Triethyloxonium Tetrafluoroborate/1,2-Dimethoxyethane – a Versatile Substitute for Trimethyloxonium Tetrafluoroborate in *O*-Methylation Reactions

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The triethyloxonium tetrafluoroborate/1,2-dimethoxyethane (TEO/DME) mixture is a versatile and cheap substitute for trimethyloxonium tetrafluoroborate in *O*-methylations of pyrrolin-2-ones, quinolones, acridones, and 1-oxo-β-carbolines. Undesired *O*-ethylation can be avoided by pre-incubation of triethyloxonium tetrafluoroborate and 1,2-dimethoxyethane for 1 h, prior to addition of the substrate. In the course of these investigations it was found that the structures assigned to the alkaloids taraxacine A and B are erroneous.

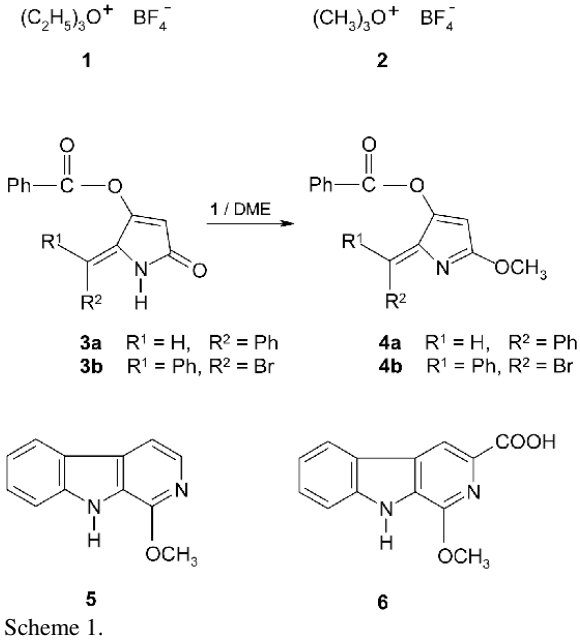
Key words: Triethyloxonium Tetrafluoroborate, *O*-Methylation, Pyridones, Alkaloids, Pyrrolin-2-ones

Introduction

Trialkyloxonium salts ("Meerwein salts"), originally described by Meerwein [1], are versatile reagents for *O*-alkylation of amides, lactams and related functional groups [2]. Both triethyloxonium tetrafluoroborate (**1** = TEO, Scheme 1) and trimethyloxonium tetrafluoroborate (**2**) are commercially available, but **2** is quite expensive. Salt **2** is most conveniently prepared from **1** by reaction with dimethyl ether [3].

Recently one of us found by chance that reactions of lactams **3a/b** with triethyloxonium tetrafluoroborate (**1**) in 1,2-dimethoxyethane did not give the expected ethoxy derivatives, but the corresponding methoxy derivatives **4a/b** (Scheme 1) [4]. No efforts were made at that time to explore the scope and limitations of this new reaction.

Inspired by a recent publication on the isolation of the new alkaloids taraxacine A and taraxacine B from *Taraxacum formosanum*, which were claimed to be the 1-methoxy-β-carbolines **5** and **6** [5], we investigated the reactions of pyrrolin-2-ones, pyridones and lactams with triethyloxonium tetrafluoroborate/1,2-dimethoxyethane (TEO/DME). In continuation of our previous research on β-carboline alkaloids [6] it was of special interest to us to find out whether this *O*-methylation protocol can also be applied to the synthesis of 1-methoxy-β-carbolines.

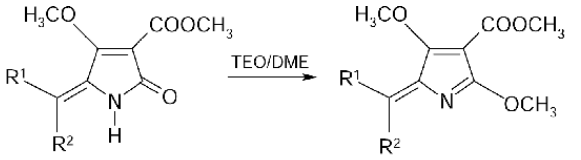


Scheme 1.

The results of our investigations on the utility of the TEO/DME reagent are presented in this paper.

Results

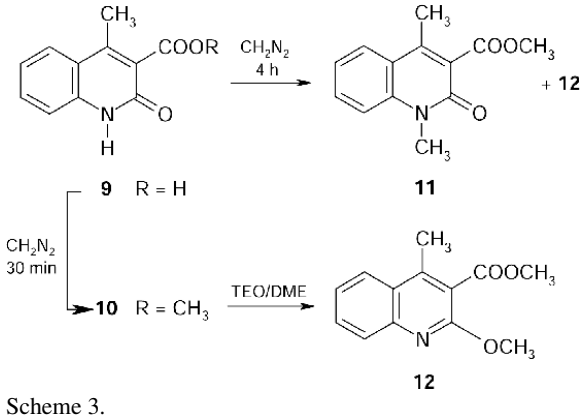
In a first set of experiments we reacted another two arylidenepyrrolin-2-ones **7a/b** [7] with the TEO/DME



7a R^1 = H, R^2 = Ph
7b R^1 = Ph, R^2 = Br

8a R^1 = H, R^2 = Ph
8b R^1 = Ph, R^2 = Br

Scheme 2.



