# Synthesis of 6-Ethyl-1,2,9-trioxopyrrolo[3,2-*f*]quinoline-8-carboxylic Acid

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*Dedicated to Professor Heinrich Nöth on the occasion of his 85th birthday*

Interaction of 6-amino-1-ethyl-4-oxoquinoline-3-carboxylic ester (**7**) with chloral hydrate and hydroxylamine hydrochloride gave the corresponding isonitroso-acetamido derivative **8** which, upon treatment with concentrated sulfuric acid, was converted regioselectively into 1,2,9-trioxopyrrolo[3,2-*f*]quinoline-8-carboxylic acid (**3**). This novel tricyclic system was isolated in good yield as a stable hydrate **3H**. Structural assignments of the new compounds are based on microanalytical and spectral (MS and NMR) data.

*Key words:* 6-Amino-1-ethyl-4-oxoquinoline-3-carboxylic Ester, Isonitroso-acetamido Derivative, Regioselective Annelation, Stable Hydrated Isatin Moiety, 1,2,9-Trioxopyrrolo[3,2-*f*]quinoline Derivatives

## Introduction

Isatin (1*H*-indole-2,3-dione, Fig. 1) is an endogenous indole found in human blood, urine [1, 2], cerebrospinal fluid [3, 4], and in many organisms. It is also present in plants of the genus *Isatis* [5], or *Calanthe discolor* LINDL. [6] or *Couroupita guianesis* Aubl. [7]. Isatin is produced by an *Alteromonas* sp. strain inhabiting the surface of embryos of the caridean shrimp *Palaemon macrodectylus*, which protects them from otherwise lethal effects of infection by the pathogenic fungus *Lagenidium callinectes* [8]. Substituted isatins are also found in plants *e. g.*, the melosatin alkaloids **1a**–**c** [9 – 11] (Fig. 1), obtained from the Caribbean tumorigenic plant *Melochia tomentosa*, as well as the isoprenyl isatins **2a** [12, 13] and **2b** [14] (Fig. 1) from fungi. A number of recent reviews have focused on the biological role of isatin and the range of biological activities (*e. g.*, anti-microbial, anti-cancer and anti-HIV), displayed by isatin and assorted isatin derivatives [15 – 18]; examples include methasizone [19], and the antitumor agents sunitinib [20 – 22] or soulieotine [23, 24] (Fig. 1). Isatins are widely employed in the synthesis of various biologically active compounds, such as functionalized indirubins [25] or regioisomeric isoindigos [26, 27], exemplified by meisoindigo (Fig. 1); the latter compound is used in China for the treatment of chronic myelocytic leukemia [28].

On the other hand, fluoroquinolones, exemplified by ciprofloxacine [29, 30] (Fig. 2), have emerged as a major class of synthetic chemotherapeutic agents which have a broad spectrum of activity against several strains of bacteria [29 – 35]. Since 1986, more than 25 fluoroquinolones have been approved by FDA, and most of those remained on the market.

Herein, we wish to report on the synthesis of a new tricyclic system **3** (Fig. 2) incorporating a 4-pyridone moiety condensed to isatin as depicted in Scheme 1. As a structural feature, the heterocyclic assembly in **3** encompasses 4-oxoquinoline (rings A, B) and isatin (rings B, C) chemotypes. Such a new hybrid heterocyclic system might display interesting biological properties.

