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SIMPLE AND CONVENIENT SYNTHESIS OF 2,3,4,5-TETRAHYDRO-1,5-DIOXOPYRROLO[1,2-*a*]QUINAZOLINE-3*a*(1*H*)-CARBOXYLIC ACIDS IN MULTI-GRAM SCALE

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Abstract – The title compounds were prepared in 70-100 grams scale by reaction of 2-amino-*N*-alkyl(aryl)benzamides with 2-oxoglutaric acid. Their structure was proved unambiguously by X-ray crystallographic study.

INTRODUCTION

Fused 4-quinazolinones are the core of both naturally occurring alkaloids and a number of synthetic drugs.[1] Among them pyrrolo[1,2-*a*]quinazolines, the structural isomers of *Peganine* system, had attracted especial attention of the chemists. As a result, derivatives with analgesic, antihypertensive and CNS depressing activities were discovered.[2] Anthranilic acid and related derivatives were often used as the suitable and readily available starting materials for preparation of pyrroloquinazolines.[3,4] Thus, alkylation of 2-aminobenzoic acids, esters or nitriles with 4-halobutanenitrile derivatives yielded pyrrolo[1,2-*a*]quinazolines via formation of the both rings at once.[3] It can be considered as the most general and effective method. Furthermore a few less common approaches were reported.[4] However, all these methods[3,4] afford the aromatic pyrroloquinazolines, while the more interesting from biologic viewpoint derivatives with partially or completely hydrogenated heterocyclic rings remain synthetically laborious. Catalytic hydroformylation of 2-(allylamino)benzamides was examined as the possible approach to hydrogenated derivatives of the target system,[5] but there were some shortcomings connected with insufficient regioselectivity of the reaction.[5]

pyrrolidinones **2**[6-9] (Figure 1). A wide variety of aliphatic 1,2- and 1,3-diamines,[6,7] (hetero)aromatic 1,2-diamines,[8] and even a few 1,4-diamines[6,9] were applied in this reaction. Moreover, certain α-amino[10] and β-amino[11] acid amides were reported to react similarly and regioselectively. The anthranilic acid amides **3** containing the β-aminoamide moiety nevertheless were not employed in the reaction, apart from the single case describing the interaction of 2-aminobenzamide and levulinic acid.[12] 2-Oxoglutaric acid **1** (R = CO_2H) seems to be the most promising oxoacid, since it gives an opportunity to bring in additional functionality, the carboxyl group, into the products of type **2**. It is very important for further derivatization and biological treatment. However, the oxoglutaric acid can react with binucleophilic substances either as 4-oxoacid[13-15] or as 2-oxoacid[16,17] dependently on the reagent nature and conditions; and examples of the both pathways were published.[13-17] Moreover, sometimes an easy decarboxylation of compounds like **2** (R = CO_2H) was observed during the reaction.[15] So, a behavior of oxoglutaric acid towards binucleophiles is not obvious. Continuing our researches[18] on the synthesis of pyrrolo[1,2-*a*]quinazolines we have examined reaction of the amides **3** with 2-oxoglutaric acid as the possible approach to the carboxylic derivatives of this core. The results obtained are reported herein.

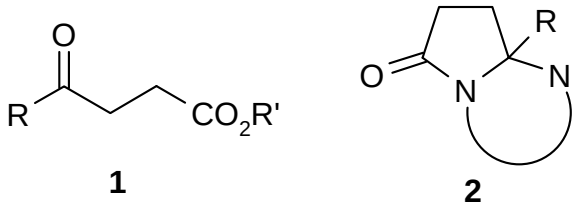
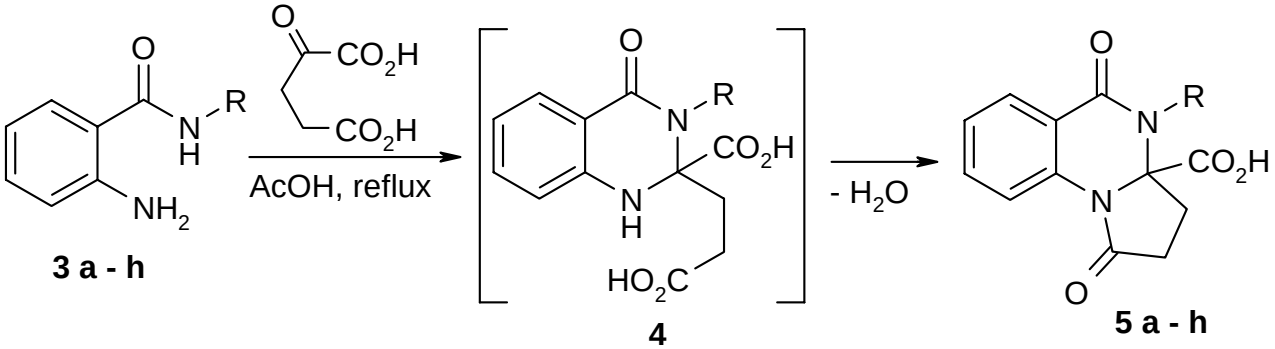


