Synthesis and Stereochemistry of 11,11a-Dihydro Derivatives of (4*S*)-2,4-Dimethyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones. A New Transannular Rearrangement Proposal

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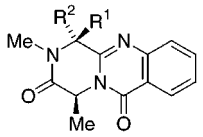
Introduction

2,4-Dihydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-diones **1** (Figure 1) contain three rings of the hexacyclic fungal metabolite *N*-acetylardeemin, which is one of the most potent known inhibitors of multidrug resistance (MDR) to antitumor agents.[1] It has been shown that this activity is retained in some compounds derived from **1a**, mainly the 1,1-dibenzyl derivatives,[2] which have been prepared by considering the N(11)═C(11a)C(1)N(2) portion of that compound as a nucleophilic or electrophilic glycine template.[3] Following our current research about this system, we wanted to study the effects on the biological activity of the pK_a and conformational changes which are associated with the hydrogenation of the N(11)═C(11a) bond. We here report the synthesis of these derivatives (**2**−**4**) by reduction of the C(1)-unsubstituted compound **1a**, as well as the *syn*- and *anti*-1-arylmethyl representatives **1b**,**c**. Alkylation of **2** at N-11 to give compounds **7** and **8** is also studied.

Results and Discussion

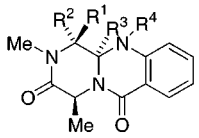
Catalytic hydrogenation of compounds **1** was discarded, since previous experiments aimed at the reductive deprotection of the N(2)−benzyl group in analogues of **1** showed that the imine function at N(11)═C(11a) is inert to these reaction conditions.[4] Thus, we investigated the reduction of **1a** with sodium borohydride/EtOH at 0 °C. Although the mechanistic details involved in imine reduction with this reagent are scarce,[5] hydride transfer to the electrophilic carbon C-11a in compound **1a** was expected to occur by axial attack, most probably directed toward the α-face, due to the asymmetric induction of the 4-methyl substituent. In fact, compound **2** was obtained diastereoselectively with the expected stereochemistry (Scheme 1).



1a $R^1 = R^2 = H$
1b R^1 = 3-indolylmethyl, $R^2 = H$
1c $R^1 = H$, R^2 = 3-chlorobenzyl

Figure 1.

Scheme 1



1a —i→ **2**, $R^1 = R^2 = R^3 = R^4 = H$
1b —i→ **3**, R^1 = 3-indolylmethyl, $R^2 = R^3 = R^4 = H$
1c —i→ **4**, R^1 = 3-chlorobenzyl, $R^2 = R^3 = R^4 = H$
1a —ii→ **5**, R^1 = H/D (0.3:0.7), R^2 = H/D (0.7:0.3), $R^3 = R^4 = D$
1c —ii→ **6**, R^1 = 3-Chlorobenzyl, $R^2 = H$, $R^3 = R^4 = D$

i: $NaBH_4$/EtOH, 0 °C, 10 h. ii: $NaBD_4$/EtOD, 0 °C, 24 h.

The boat conformation of the piperazine ring in compound **1a**, which is anchored by the pseudoaxial disposition of the C(4)-methyl substituent in order to avoid the steric interaction with the C(6)═O group,[6] is maintained in the 11,11a-dihydroderivative **2**, as proved by the observation of a significant NOE at the H_{1ax} signal after irradiation of the C(4)-Me protons. The new H-11a proton has an α-axial disposition according to the $J^{1,3}(H_{1ax-11a})$ and $J^{1,3}(H_{1eq-11a})$ coupling constants values (10.0 and 3.7 Hz, respectively), since the alternative *β*-equatorial disposition for this proton would give very similar $J^{1,3}$ values. The *N*-methyl substituent adopts a pseudoequatorial disposition (see Figure 2).

As expected, the same treatment on the syn-isomer **1b**[7] gave compound **3** in which, according to NOE experiments, the hydride transfer was also directed toward the α-face. The reduction of **1c**[7] afforded compound **4**, which showed a ^{1}H NMR spectrum very similar to that of compound **3**, with a $J^{1,3}(H_{1eq-11a})$ value of 3.2 Hz, which could be consistent with addition of hydride from the face opposite to the benzyl group. However, the NOEs observed after irradiation of significant protons (Figure 2) only support structure **4**, involving epimerization at the C-1 carbon atom.

