Pergamon

Tetrahedron 58 (2002) 9179–9185

TETRAHEDRON

Synthesis of 4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid ethyl ester and its isomer 1-oxo-2,9-dihydro-1*H*-β-carboline-4-carboxylic acid ethyl ester

Jan Bergman* and Stanley Rehn

Unit for Organic Chemistry, Department of Biosciences, Karolinska Institute, and Södertörn University College, Novum Research Park, SE-141 57 Huddinge, Sweden

Received 18 July 2002; revised 29 August 2002; accepted 19 September 2002

Abstract—4-Oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid ethyl ester was obtained when TosMIC was reacted with 3-methylene-oxindole acetic acid ethyl ester. An alternative synthesis to this pyrroloquinolone was performed via a reduction of a 2,3,4-trisubstituted pyrrole obtained in turn by treatment of a vinyl sulfone with ethyl isocyanoacetate under basic conditions. A β-carboline, isomeric with the pyrroloquinolone, was synthesised utilizing a tosylimine.

1. Introduction

Several spiro derivatives of oxindole, such as the alkaloid horsfiline,[1] **1**, and spirotryprostatin A,[2] **2**, have pharmacologically interesting properties such as cell cycle inhibition at the G2/M phase. The ring systems of the horsfiline, spiropyrrolidinyloxindole and the related pyrroloquinolones **3**–**5** (Fig. 1) have attained great interest and these tricyclic structures form the core structure of a number of biologically significant molecules. One recent well-published example is martinelline **7**[3] containing a [3,2-*c*] fused pyrrole moiety. Jones et al.[4] have synthesized [3,2-*c*] **3** and [3,4-*c*] **4** fused pyrroloquinolones by utilising an intramolecular aryl radical cyclisation route. Nevertheless, very few synthetic procedures leading to pyrrolo[2,3-*c*]quinolones **5** have been reported, although this ring system does occur as moieties in certain alkaloids.[5] Very recently Kafka et al. have reported the preparation of some derivatives of **5**, notably **6**.[6]

We felt that the readily available (from isatin and triethyl phosphonoacetate)[7] compound **8a** (Scheme 1) and *p*-toluenesulfonylmethyl isocyanide (TosMIC) might give rise to interesting heterocyclic spiro compounds. The ester **8a** has been used for preparation of several spiro oxindoles, such as **9** and **10** (Fig. 2). At the drawing board we speculated that the spiro derivative **12** (Scheme 1) might be obtained. However we also realized that the very structure of **12** might render it sensitive to secondary reactions including cleavage of the oxindole moiety.[8] Several reactions of this type are known like the Bedford cleavage[9] and the ready conversion of the *O*-acetate of isatine-3-oxime to 2-isocyanatobenzonitrile and *N*, *N*′-bis (2-cyanophenyl) urea[10] as well as the conversion of 3,3,5,7-tetranitro-oxindole to 3,5,7-trinitroindazole.[11]

2. Results and discussion

The product (74% yield) from the reaction between oxindole **8a** and TosMIC had the composition $C_{14}H_{12}N_2O_3$. The ^{1}H NMR contained, in addition to a 1,2-disubstituted benzene ring and an ethoxycarbonyl group, three signals (two NH and a CH at 7.98 ppm). With this information the pyrroloquinolone **14a** (Scheme 1) was proposed and the rationalization in Scheme 1 was outlined. An initial Michael addition would lead to adduct **11**, following the outlined pathway (a) in Scheme 1. After loss of *p*-toluenesulfinate cyclisation would give compound **12**. Cleavage of the oxindole moiety, promoted by the basic conditions, results in compound **13**, which recyclises to the pyrroloquinolone **14**. Using the corresponding methyl ester **8b**, prepared in the same manner as the ethyl ester **8a**, we obtained the methyl ester pyrroloquinolone **14b** in 52% yield. When oxindole **8c**[12] was treated under the same conditions as above, a related structure, **14c**, was isolated in 79% yield. At the same time an alternative structure, namely the β-carboline **15** can be discussed, which might be formed via adduct **11**, followed by ring closure and proton shift to yield the hypothetical molecule **16**, which might yield the epoxide **17** via valence tautomerism (Scheme 1). The

Keywords: pyrroloquinolone; TosMIC; β-carboline; tosylimine.

* Corresponding author. Tel.: +46-8-608-9204; fax: +46-8-608-1501; e-mail: jabe@cnt.ki.se

