Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2010, **20**, 83–85

Mendeleev Communications

Synthesis of substituted 2-alkyl-5-hydroxy-1-oxo-1,2-dihydroisoquinolines and their new condensed structures

Dmitry N. Platonov, Galina P. Okonnishnikova and Yury V. Tomilov*

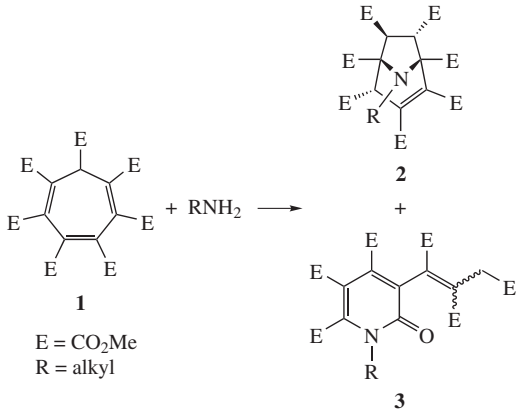
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 495 135 5328; e-mail: tom@ioc.ac.ru

DOI: 10.1016/j.mencom.2010.03.006

Original methods were developed for the synthesis of 1,2-dihydroisoquinoline derivatives by means of the cyclization of N-substituted hexamethoxycarbonyl-3-propenylpyridin-2-ones either upon action of bases or directly by reaction of hepta-(methoxycarbonyl)cycloheptatrienyl potassium with primary amines.

Pyridin-2-ones and 1,2-dihydroisoquinolines are widely used as central fragments in the synthesis of alkaloids and other biologically active substances.[1] In spite of a variety of methods for their synthesis, the development of new pathways to such functionalized compounds is of considerable current interest.

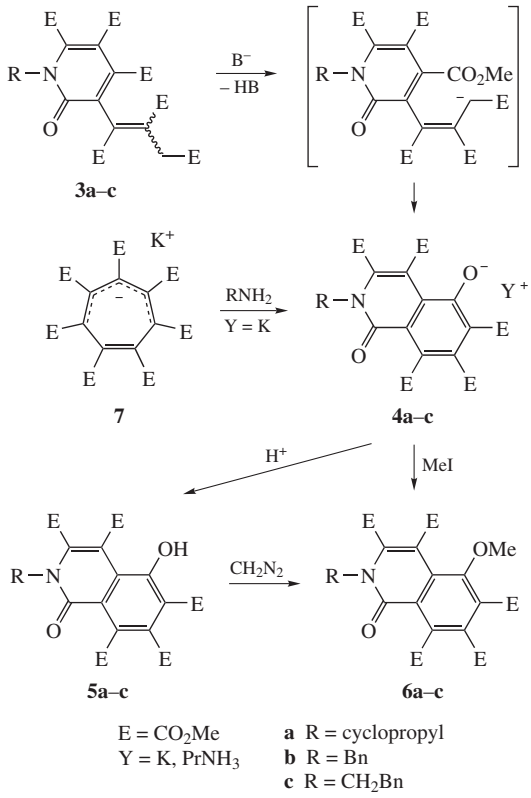
Recently,[2] we have found that the reaction of heptamethyl ester of cycloheptatrieneheptacarboxylic acid **1** with primary amines is dependent on the reaction conditions and leads to the formation of N-substituted (heptamethoxycarbonyl)nortrop-2-enes **2** and/or 3-(1-propenyl)pyridin-3-ones **3**, which contain six ester groups in a molecule (Scheme 1). In methanol, only the formation of 3-propenylpyridin-3-ones as a mixture of *E*- and *Z*-isomers was observed.