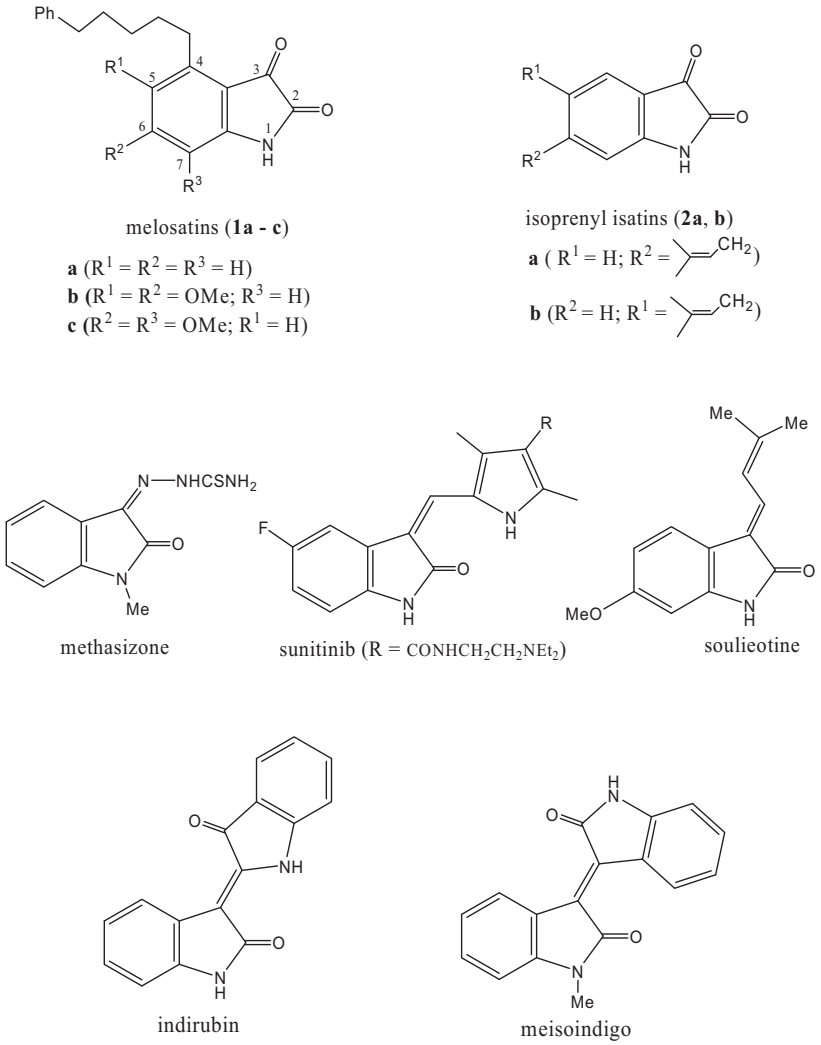



Fig. 1. Selected natural and synthetic isatin derivatives.

## Results and Discussion

The synthetic strategy towards the target tricyclic system **3** commenced with the preparation of ethyl 6-amino-1-ethyl-4-oxoquinoline-3-carboxylate (**7**), followed by annelating the pyrrolidine-2,3-dione moiety as outlined in Scheme 1. Thus, treatment of 4-nitroaniline with diethyl ethoxymethylenemalonate gave the respective enamine derivative **4** which was then cyclized into 4-oxoquinoline-3-carboxylate **5** under Gould–Jacobs′ reaction conditions [36]. Subsequent *N*(1)-ethylation of **5** to obtain **6**, followed by nitro-group reduction, produced the desired 6-amino-4-oxoquinoline **7**. The preparation and satisfactory microanalysis of compounds **4** [37, 38], **5** [37, 38] and **6** [39, 40] were previously reported, but their MS and NMR spectral data are lacking. Compound **7** was prepared (for use as synthon) by reduction of **6** with iron and ammonium chloride solution, but was not characterized [41]. Since compound **7** served herein as key intermediate, it was characterized and transformed into **3** (Scheme 1) using the classical Sandmeyer methodology [42 – 46]. It follows that interaction of **7** with chloral hydrate and hydroxylamine hydrochloride delivered the corresponding new isonitroso-acetamido derivative **8**. Finally, this penultimate intermediate **8**

