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Synthesis of structurally constrained 4-quinazolinone derivatives with a tetrahedral C-2 atom present in three rings

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ABSTRACT

The reaction of 2-aminobenzamides with 2-oxocyclopentane-, 2-oxocyclohexane-, and 2-oxocycloheptaneacetic acids esters was found to give 7a,8,9,10-tetrahydrocyclopenta[2,3]pyrrolo[1,2-*a*]quinazoline-6,12(7*H*,11*H*)-diones, 7,7a,8,9,10,11-hexahydro-6*H*-indolo[1,7*a*-*a*]quinazoline-6,13(12*H*)-diones, and 7a,8,9,10,11,12-hexahydrocyclohepta[2,3]pyrrolo[1,2-*a*]quinazoline-6,14(7*H*,13*H*)-diones, respectively. The relative configuration with the *cis*-fused butyrolactam and cycloalkane rings was assigned to the prepared compounds on the basis of an X-ray crystallographic study.

1. Introduction

Fused 4-quinazolinones are the core of naturally occurring alkaloids and a number of synthetic drugs (for recent reviews see Refs. 1–6). Among them compounds with partially or completely hydrogenated heterocyclic rings are of especial interest for biology and medicine. However, quinazoline derivatives containing a tetrahedral C-2 atom being simultaneously a member of more than two rings are very rare. To the best of our knowledge, two such substances were isolated during a study of intramolecular nitrene trapping processes,[7–9] and a few compounds were prepared by a cycloaddition reaction between isoindolo[1,2-*a*]quinazolines and maleimides.[10,11] Apparently, these works were not aimed specially at the synthesis of the aforementioned quinazoline derivatives and were rather devoted to researches on other topics. So, elaboration of new general approach to this type of structurally constrained quinazolines seems to be of interest.

Previously we have reported the preparation of pyrroloquinazoline carboxylic acids **1** (Fig. 1) from 2-aminobenzamides and 2-oxoglutaric acid.[12] Continuing this research we have turned our attention to 2-oxocycloalkaneacetic acid esters **2a**–**c** also consisting of the 4-oxoacid moiety. Historically an interest in these

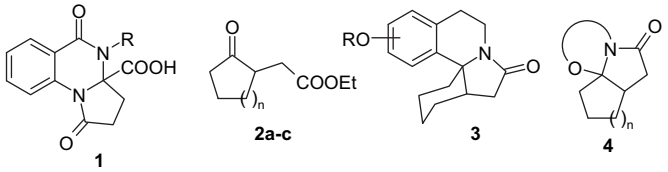

Figure 1. For compounds **2** *n*=**a**: 1, **b**: 2, **c**: 3.

acid derivatives, and first of all in the six-member one **2b**, arose from the synthesis of *Erythrina* alkaloids. Thus, its reaction with alkoxy substituted 2-phenylethanamines allowed straightforward construction of the erythrinane skeleton **3**,[13–18] which nowadays is recognized as the method of choice.[19–21] Furthermore, several amines with a tethered nucleophilic carbon atom of non-benzoic nature were also employed successfully in the reaction.[22–24] Moreover, condensation of the esters **2a**,**b** with aminoalcohols yielding tricyclic compounds of the common structure **4** was investigated as well.[25–31] A wide variety of different 1,2-[25–29] and 1,3-aminoalcohols[30,31] were used. In particular, in the case of chiral phenylglycinol or related aminoalcohols, the reaction occurred stereoselectively, and further reductive cleavage of the

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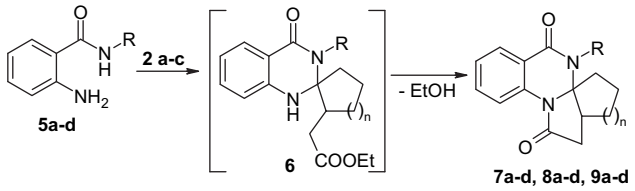
phenylglycinol fragment afforded enantiopure compounds that could be successfully applied as the ligands for the catalytic enantioselective additions to carbonyl group.[25–27] At the same time the reactivity of the oxoesters **2** toward diamines is less studied.[32] There is the only paper[32] describing their reactions with ethanediamine, propanediamine, and butanediamine; all proceeded by the analogy with aminoalcohols. Finally, an interaction of the oxoesters **2a**,**b** with certain amino acid derivatives of norbornene core has been reported recently.[33,34] It resulted in complex, but separable mixtures of different products. So, a synthetic utility of the oxoesters **2a**,**b** in the reactions with *C*,*N*- and *O*,*N*-binucleophilic compounds is well documented,[13–31] whereas their behavior toward *N*,*N*-binucleophiles is studied insufficiently.[32–34] The anthranilic acid amides **5a–d** (Scheme 1) contain the formal 1,3-diamine moiety and can be considered as *N*,*N*-binucleophilic reagents. So, continuing our researches on the synthesis of fused quinazolines[12,35–38] we have examined the reaction of compounds **5** with the oxoesters **2** as the possible route to the structurally constrained quinazoline derivatives. The results obtained are reported herein.



Scheme 1. R=**a**: CH_3, **b**: C_2H_5, **c**: $PhCH_2$, **d**: Ph. n=**7**: 1, **8**: 2, **9**: 3.