Scheme 3.

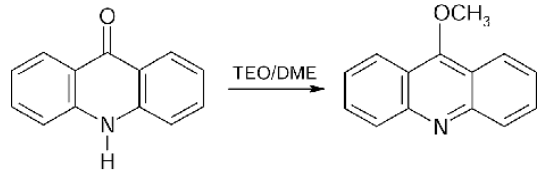
mixture. As expected, we obtained the methoxy derivatives **8a/b** exclusively (Scheme 2). The products were identified by comparison with authentic samples, which had been prepared by alternative routes [8].

In order to investigate the generality of this reaction we reacted various compounds containing pyridone, 1-oxo-β-carboline, and acridone partial structures, as well as simple lactams with TEO/DME.

The methyl quinolonecarboxylate **10** was conveniently prepared from the known carboxylic acid **9** [9] by treatment with diazomethane in methanol for 30 min. Prolonged reaction of **9** or **10** with diazomethane, however, gave a separable mixture of *N*-methyl derivative **11** and methoxyquinoline **12**. Reaction of quinolone **10** with the TEO/DME mixture resulted in the exclusive formation of the methoxyquinoline **12** [10] in high yield (Scheme 3).

Acridone (**13**) was converted to methoxyacridine (**14**) in an analogous manner, albeit in low yield (Scheme 4). Comparison of the spectroscopic data of the product with those published by Galy [11] for both the *O*-methyl and the *N*-methyl derivatives, obtained by methylation of **13** with methyl iodide under phase transfer conditions, confirmed our assignment.

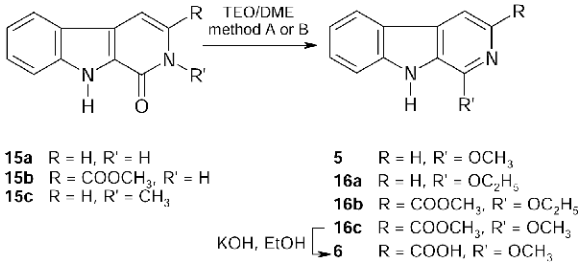
Finally, we investigated the reactions of 1-oxo-β-carbolines with the TEO/DME reagent in order



13 **14**

Scheme 4.

to work out the first total syntheses of the alkaloids taraxacine A (claimed to have structure **5**) and taraxacine B (claimed to have structure **6**). Reaction of 1-oxo-β-carboline **15a** [6a] with the TEO/DME reagent gave a 7 : 3 mixture of 1-ethoxy-β-carboline **16a** and 1-methoxy-β-carboline (**5**), the putative alkaloid taraxacine A. Selective formation of the methoxy-β-carboline **5** could be achieved by a preincubation of triethyloxonium tetrafluorobarate with the solvent 1,2-dimethoxyethane for 1 h. The structure of **5** was unambiguously confirmed by ^{1}H NMR, ^{13}C NMR and HMBC experiments, with the methoxy group giving typical resonances at 4.09 (^{1}H NMR) and 52.9 ppm (^{13}C NMR); a methyl group located at the indole nitrogen should resonate at about 4 and 30 – 35 ppm, and a methyl group at the pyridone nitrogen at about 3.5 and 30 – 35 ppm. But to our surprise, the spectroscopic data (^{1}H NMR, IR, UV, MS) were not at all in accordance with the data presented for taraxacine A in [5]. Moreover, the authors of literature [5] claim that the data of the alkaloid coincide well with those of a synthetic sample of 1-methoxy-β-carboline published earlier by Ohmoto [12] – an assertion that is simply false! And into the bargain, the few data (melting point, MS, IR) presented by Ohmoto [12] are not consistent with our data. Since Ohmoto prepared the putative 1-methoxy-β-carboline by reaction of 1-oxo-β-carboline **15a** with diazomethane, we reexamined this synthesis. The reaction gave two separable products, 1-methoxy-β-carboline (**5**) and **15c**, the product of methylation at the pyridone nitrogen. Ohmoto obviously described product **15c**, but assigned the structure **5** to it. Our analytical data of **15c** (melting point, IR) are in good agreement with values published earlier [13, 14] for the same compound prepared on other ways, and as expected the *N*-methyl group resonates at 3.62 (^{1}H NMR) and 31.1 ppm (^{13}C NMR). Compound **15c** can clearly be distinguished from the imaginable isomer bearing the methyl group at the indole nitrogen by its melting point (found: 256 °C; lit. [14]: 264 – 265 °C, isomer: 242 – 242.5 °C).



Scheme 5.