To explore a mechanism that could explain the inversion of the C-1 stereocenter in the reduction of **1c** to

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(3) (a) Martín-Santamaría, S.; Buenadicha, F. L.; Espada, M.; Söllhuber, M.; Avendaño, C. *J. Org. Chem.* **1997**, *62*, 6425. (b) Martín-Santamaría, S.; Espada, M.; Avendaño, M. *Tetrahedron* **1997**, *53*, 16795. (c) Bartolomé, M. T.; Buenadicha, F. L.; Avendaño, C.; Söllhuber, M. *Tetrahedron: Asymmetry* **1998**, *9*, 249. (d) Buenadicha, F. L.; Avendaño, C.; Söllhuber, M.; *Tetrahedron: Asymmetry* **1998**, *9*, 4275. (e) Fernández, M.; Heredia, M. L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1998**, *54*, 2777. (e) Martín-Santamaría, S.; Espada, M.; Avendaño, C. *Tetrahedron* **1999**, *55*, 1755.

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(6) (a) Rajappa, S.; Advani, B. G. *Tetrahedron* **1973**, *29*, 1299. (b) Rajappa, S.; Advani, B. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2122. (c) Suguna, K.; Ramakumar, S.; Rajappa, S. *Acta Crystallogr. B* **1982**, *B38*, 1654.

(7) Compounds **1b**,**c** were obtained by following a previously reported procedure.[2a]

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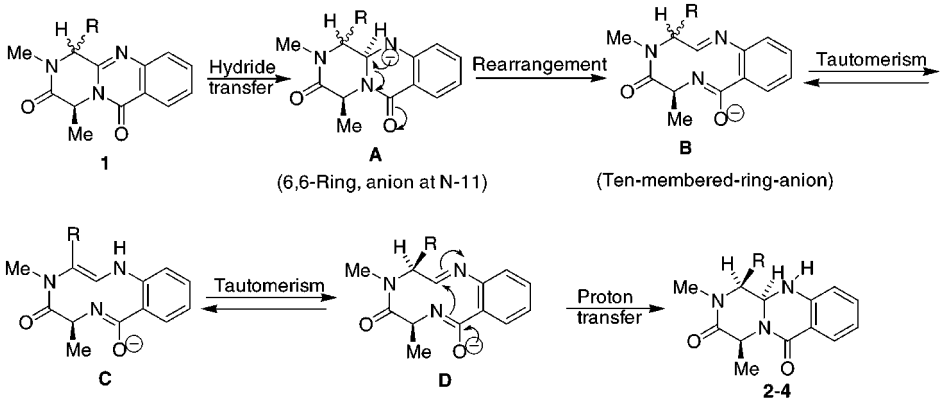
Scheme 2



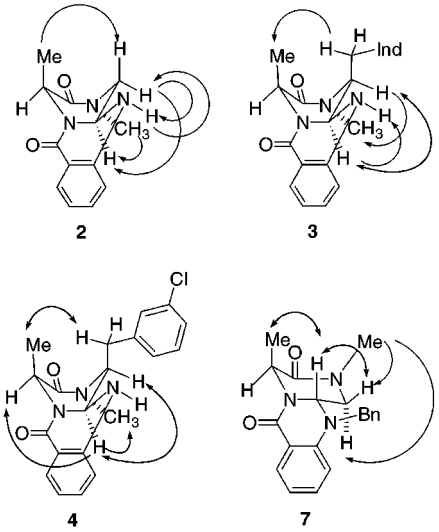


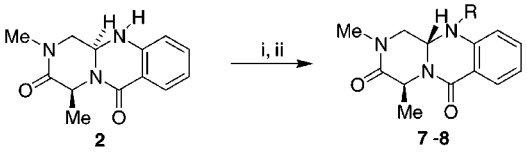
Figure 2.

compound **4**, we carried out the reaction of **1a** and **1c** with $NaBD_4$ and EtOD and obtained compounds **5** and **6**.[8]

From all these experiments we propose that anions **A**[9] (Scheme 2), formed by hydride transfer to compounds **1**, rearrange to the 10-membered-ring lactam anions **B** through cleavage of the C(11a)−N(5) bond. These species should be sufficiently long-lived to equilibrate to **D** through the intermediacy of enamine **C**, which give compounds **2**−**4** by transannular cyclization with subsequent protonation. The partial deuteration at C-1 produced in the reduction of **1a** to **5** contrasts with the absence of deuteration at this position in compound **6**. This different result may imply that intermediate **C** has a longer life for R = H than for R = 3-chlorobenzyl, allowing the interchange N(11)−H → N(11)D to occur before species **C** tautomerizes to **D**.