Scheme 1

Here, we report that the action of bases upon propenylpyridinones leads to their cyclization into 1-oxodihydroisoquinolin-5-olates **4a–c**, which give 5-hydroxyhydroisoquinolin-1-ones **5a–c** in high yields after treatment with an acid (Scheme 2). The process of cyclization does not depend on the isomeric composition of starting propenylpyridinones **3a–c**, which is apparently due to both isomers giving the same anion after deprotonation of the activated methylene group. The formed anion is able to gain the configuration favouring cyclization to **4a–c** at the ester group atattched to C(4) of the pyridine cycle. A similar cyclization was previously reported in the synthesis of substituted 10-hydroxyphenanthrenes.[3]

The rate of cyclization of propenylpyridinones **3** to dihydroxyisoquinolin-5-olates **4** depends on the strength of the base used. With strong bases like KOH, the reaction takes only several minutes while with primary amines it completes in 10–20 h.



Scheme 2

Thus, refluxing pyridinone **3a** with isopropylamine in methanol gives isopropylammonium salt **4a** (Y = $PrNH_3$) as the only product in 91% yield.† The structure of the product was confirmed by ^1H and ^{13}C NMR spectra and X-ray data (Figure 1).‡

Acidification of dihydroisoquinolin-5-olates **4** with mineral acid solutions affords hydroxy derivatives **5a–c** as stable crystalline compounds in high yields.§

Since the possibility of cyclization of propenylpyridinones **3** into dihydroisoquinolin-5-olates is determined by their deprotonation degree, we have studied a direct reaction of heptamethoxycarbonylcyclohepta-2,4,6-trien-1-yl potassium **7** with cyclopropylamine. It was shown previously[4] that salt **7** was a stable compound easily formed from cycloheptatriene **1** upon treatment with potassium *tert*-butylate. It was found that the reaction of cyclopropylamine with cycloheptatrienyl potassium **7** in acetonitrile solution at 5 °C during 16 h leads to the

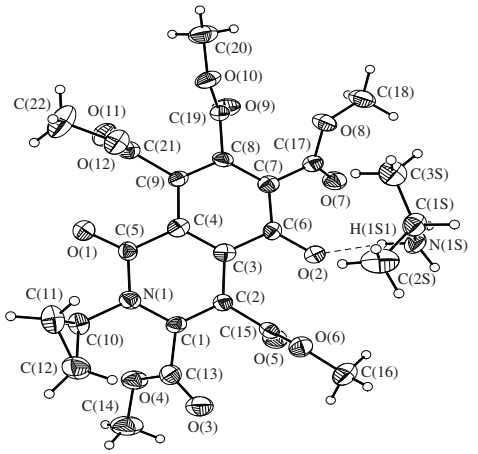


Figure 1 Crystal structure of **4a** as thermal ellipsoids drawn at 50% probability level. Selected bond lengths (Å): C(3)–C(6) 1.444(8), C(6)–C(7) 1.426(8), C(6)–O(2) 1.293(7), C(1S)–C(2S) 1.524(9), C(1S)–C(3S) 1.507(9), C(1S)–N(1S) 1.472(8), O(2)···HN(1S) 1.81.

formation of potassium dihydroisoquinolin-5-olate **4a** (Y = K) in a yield of ≥ 85%. Acidification of the resulting potassium phenolate to pH 1–2 gives phenol **5a**. Its reaction with methyl iodide in refluxing acetonitrile during 15 h gives methoxy derivative **6a** in 88% yield (Scheme 2).¶

These results allowed us to develop a convenient preparative method to obtain 5-hydroxydihydroisoquinolines **5** starting from heptamethyl cycloheptatrieneheptacarboxylate **1**. This compound was treated with methanolic KOH; then, a primary amine was added and the reaction mixture was stirred for 15 h at room temperature. After acidification to pH 1–2, the reaction mixture was extracted with chloroform and pure compounds **5a–c** were obtained in high yields.§ The acidity of phenolic protons in compounds **5** is quite high, their treatment with diazomethane in diethyl ether leads to the formation of methoxy derivatives **6a–c** in a quantitative yield.¶