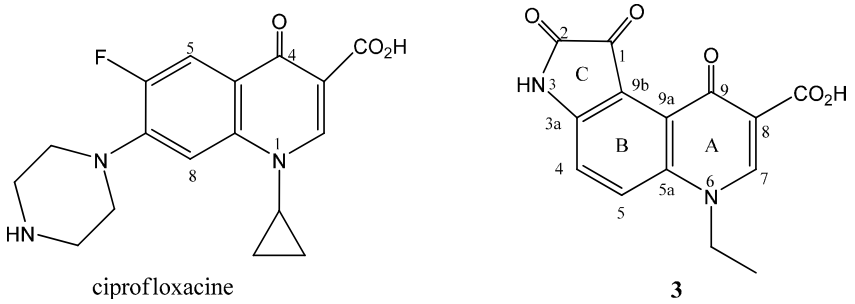
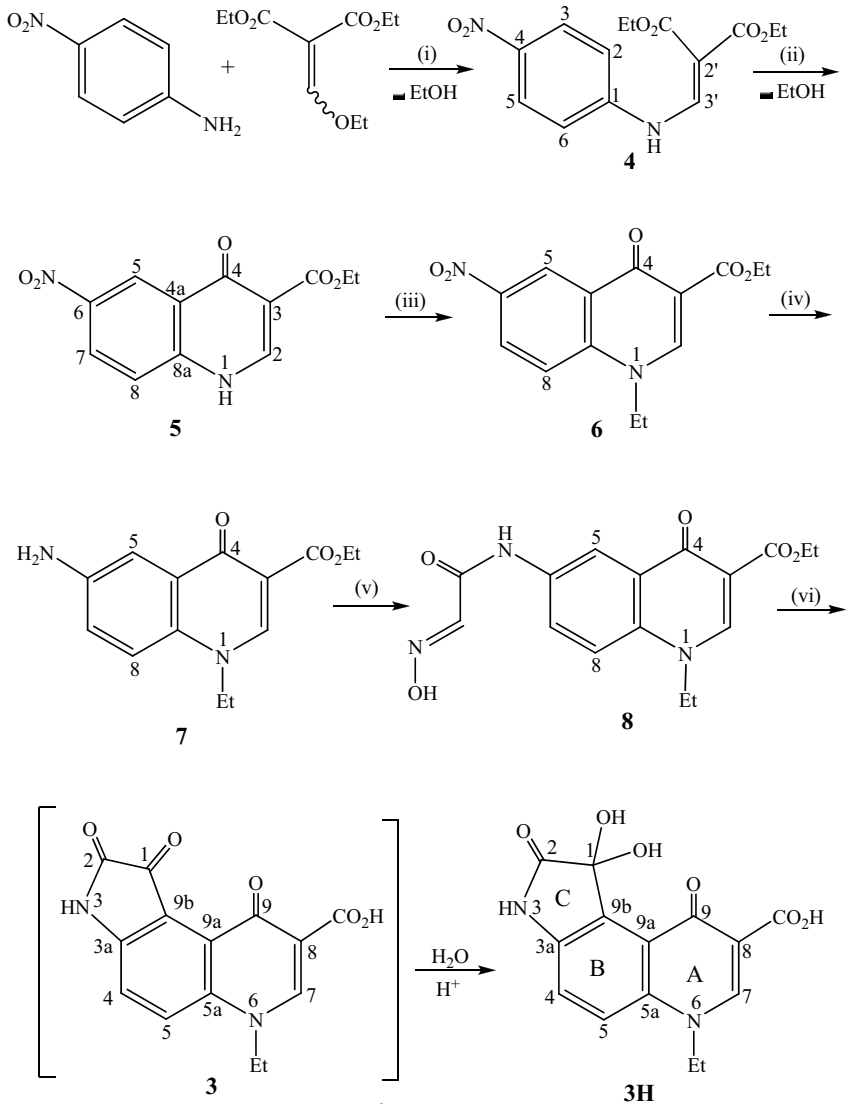



Fig. 2. A representative fluoroquinolone and an isatin-quinolone hybrid **3**.




Scheme 1. (i) 130 – 140 °C, 2 h; (ii) $(Ph)_2O$, 240 °C, 1 h; (iii) $K_2CO_3$, EtI, EtOH / reflux, 10 h; (iv) $SnCl_2$, conc. HCl / 10 – 12 h, r. t.; (v) $CCl_3$-$CH(OH)_2$, $NH_2OH$, HCl, $Na_2SO_4$, $H_2O$ / reflux, 8 h; (vi) 95 % $H_2SO_4$ / 90 °C, 1 h.

then underwent, in conc. $H_2SO_4$, regioselective intramolecular cyclization at carbon-5 to furnish the respective new product **3H** in 24 % overall yield. Compound **3H**, an angular tricyclic heterocycle, is a stable hydrate of the targeted annelated isatin **3**. To the best of our knowledge, isolable and stable monohydrated isatins (*i. e.* 3,3-dihydroxyindolin-2-ones) are hitherto undescribed in the literature. Hence, compound **3H** represents the first 4-quinolone-based tricyclic system incorporating a stable hydrated isatin moiety (rings B/C, Scheme 1).

