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Synthesis of Certain Pyrrolo[2,3-b]pyridine-5-carboxylic Acid Derivatives as Potential Antimicrobial Agents

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Summary. A synthetic approach to new 1-benzyl-7-alkyl-2,3-dimethyl-4-oxopyrrolo[2,3-b]pyridine-5-carboxylic acids using 5,6-dimethyl-2,4-dioxopyrrolo[2,3-d][1,3]oxazine as the starting material is reported. The antimicrobial activity of these compound is reported.

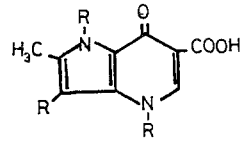
Keywords. Synthesis; Pyrrolo[2,3-b]pyridine; Cyclization.

Synthese von Pyrrolo[2,3-b]pyridin-5-carbonsäure-Derivaten als potentielle antimikrobielle Substanzen

Zusammenfassung. Die Synthese von neuen 1-Benzyl-7-alkyl-2,3-dimethyl-4-oxopyrrolo[2,3-b]-pyridin-5-carbonsäuren durch Verwendung von 5,6-Dimethyl-2,4-dioxopyrrolo[2,3-d][1,3]oxazinen als Ausgangsmaterial wird beschrieben. Die antimikrobielle Aktivität dieser Substanzen wurde geprüft.

Introduction

In previous communications [1, 2], we reported the synthesis and antimicrobial properties of pyrrolo[3,2-b]pyridine-6-carboxylic acids (**1**) and pyrrolo[3,4-b]pyridine-3-carboxylic acids (**2**).



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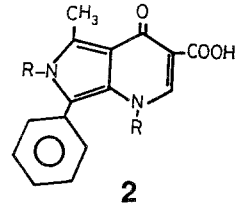

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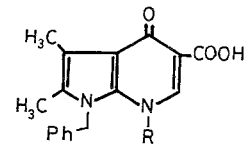
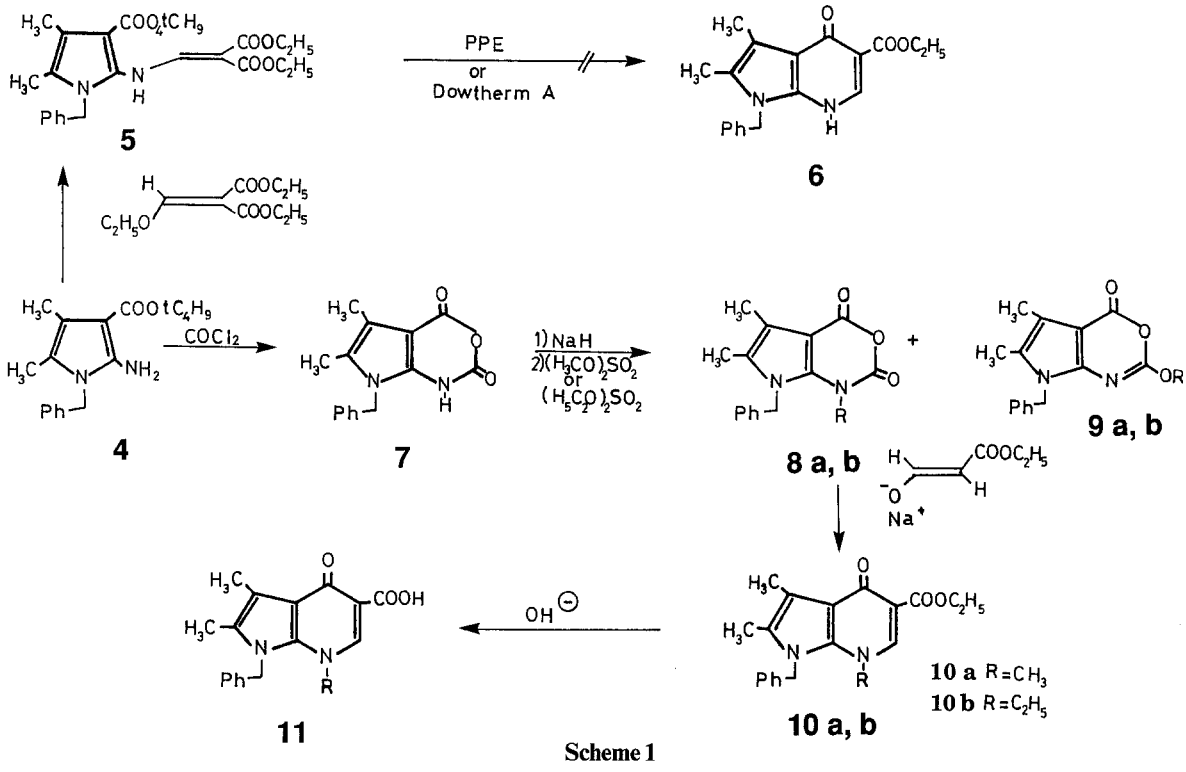