0040–4020/02/$ - see front matter
PII: S0040-4020(02)01197-3

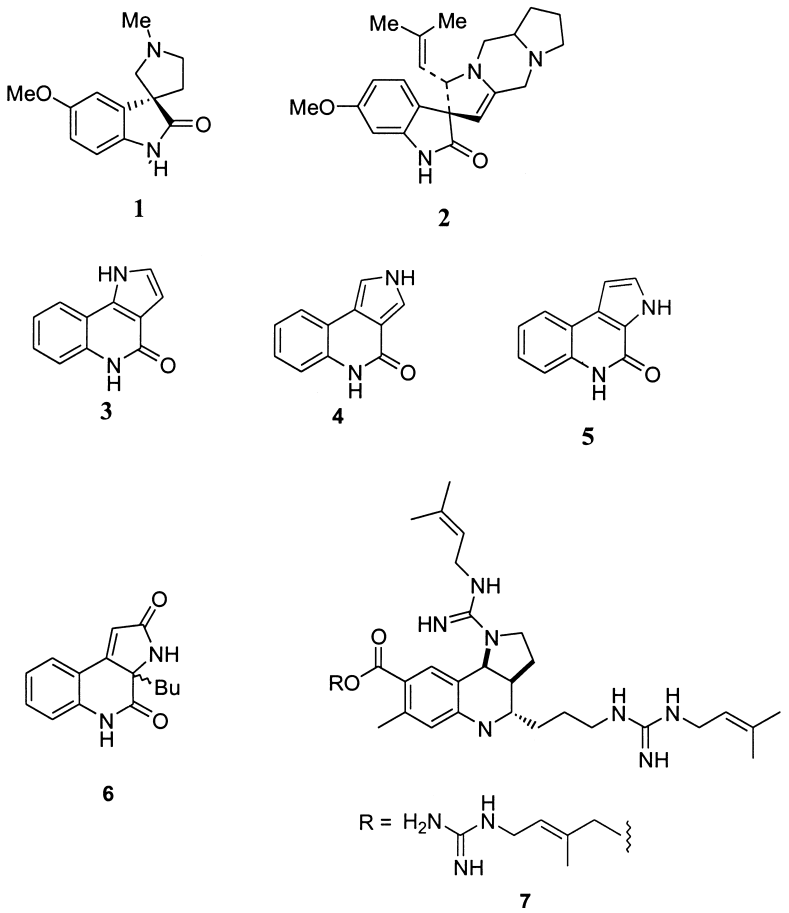
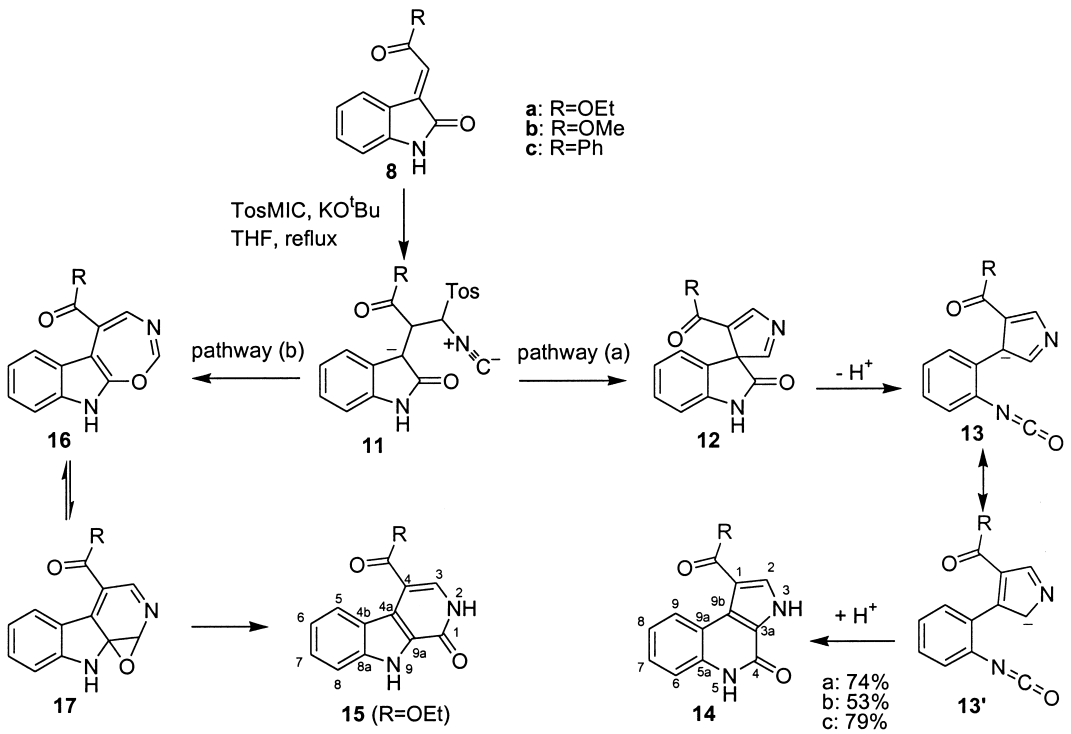
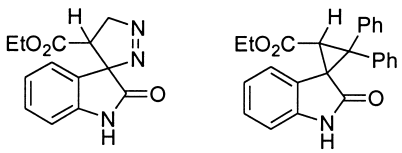


Figure 1.

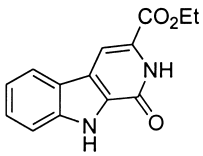


Scheme 1.



9 **10**

Figure 2.



18

Figure 3.

epoxide **17** opens and finally tautomerises to the β-carboline **15**.