2. Results and discussion

It was found that reaction of derivatives **5a–d** with the oxoesters **2a–c** in acetic acid at reflux afforded condensed quinazolines **7–9** in 40–70% yields. Obviously, compounds **7–9** were formed through the intermediate cyclic aminals **6** by means of intramolecular acylation of the secondary amine with the ester group. The adducts of type **6** are the well known products for the reactions of 2-aminobenzamides with cyclic carbonyl compounds.[39–46] Also it should be noted that all compounds **7–9** are the representatives of novel hitherto unknown heterocyclic cores, namely cyclopenta[2,3]pyrrolo[1,2-*a*]quinazoline, indolo[1,7*a*-*a*]quinazoline, and cyclohepta[2,3]pyrrolo[1,2-*a*]quinazoline, respectively.

The structure of the prepared compounds **7–9** was confirmed by ^1H and ^{13}C NMR data. Among the spectral data the signal of 2-C of the quinazoline moiety observed in the ^{13}C NMR spectra at 80–90 ppm deserves to be mentioned as the most remarkable attribute of the tetracyclic system formation. However, the reaction of amides **5** with the oxoesters **2** appeared to occur diastereoselectively yielding compounds **7–9** with definite relative configuration of the two stereocenters; or in other words with either *cis*- or *trans*-fusion of the butyrolactam and cycloalkane rings. The spectral methods did not allow the stereochemical assignment. Hence, to solve this question and to be absolutely sure in the structure of the prepared derivatives **7–9** an X-ray crystallographic study was performed for compound **9c** (Fig. 2). It revealed clearly the butyrolactam and cycloheptane rings to be *cis*-fused. Following the analogy the same relative configuration was assigned throughout the whole series of compounds **7–9**. Thus, they should be formulated as the racemates of the pair of enantiomeric structures **A** and **B** (Fig. 3). Noteworthy, the stereochemical outcome observed is in agreement with the published data.[15–18,20,25–30] Thus, during the synthesis of *erythrina* alkaloids **3**[15–18,20] and aminoalcohol adducts **4**[25–30] all cases where the stereochemistry was assigned resulted in the similar *cis*-fused compounds.

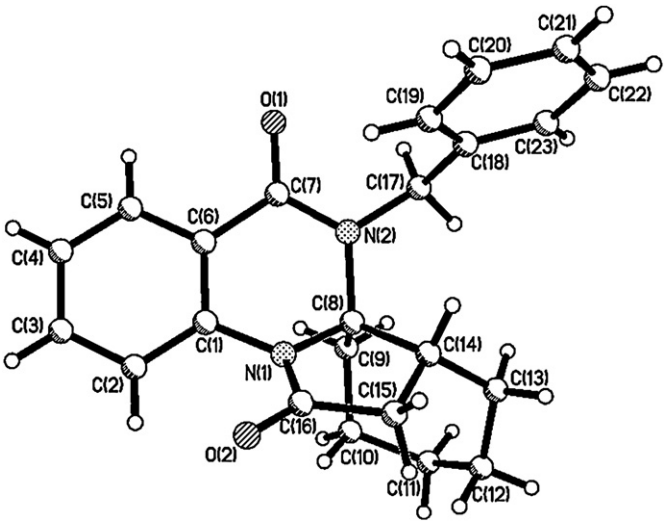


Figure 2. X-ray molecular structure of compound **9c** with the atom numbering used in the crystallographic analysis.

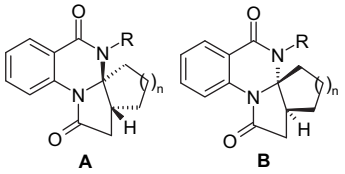


Figure 3. The relative configuration of compounds **7–9**.

There are a few points regarding the crystal structure of derivative **9c** that are worth of comment. According to the crystal data[†] the asymmetric part of crystal unit cell contains the two enantiomeric molecules **A** and **B** with very close geometric parameters. So, the further data are given for one of the molecules. The pyrimidine ring is in the distorted chair conformation with the atoms N(2) and C(8) deviated from the least-squared plane of the rest of the atoms of the ring at 0.19 Å and 0.64 Å, respectively. The following puckering parameters[47] have been calculated: S=0.59, Θ=45.9°, ψ=19.0°. The butyrolactam moiety is planar (with precision of 0.04 Å). Simultaneously, the cycloheptane ring adopts the chair conformation with the coplanar atoms C(9), C(10), C(12), and C(13) (with precision of 0.05 Å) and the atoms C(11), C(8), and C(14) deviated from their plane at −0.65 Å, +0.99 Å, and +1.13 Å, respectively.

In conclusion, the present investigation has resulted in the simple straightforward synthesis of the new structurally constrained quinazoline derivatives **7–9**. The reaction occurs stereoselectively leading to the products with the *cis*-fused lactam and cycloalkane moieties. This selectivity is suggested to be controlled kinetically. Thus, in the initial adducts **6** an easy inversion of the relative configuration can be achieved at the expense of the ring-chain tautomerism of the aminal fragment.[40] Perhaps, the intermediates **6** with the *cis*-oriented secondary amine and acetic acid residues undergo faster cyclization comparing to the corresponding *trans*-stereoisomers, therefore shifting the equilibrium between the stereoisomers **6** and yielding compounds of structures **A** and **B**.