3

As a result of our continued interest in fused pyrrolopyridines as potential antimicrobial agents, we now wish to report the synthesis of a new series of 4-oxopyrrolo[2,3-b]pyridine-5-carboxylic acids (**3**). These compounds, due to their higher similarity with the quinolone antimicrobial agents would in principle be expected to show antimicrobial activity.

Results and Discussion

In the first synthetic approach to compounds **3** 1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole (**6**) [3] was condensed with diethyl ethoxymethylene malonate to give the triester **5** (Scheme 1). The use of Dowetherm^R A [4] or polyphosphoric ester [5] for cyclization of **5** proved unsuccessful to obtain pyrrolo[2,3-b]pyridine **6**.

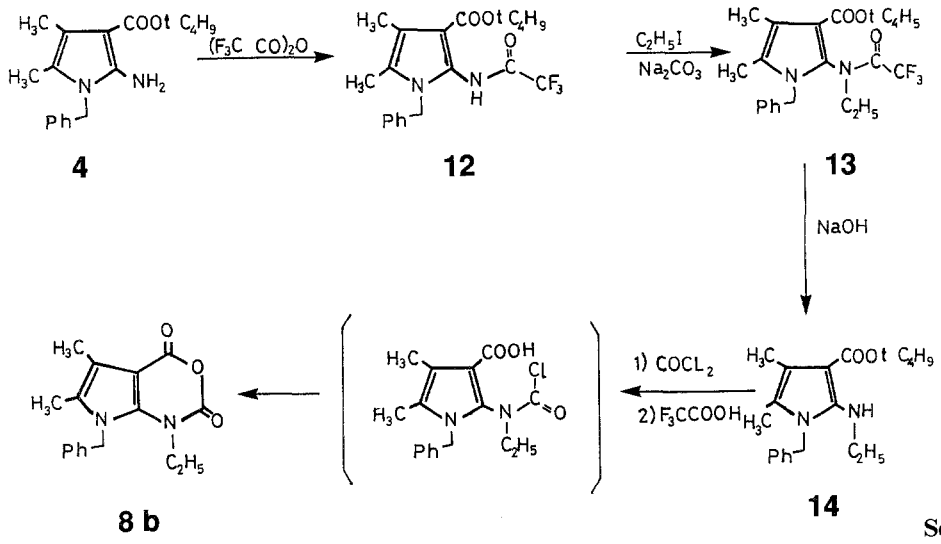


Scheme 1

An alternative method to prepare the target compounds would involve the preparation of pyrrolo[2,3-d][1,3]oxazines (**7**) as precursor, via the reaction of N-1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole (**4**) with phosgene in toluene solution (Scheme 1). Direct alkylation of **7** was achieved by treating a solution of **7** in dimethylformamide with sodium hydride. The resulting metallated derivatives were then treated with dimethyl sulphate to yield a mixture of N-methylated and O-methylated products **8 a** and **9 a**, respectively, in a 6 : 4 ratio as indicated by the ^{1}H-NMR spectrum of the crude products. This ratio was derived by integrating the O-methyl peak at 3.97 ppm and the N-methyl peak at 3.57 ppm. Three recrystallizations of the crude product from absolute ethanol yielded 7-benzyl-2,4-dioxo-1,5,6-trimethylpyrrolo[2,3-d][1,3]oxazine (**8 a**) in 42% yield. Similarly, 7-benzyl-5,6-dimethyl-2,4-dioxo-1-ethylpyrrolo[2,3-d][1,3]oxazine (**8 b**) was obtained by treating compound **7** with diethylsulphate. Condensation of compounds **8** under an inert atmosphere with sodioethylformyl acetate [6] in dimethylformamide afforded the cyclized products **10 a, b**. Hydrolysis of the latter compounds with sodium hydroxide gave the target compounds **3** in moderate yields (Scheme 1).

An alternative approach for the synthesis of N-methylated compound **8 b** was achieved by acylation of 2-amino-1-benzyl-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole

(**4**) with trifluoroacetic anhydride to give the corresponding trifluoracetomide **12** which was alkylated with ethyliodide in dimethylformamide in the presence of anhydrous sodium carbonate to yield 1-benzyl-3-*t*-butoxycarbonyl-4,5-dimethyl-2-(N-trifluoroacetyl-N-ethyl)-aminopyrrole (**13**). Hydrolysis of **13** was accomplished by refluxing in normal aqueous/alcoholic sodium hydroxide to give secondary amine **14**. Cyclization of **14** in trifluoroacetic acid gave 7-benzyl-5,6-dimethyl-2,4-dioxo-1-ethylpyrrolo[2,3-d][1,3]oxazine (**8 b**) through the cleavage of the *t*-butylester (Scheme 2).



Scheme 2

The carboxylic acids **11 a, b** were found to exhibit a relatively broad spectrum of antimicrobial activity when tested *in vitro*. The minimum inhibitory concentrations ranged from 16–32 micrograms per milliliter for most of the bacteria that were selected for testing.

Experimental Part

Melting points were determined on a Thomas-Hoover melting point apparatus (capillary method) and are uncorrected. ^{1}H-NMR spectra were obtained on a Varian EM-390 spectrometer using *TMS* as an internal standard. The microanalytical data were in full agreement with the molecular formula.

Diethyl N-[1-Benzyl-3-t-butoxycarbonyl-4,5-dimethylpyrrolo-2-yl]-aminomethylenemalonate (**5**)

A mixture of 1-benzyl-2-amino-3-*t*-butoxycarbonyl-4,5-dimethylpyrrole (**4**) (30.0 g, 0.1 mol) and diethyl ethoxymethylenemalonate (18.30 g, 0.12 mol) was heated at 140-155°C for 3 h with stirring under nitrogen atmosphere. To the cooled reaction mixture methanol (50 ml) was added and the mixture stored in a freezer overnight. The yellow crystals separated were collected and recrystallized from methanol/water (8 : 2) to give yellow crystals. Yield 66%. M.p. 124–126°C. $C_{24}H_{30}H_2H_6$. NMR ($CDCl_3$): 1.15 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.28 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.55 (9 H, s, 3·CH_3 of *t*-butoxy), 2.06 (3 H, s, 4-CH_3), 2.25 (3 H, s, 5-CH_3), 4.05 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.25 (2 H, q, J = 7.0 Hz, CH_2CH_3), 4.3 (2 H, s, benzylic methylene), 6.85–7.45 (5 H, m, *Ar*-H), 7.85 (1 H, d, J = 13.5 Hz, olefinic CH), 10.50 (1 H, d, J = 13.5 Hz, NH).

Ethyl 1-Benzyl-2,3-dimethyl-4-oxopyrrolo[2,3-b]pyridine-5-carboxylate (**6**)

A mixture of **5** (3.0 g, 0.007 mol) and polyphosphoric acid ester (15 g) was heated with stirring at 90–100°C for 4 h. The reaction mixture was cooled and poured over ice-water (150 ml) and neutralized

with aqueous sodium hydroxide (10%). Insoluble tary material was extracted with CH_2Cl_2 (100 ml) and washed with saturated sodium chloride solution (2 × 50 ml). The organic layer was dried over sodium sulphate, evaporated in vacuo to yield a tary unidentified residue.