Further transformations are observed in the reactions of cycloheptatriene **1** with both ethanolamine and ethylenediamine. In this case, no formation of bicyclic compounds similar to **2** is observed in either of the solvents used, and the reactions specifically progress towards the formation of the respective 3-vinylpyridin-2-ones. However, the process does not stop at this point. In case of ethanolamine, product **3d** instantly undergoes further cyclization to lactone **8a**, which is easily isolated from the reaction mixture by crystallization in a yield of 77–80%.[2] It should be noted that lactone **8a** is obtained as the *E*-isomer only (Scheme 3). Its structure was established by X-ray diffraction analysis, but crystals were not of good quality and constituted thin needles having a very low reflecting power.†† Upon treatment of **8a** with a base, the second fragment containing an

† *Isopropylammonium 2-cyclopropyl-3,4,6,7,8-penta(methoxycarbonyl)-1-oxo-1,2-dihydroisoquinolin-5-oate* **4a** (Y = $PrNH_3$). The mixture of dihydropyridinone **3a** (315 mg, 0.6 mmol) and 2-aminopropane (83 mg, 1.4 mmol) in methanol (10 ml) was refluxed for 14 h. Evaporation *in vacuo* and crystallisation of the residue from acetonitrile gave salt **4a** as light yellow crystals, yield 91%, mp 181–182 °C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.79, 1.07 (both m, 2×2H, CH_2CH_2), 1.09 (d, 6H, 2Me, *J* 6.5 Hz), 3.18 (tt, 1H, CH in cyclopropyl, J_{cis} 7.1 Hz, J_{trans} 4.0 Hz), 3.24 (sp, 1H, NCH, *J* 6.5 Hz), 3.78, 3.80, 3.83, 3.91, 3.94 (all s, 5×3H, 5OMe), 6.93 (br. s, 3H, CN^+H_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 8.7 (CH_2CH_2), 21.8 (2Me), 31.5 (CH in cyclopropyl), 43.9 (CH in Pr), 52.6, 52.8, 52.9, 52.9, 53.2 (5OMe), 113.2 (4-C), 118.2, 118.4 (4a-C, 6-C), 126.0, 128.4, 132.4, 134.3 (3-C, 7-C, 8-C, 8a-C), 161.1, 162.5, 163.5, 167.7, 169.1, 169.4, 169.6 (1-C, 5-C, 5COO). Found (%): C, 54.63; H, 5.23; N, 5.13. Calc. for $C_{25}H_{30}N_2O_{12}$ (%): C, 54.54; H, 5.49; N, 5.09.

Potassium 2-cyclopropyl-3,4,6,7,8-penta(methoxycarbonyl)-1-oxo-1,2-dihydroisoquinolin-5-oate **4a** (Y = K). The mixture of heptamethoxycarbonylcyclohepta-2,4,6-trien-1-yl potassium[4] (485 mg, 0.9 mmol) and cyclopropylamine (80 mg, 1.4 mmol) in acetonitrile (2.5 ml) was kept at 5 °C for 16 h. Evaporation *in vacuo* and crystallisation of the residue from benzene gave salt **4a** (Y = K) as yellow crystals, yield 85%, mp 241–242 °C (decomp.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.89, 1.18 (both m, 2×2H, CH_2CH_2), 3.34 (tt, 1H, CH in cyclopropyl, J_{cis} 7.1 Hz, J_{trans} 4.1 Hz), 3.93, 3.96, 3.97, 3.99, 4.00 (all s, 5×3H, 5OMe). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 8.7 (CH_2CH_2), 31.5 (CH in cyclopropyl), 52.2, 52.9, 53.0, 53.1, 53.3 (5OMe), 114.5 (4-C), 125.8, 125.9 (4a-C, 6-C), 128.8, 132.6, 133.4, 133.5 (3-C, 7-C, 8-C, 8a-C), 161.9, 162.9, 163.0, 169.0, 169.9, 170.5, 171.1 (1-C, 5-C, 5COO). Found (%): C, 50.11; H, 3.63; N, 2.52. Calc. for $C_{22}H_{20}KNO_{12}$ (%): C, 49.90; H, 3.81; N, 2.65.