[†] Full crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 725605. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3. Experimental

3.1. General

2-Aminobenzamides **5a**–**d**[48–51] and the oxoesters **2a**–**c**[52–54] were prepared as reported. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian UNITY*plus* 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer in DMSO-d_6 solutions. Chemical shifts (δ) are given in parts per million downfield from internal Me_4Si. *J* values are in hertz. Elemental analyses were performed at the Microanalytical Department of the Institute of Organic Chemistry, NAS, Kiev, Ukraine. The purity of all compounds prepared was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

3.2. Condensed 4-quinazolinones 7a–d, 8a–d, and 9a–d. General procedure

A solution of compounds **5a**–**d** (4.0 mmol) and the oxoesters **2a**–**c** (4.8 mmol) in acetic acid (10 mL) was heated at reflux for 7–8 h. Upon cooling it was poured into water (20 mL) resulting in separation of an oil, which slowly solidified. The solid was filtered, washed with water (5 mL), and recrystallized from an appropriate solvent yielding derivatives **7a**,**c**,**d**, **8a**–**d**, and **9a**,**c**. In the cases of compounds **7b**, **9b**,**d** the oil obtained did not solidify. So, it was taken up into CH_2Cl_2 (20 mL), the solution was washed with water (20 mL), dried (Na_2SO_4), and evaporated in vacuo. The residue was subjected to column chromatography on silica gel using gradient elution $CHCl_3 \rightarrow$ MeOH. Evaporation of the main fraction under reduced pressure afforded derivatives **7b**, **9b**,**d** as clear yellow oils.

*3.2.1. 7a,8,9,10-Tetrahydro-11-methylcyclopenta[2,3]pyrrolo[1,2-a]quinazoline-6,12(7H,11H)-dione (**7a**).* Yield 0.62 g, 61%. Beige powder; mp 121 °C (from EtOH). Found: C, 70.27; H, 6.40; N, 10.85. $C_{15}H_{16}N_2O_2$ requires C, 70.29; H, 6.29; N,10.93. ν_{max} (KBr) 2936, 2866, 1712, 1648, 1602, 1484, 1468, 1392, 1344, 1240, 1218, 764, 698 cm^{-1}. δ_H 1.52 (1H, m, 9-H), 1.67 (3H, m, 9-H, 8-CH_2), 1.85 (1H, m, 10-H), 1.95 (1H, m, 10-H), 2.37 (1H, dd, J^2 18.5, J^3 4.5, 7-H), 2.95 (1H, dd, J^2 18.5, J^3 11.0, 7-H), 3.00 (3H, s, NCH_3), 3.17 (1H, m, 7*a*-H), 7.32 (1H, t, *J* 8.0, 2-H), 7.60 (1H, t, *J* 8.0, 3-H), 7.84 (1H, d, *J* 8.0, 1-H), 7.91 (1H, d, *J* 8.0, 4-H). δ_C 23.3 (8-C), 28.0 (7*a*-C), 33.4 (9-C), 35.8 (10-C), 37.6 (NCH_3), 37.7 (7-C), 89.3 (10*a*-C), 121.4 (12*a*-C), 121.9 (4-C), 125.6 (2-C), 128.2 (1-C), 133.1 (3-C), 135.9 (4*a*-C), 161.9 (12-CO), 172.9 (6-CO).

*3.2.2. 11-Ethyl-7a,8,9,10-tetrahydrocyclopenta[2,3]pyrrolo[1,2-a]quinazoline-6,12(7H,11H)-dione (**7b**).* Yield 0.54 g, 50%. Yellow oil. Found: C, 70.87; H, 6.73; N, 10.29. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36. R_f ($CHCl_3 \rightarrow$3:1 $CHCl_3$/MeOH) 0.51. ν_{max} (KBr) 2932, 2862, 1712, 1650, 1558, 1540, 1488, 1470, 1400, 1362, 1344, 1220, 766, 698 cm^{-1}. δ_H 1.31 (3H, t, *J* 7.0, CH_3), 1.59 (2H, m, 9-CH_2), 1.75 (2H, m, 8-CH_2), 2.03 (1H, m, 10-H), 2.13 (1H, m, 10-H), 2.39 (1H, m, 7-H), 2.92 (1H, m, NCH_2), 3.06 (2H, m, 7-H, 7*a*-H), 3.99 (1H, m, NCH_2), 7.29 (1H, t, *J* 8.0, 2-H), 7.54 (1H, t, *J* 8.0, 3-H), 7.90 (1H, d, *J* 8.0, 1-H), 8.08 (1H, d, *J* 8.0, 4-H). δ_C 15.4 (CH_3), 23.0 (8-C), 33.9 (7*a*-C), 37.3 (9-C), 37.5 (10-C), 37.6 (7-C), 37.9 (NCH_2), 89.4 (10*a*-C), 121.8 (12*a*-C), 122.1 (4-C), 125.7 (2-C), 128.1 (1-C), 133.0 (3-C), 135.8 (4*a*-C), 161.8 (12-CO), 172.9 (6-CO).

