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Pictet-Spengler Synthesis of Some Thiophene[*c*]-Fused *β*-Carbolines

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Summary. 5-(Substituted) thieno[2′,3′:5,6]pyrido[3,4-*b*]indoles were synthesized *via* cyclocondensation of 3-(3-aminothien-2-yl)indole with the appropriate aldehyde in the presence of boron trifluoride etherate under *Pictet-Spengler* reaction conditions. The constitution of the new compounds is evidenced from analytical and spectral (NMR and MS) data.

Keywords. 3-(3-Aminothien-2-yl)indole; *Pictet-Spengler* reaction; Thieno[2,3-*c*]-*β*-carbolines.

Introduction

The *β*-carboline ring system (*e.g.*, in the *Harmala* alkaloids: harman (**1**) and norharman (**2**), Fig. 1) is among the most commonly encountered alkaloid frameworks in the terrestrial environment [1, 2]. Recently, there is a wealth of research work oriented toward the synthesis and bioassay of variant derivatized *β*-carbolines [3]. On the other hand, thienopyridines have been evaluated as calcium regulators, 5-lipoxygenase inhibitors, and as carbonic anhydrase inhibitors [4]. The pharmacological interest in thienopyridine systems stemmed from their potential bioisosterism with quinoline and isoquinoline entities. In this respect, notable replacement of benzene nucleus by thiophene in chemical mimic was reviewed [5].

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We became interested in thiophene-fused carbolines for which limited data were cited in literature. Reports on synthetic thienopyridoindoles are confined to tetrahydropyrido[4,3-*b*]thieno[3,2-*e*]indoles in which the thiophene ring is condensed with the indole moiety. Such compounds showed antidepressant activity (*e.g.*, **3**) [6] or constitute useful central nervous system agents (*e.g.*, **4**) [7], while others are topical compounds for cosmetic and medical treatment of skin disorders such as psoriasis (*e.g.*, **5**, Fig. 1) [8].

However, thienopyridoindoles in which the thiophene ring is condensed with the pyridine moiety (*e.g.*, **6**, Fig. 2) are hitherto undescribed in literature. The latter ring system **6** is isosteric with that of synthetic "isoneocryptolepine" (**7**) which has quite recently been described as an interesting lead compound in the search for new antiplasmodial drugs [9]. Noteworthy is that **7** is isomeric with the closely related naturally occurring indoloquinoline alkaloids (cryptolepines **8**–**10**, Fig. 3) isolated from the roots of the West African shrub *Cryptolepis sanguiolenta* [10] and used in African folk medicine as antiviral, antitumor, antibacterial, and antimalarial agents [11, 12].

Accordingly, the present study deals with the synthesis and properties of model tetracyclics in which thienopyridine is condensed with indole, namely, thieno[2′,3′:5,6]pyrido[3,4-*b*]indoles (**15a**–**15c**, Scheme 1).

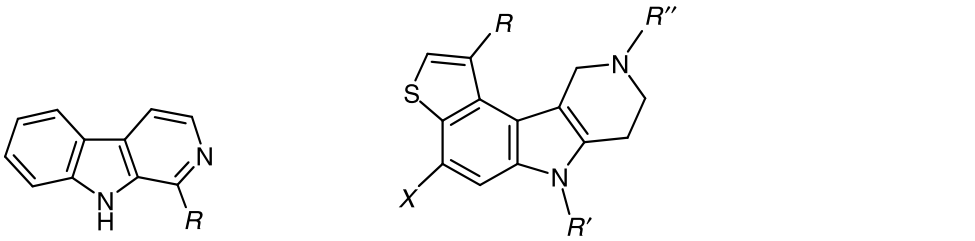


Fig. 1. Formulae of *Harmala* alkaloids and their derivatives

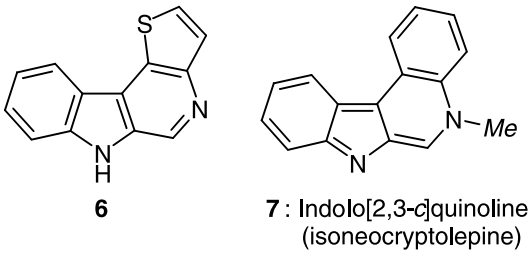


Fig. 2. Comparison of isosteric ring structures of thienopyridoindole and indolo[2,3-*c*]quinoline