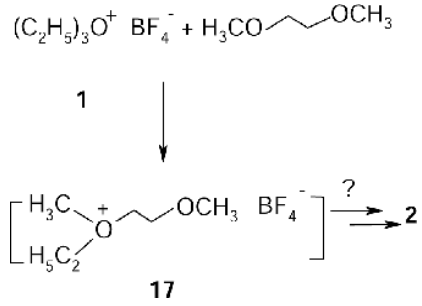
Unfortunately, the ^{1}H NMR data published for taraxacine A either do not coincide with those of **15c**, three very low-fielded proton resonances appearing inscrutable. Since the authors of literature [5] did not provide any information on the alkaloids on request, the correct structure of this alkaloid remains unsolved.

A reactivity similar to the one described above for the unsubstituted 1-oxo-β-carboline **15a** was observed for the corresponding 1-oxo-β-carboline carboxylate **15b** [6e]. Reaction with the TEO/DME reagent gave a mixture of 1-ethoxy-β-carboline **16b** and 1-methoxy-β-carboline **16c**, but pre-incubation of the reagents, as described above, once again resulted in the exclusive formation of the 1-methoxy-β-carboline **16c**. Hydrolysis of the ester group with KOH in ethanol gave the carboxylic acid **6** (Scheme 5). Here again the spectroscopic data of our synthetic product **6** did not coincide with those published for the alkaloid taraxacine B, to which the constitution of **6** was formerly assigned. Consequently, the correct structure of taraxacine B also remains to be elucidated.

Simple aliphatic lactams such as 2-pyrrolidone and 2-piperidone failed to give well-defined products with the TEO/DME reagent.

Discussion of the Mechanism of *O*-Alkylation

Triethyloxonium tetrafluoroborate (**1**) obviously performs an *O*-ethylation of the solvent 1,2-dimethoxyethane to give an intermediate mixed oxonium ion **17** [2a]. This oxonium ion might itself act as an alkylating agent, showing a higher tendency for releasing the methyl group than the ethyl group. GLC/MS analysis of the organic fraction of one of the reactions revealed that both 1-ethoxy-2-methoxyethane and 1,2-diethoxyethane are formed in the course of the reaction. This finding supports our hypothesis that *O*-ethylation of 1,2-dimethoxyethane is a crucial step in generating a reactive methylating agent. In some cases both methoxy and ethoxy derivatives were



Scheme 6.

formed. The ethoxy products might arise either from unreacted triethyloxonium tetrafluoroborate or from unselective reactivity of intermediate **17**. As a pre-incubation of triethyloxonium tetrafluorobarate with 1,2-dimethoxyethane prior to addition of the lactams resulted in exclusive formation of the methoxy products, we assume that triethyloxonium tetrafluoroborate quantitatively reacts with 1,2-dimethoxyethane on standing for 1 h to give oxonium salts (mixed oxonium salts or even trimethyloxonium tetrafluoroborate) which exclusively transfer methyl groups to the substrates (Scheme 6).

Conclusion

The triethyloxonium tetrafluoroborate/1,2-dimethoxyethane (TEO/DME) mixture is a versatile and cheap substitute for trimethyloxonium tetrafluoroborate in *O*-methylations of pyrrolin-2-ones, quinolones, acridones, and 1-oxo-β-carbolines. In most of the cases *O*-methylation occurs exclusively. In cases where both methoxy and ethoxy derivatives are obtained upon simply mixing the components, the reaction can be driven towards the methoxy derivatives by pre-incubation of triethyloxonium tetrafluoroborate and 1,2-dimethoxyethane for 1 h, followed by addition of the substrate.

Experimental Section

Thin layer chromatography (TLC) was performed on Macherey-Nagel pre-coated plastic silica gel plates with fluorescent indicator; the spots were visualized by UV illumination. Flash column chromatography was carried out using silica gel 0.040 – 0.063 mm (Merck). Melting points were determined by using a Büchi mp B-540 apparatus and are uncorrected. Infrared spectra were measured as potassium bromide plates on an FT-IR spectrometer PARAGON 1000 (Perkin Elmer). ^{1}H and ^{13}C NMR spectra (internal standard tetramethylsilane) were recorded in [D_6]DMSO as the sol-

vent on an FT NMR spectrometer Elipse 400 (JEOL) or an FT NMR spectrometer Elipse 500 (JEOL). Mass spectra were recorded with a Hewlett Packard 5989A mass spectrometer employing both EI (70 eV) and CI mode. HRMS was performeded with a JMS-GCMATE II (JEOL) mass spectrometer. Microanalyses were carried out with a CHN analyzer Elementar Vario EL.

General method A: direct O-methylation

A stirred solution/suspension of reactant (1 equiv.) and triethyloxonium tetrafluoroborate (1.5 equiv.) in 20 mL of 1,2-dimethoxyethane was heated at 65 °C for the time given below (30 min to 4 h). The solution was washed with an aqueous saturated solution of $KHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure to give the crude product. Purification was performed as described for the resp. products below.