The new compounds **7**, **8** and **3H** were characterized by elemental analyses, IR, MS and NMR spectral data. These data, detailed in the Experimental Section, are consistent with the suggested structures. Thus, the mass spectra display the correct molecular ion peaks for which the measured high-resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the $^1$H and $^{13}$C signal assignments to the different carbons and their attached, and/or neighboring hydrogens. For compounds **5**–**8**, long-range correlations are observed between 5-H and each of C-8a and C-4; likewise, 2-H is correlated with each of C-8a, C-4 and *C*$O_2$Et, while 8-H is correlated with C-4a and C-6. For compound **3H**, long-range correlations are also observed between 4-H and each of C-9b and C-5a; likewise, 5-H is correlated with C-3a and C-9a, while 7-H is correlated with C-5a, C-9 and *C*$O_2$H. The NMR spectra of **3H** reveal that carbon-1 resonates at $\delta = 92.5$ ppm, a value expected for an $sp^3$ carbon flanked by two electronegative oxygen atoms, while the two hydrogens of the geminal hydroxy groups at C-1 resonate as a broad signal at $\delta = 7.35$ ppm (exchangeable with $D_2O$). Both of the latter $^1$H and $^{13}$C signals constitute diagnostic criteria in support of the existence of the keto group as a stable hydrated form. The $^1$H signal at $\delta = 14.81$ ppm belongs to the acidic $CO_2H$ formed by acid-catalyzed hydrolysis of the ester group in compound **8** during its cyclocondensation reaction.

Functionalized indirubins [25] and isoindigos [26, 27] (Fig. 1) are receiving considerable interest as lead structures for the development of new antitumor agents. Our prime interest has been related to condensation reactions of the annelated isatin **3H** with indoxyl-3-acetates, and with the active methylene group of (substituted) oxindoles. Based on such reactions of **3H**, the preparation of annelated isoindigos and annelated indirubins for assessment of their antiprolifertive activities is currently under way.

## Experimental Section

The following chemicals used in this study were purchased from Acros and were used as received: diethyl ethoxymethylenemalonate, *p*−nitroanilines, diphenyl ether, iodoethane, chloral hydrate, hydroxylamine hydrochloride, and anhydrous $SnCl_2$. $^1$H and $^{13}$C NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III). Chemical shifts are expressed in ppm ($\delta$ units), with TMS as internal standard; *J* values for $^1$H-$^1$H coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were acquired (in positive mode) using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-4 (7-Tesla) instrument. The samples were dissolved in acetonitrile, diluted in spray solution (methanol-water 1 : 1 $v/v$ + 0.1 % formic acid) and infused using a syringe pump with a flow rate of 2 $\mu$L min$^{-1}$. External calibration was conducted using arginine clusters in a mass range $m/z = 175 - 871$. Elemental analyses were performed on a Euro Vector elemental analyzer, model EA 3000.