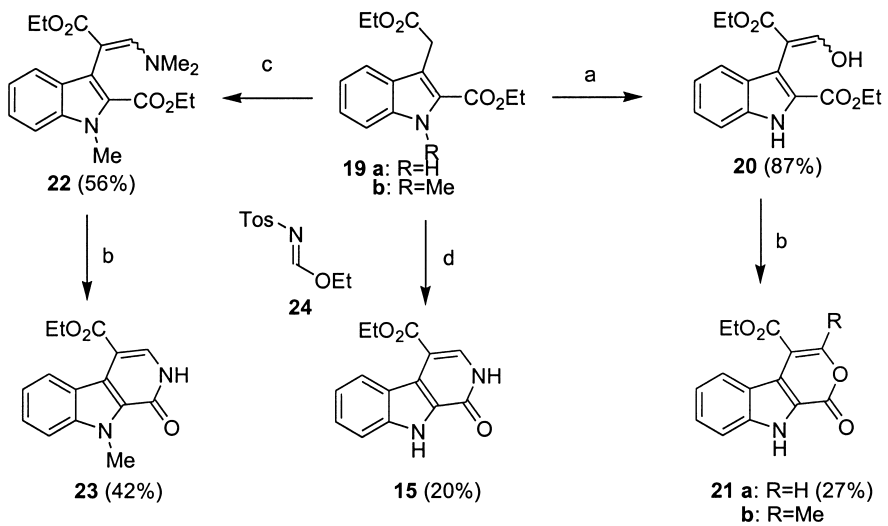
When the proton NMR spectrum of the β-carboline **15** was compared with the proton NMR spectrum of the pyrroloquinolone **14a** it showed the same pattern. Nevertheless, it differed to some extent, as the NH signals in the pyrroloquinolone **14a** were farther apart than in the β-carboline **15**. The hydrogen at position 9 in pyrroloquinolone **14a** and the corresponding hydrogen at position 5 in β-carboline **15** resonated at 9.23 and 8.83 ppm, respectively. The higher value for **14a** indicates that the carbonyl oxygen is closer in space to this hydrogen than for β-carboline **15**, i.e. the pyrroloquinolone is more bent than the β-carboline.

2.1. Synthesis of the β-carboline 15

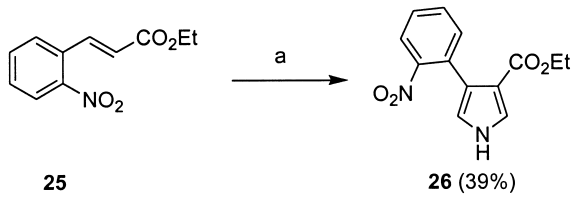
β-Carbolines are ubiquitous in nature and several synthetic strategies have been developed over the years, owing to the wide range of biological activity that several β-carbolines exhibit. The most common way of preparing β-carbolines is the Pictet–Spengler type of reaction.[13] To prepare the hitherto unknown β-carboline **15** (its regioisomer **18**, Fig. 3, is known[14]) it was not possible to use the Pictet–Spengler reaction, and therefore a new approach had to be developed. A suitable starting point for compound **15** would be the diethyl ester **19a**, available by Fischer indolisation according to Robinson.[15] To insert the desired C–N fragment we formylated according to Rozhkov.[16] When the required ring closure to the pyridone was tried with ammonia, this only gave the enol **20** back (after acidic work up), which probably was due to an initial deprotonation of the enol (Scheme 2). However, when the enol **20** was refluxed in DMF containing H_4NOAc and a catalytic amount of *p*-toluenesulfonic acid, lactonisation to the reported[17] indolopyrone **21a** occurred. Whereas Mashelkar and Usgaonkar reported a melting point of 80°C, we found that **21a** decomposed at 240°C, which correlates better to compound **21b**, which melts at 220°C, reported by the same authors.[18] To avoid the acidity a dimethylvinylamino group was introduced using *N*,*N*-dimethylformamide dimethyl acetal, DMFDMA, but unfortunately this reagent also simultaneously methylated[19] the indole nitrogen to yield **22**. From this reaction we also isolated the known *N*-methylated diethylester **19b**[20] in 23% yield. When compound **22** was refluxed in DMF with ammonium acetate as a source of ammonia, the β-carboline **23** could be isolated in 42% yield. To avoid methylation of the indole nitrogen a new strategy was developed. Thus the tosyl imidate **24**[21] was now used as source of the C–N fragment, which after a nucleophilic attack from the diethyl ester **19a** had an effect on the 2-carbethoxy unit that resulted in ring closure to the desired previously unknown fused indolo pyridone **15** in a modest yield (20%) (Scheme 2).

2.2. Alternative synthesis of the pyrroloquinolone 14a

To obtain the pyrroloquinolone **14a** we disconnected the amide bond. The synthon of this retrosynthetic step is a 2,3,4-trisubstituted pyrrole, where the 2 and 4-positions consist of carbalkoxy groups and the 3-position of an *o*-nitrophenyl moiety. Reacting TosMIC with *o*-nitrophenyl cinnamic acid ethyl ester **25**[22] (Scheme 3), prepared via a Horner–Wadsworth–Emmons reaction, yielded the 4-(*o*-nitrophenyl)-3-carbethoxy pyrrole **26**. To introduce the second carbalkoxy group on the 3,4-disubstituted pyrrole **26** several acylation reagents such as trichloroacetyl chloride,[23]



Scheme 2. (a) NaH, ethylformate, Et_2O; (b) NH_4OAc, *p*-TosOH, DMF, reflux; (c) DMFDMA, DMF, heat; (d) NaH, **24**, Et_2O.