7-Benzyl-5,6-dimethyl-2,4-dioxopyrrolo[2,3-d][1,3]oxazine (**7**)

A solution of **4** (23.0 g, 0.08 mol) in tetrahydrofuran (50 ml) was added over 20 min to a rapidly stirred cold solution of 12.5% phosgene in toluene (75 ml). After the addition was completed the ice-bath was removed and the resulting mixture was refluxed for 30 min. After cooling in an ice-bath the precipitated solid was collected by filtration, washed with diethyl ether, and air dried. Yield: 91%. M.p. 198–200°C. $C_{15}H_{14}N_2O_3$. NMR (*DMSO-d_6*): 1.93 (3 H, s, 4 CH_3), 2.15 (3 H, s, 5-CH_3), 5.25 (2 H, s, benzylic methylene), 6.90–7.45 (5 H, m, *Ar*-H), 12.25 (1 H, s, broad NH).

7-Benzyl-1,5,6-trimethylpyrrolo[2,3-d][1,3]oxazine (**8 a**)

To a stirred solution of **7** (5.50 g, 0.02 mol) in dimethylformamide (25 ml) in an ice-bath, a suspension of sodium hydride (0.5 g, 0.02 mol) in *DMF* was added. After hydrogen evolution had ceased, dimethyl sulphate (2.6 g, 0.025 mol) was added dropwise and the resulting mixture was stirred at ambient temperature for 48 h. The dimethylformamide solution was concentrated in vacuo and the residue was poured into ice/water, the off white precipitate was collected by filtration, washed with water and air dried. The crude product was suspended in methanol (15 ml), filtered and air dried to yield a mixture of N-methylated (**8 a**) and O-methylated (**9**) products. Three crystallizations from ethanol gave **8 a**. Yield 42%. M.p. 181–182°C (ethanol). $C_{16}H_{16}N_2O_3$. NMR ($CDCl_3$): 2.15 (3 H, s, 4-CH_3), 2.30 (3 H, s, 5-CH_3), 3.35 (3 H, s, 1-CH_3), 5.4 (2 H, s, benzylic methylene), 6.90–7.40 (5 H, m, *Ar*-H).

7-Benzyl-5,6-dimethyl-2,4-dioxo-1-ethylpyrrolo[2,3-d][1,3]oxazine (**8 b**) *Method A*

To a cooled solution of **7** (5.50 g, 0.02 mol) in dimethylformamide (25 ml) a suspension of sodium hydride (0.5 g, 0.025 mol) in *DMF* (5 ml) was added. After hydrogen evolution had ceased, diethyl sulphate (2.2 g, 0.052 mol) was added dropwise and the resulting mixture was stirred at ambient temperature for 48 h. The dimethylformamide solution was concentrated and poured into ice-water. The semi-solid precipitate was extracted with methylene chloride, washed with water, and air dried. Yield 42%. M.p. (ethanol) 179–180°C. $C_{17}H_{18}N_2O_3$. NMR ($CDCl_3$): 1.25 (3 H, t, J = 7.2 Hz, 5-CH_2CH_3), 2.30 (3 H, s, 6-CH_3), 3.90 (2 H, 9, J = 7.2 Hz, CH_2-CH_2), 5.30 (2 H, s, benzylic methylene), 6.90–7.55 (5 H, m, *Ar*-H).

1-Benzyl-3-t-butoxycarbonyl-4,5-dimethyl-2-trifluoroacetylaminopyrrole (**12**) *Method B*

To a mixture of **4** (30.0 g, 0.1 mol) and pyridine (8.3 g, 0.15 mol) in acetone (100 ml) cooled in an ice-bath, trifluoroacetic anhydride (21.5 g, 0.103 mol) was added dropwise while stirring. After the addition was completed, the solution was stirred for 2 h while cooling and then poured over ice-water (300 ml). The insoluble amide precursor was collected air dried. Yield 64%. M.p. (methanol-H_2O, 8/1), 163–164°C. $C_{20}H_{23}F_3N_2O_3$. NMR ($CDCl_3$): 1.54 (9 H, s, *t*-C_4H_9), 2.05 (3 H, s, 4-CH_3), 2.16 (3 H, s, 5-CH_3), 5.00 (2 H, s, benzylic methylene), 6.75–7.50 (5 H, m, *Ar*-H), 8.8–9.0 (1 H, br.s, NH).