To support the mechanism above outlined, we plannned alkylation of compound **2** in basic media. If anions **A**, which are also intermediates in these reactions, do not rearrange, the corresponding derivatives would have an unaltered configuration at the stereocenter C-11a. However, after treatment of **2** with sodium hydride and benzyl bromide or diphenylmethyl bromide as alkylating reagents, we obtained compounds **7** and **8**, respectively, in which the H-11a proton is in a β disposition.

Scheme 3



i: NaH, THF, 0 °C. ii: RBr

The mutual NOEs between H-11a and C(4)-Me protons in compound **7** showed their syn-relationship and confirm the rearrangement of the 6,6-ring *N*-anions **A** to the 10-membered ring *O*-anions **B**. The piperazine ring in this compound has a quasi-planar-chair conformation, since irradiation of the C(4)Me protons does not affect the C(1)−H signal. Furthermore, the *N*-benzyl substituent adopts a pseudoequatorial configuration (Figure 2). The epimerization at C-11a accounts for a conformational rotation around the C(1)−C(11a) bond in species **D** (Scheme 2), and in this conformation, the *si*-face of the C(11a)═N(11) bond is suitably disposed for the transannular cyclization−alkylation that produce the inverted configuration at C-11a in compound **7**. A similar structure was observed in compound **8**, in which the most significant NOE effect was the enhancement of the H_{11a} signal after irradiation of the C(4)-Me protons (Scheme 3).

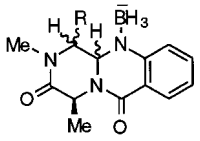
A close precedent to the rearrangement **A** ⇌ **B** was reported for electrochemical reduction of pyrimidines to 1,2-dihydropyrimidines.[10] The unusual conformational properties of medium-sized-ring systems, such as the proposed intermediates **B**−**D**, have been reported in an intraannular tandem nucleophile−electrophile addition of a 10-membered-ring lactam.[11] However, as far as we know, this behavior is unknown in more functionalyzed compounds such as those described in this work.

Experimental Section

Melting points are uncorrected. IR spectra were recorded with all solid compounds compressed into KBr pellets. NMR spectra were recorded at 250 MHz for ^1H and 62.5 MHz for ^{13}C in $CDCl_3$,

(8) Compounds **5** and **6** were obtained as crude products with traces of the corresponding starting material, their ^1H NMR spectra being compared with those of compounds **2** and **4**, respectively.

(9) Anions **A** represent intermediates



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with TMS as internal reference (Servicio RMN, Universidad Complutense). Elemental analyses were obtained from the Servicio de Microanálisis, UCM. Optical rotations were determined at 25 °C in $CHCl_3$ or EtOH at 589 nm. Separations by flash chromatography were performed on alumina (63−200 μm) for compounds **2**−**4** or silica gel (35−70 mm) for compounds **7** and **8**. Tetrahydrofuran was freshly distilled from sodium benzophenone. All reagents were of commercial quality and were used as received.

General Procedure for the Reduction of 1 with Sodium Borohydride. To a cold (0 °C), magnetically stirred solution of **1** (0.41 mmol) in absolute EtOH (25 mL) was added 2 mmol of $NaBH_4$. The reaction mixture was maintained 10 h at this temperature, the solvent was evaporated, and the residue was diluted with ethyl acetate and washed with 1 N NaOH (10 mL). The organic layer was then dried ($MgSO_4$) and concentrated. Chromatography of this material on alumina (EtOAc/MeOH, 99:1) provided compounds **2**−**4**. Deuteration experiments were performed similarly ($NaBD_4$/EtOD), and after evaporation of the solvent, the crude products were analyzed by ^{1}H NMR.