Figure 1

RESULTS AND DISCUSSION

Treatment of the compounds **3a-h**[19] with 2-oxoglutaric acid in the refluxing acetic acid was found to give pyrrolo[1,2-*a*]quinazoline-3*a*-carboxylic acids **5a-h** in 70-90 % yields (Scheme 1). Furthermore, the reaction occurred very smoothly and the isolation procedure appeared to be quite simple, thus allowing



Scheme1. R = **a**: CH_3; **b**: C_2H_5; **c**: *i*-C_3H_7; **d**: *n*-C_3H_7; **e**: *cyclo*-C_3H_5; **f**: C_6H_5; **g**: $C_6H_5CH_2$; **h**: 2-furyl-CH_2

easy scale up and preparation of derivatives **5a-h** in 70 – 100 grams amount. Apparently, compounds **5a-h** were formed through the intermediate adducts **4** by means of intramolecular acylation of the amino group with the carboxyl. Noteworthy, in the case of certain aliphatic amino acid amides the corresponding analogues of **4** were isolated, and relatively drastic conditions were required for their cyclization.[10]

The structure of the obtained compounds **5** was initially deduced from ^{1}H and ^{13}C NMR spectroscopy data and then confirmed unambiguously by X-ray crystallographic study carried out for derivative **5f** (Figure 2). As regards the spectral data the signal of 3*a*-C at 79-81 ppm and the doublet of 9-H at 8.2-8.3 ppm, shifted downfield due to deshielding by the magnetically anisotropic carbonyl at position 1, should be mentioned as the most remarkable attributes of tricyclic system formation. According to the crystal data, the benzene ring C6-C11 as well as the atoms C5 and N1 are almost coplanar (deviations from the least-square plane do not exceed 0.05 Å). The atoms N2 and C4 are deviated from this plane at +0.16 Å and +0.69 Å, respectively. So, the ring N1-C4-N2-C5-C6-C11 is in the half-boat conformation. At the same time the pyrrolidine ring N1-C1-C2-C3-C4 adopts an envelope conformation with coplanar (with precision of 0.01 Å) arrangement of C4,N1,C1,C2 atoms and C3 deviated from their plane at 0.34 Å (in opposite side in respect of the carboxyl). The planar fragments of heterocyclic rings (N1-C11-C6-C5 and C4-N1-C1-C2) form an angle 28º. Furthermore, there is a shortened intramolecular contact between O1 and H10; the distance O1-H10 is 2.43 Å while the sum of their van der Waals radii is 2.72 Å. This is in complete agreement with the mentioned deshielding of the proton observed in ^{1}H NMR spectra.

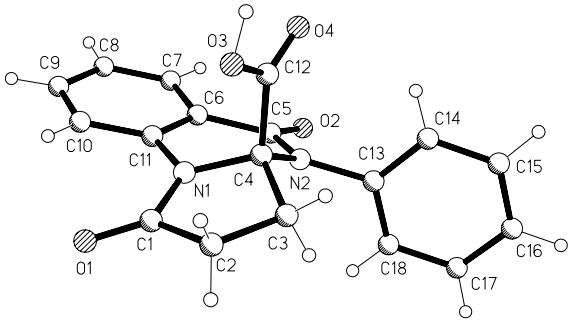


Figure 2. X-Ray molecular structure of compound **5f** with the atom numbering used in the crystallographic analysis

To resume, the straightforward synthesis of new hydrogenated pyrrolo[1,2-*a*]quinazoline derivatives **5a-h** has been elaborated. It utilizes cheap and readily available starting materials and convenient procedure providing the target compounds **5** in multi-gram scale. 2-Oxoglutaric acid has been shown to react with 2-aminobenzamides **3** exclusively as the 4-oxoacid. Further investigations on the reactivity of derivatives **5**, possibility of their additional functionalization, and applicability of this core for peptidomimetics chemistry are in progress.