General method B: O-methylation after pre-incubation

A solution of triethyloxonium tetrafluoroborate (1.5 equiv.) in 20 mL of 1,2-dimethoxyethane was stirred for 1 h at r. t. Then the reactant (1 equiv.) was added, the mixture was stirred for 2 h and then washed with a saturated aqueous solution of $KHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$. The volatiles were removed under reduced pressure to give the crude product. Purification was performed as described for the resp. products below.

*(Z)-2,4-Dimethoxy-5-(1-phenylmethylidene)-5H-pyrrole-3-carboxylic acid methyl ester (**8a**)*

Using general method A with a reaction time of 30 min, **7a** (0.52 g, 2.0 mmol) and triethyloxonium tetrafluoroborate (0.57 g, 3.0 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 3) yielded **8a** (0.20 g, 40 %) as yellow needles; m. p. 72 °C (EtOH) (lit. [8]: 67 °C). The spectroscopic data are in full accordance with those reported in literature [8].

*(Z)-5-(1-Bromo-1-phenylmethylidene)-2,4-dimethoxy-5H-pyrrole-3-carboxylic acid methyl ester (**8b**)*

Using general method A with a reaction time of 30 min, **7b** (0.68 g, 2.0 mmol) and triethyloxonium tetrafluoroborate (0.57 g, 3.0 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 3) gave **8b** (0.35 g, 50 %) as yellow plates; m. p. 111 °C (MeOH) (lit. [8]: 105 °C). The spectroscopic data are in full accordance with those reported in literature [8].

*4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid methyl ester (**10**)*

A suspension of **9** (0.10 g, 0.50 mmol) in 30 mL of CH_3OH was treated with an excess (about 5 equiv.) of an ethereal solution of diazomethane. After 30 min the volatiles were removed under reduced pressure, and the residue was recrystallized from diisopropyl ether – EtOH (1 : 1) to give **10** (50 mg, 47 %) as white plates; m. p. 258 °C. – IR (KBr): ν (cm^{-1}) = 3443, 2952, 1732, 1650, 1428, 1057. – ^{1}H NMR: δ (ppm) = 12.1 (s, 1 H, NH), 7.81 (dd, 1 H, J = 8.3, 1.2 Hz, 5-H), 7.58 (ddd, 1 H, J = 8.3, 7.1, 1.2 Hz, 7-H), 7.34 (dd, 1 H, J = 8.3, 1.2 Hz, 8-H), 7.27 (ddd, 1 H, J = 8.3, 7.1, 1.2 Hz, 6-H), 3.84 (s, 3 H, O-CH_3), 2.40 (s, 3 H, CH_3). – ^{13}C NMR: δ (ppm) = 166.6 (C=O), 158.5 (C-2), 144.7 (C-4), 138.0 (C-8a), 131.3 (C-7), 126.2 (C-3), 125.5 (C-5), 122.2 (C-6), 118.4 (C-4a), 115.5 (C-8), 52.2 (O-CH_3), 16.0 (4-CH_3). – MS (EI, 70 eV): *m/z* (%) = 217 (22) $[M]^+$, 186 (16), 167 (14), 149 (100), 127 (20), 94 (16), 85 (23), 71 (38), 55 (35). – MS (CI): *m/z* (%) = 218 (100) $[M+H]^+$, 202 (9), 186 (18), 160 (11). – $C_{12}H_{11}NO_3$: calcd. C 66.35, H 5.10, N 6.45; found C 66.09, H 5.05, N 6.34.

*1,4-Dimethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid methyl ester (**11**)*

A stirred suspension of **9** (0.20 g, 1.0 mmol) in 50 mL of CH_3OH-dioxane (1 : 1) was treated with an excess of an ethereal solution of diazomethane. After 4 h the volatile components were removed under reduced pressure to give a mixture of **11** and **12**. The residue was separated by flash column chromatography (EtOAc – cyclohexane, 1 : 1) to give **12** (55 mg, 25 %; R_f = 0.76) as the first fraction, and **11** (30 mg, 15 %; R_f = 0.29) as the second fraction.