(4*S*,11a*S*)-2,4-Dimethyl-2,4,11,11a-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (2). It was obtained as a white solid: mp 159−161 °C; yield 32%; $[\alpha]^{25}_D$ +158 (*c* 0.50, EtOH); IR 3457, 1678, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (d, 3H, J = 6.9, Me-4), 3.09 (s, 3H, Me−N), 3.43 (dd, 1H, J = 12.5 and 3.7 Hz, eq H-1), 3.89 (dd, 1H, J = 12.5 and 10.0 Hz, ax H-1), 4.21 (s, 1H, NH), 4.92 (q, 1 H, J = 6.9 Hz, H-4), 5.11 (dd, 1 H, J = 10.0 and 3.7 Hz, H-11a), 6.71 (d, 1H, J = 7.7 Hz, H-10), 6.95 (7, 1H, J = 7.4 Hz, H-8), 7.34 (t, 1H, J = 7.6 Hz, H-9), 7.94 (d, 1H, J = 7.1 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 20.6 (Me-4), 34.9 (Me-N), 51.0 (C-1), 52.0 (C-4), 64.9 (C-11a), 115.1 (C-10), 117.2 (C-6a), 120.7 (C-8), 128.8 (C-7), 138.8 (C-9), 146.3 (C-10a), 162.7 (C-6), 169.7 (C-3). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.67; H, 6.12; N, 17.14. Found: C, 63.61; H, 6.12; N, 16.89.

(4*S*,11a*S*)-2,4-Dimethyl-1-(3-indolylmethyl)-2,4,11,11a-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (3). It was obtained as a white solid: mp 178−180 °C; yield: 42%; $[\alpha]^{25}_D$ +39.7 (*c* 0.35, EtOH); IR 3489, 1694, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85 (d, 3H, J = 6.9 Hz, Me-4), 2.70 (s, 3H, N−Me), 3.09−3.18 (m, 1H, CH_2), 3.70−3.85 (m, 2H, H-1, CH_2), 4.35 (s, 1H, H-11), 4.77 (q, 1H, J = 6.9 Hz, H-4), 5.32 (d, 1H, J = 3.1 Hz, H-11a), 6.62 (d, 1H, J = 7.8 Hz, H-10), 6.90 (t, 1H, J = 7.4 Hz, H-8), 7.10 (d, 1H, J = 2.2 Hz, H-2′), 7.23−7.28 (m, 3H, H-9,5′,6′), 7.43 (d, 1H, J = 8.0 Hz, H-7′), 7.63 (d, 1H, J = 7.6 Hz, H-4′), 7.96 (d, 1H, J = 6.6 Hz, H-7), 8.29 (s, 1H, H-1′); ^{13}C NMR ($CDCl_3$) δ 21.0 (Me-4), 26.4 (CH_2), 35.7 (N−Me), 52.9 (C-4), 61.4 (C-1), 68.2 (C-11a), 11.3 (C-3′), 111.7 (C-7′), 114.3 (C-10), 115.3 (C-6a), 118.1 (C-4′), 119.9 (C-8*), 119.9 (C-5′*), 122.5 (C-6′), 123.4 (C-2′), 126.8 (C-7), 133.9 (C-9), 136.3 (C-7a′), 145.9 (C-10a), 164.8 (C-6), 169.2 (C-3). Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.59; H, 5.88; N, 14.97. Found: C, 70.67; H, 5.68; N, 14.82.

(4*S*,11a*S*)-2,4-Dimethyl-1-(3-chlorobenzyl)-2,4,11,11a-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**4**). It was obtained as a white solid: mp 212−214 °C; yield: 61%; $[\alpha]^{25}_D$ +13.3 (*c* 0.20, EtOH); IR 3409, 1699, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81 (d, 3H, J = 6.7 Hz, Me-4), 2.63 (s, 3H, N−Me), 2.95 (m, 1H, CH_2), 3.45−3.67 (m, 2H, H-1, CH_2), 4.44 (s, 1H, NH), 4.72 (q, 1H, J = 6.7 Hz, H-4), 5.29 (d, J = 3.2 Hz, 1H, H-11a), 6.63 (d, 1H, J = 7.9 Hz, H-10), 6.89 (t, 1H, J = 7.3 Hz, H-8); 7.14 (m, 1H, H-6′), 7.24−7.35 (m, 4H, H-9,2′,4′,5′), 7.92 (d, 1H, J = 6.6 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 20.9 (Me-4), 33.8 (N−Me), 35.8 (CH_2), 53.0 (C-4), 63.2 (C-1), 68.2 (C-11a), 114.1 (C-10), 114.9 (C-6a), 119.9 (C-8), 127.3 (C-4′*), 127.7 (C-6′*), 128.5 (C-7*), 129.2 (C-2′*), 130.2 (C-5′*), 133.9 (C-3′), 134.7 (C-1′), 139.8 (C-9), 145.7 (C-10a), 164.6 (C-6), 169.1 (C-3). Anal. Calcd for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.41; N, 11.37. Found: C, 64.76; H, 5.60; N, 11.46.