*Diethyl 2-[(4-nitrophenylamino)methylene]malonate (**4**)*

A mixture of *p*-nitroaniline (13.8 g, 0.1 mol) and diethyl ethoxymethylenemalonate (21.6 g, 0.1 mol) was heated at 130–140 °C for 2 h, during which time the resulting EtOH was distilled off. Thereafter, the reaction mixture was cooled to r. t., the residual solid was collected under suction and recrystallized from ethyl acetate to give **4**. Yield: 22.8 g (74 %); m. p. 142 – 143 °C (lit. [37]: m. p. 142 – 143 °C). – HRMS ((+)-ESI): $m/z = 309.10811$ (calcd. 309.10866 for $C_{14}H_{17}N_2O_6$, $[M+H]^+$), 331.09006 (calcd. 331.09061 for $C_{14}H_{16}NaN_2O_6$, $[M+Na]^+$). – $^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.36$, 1.40 [2 t, $J$ = 7.1 Hz, 7.1 Hz, 6H, 2 ($CH_3CH_2$)], 4.29, 4.34 (2 q, $J = 7.1$, 7.1 Hz, 4H, 2 ($CH_2$Me)), 7.23 (d, $J = 9$ Hz, 2H, 2-H/6-H), 8.28 (d, $J$ = 9 Hz, 2H, 3-H/5-H), 8.51 (d, $J = 13.2$ Hz, 1H, 3′-H), 11.20 (d, $J = 13.2$ Hz, 1H, N-H/exchangeable with $D_2O$). – $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta = 14.2$, 14.4 (2 $CH_3CH_2$), 60.6, 61.0 (2 O$CH_2$Me), 97.1 (C-2′), 116.4 (C-2/C-6), 126.0 (C-3/C-5), 143.9 (C-4), 144.6 (C-1), 149.7 (C-3′), 165.1, 168.6 (2 *C*$O_2$Et).

*Ethyl 6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**5**)*

Compound **4** (5 g, 0.016 mol) was added to diphenyl ether (50 mL), and the mixture was refluxed for 1 h. The solution was then cooled, the resulting precipitate collected by suction filtration, washed with cyclohexane, dried, and recrystallized from DMF to give pure **5**. Yield: 4.11 g (98 %); m. p. > 320 °C (lit. [38]: m. p. > 320 °C). – HRMS ((+)-ESI): $m/z = 263.06625$ (calcd. for 263.06680

$C_{12}H_{11}N_2O_5$, $[M+H]^+$), 285.04819 (calcd. 285.04874 for $C_{12}H_{10}NaN_2O_5$, $[M+Na]^+$). – $^1$H NMR (500 MHz, $CF_3CO_2D$): $\delta = 1.41$ (t, $J = 7.1$ Hz, 3H, $CH_3CH_2$), 4.59 (q, $J = 7.1$ Hz, 2H, $CH_2$Me), 8.30 (d, $J = 9.3$ Hz, 1H, 8-H), 8.83 (dd, $J = 2.3$ Hz, 9.3 Hz, 1H, 7-H), 9.40 (s, 1H, 2-H), 9.41 (d, $J = 2.3$ Hz, 1H, 5-H), 11.50 (s, 1H, N-H/exchangeable with $D_2O$). – $^{13}$C NMR (125 MHz, $CF_3CO_2D$): $\delta = 14.3$ ($CH_3CH_2O$), 67.6 ($OCH_2$Me), 108.7 (C-3), 122.4 (C-4a), 123.6 (C-8), 124.0 (C-5), 133.0 (C-7), 144.1 (C-8a), 149.6 (C-6), 150.4 (C-2), 169.3 ($CO_2$Et), 176.9 (C-4).

*Ethyl 1-ethyl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylate (**6**)*

A stirred mixture of compound **5** (5 g, 0.019 mol), $K_2CO_3$ (8 g, 0.058 mol), iodoethane (24.96 g, 0.162 mol), and EtOH (20 mL) was refluxed for 10 h. The reaction mixture was then evaporated to dryness and extracted with $CH_2Cl_2$ ($2 \times 20$ mL). The combined $CH_2Cl_2$ extracts were washed with $H_2O$, dried, and evaporated to dryness. The residual solid was recrystallized from EtOH to yield **6**. Yield: 4.3 g (83 %); m. p. 229 – 231 °C (decomp.) (lit. [39]: m. p. 230 – 232 °C (decomp.)). – HRMS ((+)-ESI): $m/z = 291.09755$ (calcd. 291.09810 for $C_{14}H_{15}N_2O_5$, $[M+H]^+$), 313.07949 (calcd. 313.08004 for $C_{14}H_{14}NaN_2O_5$, $[M+Na]^+$). – $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta = 1.30$ (t, $J = 7.1$ Hz, 3H, $OCH_2CH_3$), 1.40 (t, $J = 7.0$ Hz, 3H, $NCH_2CH_3$), 4.26 (q, $J = 7.1$ Hz, 2H, $OCH_2$Me), 4.46 (q, $J = 7.0$ Hz, 2H, $NCH_2$Me), 8.1 (d, $J = 9.0$ Hz, 1H, 8-H), 8.50 (dd, $J = 9.0$ Hz, 2.8 Hz, 1H, 7-H), 8.78 (s, 1H, 2-H), 8.90 (d, $J = 2.8$ Hz, 1H, 5-H). – $^{13}$C NMR (125 MHz, $[D_6]$DMSO): $\delta = 14.6$ ($OCH_2CH_3$), 14.7 ($NCH_2CH_3$), 49.0 ($NCH_2$Me), 60.6 ($OCH_2$Me), 112.2 (C-3), 119.8 (C-8), 122.8 (C-5), 127.1 (C-7), 128.4 (C-6), 143.0 (C-8a), 144.1 (C-4a), 150.8 (C-2), 164.4 ($CO_2$Et), 172.5 (C-4).