Data of **11**: white solid, m. p. 89 °C. – IR (KBr): ν (cm^{-1}) = 3445, 2954, 1733, 1634, 1592, 1457, 1159. – ^{1}H NMR: δ (ppm) = 7.91 (dd, 1 H, J = 8.3, 1.1 Hz, 5-H), 7.72 (ddd, 1 H, J = 8.3, 7.1, 1.1 Hz, 7-H), 7.59 (dd, 1 H, J = 8.3, 1.1 Hz, 8-H), 7.37 (ddd, 1 H, J = 8.3, 7.1, 1.1 Hz, 6-H), 3.85 (s, 3 H, O-CH_3), 3.64 (s, 3 H, N-CH_3), 2.42 (s, 3 H, 4-CH_3). – ^{13}C NMR: δ (ppm) = 166.5 (C=O), 157.9 (C-2), 143.1 (C-4), 138.9 (C-8a), 131.7 (C-7), 126.1 (C-5), 125.7 (C-3), 122.4 (C-6), 119.3 (C-4a), 115.0 (C-8), 52.2 (O-CH_3), 29.1 (N-CH_3), 15.9 (4-CH_3). – MS (EI, 70 eV): *m/z* (%) = 231 (72) $[M]^+$, 199 (81), 173 (37), 143 (100), 115 (22), 103 (13), 86 (9), 77 (19), 51 (13). – MS (CI): *m/z* (%) = 232 (100) $[M+H]^+$, 200 (23). – $C_{13}H_{13}NO_3$: calcd. C 67.52, H 5.67, N 6.06; found C 67.55, H 5.88, N 5.87.

*2-Methoxy-4-methylquinoline-3-carboxylic acid methyl ester (**12**)*

Using general method A with a reaction time of 30 min, **10** (0.11 g, 0.50 mmol) and triethyloxonium tetrafluoroborate

(0.14 g, 0.75 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 1) yielded **12** as a white powder (45 mg, 85 %); m. p. 81 °C (lit. [10]: no data given). – IR (KBr): ν (cm^{-1}) = 3436, 2954, 1731, 1606, 1447, 1327, 1060. – ^{1}H NMR: δ (ppm) = 8.07 (dd, 1 H, J = 8.3, 1.0 Hz, 5-H), 7.82 (dd, 1 H, J = 8.3, 1.0 Hz, 8-H), 7.75 (ddd, 1 H, J = 8.3, 7.0, 1.0 Hz, 7-H), 7.53 (ddd, 1 H, J = 8.3, 7.0, 1.0 Hz, 6-H), 4.00 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 2.57 (s, 3 H, 4-CH_3). – ^{13}C NMR: δ (ppm) = 166.8 (C-2), 157.4 (C=O), 145.3 (C-8a), 144.3 (C-3), 130.7 (C-7), 127.3 (C-8), 124.8 (C-5), 124.8 (C-6), 123.8 (C-4a), 118.6 (C-4), 53.6 (CH_3), 52.6 (O-CH_3), 15.6 (4-CH_3). – MS (EI, 70 eV): *m/z* (%) = 231 (44) $[M]^+$, 217 (19), 200 (41), 186 (41), 171 (30), 159 (23), 143 (61), 129 (19), 115 (24), 102 (18), 91 (24), 77 (24), 69 (17), 58 (100). – MS (CI): *m/z* (%) = 232 (100) $[M+H]^+$, 214 (16), 200 (65). – $C_{13}H_{13}NO_3$: calcd. C 67.52, H 5.67, N 6.06; found C 67.76, H 5.99, N 5.76.

*9-Methoxy-dibenzo[b,e]pyridine (**14**)*

Using general method A with a reaction time of 4 h, acridone (**13**) (0.20 g, 1.0 mmol) and triethyloxonium tetrafluoroborate (0.28 g, 1.5 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 1) gave **14** as a yellow solid (35 mg, 16 %); m. p. 75 °C (lit. [11]: 65 °C). The spectroscopic data are in full accordance with those reported in literature [11].

*1-Ethoxy-9H-pyrido[3,4-b]indole (**16a**)*

Using general method A with a reaction time of 2 h, **15a** (0.10 g, 0.50 mmol) and triethyloxonium tetrafluoroborate (0.14 g, 0.75 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product, a mixture of **16a** and **5**. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 3) gave **16a** as the first fraction (45 mg, 39 %; R_f = 0.33), and **5** (25 mg, 23 %; R_f = 0.25) as the second fraction.

Data of **16a**: white solid, m. p. 127 °C. – IR (KBr): ν (cm^{-1}) = 3129, 2970, 2896, 1629, 1415, 1381, 1100. – ^{1}H NMR: δ (ppm) = 11.63 (s, 1 H, NH), 8.13 (dd, 1 H, J = 8.0, 1.0 Hz, 5-H), 7.84 (d, 1 H, J = 5.5 Hz, 3-H), 7.68 (d, 1 H, J = 5.5 Hz, 4-H), 7.57 (dd, 1 H, J = 8.0, 1.0 Hz, 8-H), 7.48 (ddd, 1 H, J = 8.0, 7.0, 1.0 Hz, 7-H), 7.21 (ddd, 1 H, J = 8.0, 7.0, 1.0 Hz, 6-H), 4.57 (q, 2 H, J = 7.1 Hz, CH_2), 1.46 (t, 3 H, J = 7.1 Hz, CH_3). – ^{13}C NMR: δ (ppm) = 151.0 (C-1), 140.4 (C-8a), 134.9 (C-3), 129.0 (C-4a), 127.7 (C-7), 124.0 (C-9a), 121.8 (C-5), 121.7 (C-4b), 119.7 (C-6), 112.7 (C-8), 109.7 (C-4), 61.5 (CH_2), 15.3 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 212 (66) $[M]^+$, 197 (67), 184 (100), 168 (18), 155 (35), 129 (24), 101 (24), 94 (59), 77 (24), 69 (18), 57 (30). – MS (CI): *m/z* (%) = 213 (100) $[M+H]^+$. – $C_{13}H_{12}N_2O$: calcd. C 73.57, H 5.70, N 13.20; found C 73.41, H 5.82, N 12.97.