General Procedure for the *N*-Alkylation of Compound 2. To a cold (0 °C), magnetically stirred suspension of NaH (1.2 mmol) in dry THF was slowly added a solution of **2** (0.49 mmol). The reaction was followed by evolution of hydrogen. The adequate halide was added 5−10 min later. The reaction mixture was maintained at room temperature during 2 h and refluxing overnight. Then, the solvent was evaporated and the residue was diluted in ethyl ether and washed with 1% HCl (2 mL). The aqueous layer was washed with ethyl ether (5 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2 mL), dried ($MgSO_4$), and concentrated. Chromatography of the residue in silica gel (EtOAc/hexane, 9:1) provided the corresponding compounds **7** and **8**.

(4*S*,11a*S*)-11-Benzyl-2,4-Dimethyl-2,4,11,11a-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (7). It was obtained as an oil: quantitative yield; $[\alpha]^{25}_D$ −127.7 (*c* 0.25, EtOH); IR 1675, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, 3H, J = 7.3 Hz, Me-4), 2.83 (s, 3H, N-Me), 3.01 (dd, 1H, J = 11.5 and 3.6 Hz, eq H-1), 3.75 (m, 1H, ax H-1), 4.50 (d, 1H, J = 16.1 Hz, CH_2Ph), 4.71 (d, 1 H, J = 16.1 Hz, CH_{2Ph}), 5.06 (dd, 1H, J = 10.5 and 3.6 Hz, H-11a), 5.41 (q, 1H, J = 7.3 Hz, H-4), 6.72 (d, 1 H, J = 8.3 Hz, H-10), 6.88 (t, 1H, J = 7.4 Hz, H-8), 7.30−7.41 (m, 6H, H-9,2′-6′), 8.00 (d, 1H, J = 7.7 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 16.2 (Me-4), 35.0 (N-Me), 51.3 (C-4), 52.1 (C-1), 54.6 (CH_2), 66.5 (C-11a), 113.9 (C-10), 115.6 (C-6a), 119.6 (C-8), 127.1 (C-2′, 6′), 128.2 (C-7*), 129.2 (C-3′, 5′), 129.2 (C-4′*), 134.4 (C-9), 136.5 (C-1′), 145.5 (C-10a), 161.3 (C-6), 168.5 (C-3). Anal. Calcd for $C_{20}H_{21}N_3O_2$: C, 71.64; H, 6.27; N, 12.54. Found: C, 71.33; H, 5.99; N, 12.53.

(4*S*,11a*S*)-11-(Diphenylmethyl)-2,4-dimethyl-2,4,11,11a-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (8). It was obtained as an oil: quantitative yield; $[\alpha]^{25}_D$ −55.5 (*c* 0.30, EtOH); IR 1656, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3H, J = 7.4 Hz, Me-4), 2.60 (dd, 1H, J = 11.5 and 3.9 Hz, eq H-1), 2.69 (s, 3H, N-Me), 3.73 (m, 1H, ax H-1), 4.94 (dd, 1H, J = 10.7 and 3.9 Hz, H-11a), 5.31 (q, 1H, J = 7.4 Hz, H-4), 6.24 (s, 1H, benzyl CH), 6.82−6.94 (m, 2H, H-8, 10), 7.24−7.44 (m, 11H, H-9,10 and phenyl protons), 8.01 (d, 1H, J = 7.8 Hz, H-7); ^{13}C NMR ($CDCl_3$) δ 15.6 (Me-4), 34.9 (N−Me), 51.5 (C-4), 52.0 (C-1), 62.4 (benzyl CH), 69.0 (C-11a), 115.8 (C-10), 117.0 (C-6a), 120.2 (C-8), 128.4 (C-7), 128.7, 128.8, 129,1, 129.2 (aromatic carbon atoms), 134.3 (C-9), 138.7 (C-1′*), 139.5 (C-1′*), 146.0 (C-10a), 162.2 (C-6), 168.7 (C-3). Anal. Calcd for $C_{26}H_{25}N_3O_2$: C, 75.91; H, 6.08; N, 10.22. Found: C, 75.80; H, 5.97; N, 10.52.

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Supporting Information Available: Figures showing NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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