‡ *Crystallographic data for* **4a** (Y = $PrNH_3$). Crystals of $C_{25}H_{30}N_2O_{12}$ (*M* = 550.51) are orthorhombic, space group $Pca2_1$, at 120(2) K: *a* = = 23.829(7), *b* = 13.374(3) and *c* = 8.533(2) Å, *V* = 2719.3(12) Å^3, *Z* = 4, *F*(000) = 1160, d_{calc} = 1.345 g cm^{-3}, μ = 0.108 mm^{-1}. Intensities of 25922 reflections were measured on an automated SMART 1000 CCD diffractometer (MoKα radiation, graphite monochromator, φ and ω-scanning techniques, θ_{max} = 28°). The structure was solved by direct methods and refined by a full-matrix least-squares method against F^2 in the anisotropic–isotropic approximation. The positions of the hydrogen atoms were calculated geometrically. The final *R* factors were as follows: R_1 = 0.0745 for 3481 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.1398 for all 1755 independent reflections, GOF = 1.101. All calculations were carried out using the SHELXTL PLUS software (Version 5.0).

CCDC 749953 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.

§ *General method for the synthesis of compounds* **5a–c**. Heptamethoxycarbonylcyclohepta-1,3,5-triene **1** (200 mg, 0.4 mmol) was added to a solution of KOH (26 mg, 0.4 mmol) in methanol (5 ml) and the mixture was stirred for 30 min. Then an amine (0.4 mmol) was added to a reaction mixture and the mixture was stirred for 6–7 h at 25 °C (TLC). The solvent was removed *in vacuo*, 5% aqueous H_2SO_4 solution was added to pH ~1.5, and the mixture was extracted with chloroform. The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo*. The products were obtained as colourless crystals.

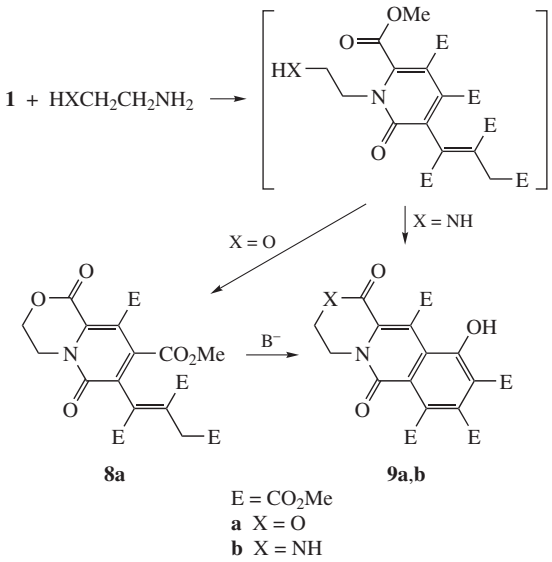
Pentamethyl 2-cyclopropyl-5-hydroxy-1-oxo-1,2-dihydroisoquinoline-3,4,6,7,8-pentacarboxylate **5a**. Yield 88%, mp 195–196 °C (MeCN). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.84, 1.11 (both m, 2×2H, CH_2CH_2), 3.21 (tt, 1H, CH in cyclopropyl, J_{cis} 7.2 Hz, J_{trans} 4.1 Hz), 3.62, 3.83, 3.90, 3.94, 3.98 (all s, 5×3H, 5OMe), 12.1 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 8.8 (CH_2CH_2), 31.7 (CH in cyclopropyl), 53.1, 53.2 (2C), 53.5, 53.9 (5OMe), 110.6, 110.7 (4-C, 6-C), 124.6, 125.0, 127.1 (4a-C, 8-C, 8a-C), 133.1, 137.3 (3-C, 7-C), 158.4, 158.5 (1-C, 5-C), 159.9, 161.9, 166.5, 167.6, 169.1 (5COO). MS, *m/z* (%): 491 (3) $[M]^+$, 432 (5) $[M - CO_2Me]^+$, 400 (11), 368 (10), 336 (11), 59 (40), 41 (100). Found (%): C, 54.00; H, 4.38; N, 2.70. Calc. for $C_{22}H_{21}NO_{12}$ (%): C, 53.77; H, 4.28; N, 2.85.