*1-Methoxy-9H-pyrido[3,4-b]indole (**5**)*

Using general method B with a reaction time of 2 h, **15a** (0.10 g, 0.50 mmol) and triethyloxonium tetrafluoroborate (0.14 g, 0.75 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 3) yielded **5** as a white solid (20 mg, 19 %); m. p. 136 °C (lit. [5]: pale yellow syrup). – IR (KBr): ν (cm^{-1}): 3173, 2991, 1633, 1559, 1437, 1287, 1105. – ^{1}H NMR: δ (ppm) = 11.71 (s, 1 H, NH), 8.14 (dd, 1 H, J = 8.0, 1.0 Hz, 5-H), 7.86 (d, 1 H, J = 5.5 Hz, 3-H), 7.70 (d, 1 H, J = 5.5 Hz, 4-H), 7.56 (dd, 1 H, J = 8.0, 1.0 Hz, 8-H), 7.49 (ddd, 1 H, J = 8.0, 7.0, 1.0 Hz, 7-H), 7.21 (ddd, 1 H, J = 8.0, 7.0, 1.0 Hz, 6-H), 4.09 (s, 3 H, CH_3). – ^{13}C NMR: δ (ppm) = 150.8 (C-1), 139.9 (C-8a), 134.4 (C-3), 128.5 (C-4a), 127.2 (C-7), 123.5 (C-9a), 121.3 (C-5), 121.2 (C-4b), 119.2 (C-6), 112.2 (C-8), 109.4 (C-4), 52.9 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 198 (23) $[M]^+$, 180 (9), 111 (15), 94 (100), 85 (25), 57 (70). – MS (CI): *m/z* (%) = 199 (100) $[M+H]^+$, 182 (11). – HRMS (EI): *m/z* = 198.0780 (calcd. 198.0793 for $C_{12}H_{10}N_2O$, $[M]^+$).

*Methylation of **15a** with diazomethane*

To a solution of **15a** (70 mg, 0.38 mmol) in 10 mL of methanol, an excess of an ethereal solution of diazomethane was added, and the mixture was stirred at r. t. for 24 h. The excess of diazomethane was destroyed by dropwise addition of acetic acid, and the volatile components were removed under reduced pressure. The residue was purified by column chromatography (EtOAc – cyclohexane, 1 : 3, then EtOAc) to give 1-methoxy-*9H*-pyrido[3,4-b]indole (**5**) as the first fraction (30 mg, 40 %), and 2-methyl-1,2-dihydro-*9H*-pyrido[3,4-b]indol-1-one (**15c**) as the second fraction (25 mg, 33 %).

Data of **15c**: white solid, m. p. 265 °C (lit. [14]: 264 – 265 °C). – IR (KBr): ν (cm^{-1}) = 3143, 1654, 1592, 1566, 1332, 1269, 979, 744, 646, 432. – ^{1}H NMR: δ (ppm) = 11.94 (s, 1 H, NH), 8.03 (dd, 1 H, J = 8.3, 1.0 Hz, 5-H), 7.52 (dd, 1 H, J = 8.3, 1.0 Hz, 8-H), 7.41 (ddd, 1 H, J = 8.3, 6.7, 1.0 Hz, 7-H), 7.39 (d, 1 H, J = 6.9 Hz, 3-H), 7.18 (ddd, 1 H, J = 8.3, 6,7, 1.0 Hz, 6-H), 7.03 (d, 1 H, J = 6.9 Hz, 4-H), 3.62 (s, 3 H, N-CH_3). – ^{13}C NMR: δ (ppm) = 155.3 (C-1), 139.3 (C-8a), 129.6 (C-3), 127.5 (C-4a), 126.3 (C-7), 123.6 (C-9a), 121.9 (C-4b), 121.3 (C-5), 119.6 (C-6), 112.5 (C-8), 99.9 (C-4), 31.1 (N-CH_3). – MS (EI, 70 eV): *m/z* (%) = 198 (100) $[M]^+$, 169 (18), 155 (15), 129 (12), 99 (7), 57 (14). – MS (CI): *m/z* (%) = 199 (100) $[M+H]^+$, 170 (10). – HRMS (EI): *m/z* = 198.0793 (calcd. 198.0814 for $C_{12}H_{10}N_2O$, $[M]^+$).