*Ethyl 6-amino-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (**7**)*

Anhydrous stannous chloride (2.5 g, 14 mmol) was added portion-wise to a stirred solution of the nitro compound **6** (1.0 g, 3.4 mmol) in conc. HCl (20 mL), cooled at 2 – 5 °C. The reaction mixture was stirred for one additional hour at 2 – 5 °C and for 20 h at r. t. Thereafter, the solution was diluted with water (200 mL) and treated portion-wise with a 40 % aqueous sodium hydroxide solution to pH ~11. The resulting faint-yellowish precipitate was collected by suction filtration, washed with water, and dried to give **7**. Yield: 0.68 g (77 %); m. p. 209 – 211 °C. – HRMS ((+)-ESI): $m/z = 261.12337$ (calcd. 261.12392 for $C_{14}H_{17}N_2O_3$, $[M+H]^+$), 283.10531 (calcd. 283.10586 for $C_{14}H_{16}NaN_2O_3$, $[M+Na]^+$). – $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta = 1.27$ (t, $J = 7.1$ Hz, 3H, $CH_3CH_2O$), 1.35 (t, $J = 7.0$ Hz, 3H, $CH_3CH_2N$), 4.20 (q, $J = 7.1$ Hz, $OCH_2$Me), 4.32 (q, $J = 7.0$ Hz, $NCH_2$Me), 5.57 (s, 2H, $NH_2$/exchangeable with $D_2O$), 7.07 (dd, $J = 9.0$ Hz, 2.5 Hz, 7-H), 7.40 (d, $J = 2.5$ Hz, 1 H, 5-H), 7.53 (d, $J = 9.0$ Hz, 1 H, 8-H), 8.50 (s, 1H, 2-H). – $^{13}$C NMR (125 MHz, $[D_6]$DMSO): $\delta = 15.0$ ($CH_3CH_2O$), 15.2 ($CH_3CH_2N$), 48.6 ($NCH_2$Me), 60.2 ($OCH_2$Me), 108.5 (C-5), 108.8 (C-2), 119.2 (C-8), 121.7 (C-7), 130.7 (C-8a), 131.3 (C-4a), 147.5 (C-2), 147.8 (C-6), 166.6 ($CO_2$Et), 174.1 (C-4). – $C_{14}H_{16}N_2O_3$(260.29): calcd. C 64.60, H 6.20, N 10.76; found C 64.42, H 6.12, N 10.58.

*Ethyl 1-ethyl-6-[2-(hydroxyimino)acetamido]-4-oxo-1,4-dihydroquinoline-8-carboxylate (**8**)*