Pentamethyl 2-benzyl-5-hydroxy-1-oxo-1,2-dihydroisoquinoline-3,4,6,7,8-pentacarboxylate **5b**. Yield 93%, mp 212–213 °C (MeCN). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.88, 3.89, 3.95, 3.96, 3.98 (all s, 5×3H, 5OMe), 5.47 (s, 2H, CH_2), 7.16 (dd, 2H, $2H_o$, ^3J 7.7 Hz, ^4J 2.2 Hz), 7.28 (m, 3H, $2H_m$, H_p), 12.1 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 48.4 (CH_2), 53.1, 53.2, 53.3, 53.5, 54.0 (5OMe), 110.8 (4-C), 125.1, 125.2, 126.9 (4a-C, 6-C, 8-C), 133.1, 135.5, 135.6, 135.8 (C_i, 3-C, 7-C, 8a-C), 158.6 (2C), 159.1, 162.1, 166.6, 167.8, 169.1 (1-C, 5-C, 5COO). MS, *m/z* (%): 509 (5) $[M - MeOH]^+$, 388 (11), 356 (15), 121 (21), 91 (100). Found (%): C, 57.45; H, 4.22; N, 2.50. Calc. for $C_{26}H_{23}NO_{12}$ (%): C, 57.67; H, 4.25; N, 2.59.

Pentamethyl 2-(2-phenylethyl)-5-hydroxy-1-oxo-1,2-dihydroisoquinoline-3,4,6,7,8-pentacarboxylate **5c**. Yield 95%, mp 175–176 °C (C_6H_6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.04 (m, 2H, CH_2), 3.88, 3.90, 3.92, 3.96, 3.97 (all s, 5×3H, 5OMe), 4.18 (m, 2H, NCH_2), 7.27 (m, 5H, Ph), 12.1 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 34.8 (CH_2), 49.2 (NCH_2), 53.1 (2C), 53.2, 53.8, 53.9 (5OMe), 110.0, 110.6 (4-C, 6-C), 125.0, 125.1, 126.8 (4a-C, 8-C, 8a-C), 132.8, 136.5, 137.7 (C_i, 3-C, 7-C), 158.5, 158.6 (1-C, 5-C), 162.3, 166.6, 166.7, 167.8, 169.1 (5COO). MS, *m/z* (%): 555 (5) $[M]^+$, 492 (10), 451 (20), 419 (50), 387 (50), 356 (20), 329 (31), 271 (26), 105 (100). Found (%): C, 57.99; H, 4.47; N, 2.49. Calc. for $C_{27}H_{25}NO_{12}$ (%): C, 58.38; H, 4.54; N, 2.52.

active methylene group undergoes cyclization. Acidification of the phenolate affords derivative **9a**.‡‡ The same compound is easily obtained as a phenolate in one pot if KOH is initially added to triene **1**.

In case of ethylenediamine, which is a quite strong base, lactam **8b** could not be detected as the propenylpyridine fragment of this compound immediately cyclised into the phenolate, which upon acidification gives condensed phenol **9b** in 90% yield (Scheme 3).



Scheme 3

Thus, using the reactions of cycloheptatrieneheptacarboxylic acid heptamethyl ester with primary amines in various basic environments we have developed a new approach to the synthesis of polyfunctionalized condensed heterocyclic compounds containing a dihydroisoquinolin-1-one fragment.