*1-Ethoxy-9H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester (**16b**)*

Using general method A with a reaction time of 2 h, **15b** (0.12 g, 0.50 mmol) and triethyloxonium tetrafluoroborate

(0.14 g, 0.75 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product, a mixture of **16b** and **16c**. Purification by flash column chromatography (EtOAc – cyclohexane 1 : 3) gave **16b** (40 mg, 30 %; R_f = 0.24) as the first fraction, and **16c** (45 mg, 35 %; R_f = 0.14) as the second fraction.

Data of **16b**: dark yellow solid, m. p. 199 °C. – IR (KBr): ν (cm^{-1}) = 3334, 2924, 2853, 1718, 1437, 1253, 1008. – ^{1}H NMR: δ (ppm) = 12.09 (s, 1 H, NH), 8.56 (s, 1 H, 4-H), 8.27 (dd, 1 H, *J* = 7.9, 1.0 Hz, 5-H), 7.62 (dd, 1 H, *J* = 7.9, 1.0 Hz, 8-H), 7.53 (ddd, 1 H, *J* = 7.9, 6.8, 1.0 Hz, 7-H), 7.27 (ddd, 1 H, *J* = 7.9, 6.8, 1.0 Hz, 6-H), 4.63 (q, 2 H, *J* = 7.2 Hz, CH_2), 3.88 (s, 3 H, O-CH_3), 1.49 (t, 3 H, *J* = 7.2 Hz, CH_3). – ^{13}C NMR: δ (ppm) = 165.8 (C=O), 149.7 (C-1), 140.4 (C-8a), 133.3 (C-3), 128.1 (C-4a), 127.9 (C-7), 125.9 (C-9a), 121.8 (C-5), 121.7 (C-4b), 120.3 (C-6), 113.4 (C-4), 112.7 (C-8), 61.7 (CH_2), 52.0 (O-CH_3), 14.8 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 270 (22) $[M]^+$, 255 (8), 242 (12), 223 (12), 182 (21), 154 (21), 127 (16), 58 (100). – MS (CI): *m/z* (%) = 271 (43) $[M+H]^+$, 187 (5), 159 (6), 117 (100). – HRMS (EI): *m/z* = 270.1034 (calcd. 270.1005 for $C_{15}H_{14}N_2O_3$, $[M]^+$).

*1-Methoxy-9H-pyrido[3,4-b]indole-3-carboxylic acid methyl ester (**16c**)*

Using general method B with a reaction time of 2 h, **15b** (0.12 g, 0.50 mmol) and triethyloxonium tetrafluoroborate (0.14 g, 0.75 mmol) in 1,2-dimethoxyethane (20 mL) gave the crude product. Purification by flash column chromatography (EtOAc – cyclohexane, 1 : 3) gave **16c** as a yellow solid (40 mg, 32 %); m. p. 198 °C. – IR (KBr): ν (cm^{-1}) = 3298, 2923, 1714, 1560, 1337, 1257, 1110. – ^{1}H NMR: δ (ppm) = 12.20 (s, 1 H, NH), 8.60 (s, 1 H, 4-H), 8.30 (dd, 1 H, *J* = 7.9, 1.0 Hz, 5-H), 7.61 (dd, 1 H, *J* = 7.9, 1.0 Hz, 8-H), 7.55 (ddd, 1 H, *J* = 7.9, 6.8, 1.0 Hz, 7-H), 7.29 (ddd, 1 H, J_1 = 7.9, 6.8, 1.0 Hz, 6-H), 4.15 (s, 3 H, CH_3), 3.90 (s, 3 H, CH_3). – ^{13}C NMR: δ (ppm) = 165.8 (C=O), 150.0 (C-1), 140.4 (C-8a), 133.3 (C-3), 128.1 (C-4a), 127.9 (C-7), 125.9 (C-9a), 121.8 (C-5), 121.7 (C-4b), 120.3 (C-6), 113.6 (C-4), 112.7 (C-8), 53.3 (CH_3), 52.0 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 256 (100) $[M]^+$, 223 (34), 198 (35), 183 (16), 168 (14), 154 (24), 127 (34). – MS (CI): *m/z* (%) = 257 (100) $[M+H]^+$. – HRMS (EI): *m/z* = 256.0893 (calcd. 256.0848 for $C_{14}H_{12}N_2O_3$, $[M]^+$).