*3.2.3. 7a,8,9,10-Tetrahydro-11-benzylcyclopenta[2,3]pyrrolo[1,2-a]-quinazoline-6,12(7H,11H)-dione (**7c**).* Yield 0.80 g, 60%. White powder; mp 136 °C (from EtOH). Found: C, 75.68; H, 6.14; N, 8.48. $C_{21}H_{20}N_2O_2$ requires C, 75.88; H, 6.06; N, 8.43. ν_{max} (KBr) 2958, 2936, 2872, 1710, 1650, 1604, 1486, 1468, 1394, 1362, 1342, 1250, 1220, 760, 742, 700 cm^{-1}. δ_H 1.45 (1H, m, 9-H), 1.54 (1H, m, 9-H), 1.63 (1H, m, 8-H), 1.73 (1H, m, 8-H), 1.98 (2H, m, 10-CH_2), 2.32 (1H, dd, J^2 18.0, J^3 2.5, 7-H), 2.61 (1H, dd, J^2 18.0, J^3 11.0, 7-H), 2.84 (1H, m, 7*a*-H), 4.30 (1H, d, *J* 16.5, NCH_2), 5.18 (1H, d, *J* 16.5, NCH_2), 7.24 (3H, m, H_R), 7.23–7.39 (3H, m, 2-H, 2H_R), 7.66 (1H, t, *J* 8.0, 3-H), 7.85 (1H, d, *J* 8.0, 1-H), 7.97 (1H, d, *J* 8.0, 4-H). δ_C 23.0 (8-C), 33.6 (9-C), 37.1 (10-C), 37.3 (7*a*-C), 37.7 (7-C), 45.3 (NCH_2), 89.7 (10*a*-C), 121.6 (12*a*-C), 122.2 (4-C), 125.9 (2-C), 126.6 (3,5-C_R), 127.4 (4-C_R), 128.5 (1-C), 129.1 (2,6-C_R), 133.4 (3-C), 136.0 (1-C_R), 138.9 (4*a*-C), 162.5 (12-CO), 172.8 (6-CO).

*3.2.4. 7a,8,9,10-Tetrahydro-11-phenylcyclopenta[2,3]pyrrolo[1,2-a]quinazoline-6,12(7H,11H)-dione (**7d**).* Yield 0.79 g, 62%. White powder; mp 170 °C (from EtOH). Found: C, 75.48; H, 5.81; N, 8.73. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80. ν_{max} (KBr) 2962, 2938, 2872, 1712, 1654, 1486, 1464, 1392, 1342, 1246, 1224, 764, 696 cm^{-1}. δ_H 1.42 (2H, m, 10-CH_2), 1.50 (1H, m, 9-H), 1.58 (1H, m, 9-H), 2.14 (2H, m, 8-CH_2), 2.33 (1H, dd, J^2 18.0, J^3 3.5, 7-H), 2.60 (1H, m, 7*a*-H), 2.99 (1H, dd, J^2 18.0, J^3 10.5, 7-H), 7.36–7.44 (4H, m, 2-H, 3H_R), 7.50 (2H, m, 2H_R), 7.68 (1H, t, *J* 8.0, 3-H), 7.89 (1H, d, *J* 8.0, 1-H), 7.96 (1H, d, *J* 8.0, 4-H). δ_C 23.6 (8-C), 33.0 (7*a*-C), 37.5 (9-C), 38.1 (10-C), 38.7 (7-C), 90.2 (10*a*-C), 122.0 (12*a*-C), 122.2 (4-C), 125.8 (2-C), 128.7 (2,6-C_R), 128.8 (1-C), 129.8 (3,5-C_R), 130.3 (4-C_R), 133.6 (3-C), 136.2 (4*a*-C), 138.0 (1-C_R), 161.9 (12-CO), 172.8 (6-CO).

*3.2.5. 7,7a,8,9,10,11-Hexahydro-12-methyl-6H-indolo[1,7a-a]quinazoline-6,13(12H)-dione (**8a**).* Yield 0.72 g, 67%. White needles; mp 114 °C (from AcOH). Found: C, 71.18; H, 6.71; N, 10.36. $C_{16}H_{18}N_2O_2$ requires C, 71.09; H, 6.71; N, 10.36. ν_{max} (KBr) 2920, 2854, 1718, 1700, 1650, 1558, 1540, 1458, 1386, 1198, 1046, 764, 708 cm^{-1}. δ_H 1.26 (1H, m, 9-H), 1.39 (1H, m, 9-H), 1.48–1.55 (3H, m, 8-H, 10-CH_2), 1.61 (1H, m, 8-H), 1.87 (1H, m, 11-H), 1.96 (1H, m, 11-H), 2.45 (1H, dd, J^2 16.5, J^3 6.5, 7-H), 2.66 (1H, dd, J^2 16.5, J^3 8.0, 7-H), 2.91 (1H, m, 7*a*-H), 3.11 (3H, s, NCH_3), 7.32 (1H, t, *J* 8.0, 2-H), 7.60 (1H, t, *J* 8.0, 3-H), 7.82 (1H, d, *J* 8.0, 1-H), 7.88 (1H, d, *J* 8.0, 4-H). δ_C 20.2 (8-C), 20.3 (9-C), 26.8 (10-C), 28.8 (NCH_3), 31.5 (11-C), 34.4 (7*a*-C), 36.4 (7-C), 79.3 (11*a*-C), 121.7 (13*a*-C), 122.2 (4-C), 125.7 (2-C), 128.2 (1-C), 133.3 (3-C), 135.8 (4*a*-C), 162.1 (13-CO), 173.6 (6-CO).