EXPERIMENTAL

The starting materials **3a-h** were prepared from the isatoic anhydride and appropriate amines according to the reported procedures.[19] 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 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in DMSO-d_6 solutions. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. *J* values are in Hz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

General procedure for preparation of compounds 5a-h: A solution of amide **3a-h** (0.35 mol) and 2-oxoglutaric acid (61.3 g, 0.42 mol) in glacial acetic acid (150 mL) was refluxed for 4-6 h. After cooling the precipitate formed was filtered, washed with water and dried at 100 ºC / 12 mm Hg to give derivatives **5a-h**. Additional portion of compounds **5a-h** can be obtained by diluting the acetic acid filtrate with water (~ 3-fold volume), filtering the separated solid and recrystallization from the appropriate solvent (usually EtOH or *i*-PrOH).

2,3,4,5-Tetrahydro-4-methyl-1,5-dioxopyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5a): (78.3 g, 86 %). mp 262 ºC (EtOH). ^{1}H NMR: δ = 2.63-2.72 (m, 4H, 2,3-CH_2), 3.07 (s, 3H, CH_3), 7.29 (t, *J* = 7.5, 1H, 7-H), 7.61 (dd, *J* = 7.5, *J* = 8.0, 1H, 8-H), 7.90 (d, *J* = 7.5, 1H, 6-H), 8.20 (d, *J* = 8.0, 1H, 9-H), 12.6 (br s, 1H, CO_2H). ^{13}C NMR: δ = 28.6 (3-C), 29.6 (CH_3), 30.6 (2-C), 79.8 (3a-C), 118.6 (9-C), 119.4 (5a-C), 125.2 (7-C), 128.5 (8-C), 133.8 (6-C), 136.2 (9a-C), 162.3 (5-CO), 171.7 (1-CO), 173.1 (CO_2H). Anal. Calcd for $C_{13}H_{12}N_2O_4$: C 60.00, H 4.65, N 10.76. Found: C 59.91, H 4.73, N 10.92.

4-Ethyl-2,3,4,5-tetrahydro-1,5-dioxopyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5b): (72.9 g, 76 %). mp 220 ºC (EtOH). ^{1}H NMR: δ = 1.28 (t, *J* = 7.2, 3H, CH_3), 2.56-2.78 (m, 4H, 2,3-CH_2), 3.15 (m, 1H, NCH_2), 3.89 (m, 1H, NCH_2), 7.22 (t, *J* = 7.6, 1H, 7-H), 7.52 (t, *J* = 7.6, 1H, 8-H), 7.92 (d, *J* = 7.6, 1H, 6-H), 8.28 (d, *J* = 7.6, 1H, 9-H), 13.60 (br s, 1H, CO_2H). ^{13}C NMR: δ = 15.5 (CH_3), 28.2 (3-C), 30.6 (2-C), 39.4 (NCH_2), 80.3 (3a-C), 118.5 (9-C), 119.6 (5a-C), 125.2 (7-C), 128.4 (8-C), 133.7 (6-C), 136.3 (9a-C), 162.2 (5-CO), 172.0 (1-CO), 173.1 (CO_2H). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C 61.31, H 5.14, N 10.21. Found: C 61.40, H 5.32, N 10.30.

2,3,4,5-Tetrahydro-4-(*i*-propyl)-1,5-dioxopyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5c): (77.6 g, 77 %). mp 243 ºC (*i*-PrOH). ^{1}H NMR: δ = 1.51 (d, *J* = 6.8, 3H, CH_3), 1.61 (d, *J* = 6.4, 3H, CH_3), 2.56-2.79 (m, 4H, 2,3-CH_2), 3.66 (m, 1H, NCH), 7.19 (t, *J* = 7.6, 1H, 7-H), 7.48 (t, *J* = 7.6, 1H, 8-H), 7.86 (d, *J* = 7.6, 1H, 6-H), 8.21 (d, *J* = 7.6, 1H, 9-H), 10.70 (br s, 1H, CO_2H). ^{13}C NMR: δ = 19.6 (CH_3), 21.9 (CH_3), 29.0 (3-C), 30.6 (2-C), 49.8 (NCH), 80.9 (3a-C), 118.5 (9-C), 121.3 (5a-C), 125.1 (7-C), 128.1 (8-C), 133.3 (6-C), 135.9 (9a-C), 161.1 (5-CO), 171.7 (1-CO), 173.0 (CO_2H). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C 62.49, H 5.59, N 9.72. Found: C 62.50, H 5.50, N 9.69.