25 **26** (39%)

Scheme 3. (a) TosMIC, NaH, Et_2O/DMSO.

oxalyl chloride[24] and trifluoroacetic acid anhydride[25] were tested. Unfortunately none of these reagents were successful. We therefore concluded that the *o*-nitrophenyl group together with the carbethoxy group were too electron withdrawing for acylations to be carried out. Therefore the 2-carboxy group have to be introduced in another way.

Using the modified method of the Barton–Zard reaction,[26] that starts from the α,β-unsaturated sulfone **27**, a 2,3,4-trisubstituted pyrrole can be achieved. The required sulfone **27** was obtained by Knoevenagel condensation of *o*-nitrobenzaldehyde with tosylacetonitrile.[27] Treating the sulfone **27** with ethyl isocyanoacetate under basic conditions yielded the trisubstituted pyrrole **28** in 72% yield (Scheme 4). Reduction of the nitro group and an intra molecular amide formation completed the comparatively unusual ring system of the desired pyrroloquinolone. Using sodium dithionite in a refluxing ethanol/water mixture, however, yielded 4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carbonitrile **29** in a lower yield (39%). Changing the conditions to iron in refluxing acetic acid, the yield of the pyrroloquinolone **29** increased to 65%. Hydrolysis to the ethyl ester was performed by refluxing the pyrroloquinolone **29** for 4 h in a 1:1 mixture of sulfuric acid and ethanol, which yielded a grey solid, that did not show any nitrile absorption in the IR spectrum. The proton NMR of the crude product revealed a 4:1 mixture of the acid **30** and the desired 4-oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid ethyl ester **31**, which proved to be identical in all respects with the product **14a** obtained by the simple condensation of oxindole **8a** and TosMIC. The total yield of **31** according to Scheme 4 was a mearge 11% as compared with 74% when prepared directly from oxindole **8a** and TosMIC. Furthermore the β-carboline **15** could not be detected in the reaction mixture. This independent synthesis thus proves that the ester **8a** when treated with TosMIC undergoes a cycloaddition to the intermediate **12a**, followed by ring opening and recyclization to eventually form the ring-expanded product **14a**.

3. Experimental

3.1. General

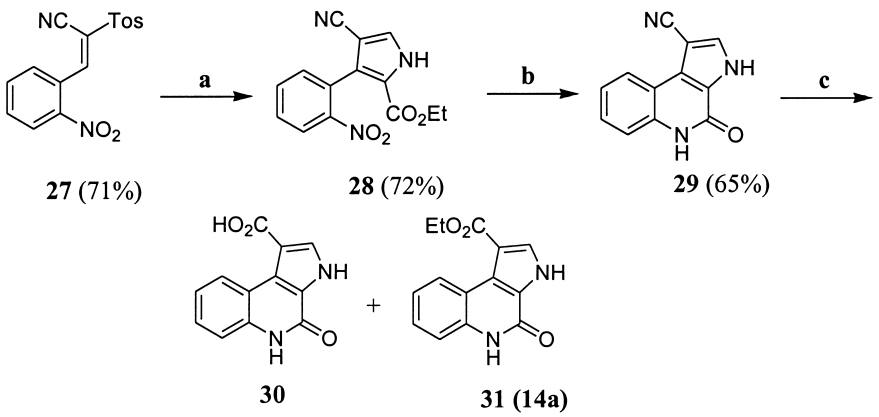
NMR spectra were recorded in DMSO-d_6 solutions, unless otherwise stated, on a Bruker DPX 300 spectrometer, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, δ values were reported in ppm and J values in Herz. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR instrument. Melting points were determined with a Buchi melting point B-545 apparatus and are uncorrected. Elemental analysis were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

3.1.1. 3-(Ethoxycarbonyl)methylene-1,3-dihydroindole-2-one, 8a. The title compound was obtained in 85% (0.1 mol scale) following the excellent procedure (Horner–Wadsworth–Emmons) given by Franke.[7] Various other inferior procedures are given in the literature.[28]

3.2. General procedure for the addition of TosMIC to compounds 8a–c

A solution of KO^{t}Bu (10 mmol) in THF (70 ml) was added to a stirred solution of **8** (10 mmol) and TosMIC (10 mmol) in THF (35 ml). The reaction was heated to reflux and the colour changed from orange to brown and finally to black. After 30 min the solid formed was collected, the THF solution was poured out on ice/water and acidified with AcOH. A brownish solid was collected by filtration. This crude product was recrystallized from AcOH.

3.2.1. 4-Oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid ethyl ester, 14a. KO^{t}Bu (1.12 g, 10 mmol) in THF (70 ml), **8a** (2.17 g, 10 mmol) and TosMIC (1.95 g, 10 mmol) in THF (35 ml). Yield 1.90 g (74%) as a white solid, mp 310–311°C (dec); δ_H 1.33 (3H, t, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 7.21 (1H, m), 7.36–7.43 (2H, m), 7.98 (1H, d, J=3.2 Hz), 9.23 (1H, d, J=8.2 Hz), 11.67 (1H, s), 12.98 (1H, s); δ_C 14.3 (q), 59.8 (t), 111.1 (s), 115.9 (d), 116.7 (s), 121.5 (d), 124.8 (s), 125.5 (s), 126.4 (d), 127.3 (d), 132.9 (d), 136.0 (s), 154.7 (s), 164.0



27 (71%) **28** (72%) **29** (65%)

30 **31 (14a)**

Scheme 4. (a) Ethyl isocyanoacetate, DBU, THF, 0°C; (b) Fe, AcOH, reflux; (c) EtOH/conc. H_2SO_4 (1:1), reflux.