1-Benzyl-3-t-butoxycarbonyl-4,5-dimethyl-2-(N-trifluoroacetyl-N-ethyl)aminopyrrole (**13**)

A mixture of **12** (10.0 g, 0.025 mol), anhydrous sodium carbonate (3.0 g, 0.03 mol), and ethyl iodide (4.1 g, 0.03 mol) in dry dimethylformamide (25 ml) was stirred at room temperature for 48 h. The mixture was poured over ice (200 g) to yield a gummy solid which was collected and air dried. Yield 86%. M.p. (methanol/H_2O: 411) 93–95°C. $C_{22}H_{27}F_3N_2O_3$. NMR ($CDCl_3$): 0.95 (3 H, t, CH_2CH_3), 1.50 (9 H, s, *t*-C_4H_9), 1.95 (3 H, s, 4-CH_3), 2.25 (3 H, s, 5-CH_3), 3.50 (2 H, m, CH_2CH_3), 5.0 (2 H, m, benzylic methylene), 6.85–7.50 (5 H, m, *Ar*-H).

1-Benzyl-3-t-butoxycarbonyl-4,5-dimethyl-2-ethylaminopyrrole (**14**)

A mixture of **13** (3.89, 0.009 mol) and 12% aqueous sodium hydroxide (15 ml) in ethanol (30 ml) was refluxed with stirring for 3 h, ethanol was removed in vacuo, and the residual aqueous layer was extracted with diethyl ether (3 × 15 ml). The combined organic layers were washed with water (10 ml), saturated sodium chloride solution (2 × 15 ml), and dried with anhydrous sodium sulphate. The solvent was then removed by evaporation in vacuo to leave an brownish oil, yield 98%. $C_{20}H_{28}N_2O_2$. NMR ($CDCl_3$): 1.03 (3 H, t, N-CH_2CH_3), 1.55 (9 H, s, *t*-C_4H_9), 1.85 (3 H, s, 4-CH_3), 2.15 (3 H, s, 5-CH_3), 2.80 (2 H, q, N-CH_2CH_3), 4.95 (2 H, s, benzylic methylene), 6.90–5.50 (5 H, m, *Ar*-H).

7-Benzyl-5,6-dimethyl-2,4-dioxo-1-ethyl-1,2,4,7-tetrahydropyrrolo[2,3-d][1,3]oxazine (**8 b**)

A solution of **14** (2.9 g, 0.0087 mol) in dry tetrahydrofuran (10 ml) was added dropwise over 10 min to phosgene (12.5%) in toluene (10 ml) while stirring in an ice-bath. After the addition was complete, the amber coloured solution was stirred at room temperature for 30 min. Trifluoroacetic acid (2 ml) was added and the solution was refluxed for 1 h. Xylene (10 ml) was added and 20 ml of solvent were removed by distillation. After cooling in an ice-bath, hexane (15 ml) was added, the precipitate was collected, washed with hexane, and air dried. The solid was suspended in absolute ethanol (15 ml) and the insoluble white product was collected and air dried to give **8 b**. Yield 86%.