*3.2.6. 12-Ethyl-7,7a,8,9,10,11-hexahydro-6H-indolo[1,7a-a]quinazoline-6,13(12H)-dione (**8b**).* Yield 0.81 g, 71%. Yellowish powder; mp 78 °C (from EtOH). Found: C, 71.68; H, 7.20; N, 9.97. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.85. ν_{max} (KBr) 2936, 2854, 1726, 1702, 1642, 1604, 1484, 1466, 1400, 1348, 1308, 1274, 1212, 1194, 1062, 780, 762, 708 cm^{-1}. δ_H 1.17 (4H, m, 9-H, CH_3), 1.41 (3H, 9-H, 8-CH_2), 1.54 (1H, m, 11-H), 1.70 (2H, m, 10-CH_2), 1.99 (1H, m, 11-H), 2.36 (1H, dd, J^2 17.5, J^3 3.5, 7-H), 2.69 (1H, dd, J^2 17.5, J^3 8.0, 7-H), 2.86 (1H, m, 7*a*-H), 3.29 (1H, m, NCH_2), 3.75 (1H, m, NCH_2), 7.34 (1H, t, *J* 8.0, 2-H), 7.61 (1H, t, *J* 8.0, 3-H), 7.68 (1H, d, *J* 8.0, 1-H), 7.88 (1H, d, *J* 8.0, 4-H). δ_C 15.5 (CH_3), 20.4 (8-C), 20.8 (9-C), 28.4 (10-C), 31.8 (11-C), 34.0 (7*a*-C), 37.3 (7-C), 37.6 (NCH_2), 80.4 (11*a*-C), 122.8 (13*a*-C), 123.4 (4-C), 126.1 (2-C), 127.9 (1-C), 133.2 (3-C), 135.7 (4*a*-C), 162.2 (13-CO), 174.4 (6-CO).

*3.2.7. 7,7a,8,9,10,11-Hexahydro-12-benzyl-6H-indolo[1,7a-a]quinazoline-6,13(12H)-dione (**8c**).* Yield 0.90 g, 65%. Colorless needles; mp 200 °C (from AcOH). Found: C, 76.38; H, 6.40; N, 8.27. $C_{22}H_{22}N_2O_2$ requires C, 76.28; H, 6.40; N, 8.09. ν_{max} (KBr) 2926, 2856, 1716, 1644, 1602, 1484, 1462, 1442, 1400, 1360, 1340, 1266, 1206, 1124, 966, 778, 740, 706 cm^{-1}. δ_H 1.20 (1H, m, 9-H), 1.34 (1H, m, 9-H), 1.44 (2H, m, 8-CH_2), 1.53 (1H, m, 11-H), 1.79 (1H, m, 10-H), 1.85 (1H, m, 10-H), 1.94 (1H, m, 11-H), 2.17 (2H, m, 7-CH_2), 2.73 (1H, m, 7*a*-H), 4.49 (1H, d, *J* 16.0, NCH_2), 5.21 (1H, d, *J* 16.0, NCH_2), 7.24 (1H, m, H_R), 7.31 (4H, m, H_R), 7.39 (1H, t, *J* 7.5, 2-H), 7.65 (1H, t, *J* 7.5, 3-H), 7.72 (1H, d, *J* 7.5, 1-H), 7.99 (1H, d, *J* 7.5, 4-H). δ_C 20.6 (8-C), 20.9 (9-C), 28.3 (10-C), 31.6 (11-C), 34.1 (7*a*-C), 37.1 (7-C), 45.2 (NCH_2), 80.7 (11*a*-C), 122.6 (13*a*-C), 123.6 (4-C), 126.4 (2-C), 127.3 (3,5-C_R),

127.5 (4-C_R), 128.3 (1-C), 129.0 (2,6-C_R), 133.6 (3-C), 136.0 (1-C_R), 139.1 (4*a*-C), 163.1 (13-CO), 174.4 (6-CO).

*3.2.8. 7,7a,8,9,10,11-Hexahydro-12-phenyl-6H-indolo[1,7a-a]quinazoline-6,13(12H)-dione (**8d**).* Yield 0.80 g, 60%. Beige powder; mp 194 °C (from *i*-PrOH). Found: C, 75.80; H, 6.06; N, 8.50. $C_{21}H_{20}N_2O_2$ requires C, 75.88; H, 6.06; N, 8.43. ν_{max} (KBr) 2952, 2924, 2852, 1734, 1652, 1590, 1494, 1484, 1464, 1380, 1346, 1318, 1204, 1136, 1072, 762, 710, 694 cm^{-1}. δ_H 1.19 (4H, m, 9-CH_2, 10-CH_2), 1.45 (2H, m, 8-CH_2), 1.96 (1H, m, 11-H), 2.23 (1H, m, 11-H), 2.39 (1H, dd, J^2 16.5, J^3 5.5, 7-H), 2.55 (1H, m, 7*a*-H), 2.75 (1H, dd, J^2 16.5, J^3 8.0, 7-H), 7.37 (1H, t, *J* 7.5, 2-H), 7.46 (5H, m, H_R), 7.68 (1H, t, *J* 7.5, 3-H), 7.91 (2H, m, 1-H, 4-H). δ_C 20.2 (8-C), 20.6 (9-C), 26.4 (10-C), 33.5 (11-C), 34.8 (7*a*-C), 36.6 (7-C), 80.5 (11*a*-C), 122.2 (13*a*-C), 122.5 (4-C), 125.9 (2-C), 128.6 (1-C), 128.8 (2,6-C_R), 129.6 (3,5-C_R), 131.0 (4-C_R), 133.8 (3-C), 136.1 (4*a*-C), 138.1 (1-C_R), 162.2 (13-CO), 173.7 (6-CO).