Results and Discussion

The synthesis of 5-(substituted) thieno[2′,3′:5,6]pyrido[3,4-*b*]indoles (**15a**–**15c**) was achieved through cyclocondensation of freshly prepared 3-(3-aminothien-2-yl)indole (**11**) with the appropriate aldehyde (*Ar*-CHO) in the presence of boron trifluoride etherate under *Pictet-Spengler* reaction conditions as depicted in Scheme 1. In this reaction, the main isolable products were identified as the respective thieno[2′,3′:5,6]pyrido[3,4-*b*]indoles (**15a**–**15c**) on the basis of their analytical and spectral data (*vide infra*). The formation of **15a**–**15c** implies the intermediacy of the corresponding imino derivatives **12B**; the electrophilic nature of the imino carbon in the latter intermediates, enhanced by the *Lewis* acid catalyst, provides the driving force for attack of the indolic C2–C3 double bond and consequent cyclization. Aromatization of the resulting tetracyclic intermediates **14a**–**14c**, *via* air-oxidation, yielded the respective target molecules **15a**–**15c** as the final products. This result is in accordance with the established pathway for *Pictet-Spengler* type reactions [13–15].

The MS and NMR spectral data are in conformity with the assigned structures **15a**–**15c**, and are given in the Experimental section. Thus, their MS spectra display the correct molecular ions for which the m/z data are in agreement with the calculated values. Assignments of the ^{1}H NMR signals to the different protons are straightforward, and ^{13}C signal assignments are based on DEPT and 2D (COSY, HMBC, HMQC) experiments; these experiments showed different correlations that helped in the full assignments of the different hydrogens and carbons. It is worth noting that the doublet, belonging to H-2 of the indole ring, is absent in the ^{1}H NMR spectra of the cyclized products. Furthermore, a long-range correlation between C-5 of the β-carboline nucleus and H-2′/H-6′ is observed in the HMBC spectrum of **15a**. Collectively, these data indicate that ring closure has taken place at C-2 of the indole nucleus.

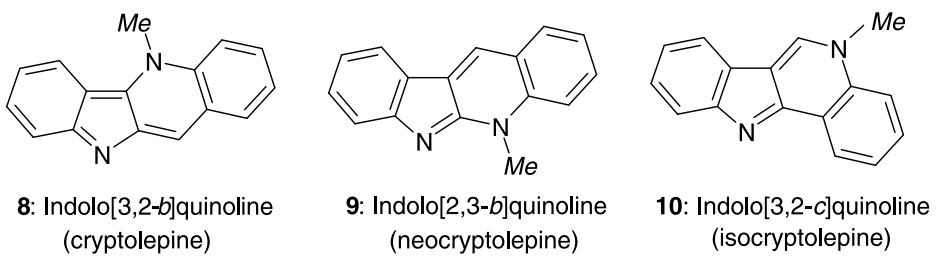
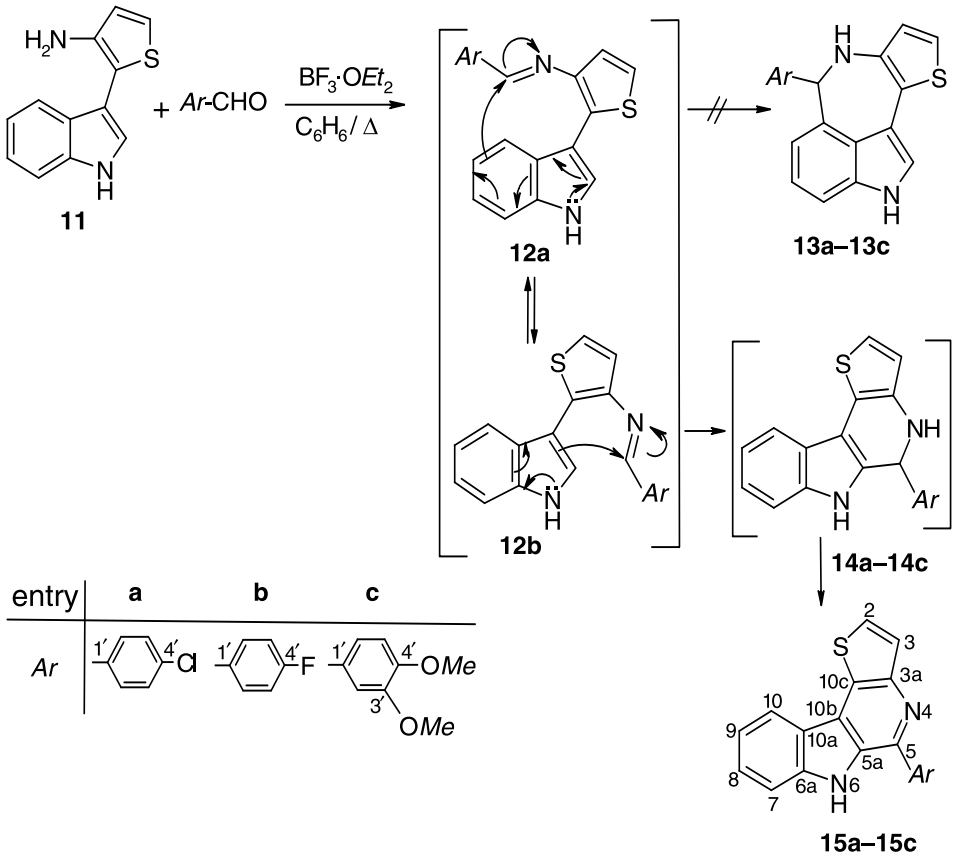