Crystalline sodium sulfate (36 g), a hot solution of the amino ester **7** (3.5 g, 0.013 mol) in 4 % aqueous hydrochloric acid (2 mL), and a solution of hydroxylamine hydrochloride (5.5 g, 0.079 mol) in water (12 mL) were added successively to a solution of chloral hydrate (4.5 g, 0.03 mol) in water (23 mL). Thereafter, the reaction mixture was refluxed with continuous stirring for 8 h, and the resulting solution was filtered while hot. The precipitated product was collected by suction filtration, washed with hot water and dried to give **8**. Yield: 3.5 g (82 %); m. p. 219 – 220 °C. – HRMS ((+)-ESI): $m/z = 332.12410$ (calcd. 332.12465 for $C_{16}H_{18}N_3O_5$, $[M+H]^+$), 354.10604 (calcd. 354.10659 for $C_{16}H_{17}NaN_3O_5$, $[M+Na]^+$). – $^1$H NMR (500 MHz, $[D_6]$DMSO): $\delta = 1.29$ (t, $J = 7.1$ Hz, 3H, $CH_3CH_2O$), 1.40 (t, $J = 7.0$ Hz, 3H, $CH_3CH_2N$), 4.23 (q, $J = 7.1$ Hz, $OCH_2$Me), 4.40 (q, $J = 7.0$ Hz, $NCH_2$Me), 7.70 (s, 1H, CH=NOH), 7.83 (d, $J = 9.1$ Hz, 1 H, 8-H), 8.13 (dd, $J = 9.1$ Hz, 2.1 Hz, 7-H), 8.58 (d, $J = 2.1$ Hz, 1H, 5-H), 8.66, (s, 1H, 2-H), 10.55 (s, 1H, N-H/exchangeable with $D_2O$), 12.26 (d, 1H, CH=NO-*H*/exchangeable with $D_2O$). – $^{13}$C NMR (125 MHz, $[D_6]$DMSO): $\delta = 14.9$ ($OCH_2CH_3$), 15.0 ($CH_3CH_2N$), 48.7 ($NCH_2$Me), 60.5 ($OCH_2$Me), 110.5 (C-3), 117.3 (C-5), 119.1 (C-8), 126.2 (C-7), 130.1 (C-6), 136.1 (C-8a), 136.9 (C-4a), 145.2 (CH=NOH), 149.6 (C-2), 161.9 (O=C–NH), 166.2 ($CO_2$Et), 174.0 (C-4). – $C_{16}H_{17}N_3O_5$ (331.32): calcd. C 58.00, H 5.17, N 12.68; found C 57.84, H 5.26, N 12.50.

*6-Ethyl-1,1-dihydroxy-2,9-dioxo-2,3,6,9-tetrahydro-1H-pyrrolo[3,2-f]quinoline-8-carboxylic acid (**3H**)*

Compound **8** (0.6 g; 1.8 mmol) was added portion-wise to 95 % sulfuric acid (4 mL) preheated at 65 – 70 °C under stirring. Thereafter, the temperature of the reaction mixture was raised to 90 °C and maintained there for 1 h. The resulting solution was then cooled to r. t., treated with crushed ice (200 g), and allowed to stand overnight. The precipitated product was filtered, washed successively with hot water and cold methanol (10 mL), and dried to give **3H**. Yield: 0.35 g (64 %); m. p. > 350 °C. – HRMS ((+)-ESI): $m/z = 305.07718$ (calcd. 305.07736 for

$C_{14}H_{13}N_2O_6$, $[M+H]^+$), 327.05912 (calcd. 327.05931 for $C_{14}H_{12}NaN_2O_6$, $[M+Na]^+$). – $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.43$ (t, $J = 7.1$ Hz, 3H, $CH_2CH_3$), 4.65 (q, $J = 7.1$ Hz, 2H, $CH_2$Me), 7.35 (s, 2H, $(HO)_2$C-1/ exchangeable with $D_2O$), 7.52 (d, $J = 9$ Hz, 1H, 4-H), 8.08 (d, $J = 9$ Hz, 1H, 5-H), 9.01 (s, 1H, 7-H), 10.70 (s, 1H, N-H/exchangeable with $D_2O$), 14.51 (s, 1H, $CO_2$H/exchangeable with $D_2O$). – $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$ = 15.1 ($CH_2CH_3$), 50.3 ($CH_2$Me), 92.5 (C-1), 108.3 (C-8), 118.4 (C-4), 121.1 (C-5), 123.8 (C-9a), 127.6 (C-9b), 135.4 (C-5a), 140.8 (C-3a), 148.8 (C-7), 166.0 ($CO_2$H), 174.4 (C-2), 177.9 (C-9). – $C_{14}H_{12}N_2O_6$ (304.25): calcd. C 55.27, H 3.98, N 9.21; found C 55.03, H 3.86, N 9.08.

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