*3.2.9. 7a,8,9,10,11,12-Hexahydro-13-methylcyclohepta[2,3]pyrrolo[1,2-a]quinazoline-6,14(7H,13H)-dione (**9a**).* Yield 0.66 g, 58%. White powder; mp 148 °C (from *i*-PrOH). Found: C, 72.05; H, 7.06; N, 9.81. $C_{17}H_{20}N_2O_2$ requires C, 71.81; H, 7.09; N, 9.85. ν_{max} (KBr) 2942, 2928, 2858, 1704, 1644, 1602, 1486, 1470, 1396, 1348, 1328, 1214, 1050, 1032, 810, 748, 704, 686 cm^{-1}. δ_H 0.98 (1H, m, 10-H), 1.25 (1H, m, 10-H), 1.38 (1H, m, 11-H), 1.63–1.71 (3H, m, 11-H, 9-CH_2), 1.84–1.92 (4H, m, 8-CH_2, 12-CH_2), 2.57 (1H, dd, J^2 18.0, J^3 11.0, 7-H), 2.81 (1H, dd, J^2 18.0, J^3 9.5, 7-H), 3.03 (3H, s, CH_3), 3.18 (1H, m, 7*a*-H), 7.30 (1H, t, *J* 8.0, 2-H), 7.60 (1H, t, *J* 8.0, 3-H), 7.88 (2H, m, 1-H, 4-H). δ_C 22.3 (10-C), 23.5 (8-C), 27.4 (9-C), 27.8 (12-C), 30.5 (11-C), 33.3 (NCH_3), 34.5 (7-C), 38.9 (7a-C), 84.5 (12*a*-C), 121.2 (14*a*-C), 122.1 (4-C), 125.6 (2-C), 128.1 (1-C), 133.2 (3-C), 135.0 (4*a*-C), 161.4 (14-CO), 172.2 (6-CO).

*3.2.10. 13-Ethyl-7a,8,9,10,11,12-hexahydrocyclohepta[2,3]pyrrolo[1,2-a]quinazoline-6,14(7H,13H)-dione (**9b**).* Yield 0.45 g, 38%. Yellow oil. Found: C, 72.49; H, 7.30; N, 9.39. $C_{18}H_{22}N_2O_2$ requires C, 72.46; H, 7.43; N, 9.39. R_f ($CHCl_3 \rightarrow$3:1 $CHCl_3$/MeOH) 0.48. ν_{max} (KBr) 2932, 2856, 1710, 1654, 1488, 1470, 1406, 1366, 1344, 1312, 1220, 768, 704 cm^{-1}. δ_H 1.09 (1H, m, 10-H), 1.33 (4H, m, 10-H, CH_3), 1.47 (1H, m, 11-H), 1.66 (1H, m, 11-H), 1.79 (3H, m, 8-H, 9-CH_2), 1.97 (2H, m, 8-H, 12-H), 2.09 (1H, m, 12-H), 2.75 (2H, m, 7-CH_2), 3.16 (2H, m, 7*a*-H, NCH_2), 3.91 (1H, m, NCH_2), 7.30 (1H, t, *J* 8.0, 2-H), 7.55 (1H, t, *J* 8.0, 3-H), 7.91 (1H, d, *J* 8.0, 1-H), 8.06 (1H, d, *J* 8.0, 4-H). δ_C 15.5 (CH_3), 22.7 (10-C), 23.7 (8-C), 28.7 (9-C), 30.4 (12-C), 33.7 (11-C), 36.5 (7-C), 37.8 (NCH_2), 38.3 (7*a*-C), 85.2 (12*a*-C), 121.8 (14*a*-C), 122.4 (4-C), 125.7 (2-C), 127.8 (1-C), 133.1 (3-C), 135.0 (4*a*-C), 161.5 (14-CO), 172.3 (6-CO).

*3.2.11. 7a,8,9,10,11,12-Hexahydro-13-benzylcyclohepta[2,3]pyrrolo[1,2-a]quinazoline-6,14(7H,13H)-dione (**9c**).* Yield 0.98 g, 68%. White powder; mp 172 °C (from *i*-PrOH). Found: C, 76.78; H, 6.73; N, 7.91. $C_{23}H_{24}N_2O_2$ requires C, 76.64; H, 6.71; N, 7.77. ν_{max} (KBr) 2920, 2856, 1718, 1640, 1602, 1488, 1468, 1406, 1374, 1350, 1228, 1132, 762, 732, 704 cm^{-1}. δ_H 1.00 (1H, m, 10-H), 1.24 (1H, m, 10-H), 1.40 (1H, m, 11-H), 1.58–1.66 (4H, m, 11-H, 9-CH_2, 12-H), 1.97 (3H, m, 8-CH_2, 12-H), 2.48 (1H, m, 7-H), 2.65 (1H, m, 7-H), 2.89 (1H, m, 7*a*-H), 4.39 (1H, d, *J* 16.5, NCH_2), 5.17 (1H, d, *J* 16.5, NCH_2), 7.23 (3H, m, H_R), 7.30–7.37 (3H, m, 2-H, H_R), 7.65 (1H, t, *J* 7.0, 3-H), 7.87 (1H, d, *J* 7.0, 1-H), 7.95 (1H, d, *J* 7.0, 4-H). δ_C 22.8 (10-C), 23.6 (8-C), 28.4 (9-C), 30.4 (12-C), 33.6 (11-C), 36.0 (7-C), 38.0 (7*a*-C), 45.6 (NCH_2), 85.4 (12*a*-C), 121.5 (14*a*-C), 122.6 (4-C), 125.9 (2-C), 126.6 (3,5-C_R), 127.3 (4-C_R), 128.2 (1-C), 129.1 (2,6-C_R), 133.6 (3-C), 135.2 (1-C_R), 139.2 (4*a*-C), 162.4 (14-CO), 172.3 (6-CO).