This work was supported by the Presidium of the Russian Academy of Sciences (Program for Basic Research 'Elaboration of Methods for the Synthesis of Chemical Substances and Creation of New Materials') and the Council on Grants of the President of the Russian Federation (grant no. NSh-3237.2008.3).

We are grateful to Dr. K. Yu. Suponitsky (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences) for the execution of X-ray diffraction analyses.

References

1 (*a*) H. Tieckelmann, in *Pyridine and Its Derivatives*, ed. R. A. Abramovitch, Interscience, New York, 1974, vol. 14, part 3, ch. 12; (*b*) T. Matsui, T. Sugiura, H. Nakai, S. Iguchi, S. Shigeoka, H. Takada, Y. Odagaki, Y. Nagao and Y. Ushio, *J. Med. Chem.*, 1992, **35**, 3307; (*c*) N. M. Mollov and H. B. Dutschewska, *Tetrahedron Lett.*, 1969, **10**, 1951.

2 Yu. V. Tomilov, D. N. Platonov and G. P. Okonnishnikova, *Tetrahedron Lett.*, 2009, **50**, 5605.

3 (*a*) S. Kobayashi, K. Kitamura, A. Miura, M. Fukuda and M. Kihara, *Chem. Pharm. Bull.*, 1972, **20**, 694; (*b*) W. Ried and R. Conte, *Chem. Ber.*, 1972, **105**, 799.

4 Yu. V. Tomilov, D. N. Platonov, R. F. Salikov and G. P. Okonnishnikova, *Tetrahedron*, 2008, **64**, 10201.

Received: 13th October 2009; Com. 09/3401

¶ *2-Cyclopropyl-3,4,6,7,8-penta(methoxycarbonyl)-1-oxo-5-methoxy-1,2-dihydroisoquinoline* **6a**. A solution of compound **4a** (Y = K) (160 mg, 0.3 mmol) and methyl iodide (71 mg, 0.5 mmol) in acetonitrile (4 ml) was refluxed for 15 h. After cooling, filtration, evaporation of the filtrate *in vacuo* and crystallisation from CH_2Cl_2–CCl_4 (10:1) compound **6a** was obtained as light yellow crystals, yield 88%, mp 154–155 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.85, 1.10 (both m, 2×2H, CH_2CH_2), 3.18 (tt, 1H, CH in cyclopropyl, J_{cis} 7.0 Hz, J_{trans} 4.1 Hz), 3.76 (s, 3H, OMe), 3.86, 3.88, 3.94, 3.96, 4.01 (all s, 5×3H, 5OMe). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 8.7 (CH_2CH_2), 31.6 (CH in cyclopropyl), 53.2, 53.3, 53.4, 53.5, 53.6 (5OMe), 64.9 (OMe), 109.9 (4-C), 125.2, 129.2 (4a-C, 8-C), 131.0, 131.2, 132.0 (7-C, 6-C, 8a-C), 138.4 (3-C), 154.0 (5-C), 160.1 (1-C), 161.9, 164.6, 165.7, 166.5, 167.7 (5COO). MS, *m*/*z* (%): 505 (3) $[M]^+$, 490 (12), 474 (10), 446 (22), 414 (20), 199 (50), 185 (60), 171 (55), 158 (47), 143 (57), 128 (65), 114 (100). Found (%): C, 54.27; H, 4.49; N, 2.85. Calc. for $C_{23}H_{23}NO_{12}$ (%): C, 54.66; H, 4.59; N, 2.77.