Fig. 3. Structures of naturally occurring indoloquinoline alkaloids



Scheme 1

It is worth noting that 3-(3-carboxamidothien-2-yl)indoles, under *Bischler-Napieralski* reaction conditions, underwent regioselective intramolecular cyclization at the benzenoid C-4 of the indole nucleus (rather than the pyrrolic C-2) to deliver the corresponding thieno[2′,3′:5,6]azepino[5,4,3-*cd*]indoles [16]. Under similar cyclization conditions, this mode of site-selectivity reversal (occurring at the C-4 locus) has also been reported for the related 3-(4-carboxamidopyrazol-5-yl)indoles [17].

Experimental

2-Chloro-3-nitrothiophene was purchased from Apollo Scientific Ltd (UK) and aryl aldehydes were purchased from Acros. Melting points were determined on an SMP2 Stuart Melting point apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with *TMS* as internal reference. Electron-impact mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV and at ion source temperature of 200°C. IR spectra were recorded as KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. Elemental analyses (C, H, N, and S) were preformed at the Microanalytical Laboratory-Inorganic Chemistry Department, Tübingen University, Germany, and the results were found to be in good agreement (±0.4%) with the calculated values.

3-(3-Aminothien-2-yl)indole (**11**)
This compound is prepared according to a reported procedure [13] that involves reduction of the corresponding 3-(3-nitrothien-2-yl)indole which, in turn, is accessible *via* coupling of indolylzinc chloride with 2-chloro-3-nitrothiophene [13]. Due to the instability of **11**, in the form of free amino group, it was freshly prepared and immediately used in the next condensation step.

5-(4-Chlorophenyl)-6H-thieno[2′,3′:5,6]pyrido[3,4-b]-indole (**15a**, $C_{19}H_{11}ClN_2S$)
A solution of 0.5 g **11** (2.2 mmol) and 0.17 g *p*-chlorobenzaldehyde (2.2 mmol) in 30 cm^3 dry benzene was stirred at 60°C for 2 h. Thereafter, 2.0 cm^3 borontrifluoride etherate were added, whereby the solution acquired an immediate orange color that changed to deep red. The resulting mixture were refluxed for 3 h, and then benzene was removed *in vacuo*. The solid residue was soaked with aqueous sodium hydroxide (5%) and water (2×20 cm^3), collected, dried, and recrystallized from methanol/diethyl ether. Yield of pure product: 0.34 g (55%), mp > 270°C (dec); MS-EI: m/z (% rel int) =

334 (M^+, 100), 298 (30), 167 (8), 149 (75), 127 (8), 99 (5); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.37$ (dd, 1H, $J = 7.3$, 7.7 Hz, H-9), 7.60 (dd, 1H, $J = 7.3$, 8.2 Hz, H-8), 7.68 (d, 2H, $J = 8.4$ Hz, H-3′/H-5′), 7.72 (d, 1H, $J = 8.2$ Hz, H-7), 7.75 (d, 1H, $J = 5.3$ Hz, H-3), 7.95 (d, 1H, $J = 5.3$ Hz, H-2), 8.08 (d, 2H, $J = 8.4$ Hz, H-2′/H-6′), 8.18 (d, 1H, $J = 7.7$ Hz, H-10), 11.8 (s, 1H, N(6)-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 113.3$ (C-7), 120.1 (C-10a), 120.8 (C-9), 122.1 (C-10), 123.1 (C-10b), 124.8 (C-3a), 125.6 (C-3), 127.1 (C-2), 128.5 (C-8), 129.3 (C-3′/C-5′), 130.3 (C-5), 131.0 (C-2′/C6′), 134.0 (C-4′), 137.5 (C-1′), 141.1 (C-6a), 141.2 (C-5a), 148.8 (C-10c) ppm.