*3.2.12. 7a,8,9,10,11,12-Hexahydro-13-phenylcyclohepta[2,3]pyrrolo[1,2-a]quinazoline-6,14(7H,13H)-dione (**9d**).* Yield 0.91 g, 66%. Yellow oil. Found: C, 76.40; H, 6.50; N, 7.92. $C_{22}H_{22}N_2O_2$ requires C, 76.28; H, 6.40; N, 8.09. R_f ($CHCl_3 \rightarrow$3:1 $CHCl_3$/MeOH) 0.84. ν_{max} (KBr) 2928, 2854, 1732, 1714, 1652, 1488, 1466, 1404, 1380, 1348, 1316, 1270, 1204, 1136, 1072, 762, 710, 694 cm^{-1}. δ_H 0.90 (1H, m, 10-H), 1.03 (1H, m, 10-H), 1.14 (1H, m, 11-H), 1.31 (1H, m, 11-H), 1.45 (3H, 8-H, 9-CH_2), 1.68 (1H, m, 8-H), 2.21 (1H, m, 12-H), 2.34 (1H, m, 12-H), 2.64–2.71 (2H, m, 7-CH_2), 3.11 (1H, m, 7*a*-H), 7.37 (1H, t, *J* 7.5, 2-H), 7.45 (3H, m, H_R), 7.52 (2H, m, H_R), 7.70 (1H, t, *J* 7.5, 3-H), 7.94 (1H, d, *J* 7.5, 1-H), 7.99 (1H, d, *J* 7.5, 4-H). δ_C 22.6 (10-C), 23.0 (8-C), 26.5 (9-C), 30.5 (12-C), 33.6 (11-C), 37.5 (7-C), 38.3 (7*a*-C), 85.6 (12*a*-C), 121.7 (14*a*-C), 122.3 (4-C), 125.7 (2-C), 128.4 (1-C), 128.8 (2,6-C_R), 129.8 (3,5-C_R), 130.9 (4-C_R), 133.7 (3-C), 135.4 (4*a*-C), 137.7 (1-C_R), 161.6 (14-CO), 172.4 (6-CO).

3.3. X-ray crystal structure determination of compound 9c

Intensities of 13,515 reflections (6341 independent, R_{int}=0.037) were measured with 'Xcalibur-3' diffractometer operating in the ω–2θ scan mode, 2θ_{max}=50°, and using graphite monochromated Mo Kα radiation (λ=0.71073 Å). Crystal data: $C_{23}H_{24}N_2O_2$, M_r=360.44, triclinic, *a*=10.735 Å, *b*=11.257 Å, *c*=16.074 Å, α=87.52°, β=83.50°, γ=86.48°, *V*=1924.9 $Å^3$, *T*=293 K, space group *P*1, *Z*=4, μ(Mo Kα)=0.080 mm^{-1}. The structure was solved by direct method with the SHELXTL program package.[55] Positions of the hydrogen atoms were calculated geometrically and refined by riding model with U_{iso}=1.2U_{eq} of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 6271 reflections was converged to wR_2=0.140, R_1=0.052 [for 3214 reflections with $F>4\sigma(F)$], *S*=0.860.

References and notes

1. Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787–9826.
2. Orfi, L.; Waczek, F.; Pato, J.; Varga, I.; Hegymegi-Barakonyi, B.; Houghten, R. A.; Keri, G. *Curr. Med. Chem.* **2004**, *11*, 2549–2553.
3. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202.
4. Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246.
5. Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627–646.
6. Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650–668.
7. Atkinson, R. S.; Fawcett, J.; Gawad, N. A.; Russell, D. R.; Sherry, L. J. S. *J. Chem. Soc., Chem. Commun.* **1984**, 1072–1073.
8. Atkinson, R. S.; Gawad, N. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 825–830.
9. Atkinson, R. S.; Gawad, N. A.; Russell, D. R.; Sherry, L. J. S. *J. Chem. Soc., Chem. Commun.* **1983**, 568–570.
10. Voitenko, Z. V.; Samoylenko, V. P. *Khim. Geterotsikl. Soedin.* **2002**, 218–226; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 197–204.
11. Samoylenko, V. P.; Voitenko, Z. V.; Donnadieu, B.; Bonnet, J.-J. *Tetrahedron* **2002**, *58*, 6103–6110.
12. Iminov, R. T.; Tverdokhlebov, A. V.; Tolmachev, A. A.; Volovenko, Y. M.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Heterocycles* **2008**, *75*, 1673–1680.
13. Mondon, A. *Chem. Ber.* **1959**, *92*, 1461–1471.
14. Mondon, A.; Hasselmeyer, G.; Zander, J. *Chem. Ber.* **1959**, *92*, 2543–2552.
15. Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062–5074.
16. Isobe, K.; Mohri, K.; Maeda, M.; Takeda, T.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2602–2604.
17. Isobe, K.; Mohri, K.; Itoh, Y.; Toyokawa, Y.; Takeda, N.; Taga, J.-I.; Tsuda, Y. *Chem. Pharm. Bull.* **1987**, *35*, 2618–2621.
18. Isobe, K.; Mohri, K.; Tokoro, K.; Fukushima, C.; Higuchi, F.; Taga, J.-I.; Tsuda, Y. *Chem. Pharm. Bull.* **1988**, *36*, 1275–1282.
19. Padwa, A.; Waterson, A. G. *J. Org. Chem.* **2000**, *65*, 235–244.
20. Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464–9467.
21. El Bialy, S. A. A.; Braun, H.; Tietze, L. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 5391–5393.
22. Mondon, A.; Hasselmeyer, G. *Chem. Ber.* **1959**, *92*, 2552–2555.
23. Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650–5651.
24. Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Org. Chem.* **1992**, *57*, 2531–2534.
25. Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467.
26. Aurich, H. G.; Soeberdt, M. *Tetrahedron Lett.* **1998**, *39*, 2553–2554.
27. Kossenjans, M.; Soeberdt, M.; Wallbaum, S.; Harms, K.; Martens, J.; Aurich, H. G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2353–2365.
28. Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57–70.

29. Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813–5817.
30. Sillanpaa, R.; Virag, M.; Stajer, G.; Bernath, G. *Acta Chem. Scand.* **1997**, *51*, 810–812.
31. Virag, M.; Gunther, G.; Bocskei, Z.; Sohar, P.; Bernath, G.; Stajer, G. *J. Mol. Struct.* **1998**, *440*, 147–154.
32. Csende, F.; Bernath, G.; Bocskei, Z.; Sohar, P.; Stajer, G. *Heterocycles* **1997**, *45*, 323–330.
33. Stajer, G.; Szabo, A. E.; Turos, G.; Sohar, P.; Sillanpää, R. *Eur. J. Org. Chem.* **2005**, 4154–4161.
34. Stajer, G.; Miklos, F.; Sohar, P.; Sillanpää, R. *Eur. J. Org. Chem.* **2001**, 4153–4156.
35. Kulik, S. N.; Kobko, A. S.; Tolmachev, A. A.; Tverdokhlebov, A. V.; Shishkin, O. V.; Chernega, A. N. *Synthesis* **2007**, 1503–1508.
36. Resnyanska, E. V.; Tverdokhlebov, A. V.; Tolmachev, A. A.; Volovenko, Y. M.; Shokol, T. V. *Heterocycles* **2004**, *63*, 797–807.
37. Volovenko, Y. M.; Resnyanskaya, E. V. *Mendeleev Commun.* **2002**, 119–120.
38. Volovenko, Y. M.; Resnyanskaya, E. V.; Tverdokhlebov, A. V. *Khim. Geterotsikl. Soedin.* **2002**, 360–366; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2002**, *38*, 324–330.
39. Ukhin, L. Y.; Kuzmina, L. G. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 1183–1191; *Russ. Chem. Bull.* **2006**, *55*, 1229–1238.
40. Maloshitskaya, O. A.; Sinkkonen, J.; Alekseyev, V. V.; Zelenin, K. N.; Pihlaja, K. *Tetrahedron* **2005**, *61*, 7294–7303.
41. Takai, H.; Obase, H.; Nakamizo, N.; Teranishi, M.; Kubo, K.; Shuto, K.; Kasuya, Y.; Shigenobu, K.; Hashikami, M.; Karashima, N. *Chem. Pharm. Bull.* **1985**, *33*, 1116–1128.
42. Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677–680.
43. Fülöp, F.; Simeonov, M.; Pihlaja, K. *Tetrahedron* **1992**, *48*, 531–538.
44. Fetisov, V. I.; Kotov, A. V.; Gordeev, P. B.; Bachurin, S. O.; Petrova, L. N.; Raevskij, O. A.; Martynov, I. V. *Dokl. Akad. Nauk* **1999**, *367*, 776–779; *Dokl. Chem.* **1999**, *367*, 201–204.
45. Tugusheva, N. Z.; Ryabova, S. Y.; Solov'eva, N. P.; Anisimova, O. S.; Granik, V. G. *Khim. Geterotsikl. Soedin.* **2001**, 962–970; *Chem. Heterocycl. Compd. (Engl. Transl.)* **2001**, *37*, 885–893.
46. Smirnov, G. A.; Sizova, E. P.; Lukyanov, O. A.; Fedyanin, I. V.; Antipin, M. Y. *Izv. Akad. Nauk, Ser. Khim.* **2003**, 2311–2319; *Russ. Chem. Bull.* **2003**, *52*, 2444–2453.
47. Zefirov, N. S.; Palyulin, V. A.; Dashevskaya, E. E. *J. Phys. Org. Chem.* **1990**, *3*, 147–154.
48. Witt, A.; Bergman, J. *Tetrahedron* **2000**, *56*, 7245–7253.
49. Gravier, D.; Dupin, J.-P.; Casadebaig, F.; Hou, G.; Boisseau, M.; Bernard, H. *Pharmazie* **1992**, *47*, 91–92.
50. Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2005**, *7*, 5285–5288.
51. Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208–1213.
52. Begley, M. J.; Cooper, K.; Pattenden, G. *Tetrahedron* **1981**, *37*, 4503–4508.
53. Moon, S.; Waxman, B. H. *J. Org. Chem.* **1969**, *34*, 288–292.
54. Sinclair, I. W.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2485–2488.
55. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *A64*, 112–122.