Pentamethyl 2-(2-phenylethyl)-5-methoxy-1-oxo-1,2-dihydroisoquinoline-3,4,6,7,8-pentacarboxylate **6c**. A solution of diazomethane in Et_2O (1 ml, ~0.5 mmol) was added in one portion to a solution of **5c** (112 mg, 0.2 mmol) in CH_2Cl_2 (4 ml) and the mixture was stirred at room temperature for 1 h. Yield 99%, mp 186–187 °C (MeCN). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.05 (m, 2H, CH_2), 3.76 (s, 3H, OMe), 3.85, 3.90, 3.93, 3.95, 4.03 (all s, 5×3H, 5CO_2Me), 4.16 (m, 2H, NCH_2), 7.29 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 34.8 (CH_2), 49.1 (NCH_2), 53.1, 53.2, 53.3, 53.4, 53.9 (5OMe), 64.9 (OMe), 109.1 (4-C), 124.9 (8-C), 131.3, 131.4, 132.1 (4a-C, 6-C, 8a-C), 137.5, 137.6, 137.7 (C_i, 3-C, 7-C), 154.0, 158.8 (1-C, 5-C), 162.2, 164.6, 165.7, 166.7, 167.9 (5COO). MS, *m*/*z* (%): 569 (10) $[M]^+$, 538 (15), 464 (29), 432 (50), 401 (40), 387 (21), 373 (25), 105 (100). Found (%): C, 58.89; H, 4.69; N, 2.40. Calc. for $C_{28}H_{27}NO_{12}$ (%): C, 59.05; H, 4.75; N, 2.46.

†† CCDC 756669 contains the supplementary crystallographic data for **8a**, which were obtained earlier.[2] These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

‡‡ *Tetramethyl 10-hydroxy-1,6-dioxo-1,3,4,6-tetrahydro[1,4]oxazino[4,3-*b*]isoquinoline-7,8,9,11-tetracarboxylate* **9a**. This compound was obtained according to the general method for the synthesis of compounds **5a**–**c**. Yield 84%, mp 226–228 °C (MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.90, 3.95, 3.98, 4.00 (all s, 4×3H, 4OMe), 4.34 (m, 2H, NCH_2), 4.63 (t, 2H, OCH_2, *J* 4.8 Hz), 12.3 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 40.0 (NCH_2), 53.1, 53.2, 53.3, 54.0 (4OMe), 65.2 (OCH_2), 111.2 (11-C), 116.9 (9-C), 124.5, 124.8, 126.3, 134.2 (6a-C, 7-C, 8-C, 10a-C), 157.0, 157.5, 159.3, 159.4 (1-C, 6-C, 10-C, 11a-C), 166.0, 166.1, 167.3, 168.7 (4COO). MS, *m*/*z* (%): 431 (4) $[M - MeOH]^+$, 400 (5), 359 (6), 283 (15), 59 (100). Found (%): C, 51.79; H, 3.51; N, 3.09. Calc. for $C_{20}H_{17}NO_{12}$ (%): C, 51.84; H, 3.70; N, 3.02.

*Tetramethyl 10-hydroxy-1,6-dioxo-1,3,4,6-tetrahydro-2*H*-pyrazino[1,2-*b*]isoquinoline-7,8,9,11-tetracarboxylate* **9b**. Yield 87%, mp > 240 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO, 300 MHz) δ: 3.47, 4.12 (both m, 2×2H, CH_2CH_2), 3.73, 3.76, 3.77, 3.80 (all s, 4×3H, 4OMe), 8.80 (br. s, 1H, NH), 11.5 (br. s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ: 36.6 (3-C), 40.3 (4-C), 51.5, 51.9, 52.5, 52.6 (4OMe), 111.7 (11-C), 120.7 (9-C), 124.2, 126.3, 129.9, 131.0 (6a-C, 7-C, 8-C, 10a-C), 152.2, 156.8, 157.5, 157.6 (1-C, 6-C, 10-C, 11a-C), 165.0, 165.1, 166.1, 166.8 (4COO). Found (%): C, 51.71; H, 3.98; N, 5.97. Calc. for $C_{20}H_{18}N_2O_{11}$ (%): C, 51.95; H, 3.92; N, 6.06.