(s); IR (KBr) 3329, 2983, 1692, 1669, 1413, 1298, 1175, 1156, 1107, 748 cm^{-1}; Anal. calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.74; H, 4.78; N, 10.88.

3.2.2. 4-Oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid methyl ester, 14b. KO^{t}Bu (0.76 g, 6.8 mmol) in THF (20 ml), **8b** (1.38 g, 6.8 mmol) and TosMIC (1.33 g, 6.8 mmol) in THF (20 ml). Yield 0.85 g (52%) as a brownish solid, mp. 365°C (dec); δ_H 3.83 (3H, s), 7.21 (1H, app. t, J=7.5 Hz), 7.36–7.43 (2H, m), 7.99 (1H, s), 9.22 (1H, d, J=8.0 Hz), 11.67 (1H, s), 12.99 (1H, s); δ_C 51.4 (q), 110.7 (s), 116.0 (d), 116.7 (s), 121.6 (d), 124.8 (s), 125.6 (s), 126.4 (d), 127.3 (d), 133.0 (d), 136.1 (s), 135.7 (s), 164.5 (s); IR (KBr) 3213, 1694, 1672, 1466, 1414, 1299, 1154, 1106, 747 cm^{-1}; Anal. calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.38; H, 4.12; N, 11.48.

3.2.3. 1-Benzoyl-3,5-dihydro-pyrrolo[2,3-*c*]quinolin-4-one, 14c. KO^{t}Bu (1.12 g, 10 mmol) in THF (100 ml), **8c** (2.49 g, 10 mmol) and TosMIC (1.95 g, 10 mmol) in THF (35 ml). Yield 2.28 g (79%) as a light brown solid, mp 308–309°C (dec); δ_H 7.18 (1H, app. t, J=8.2 Hz), 7.37–7.46 (2H, m), 7.52–7.57 (2H, m), 7.62–7.67 (2H, m), 7.82–7.85 (2H, m), 8.83 (1H, d, J=7.9 Hz), 11.75 (1H, s), 13.07 (1H, s); δ_C 116.0 (d), 116.8 (s), 119.5 (s), 121.4 (d), 125.2 (s), 126.0 (s), 126.1 (d), 127.4 (d), 128.4 (d), 129.2 (d), 132.0 (d), 135.0 (d), 136.2 (s), 140.0 (s), 154.8 (s), 190.9 (s); IR (KBr) 3356, 2873, 1663, 1630, 1407, 1296, 1112, 884 cm^{-1}; Anal. calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 74.92; H, 4.25; N, 9.78.

3.2.4. 1-Oxo-2,9-dihydro-1*H*-β-carboline-4-carboxylic ethyl ester, 15. A solution of diethyl ester **19a** (2.00 g, 7 mmol) and sulfone amide **24** (3.30 g, 14 mmol) in THF (30 ml) was added dropwise for 1 h to a cold (0°C) suspension of NaH 60% w/w (0.44 g, 18 mmol) in THF (10 ml). The reaction was allowed to reach rt and quenched after 22 h by adding approximately 10 g of ice. The mixture was brought to 0°C and treated with 50% AcOH (10 ml), extracted with $CHCl_3$ (3×50 ml), evaporated and triturated with hot Et_2O to yield a yellow solid (0.38 g, 20%). An analytically pure sample was obtained by recrystallization from AcOH, mp 307–310°C (dec); δ_H 1.36 (3H, t, J=7.1 Hz), 4.37 (2H, q, J=7.1 Hz), 7.18 (1H, app. t, J=8.3 Hz), 7.43 (1H, app. t, J=8.3 Hz), 7.56 (1H, d, J=8.3 Hz) 7.88 (1H, s), 8.78 (1H, d, J=8.3 Hz), 12.00 (1H, s), 12.28 (1H, s); δ_C 14.2 (q), 60.3 (t), 106.45 (s), 112.4 (d), 119.7 (d), 120.3 (s), 121. 4 (s), 125.6 (d), 126.4 (d), 127.8 (s), 131.7 (d), 139.5 (s), 155.6 (s), 165.1 (s); IR (KBr) 3462, 3222, 3152, 1684, 1655, 1291, 1103, 749 cm^{-1}; Anal. calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.69; H, 4.70; N, 10.99.

3.2.5. 3-(1-Ethoxycarbonyl-2-hydroxy-vinyl)1*H*-indole-2-carboxylic ethyl ester, 20. A solution of ethyl formate (11 ml, 137 mmol) and diethyl ester **19a** (2.75 g, 10 mmol) in ether (20 ml) was added dropwise to a suspension of 95% w/w NaH (1.65 g, 66 mmol) over 10 min. After 3.5 h MeOH (2 ml) was added and the reaction was cooled to 0°C whereupon 50% AcOH (10 ml) was added. The mixture was extracted with Et_2O (2×50 ml) and the combined organic phases were washed with water (50 ml) and sat. aq. $NaHCO_3$ (50 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography and yielded 2.64 g (87%) of **20**. This material was used without further purification in the next reaction. The NMR spectrum showed the presence of two tautomers.