5-(4-Fluorophenyl)-6H-thieno[2′,3′:5,6]pyrido[3,4-b]indole (**15b**, $C_{19}H_{11}FN_2S$)

A solution of 0.5 g **11** (2.2 mmol) and 0.31 g *p*-fluorobenzaldehyde (2.2 mmol) in 30 cm^3 dry benzene was stirred at 60°C for 2 h. Thereafter, 2.0 cm^3 borontrifluoride etherate were added, whereby the solution acquired an immediate orange color that changed to deep red. The resulting mixture was refluxed for 3 h, and benzene was removed *in vacuo*. The solid residue was soaked with aqueous sodium hydroxide (5%) and 20 cm^3 water, collected, dried, and recrystallized from methanol/diethyl ether. Yield of pure product: 0.34 g (45%), mp 268–270°C; MS-EI: m/z (% rel int) = 318 (M^+, 100), 281 (20), 159 (23), 149 (35), 137 (19); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 7.45$ (dd, 1H, $J = 6.9$, 7.5 Hz, H-9), 7.60 (dd, 2H, $J = 6.2$, 8.1 Hz, H-2′/H-6′), 7.75 (dd, 2H, $J = 8.1$, 8.2 Hz, H-3′/H-5′), 7.85 (d, 1H, $J = 5.5$ Hz, H-3), 8.05 (d, 1H, $J = 8.4$ Hz, H-7), 8.05 (dd, 1H, $J = 6.9$, 8.4 Hz, H-8), 8.20 (d, 2H, $J = 7.5$ Hz, H-10), 8.34 (d, 1H, $J = 5.5$ Hz, H-2), 12.5 (s, 1H, N(6)-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 113.8$ (C-7), 117.0 (d, $^2J_{C-F} = 22.5$ Hz, C-3′/C-5′), 119.0 (C-10a), 120.2 (C-9), 122.2 (C-10), 123.1 (C-8), 126.6 (C-3a), 126.8 (C-10b), 129.5 (C-5), 131.3 (C-3), 132.3 (C-2), 133.0 (d, $^3J_{C-F} = 7.5$ Hz, C-2′/C-6′), 137.8 (C-1′), 140.6 (C-6a), 143.8 (C-5a), 143.9 (C-10c), 164.2 (d, $^1J_{C-F} = 24.8$ Hz, C-4′) ppm.

5-(3,4-Dimethoxyphenyl)-6H-thieno[2′,3′:5,6]pyrido[3,4-b]-indole (**15c**, $C_{21}H_{16}N_2O_2S$)

A solution of 0.5 g **11** (2.2 mmol) and 0.31 g 3,4-dimethoxybenzaldehyde (2.2 mmol) in 30 cm^3 dry benzene was stirred at 60°C for 2 h. Thereafter, 2.0 cm^3 borontrifluoride etherate were added, whereby the solution acquired an immediate orange color that changed to deep red. The resulting mixture were refluxed for 3 h, and benzene was removed *in vacuo*. The solid residue was soaked with aqueous sodium hydroxide (5%) and 20 cm^3 water, collected, dried, and recrystallized from methanol/diethyl ether. Yield of pure product: 0.34 g (45%), mp 220–221°C; MS-EI: m/z (% rel int) = 360 (M^+, 100), 345 (14), 329 (14), 315 (15), 301 (10), 274 (8), 181 (12), 165 (7), 143 (7), 137 (6); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 3.86$ (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 7.19 (d, 1H, $J = 8.8$ Hz, H-5′), 7.37 (dd, 1H, $J = 6.8$, 7.8 Hz, H-9), 7.58 (s, 1H, H-2′), 7.60 (d, 1H, $J = 8.8$ Hz, H-6′), 7.63 (dd, 1H, $J = 6.8$, 8.1 Hz, H-8), 7.72 (d, 1H, $J = 5.4$ Hz, H-3), 7.75 (d, 1H, $J = 8.1$ Hz, H-7), 7.95 (d, 1H, $J = 5.4$ Hz, H-2), 8.15 (d, 1H, $J = 7.8$ Hz, H-10), 11.8 (s, 1H, N(6)-H) ppm; ^{13}C NMR (75 MHz, *DMSO*-d_6): $\delta = 56.0$, 56.2 (3′OCH_3/4′–OCH_3), 112.4 (C-2′), 112.6 (C-5′), 113.4 (C-7), 120.2 (C-10a), 120.6 (C-9), 121.7 (C-6′), 122.0 (C-10), 122.7 (C-10b), 124.0 (C-3a), 125.6 (C-3), 126.6 (C-2), 128.2 (C-8), 130.3 (C-5), 131.2 (C-1′), 141.0 (C-6a), 142.6 (C-5a), 148.6 (C-10c), 149.4, 150.0 (C-3′/C-4′) ppm.

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