2,3,4,5-Tetrahydro-1,5-dioxo-4-propylpyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5d): (84.7 g, 84 %). mp 196 ºC (*i*-PrOH). ^{1}H NMR: δ = 0.98 (t, *J* = 7.2, 3H, CH_3), 1.59 (m, 1H, CH_2), 1.81 (m, 1H, CH_2), 2.53-2.85 (m, 4H, 2,3-CH_2), 2.98 (m, 1H, NCH_2), 3.78 (m, 1H, NCH_2), 7.21 (t, *J* = 7.6, 1H, 7-H), 7.51 (t, *J* = 7.6, 1H, 8-H), 7.93 (d, *J* = 7.6, 1H, 6-H), 8.30 (d, *J* = 7.6, 1H, 9-H), 12.9 (br s, 1H, CO_2H). ^{13}C NMR: δ = 11.8 (CH_3), 23.1 (CH_2), 28.3 (3-C), 30.6 (2-C), 46.3 (NCH_2), 80.4 (3a-C), 118.5 (9-C), 119.5 (5a-C), 125.1 (7-C), 128.5 (8-C), 133.8 (6-C), 136.3 (9a-C), 162.6 (5-CO), 172.0 (1-CO), 173.1 (CO_2H). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C 62.49, H 5.59, N 9.72. Found: C 62.21, H 5.48, N 9.69.

4-Cyclopropyl-2,3,4,5-tetrahydro-1,5-dioxopyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5e): (89 g, 89 %). mp 201 ºC (*i*-PrOH). ^{1}H NMR: δ = 0.83 (m, 2H, H_R), 0.96 m, (2H, H_R), 2.62 (m, 3H, 2,3-CH_2), 2.85 (m, 2H, 2-CH_2, NCH), 7.21 (t, *J* = 7.6, 1H, 7-H), 7.49 (t, *J* = 7.6, 1H, 8-H), 7.88 (d, *J* = 7.6, 1H, 6-H), 8.20 (d, *J* = 7.6, 1H, 9-H), 10.56 (br s, 1H, CO_2H). ^{13}C NMR: δ = 6.9 (CH_2), 9.1 (CH_2), 26.1 (NCH), 27.7 (3-C), 30.7 (2-C), 80.6 (3a-C), 118.7 (9-C), 121.0 (5a-C), 125.3 (7-C), 128.5 (8-C), 133.5 (6-C), 135.9 (9a-C), 162.9 (5-CO), 172.7 (1-CO), 173.0 (CO_2H). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C 62.93, H 4.93, N 9.78. Found: C 62.83, H 5.16, N 9.70.

2,3,4,5-Tetrahydro-1,5-dioxo-4-phenylpyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5f): (87.9 g, 78 %). mp 146 ºC (EtOH). ^{1}H NMR: δ = 2.18 (m, 2H, 3-CH_2), 2.61 (m, 1H, 2-CH_2), 2.71 (m, 1H, 2-CH_2), 7.32 (t, *J* = 8.0, 1H, 7-H), 7.41 (m, 3H, H_R), 7.47 (m, 2H, H_R), 7.66 (t, *J* = 8.0, 1H, 8-H), 7.94 (d, *J* = 8.0, 1H, 6-H), 8.27 (d, *J* = 8.0, 1H, 9-H), 11.16 (br s, 1H, CO_2H). ^{13}C NMR: δ = 28.4 (3-C), 30.8 (2-C), 80.9 (3a-C), 118.8 (9-C), 120.3 (5a-C), 125.4 (7-C), 128.5 (8-C), 128.9 (4-C_R), 129.6 (3,5-C_R), 129.7 (2,6-C_R), 134.2 (6-C), 136.4 (9a-C), 137.6 (1-C_R), 162.2 (5-CO), 172.3 (1-CO), 173.0 (CO_2H). Anal. Calcd for $C_{18}H_{14}N_2O_4$: C 67.08, H 4.38, N 8.69. Found: C 67.19, H 4.16, N 8.84.