3.2.6. 1-Oxo-1,9-dihydro-pyrano[3,4-*b*]indole-4-carboxylic acid ethyl ester, 21a. The ester **19** (1.0 g, 3 mmol) and H_4NOAc (1.02 g, 17 mmol) and catalytic amounts of TosOH (63 mg) were refluxed for 220 min in DMF (25 ml). Addition of ice up to the double volume quenched the reaction. A brown-red solid (0.23 g, 27%) was collected, mp: 240°C (dec); δ_H 1.36 (3H, t, J=7.1 Hz), 4.39 (2H, q, J=7.1 Hz), 7.24 (1H, app. t, J=8.4 Hz), 7.49 (1H, app. t, J=8.3 Hz), 7.58 (1H, d, J=8.3 Hz), 7.84 (1H, s), 8.60 (1H, d, J=8.4 Hz), 12.77 (1H, s); δ_C 14.1 (q), 61.1 (t), 110.6 (s), 112.9 (d), 119.5 (s), 120.8 (d), 121.0 (s), 121.1 (s), 125.3 (d), 127.7 (d), 140.2 (s), 149.9 (d), 155.5 (s), 164.1 (s); IR (KBr) 3923, 3272, 1728, 1695, 1289, 1069, 757 cm^{-1}; Anal. calcd for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.22; H, 4.43; N, 5.43.

3.2.7. 3-(2-Dimethylamino-1-ethoxycarbonyl-vinyl)-1-methyl-1*H*-indole-2-carboxylic ethyl ester, 22. A solution of the diethyl ester **19a** (3.2 g, 11 mmol) in DMFDMA (7 ml, 52 mmol) was refluxed for 28 h. After quenching with water (200 ml) the reaction mixture was extracted with Et_2O (4×50 ml) and the combined Et_2O phase was washed with water (3×30 ml) dried ($MgSO_4$) and evaporated to yield a brownish oil (3.72 g). Purification by flash chromatography gave 0.8 g of **19b** and 2.17 g (56%) of the vinylamine **22** as a brownish solid. This material was used without further purification in the next reaction. The NMR spectrum showed the presence of two tautomers.

3.2.8. 9-Methyl-1-oxo-2,9-dihydro-1*H*-β-carboline-4-carboxylic ethyl ester, 23. The vinylamine **22** (0.7 g, 2 mmol), H_4NOAc (0.81 g, 11 mmol) and catalytic amounts of *p*-TosOH (20 mg) were refluxed in DMF (10 ml) for 7 days. Ice was then added until a solid appeared and the mixture was the subsequently cooled to 0°C whereupon a light brownish solid was collected. The solid was then washed with ice cold EtOH (5 ml) to yield 0.24 g of **23** (42%), mp 252–254°C; δ_H 1.35 (3H, t, J=7.1 Hz), 4.24 (3H, s), 4.34 (2H, q, J=7.1 Hz), 7.22 (1H, app. t, J=8.3 Hz), 7.50 (1H, app. t, J=8.4 Hz), 7.61 (1H, d, J=8.4 Hz), 7.81 (1H, s), 8.79 (1H, d, J=8.3 Hz), 11.98 (1H, s); δ_C 14.2 (q), 31.0 (q), 60.4 (t), 106.3 (s), 110.2 (d), 119.9 (d), 120.3 (s), 120.9 (s), 125.8 (d), 126.3 (s), 126.7 (d), 131.9 (d), 140.6 (s), 156.3 (s), 165.9 (s); IR (KBr) 2904, 2850, 1715, 1646, 1462, 1282, 1217, 1141. 1086, 747 cm^{-1}; Anal. calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.36. Found: C, 66.64; H, 5.23; N, 10.28.

3.2.9. 4-(2-Nitrophenyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester, 26. A solution of *o*-nitrophenyl cinnamic acid ethyl ester **25** (1.01 g, 4.5 mmol) and TosMIC (1.06 g, 5.5 mmol) in Et_2O (30 ml) and DMSO (10 ml) was added dropwise during 40 min to a suspension of 60% w/w NaH (0.50 g, 12.5 mmol) in Et_2O (10 ml) at 0°C. Stirring was continued for 75 min and then the reaction was quenched by adding ice followed by 1 M KOH (40 ml). The mixture was extracted with $CHCl_3$ (3×30 ml), dried ($MgSO_4$) and

evaporated to yield a crude product that was recrystallized from $CHCl_3$/hexane to yield 0.46 g (39%) of **26** as a brown solid, mp 161–163°C; δ_H 1.05 (3H, t, J=7.1 Hz), 3.96 (2H, q, J=7.1 Hz), 6.95 (1H, t, J=2.3 Hz), 7.38–7.55 (3H, m), 7.66 (1H, d, J=7.5 Hz), 7.97 (1H, d, J=8.1 Hz), 11.64 (1H, s); δ_C; 13.9 (q), 58.8 (t), 112.5 (s), 119.4 (d), 120.8 (s), 123.8 (d), 125.2 (d), 127.7 (d), 130.4 (s), 132.6 (d), 133.0 (d), 149.1 (s), 163.7 (s); IR (KBr) 3290, 1674, 1527, 1355, 1322, 1165, 1138, 752 cm^{-1}; Anal. calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; N, 10.76. Found: C, 59.88; N, 10.63.

