine CNS effects upon chronic treatment in rats: Lack of change in concentration–EEG effect relationship. *Eur. J. Pharm. Sci*. **2000**, *12*, 141–150; (c) Ndikum-Moffor, F. M.; Munson, J. W.; Bokinkere, N. K.; Brown, J. L.; Richards, N.; Roberts, S. M. Immunochemical detection of hepatic cocaine-protein adducts in mice. *Chem. Res. Toxicol*. **1998**, *11*, 185–192.
4. (a) Krasnov, K. A.; Kartsev, V. G. Stereoselective modification of cytisine: T-reaction for construction of benzoannelated anagyrine skeleton. *Heterocycles* **2007**, *71*, 19–25; (b) Lancaster, M.; Smith, D. J. H. Preparation and some reactions of benzazetidines. *J. Chem. Soc. Chem. Commun*. **1980**, 471–472; (c) Ferles, M.; Kocian, O. Quinoline and isoquinoline derivatives. V. Reduction of 2-, 3 and 4-quinolinecarbonitrile and 3- and 4-quinolinecarbonitrile methyl methosulfates with triethylammonium formate. *Collect. Czech. Chem. Commun*. **1979**, *44*, 2238–2242; (d) Grob, C. A.; Renk, E. Die synthese von ergolin-derivaten. Benz[cd]indol-reihe. *Helv. Chim. Acta* **1961**, *44*, 1531–1541; (e) Uhle, F. C.; Jacobs, W. A. The ergot alkaloids, XX: The synthesis of dihydro-*dl*-lysergic acid: A new synthesis of 3-substituted quinolines. *J. Org. Chem*. **1945**, *10*, 76–86.
5. (a) Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. The *tert*-amino effect in the synthesis of hetaryl- and arylsulfonyl-substituted pyrrolo- and pyrido[1,2-*a*]quinoline derivatives and their pyrazolo annulated analogues. *Synthesis* **2005**, 2161–2170; (b) Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. A novel *tert*-amino effect based approach to 1,2,3,4-tetrahydroquinoline-2-spirocycloalkanes. *Tetrahedron* **2006**, *62*, 9146–9152; (c) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Shivanyuk, A. N.; Tolmachev, A. A. A one-pot fusion of nitrogen-containing heterocycles. *Synthesis* **2007**, 2872–2886.
6. (a) Meth-Cohn, O., Suschitzky, H. Heterocycles by ring closure of *o*-substituted *tert*-anilines: *tert*-Amino effect. *Adv. Heterocycl. Chem.* **1972**, *14*, 211–278; (b) Meth-Cohn, O. The *t*-amino effect: Heterocycles formed by ring closure of *ortho*-substituted *t*-anilines. *Adv. Heterocycl. Chem*. **1996**, *65*, 1–37; (c) Verboom, W.; Reinhoudt, D. N. *Tert*-amino effect in heterocyclic

synthesis: Ring closure reactions of *N*,*N*-dialkyl-1,3-dien-1-amines. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311–324.

7. (a) Eltsov, O. S.; D'yachenko, E. V.; Glukhareva, T. V.; Morzherin, Y. Synthesis of spirocyclic 4,5,5a,6,7,8-hexahydro-1*H*-pyrazolo[3,4-*e*]indolizine derivatives. *Mendeleev Commun*. **2005**, 119–120; (b) D'yachenko, E. V.; Glukhareva, T. V.; Nikolaenko, E. F.; Tkachev, A. V.; Morzherin, Y. *tert*-Amino effect in heterocyclic chemistry: Synthesis of hydrogenated spiro derivatives of quinolines. *Russ. Chem. Bl*. **2004**, *53*, 1240–1247; (c) Elias, O.; Karolyhazy, L.; Horvath, G.; Harmat, V.; Matyus, P. Novel *ortho*- and *peri*-fused pyridazine ring systems. *Theochem*. **2003**, 666–667; (d) Glukhareva, T. V.; D'yachenko, E. V.; Morzherin, Y. Synthesis of spiro derivatives of pyrrolo[1,2-*a*]quinoline. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 1426–1427; (e) Kaval, N.; Halasz-Dajka, B.; Vo-Thanh, G.; Dehaen, W.; Van der Eycken, J.; Matyus, P.; Loupy, A.; Van der Eycken, E. An efficient microwave-assisted solvent-free synthesis of pyrido-fused ring systems applying the *tert*-amino effect. *Tetrahedron* **2005**, *61*, 9052–9057; (f) Deeva, E. V.; Glukhareva, T. V.; Zybina, N. A.; Morzherin, Y. Stereoselective synthesis of spiro derivatives of 2,4-dimethyl-2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine. *Russ. Chem. Bl*. **2005**, *54*, 1537–1538; (g) Deeva, E. V.; Glukhareva, T. V.; Tkachev, A. V.; Morzherin, Y. Stereoselective synthesis of spirofused 3-substituted 2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine using the *tert*-amino effect. *Mendeleev Commun*. **2006**, *2*, 82–83; (h) Vlaskina, N. M.; Suzdalev, K. F.; Babakova, M. N.; Mezheritskii, V. V.; Kartsev, V. G. Use of the *tert*-amino effect in the synthesis of spirocyclic fused α-carbolines. *Russ. Chem. Bl*. **2006**, *55*, 384–386; (i) Devi, I.; Baruah, B.; Bhuyan, P. J. α-Cyclization of tertiary amines: Synthesis of some novel annelated quinolines via a three-component reaction under solvent-free conditions. *Synlett* **2006**, 2593–2596.
8. (a) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. Chlorotrimethylsilane-mediated synthesis of 2-aryl-1-chloro-1-heteroarylalkenes. *Synthesis* **2007**, 3163–3170, and references cited therein.
9. (a) Fillion, E.; Wilsily, A. Asymmetric synthesis of all-carbon benzylic quaternary stereocenters via Cu-catalyzed conjugate addition of dialkylzinc reagents to 5-(1-arylalkylidene) Meldrum's acids. *J. Am. Chem. Soc*. **2006**, *128*, 2774–2775; (b) Li, J.-H.; Li, Z.-G.; Chen, Q.-G. Michael addition of nitromethane to isopropylidene 5-alkylidenemalonates. *J. Chem. Res. Synop*. **2004**, 758–759; (c) Jones, G.; Pitman, M. A.; Lunt, E.; Lythgoe, D. J.; Abarca, B.; Ballesteros, R.; Elmasnaouy, M. Triazolopyridines, 18: Nucleophilic substitution reactions on triazolopyridines; a new route to 2,2′-bipyridines. *Tetrahedron* **1997**, *53*, 8257–8268; (d) Aleksandrov, A. M.; Pehk, T. J.; Petrenko, A. E.; Watson, W. H. Accessible route to 4-substituted "bird-cage" hydrocarbon derivatives. *J. Org. Chem*. **1994**, *59*, 3709–3711; (e) Troxler, T.; Scheffold, R. Asymmetric catalysis by vitamin B12: The isomerization of achiral cyclopropanes to optically active olefins. *Helv. Chim. Acta* **1994**, *77*, 1193–1202.