2,3,4,5-Tetrahydro-1,5-dioxo-4-benzylpyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5g): (101 g, 86 %). mp 129 ºC (EtOH). ^{1}H NMR: δ = 2.30 (m, 1H, 3-CH_2), 2.60-2.75 (m, 3H, 2,3-CH_2), 4.35 (d, *J* = 16.8, 1H, NCH_2), 5.22 (d, *J* = 16.8, 1H, NCH_2), 7.23 (m, 1H, H_R), 7.32 (m, 5H, 7-H, 4H_R), 7.65 (dd, *J* = 7.6, *J* = 8.4, 1H, 8-H), 7.95 (d, *J* = 7.6, 1H, 6-H), 8.29 (d, *J* = 8.4, 1H, 9-H), 12.60 (br s, 1H, CO_2H). ^{13}C NMR: δ = 28.2 (3-C), 30.5 (2-C), 47.4 (NCH_2), 80.7 (3a-C), 118.6 (9-C), 119.2 (5a-C), 125.3 (7-C), 127.1 (3,5-C_R), 127.3 (4-C_R), 128.7 (8-C), 128.9 (2,6-C_R), 134.1 (6-C), 136.5 (9a-C), 139.2 (1-C_R), 163.1 (5-CO), 171.9 (1-CO), 173.2 (CO_2H). Anal. Calcd for $C_{19}H_{16}N_2O_4$: C 67.85, H 4.79, N 8.33. Found: C 67.80, H 4.60, N 8.49.

4-(2-Furylmethyl)-2,3,4,5-tetrahydro-1,5-dioxopyrrolo[1,2-*a*]quinazoline-3*a*(1*H*)-carboxylic acid (5h): (85.6 g, 75 %). mp 134 ºC (EtOH). ^{1}H NMR: δ = 2.61-2.77 (m, 4H, 2,3-CH_2), 4.26 (d, *J* = 16.4, 1H, NCH_2), 5.12 (d, *J* = 16.4, 1H, NCH_2), 6.30 (m, 2H, 3,4-H_R), 7.23 (t, *J* = 7.6, 1H, 7-H), 7.37 (d, *J* = 1.1, 1H, 5-H_R), 7.53 (t, *J* = 7.6, 1H, 8-H), 7.95 (d, *J* = 7.6, 1H, 6-H), 8.31 (d, *J* = 7.6, 1H, 9-H), 12.60 (br s, 1H,

CO_2H). ^{13}C NMR: δ = 28.3 (3-C), 30.5 (2-C), 40.6 (NCH_2), 80.4 (3a-C), 108.5 (4-C_R), 111.1 (3-C_R), 118.6 (9-C), 119.1 (5a-C), 125.4 (7-C), 128.7 (8-C), 134.2 (6-C), 136.4 (9a-C), 142.6 (5-C_R), 151.7 (2-C_R), 162.6 (5-CO), 171.8 (1-CO), 173.1 (CO_2H). Anal. Calcd for $C_{17}H_{14}N_2O_5$: C 62.58, H 4.32, N 8.58. Found: C 62.60, H 4.40, N 8.43.

X-Ray crystal structure determination of compound 5f: Crystallographic measurements were performed at 296 K on a Bruker Smart APEX II diffractometer. The intensities of 9995 reflections (3231 unique) were collected within the range $2.6 < \theta < 26.4$ ($-11 < h < 10$, $-19 < k < 19$, $-13 < l < 14$) using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Crystal data: $C_{18}H_{16}N_2O_5$, M_r = 340.33, monoclinic, *a* = 8.9563(3), *b* = 15.5928(4), *c* = 11.4243(3) Å, β = 98.705(2)°, V = 1577.07(8) $Å^3$, Z = 4, space group $P2_1/n$, μ(Mo-Kα) = 0.106 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares technique in anisotropic approximation using SHELXS97[20] and SHELXL97[21] program packages. Hydrogen atoms were located in the difference Fourier maps and refined isotropically. In the refinement 2273 reflections with $I > 2\sigma(I)$ were used. Convergence was obtained at R1 = 0.042, *w*R2 = 0.090, GOF = 1.02. Full crystallographic parameters have been deposited at Cambridge Crystallographic Data Center as supplementary publication number CCDC 663489.

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