3.2.10. 3-(2-Nitrophenyl)-2-(toluene-4-sulfonyl)-acrylonitrile, 27. *p*-Nitrobenzaldehyde (3.04 g, 20 mmol) and tosylacetonitrile (3.93 g, 20 mmol) were dissolved in ethanol (60 ml) and piperidine (0.5 ml) was added. After 1.5 h of reflux the mixture was allowed to cool to 25°C and light brownish needles (4.36 g, 66%) were collected. After partial concentration a second crop 0.37 g was obtained. Total yield: 71%, mp 152–153°C (lit.,[27] 149°C); δ_H 2.46 (3H, s), 7.61 (2H, d, J=8.1 Hz), 7.85–7.94 (6H, m), 9.02 (1H, s); δ_C 21.2 (q), 111.8 (s), 117.8 (s), 125.4 (d), 126.8 (s), 128.3 (d), 130.2 (d), 130.8 (d), 133.0 (d), 134.0 (s), 134.9 (d), 146.5 (s), 147.3 (s), 153.8 (d); IR (KBr) 3421, 1524, 1342, 1155, 735, 674, 574 cm^{-1}.

3.2.11. 4-Cyano-3-(2-nitro-phenyl)-1*H*-pyrrole-2-carboxylic acid methyl ester, 28. DBU (2.93 g, 19 mmol) and ethyl isocyanoacetate (1.82 g, 16 mmol) were added dropwise during 5 min to a cold, 0°C, solution of tosyl acrylonitrile **27** (5.26 g, 16 mmol) in dry THF (60 ml). The reaction mixture was allowed to reach room temperature during the night. After 20 h the reaction was quenched with 1 M $HCl_{(aq)}$ (50 ml) and extracted with $CHCl_3$ (50 ml). The water phase was extracted with $CHCl_3$ (2×50 ml) and the combined organic phases were washed with water (2×50 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated. The crude product was recrystallized from $CHCl_3$ to yield a light yellow solid (3.30 g, 72%), mp: 142–143°C; δ_H 0.98 (3H, t, J=7.1 Hz), 4.02 (2H, q, J=7.1 Hz), 7.53 (1H, dd, J=7.6, 1.4 Hz), 7.70 (1H, td, J=7.6, 1.4 Hz), 7.81 (1H, td, J=7.6, 1.3 Hz), 7.98 (1H, s), 8.12 (1H, dd, J=8.1, 1.2 Hz), 13.03 (1H, s); δ_C 13.8 (q), 60.8 (t), 95.2 (s), 115.0 (s), 119.9 (s), 124.3 (d), 127.0 (s), 128.3 (s), 129.7 (d), 130.6 (d), 132.7 (d), 133.2 (d), 149.0 (s), 159.1 (s); IR (KBr) 3259, 2232, 1683, 1526, 1354, 1279, 1188, 1138, 1013, 759 cm^{-1}; Anal. calcd for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.86; H, 3.94; N, 14.70.

3.2.12. 4-Oxo-4,5-dihydro-3-*H*-pyrrolo[2,3-*c*]quinoline-1-carbonitrile, 29. The pyrrole derivative **28** (0.27 g, 1 mmol) and iron (0.52 g, 10 mmol) were refluxed in AcOH (15 ml). After 40 min the blackish refluxing mixture was filtered and allowed to cool to room temperature, whereupon a white solid (0.13 g, 65%) of **29** was collected, mp 361–365°C (dec); δ_H 7.28 (1H, app. t, J=7.9 Hz), 7.43 (1H, app. t, J=8.2 Hz), 7.48 (1H, d, J=8.2 Hz), 8.06 (1H, s), 8.26 (1H, d, J=7.9 Hz), 11.30 (1H, s), 12.89 (1H, s); δ_C 86.3 (s), 115.5 (s), 116.4 (d), 116.5 (s), 121.6 (d), 122.3 (d), 123.4 (s), 126.5 (s), 128.0 (d), 134.6 (d), 135.0 (s), 154.3 (s); IR (KBr) 3422 (NH), 2224 (CN), 1662 (CO), 1409, 1137, 767, 740 cm^{-1}; Anal. Calcd for $C_{12}H_7N_3O$: C, 68.89; H, 3.37; N, 20.09. Found: C, 68.75; H, 3.46; N, 19.88.