*1-Methoxy-9H-pyrido[3,4-b]indole-3-carboxylic acid (**6**)*

A solution of **16c** (0.50 g, 2.0 mmol) and KOH (0.28 g, 5.0 mmol) in 20 mL of EtOH was heated at 90 °C for 4 h, then the solvent was evaporated under reduced pressure, and hydrochloric acid (10 mL, 10 %) and water (20 mL) were added to the residue. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (EtOAc – cyclohexane, 1 : 1) to give **6** as a pale yellow solid (0.20 g, 42 %); m. p. 194 °C (lit. [5]: pale yellow syrup). – IR (KBr): ν (cm^{-1}) = 3441, 3283, 2924, 1683, 1396, 1264, 1103. – ^{1}H NMR: δ (ppm) = 12.14 (s, 1 H, NH), 8.57 (s, 1 H, 4-H), 8.28 (dd, 1 H, *J* = 7.9, 1.0 Hz, 5-H), 7.61 (dd, 1 H, *J* = 7.9, 1.0 Hz, 8-H), 7.54 (ddd, 1 H, *J* = 7.9, 6.8, 1.0 Hz, 7-H), 7.28 (ddd, 1 H, *J* = 7.9, 6.8, 1.0 Hz, 6-H), 4.17 (s, 3 H, CH_3). – ^{13}C NMR: δ (ppm) = 167.0 (C=O), 150.3 (C-1), 140.9 (C-8a), 134.2 (C-3), 128.7 (C-4a), 128.2 (C-7), 126.2 (C-9a), 122.1 (C-5), 122.0 (C-4b), 120.6 (C-6), 113.5 (C-4), 113.0 (C-8), 53.8 (CH_3). – MS (EI, 70 eV): *m/z* (%) = 242 (28) $[M]^+$, 198 (24), 183 (13), 155 (10), 127 (12), 101 (15), 86 (13), 71 (26), 58 (100). – MS (CI): *m/z* (%) = 243 (100) $[M+H]^+$, 225 (16), 117 (16). – HRMS (EI): *m/z* = 242.0688 (calcd. 242.0692 for $C_{13}H_{10}N_2O_3$, $[M]^+$).

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[1] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, E. Pfeil, *J. prakt. Chem.* **1937**, *147*, 257 – 285.
[2] a) H. Meerwein, in *Houben-Weyl, Methoden der organischen Chemie* (4th ed.), Vol. 6/3, Thieme, Stuttgart **1965**, pp. 325 – 365; b) S. Pichlmair, *Synlett* **2004**, 195 – 196.
[3] H. Meerwein, *Org. Synth.* **1966**, *46*, 120 – 121.
[4] H. Poschenrieder, H.-D. Stachel, G. Höfner, P. Mayer, *Eur. J. Med. Chem.* **2005**, *40*, 391 – 400.
[5] Y.-L. Leu, L.-S. Shi, A. G. Damu, *Chem. Pharm. Bull.* **2003**, *51*, 599 – 601.
[6] a) F. Bracher, D. Hildebrand, *Liebigs Ann. Chem.* **1992**, 1315 – 1319; b) F. Bracher, D. Hildebrand, *Tetrahedron* **1994**, *50*, 12329 – 12336; c) F. Bracher, J. Daab, *Synth. Commun.* **1995**, *25*, 1557 – 1562; d) F. Bracher, A. Puzik, *J. Heterocyclic Chem.* **2004**, *41*, 173 – 176; e) F. Bracher, D. Hildebrand, H. Häberlein, *Nat. Prod. Res.* **2004**, *18*, 391 – 396; f) B. Pohl, T. Luchterhandt, F. Bracher, *Synth. Commun.* **2007**, *37*, 1273 – 1280.
[7] a) H.-D. Stachel, K. K. Harigel, H. Poschenrieder, H. Burghard, *J. Heterocyclic Chem.* **1980**, *17*, 1195 – 1199; b) H.-D. Stachel, H. Poschenrieder, *Arch. Pharm. (Weinheim)* **1985**, *318*, 311 – 318.
[8] H.-D. Stachel, H. Poschenrieder, E. Immerz-Winkler, *J. Heterocyclic Chem.* **1983**, 20, 935 – 941.
[9] R. Camps, *Arch. Pharm.* **1902**, *240*, 135 – 146.
[10] A. Cappelli, M. Anzini, S. Vomero, L. Mennuni, F. Makovec, E. Doucet, M. Hamon, M. C. Menzioni,

P. G. De Benedetti, G. Giorgi, C. Ghelardini, S. Collina, *Bioorg. Med. Chem*. **2002**, *10*, 779 – 801.

[11] J. P. Galy, J. Elguero, E. J. Vincent, A. M. Galy, J. Barbe, *Synthesis* **1979**, 944 – 946.

[12] T. Ohmoto, T. Nikaido, K. Koike, K. Kohda, U. Sankawa, *Chem. Pharm. Bull*. **1988**, *36*, 4588 – 4592.

[13] a) W. O. Kermack, *J. Chem. Soc. Trans*. **1922**, *121*, 1872 – 1896; b) U. C. Mashelkar, R. U. Usgaonkar, *Chem. & Ind*. **1978**, 35 – 36.

[14] J. R. Johnson, A. A. Larsen, A. D. Holley, K. Gerzon, *J. Am. Chem. Soc*. **1947**, *69*, 2364 – 2370.