Ethyl 1-Benzyl-2,3-dimethyl-7-ethyl-4-oxopyrrolo[2,3-d]pyridine-5-carboxylate (**10 b**)

A solution of **8 b** (240 mg, 0.0085 mol) in dimethylformamide (20 ml) was added to a stirred solution of sodioethylformylacetate (353 mg, 0.0025 mol) in dimethylformamide (30 ml) under an inert atmosphere. The resulting mixture was cooled to room temperature and dimethylformamide was removed in vacuo followed by benzene azotrope to remove trace dimethylformamide. The dark brown residue was taken up in water, and the aqueous solution was extracted with three portions of ether, then acidified to *pH* 2 with concentrated HCl, and extracted with four portions of chloroform. The chloroform extract was dried over $MgSO_4$, and concentrated in vacuo to give yellow crystals. Yield 40%. M.p. 193–194°C (methanol). $C_{21}H_{24}N_2O_3$. NMR ($CDCl_3$): 1.38 (6 H, t, 2 × CH_3 and CH_2-CH_3), 2.15 (3 H, s, 3-CH_3), 2.50 (3 H, s, 2-CH_3), 3.85 (2 H, distorted quartet, N-C_2H_5), 4.28 (2 H, s, $COOCH_2CH_3$), 5.28 (2, s, benzylic methylene), 6.50–7.50 (5 H, m, *Ar*-H), 7.82 (1 H, s, CH).

1-Benzyl-2,3-dimethyl-7-ethyl-4-oxopyrrolo[2,3-b]pyridine-5-carboxylic acid (**11 b**)

A mixture of **10 b** (0.2 g) and sodium hydroxide (0.2 g, 0.005 mol) in water (100 ml) was refluxed until a homogenous solution was achieved. After cooling the solution was filtered and acidified by dropwise addition of 6*N* hydrochloric acid. The white precipitate was collected, washed with water and dried. Yield 96%. M.p. 213–215°C (methanol). $C_{19}H_{20}N_2O_3$. NMR ($CDCl_3$): 1.45 (3 H, t, CH_2CH_3), 2.20 (3 H, s, 3-CH_3), 2.45 (3 H, s, 2-CH_3) 4.10 (2 H, q, CH_2CH_3), 5.35 3 H, s, benzylic methylene), 6.60–7.35 (5 H, m, *Ar*-H), 8.10 (1 H, s, C_6H).

1-Benzyl-2,3,7-trimethyl-4-oxopyrrolo[2,3-b]pyridine-5-carboxylic acid (**11 a**)

A solution of compound **8 a** (230 mg, 0.008 mol) in dimethylformamide (20 ml) was treated similarly according to the procedure described for **10 b**. The oily product of ethyl-1-benzyl-2,3,7-trimethyl-4-oxopyrrolo[2,3-b]pyridine-5-carboxylate (**10 a**) was refluxed with a solution of sodium hydroxide (0.2 g, 0.005 mol) in water (100 ml) until a homogenous solution was achieved, work up as described for compound **11 b** afforded a white powder. Yield 92%. M.p. 261–263°C (methanol). $C_{18}H_{18}N_2O_3$. NMR ($CDCl_3$): 1.45 (3 H, t, CH_2CH_3), 2.20 (3 H, s, 3-CH_3), 2.45 (3 H, s, 2-CH_3), 4.1 (2 H, q, CH_2CH_3), 5.35 (2 H, s, benzylic methylene), 6.60–7.33 (5 H, m, *Ar*-H), 8.10 (1 H, s, C_6-H). The carboxylic acid proton merged into the base line.

References

[1] Bayomi S. M., Price K. E., Sowell J. W. (1985) J. Heterocycl. Chem. **22**: 83
[2] Bayomi S. M., Price K. E., Sowell J. W. (1985) J. Heterocycl. Chem. **22**: 729
[3] Laks J. S., Ross J. R., Bayomi S. M., Sowell J. W. (1985) Synthesis: 291
[4] Balszkiewler P., Vorbruggen H., Kessler H. L. (1976) Schering AG Dos. 2,447,447; Chem. Abstr. **85**: 46627
[5] Okumura K., Adachi T., Tomie M., Kondo K., Inoue I. (1972) J. Chem. Soc., Perkin Trans. I: 173
[6] Mitscher L. A., Flynn D. L., Eugene Gracey H., Drake S. D. (1979) J. Med. Chem. **22**: 1354
[7] Deuchl W. (1952) Helv. Chim. Acta **35**: 1587

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