3.2.13. 4-Oxo-4,5-dihydro-3*H*-pyrrolo[2,3-*c*]quinoline-1-carboxylic acid ethyl ester, 31=14a. The pyrroloquinolone **29** (0.22 g, 1 mmol) was refluxed in a 1:1 mixture of ethanol (15 ml) and sulfuric acid (15 ml) for 3 h 40 min, whereupon the reaction mixture was poured out on a water-ice mixture (150 ml) and a grey solid was collected, which was portioned between sat. aq. $NaHCO_3$ (50 ml) and $CHCl_3$ (50 ml). The organic phase was then evaporated to yield compound **31**; δ_H 1.34 (3H, q, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 7.21 (1H, app. t, J=8.3 Hz), 7.38 (1H, app. t, J=8.2 Hz), 7.44 (1H, d, J=8.2 Hz), 7.97 (1H, d, J=3.3 Hz), 9.22 (1H, d, J=8.3 Hz), 11.70 (1H, s), 13.00 (1H, s); δ_C 14.3 (q), 59.8 (t), 111.0 (s), 116.0 (d), 116.7 (s), 121.5 (d), 124.7 (s), 125.5 (s), 126.4 (d), 127.2 (d), 133.0 (d), 136.1 (s), 154.7 (s), 164.0 (s).

References

1. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527–6530.
2. (a) Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138–1140. (b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
3. (a) Hadden, M.; Nieuwenhuyzen, M.; Osborne, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron Lett.* **2001**, *42*, 6417–6419. (b) Mahmud, H.; Lovely, C. J.; Rasika Dias, H. V. *Tetrahedron* **2001**, *57*, 4095–4105. (c) Ma, D.; Xia, C.; Jiang, J.; Zhang, J. *Org. Lett.* **2001**, *3*, 2189–2191. (d) Frank, K. E.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 655–666.
4. (a) Ho, T. C. T.; Jones, K. *Tetrahedron* **1997**, *53*, 8287–8294. (b) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951–8955. (c) Escolano, C.; Jones, K. *Tetrahedron* **2002**, *58*, 1453–1464.
5. Eiter, K.; Nagy, M. *Monatsh.* **1949**, *80*, 607–621.
6. Klásek, A.; Kafka, S.; Polis, J.; Košmrlj, J. Nineth Blue Danube Symposium on Heterocyclic Chemistry, June 16–20, 2000.
7. Franke, A. *Liebigs Ann. Chem.* **1978**, 717–725.
8. Bennett, G. B.; Mason, R. B.; Shapiro, M. J. *J. Org. Chem.* **1978**, *43*, 4383–4385.
9. Bedford, G. R.; Partridge, M. W. *J. Chem. Soc.* **1959**, 1633–1634.
10. (a) Beckmann, E.; Bark, E. *J. Prakt. Chem* **1922**, *105*, 327–349. (b) Borsche, W.; Jacobs, W. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 354–363. (c) Borsche, W.; Sander, W. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 2815–2826. (d) Borsche, W.; Weußmann, H.; Fritzsche, A. *Ber. Dtsch. Chem. Ges.* **1924**, *57*, 1149–1152.
11. Bergman, J.; Bergman, S.; Brimert, T. *Tetrahedron* **1999**, *55*, 10447–10466.
12. Lindwall, H. G.; Maclennan, J. S. *J. Am. Chem. Soc.* **1932**, *54*, 4739–4744.
13. Love, B. E. *Org. Prep. Proc. Int.* **1996**, *28*, 1–64.
14. King, H.; Stiller, E. T. *J. Chem. Soc.* **1937**, 466–473.
15. Robinson, J. R.; Good, N. E. *Can. J. Chem.* **1975**, *35*, 1578–1581.
16. Rozhkov, V. S.; Smushkevich, Y. I.; Suvorov, N. N. *J. Heterocycl. Chem.* **1980**, 45–48, Transl. from *Khim. Get. Soed.* **1980**, 55–58.
17. Mashelkar, U. C.; Usgaonkar, R. N. *Chem. Ind. (London)* **1978**, 35–36.

18. Mashelkar, U. C.; Usgaonkar, R. N. *Indian J. Chem. Sect. B* **1978**, *16B*, 782–785.
19. (a) Stanovinik, B.; Tišler, M.; Hribar, A.; Barlin, G. B.; Brown, D. J. *Aust. J. Chem.* **1981**, *34*, 1729–1738. (b) Middleton, R. W.; Monney, H.; Parrick, J. *Synthesis* **1984**, 740–743.
20. Gray, N. M.; Dappen, M. S.; Cheng, B. K.; Cordi, A. A.; Biesterfeldt, J. P. *J. Med. Chem.* **1991**, *34*, 1283–1292.
21. Anglada, L.; Marquez, M.; Sacristan, A.; Ortiz, J. A. *Eur. J. Med. Chem. Chim. Ther.* **1988**, *23*, 97–100.
22. Sinisterra, J. V.; Mouloungui, Z.; Dekmas, M.; Gaser, A. *Synthesis* **1985**, 1097–1100.
23. Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1972**, *37*, 3618–3622.
24. Treibs, A.; Kreuzer, F-H. *Liebigs Ann. Chem.* **1969**, *721*, 105–115.
25. Bergman, J.; Renström, L.; Sjöberg, B. *Tetrahedron* **1980**, *36*, 2505–2512.
26. (a) Barton, D. H.; Kervagoret, J.; Zard, S. Z. *Tetrahedron* **1990**, *46*, 7587–7598. (b) Fumoto, Y.; Uno, H.; Murashima, T.; Ono, N. *Heterocycles* **2001**, *54*, 705–720.
27. Köppen-Kastrop, P.; Tröger, J. *J. Prakt. Chem.* **1922**, *104*, 335–367.
28. Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613, and references therein.