Monatshefte für Chemie 127, 91–95 (1996)

Monatshefte für Chemie
Chemical Monthly

3-Alkylpyridines III [1]. Total Synthesis of Both Enantiomers of the Antineoplastic Marine Alkaloid Niphatesine D[#]

F. Bracher* and **T. Papke**

Institut für Pharmazeutische Chemie der Technischen Universität Braunschweig, D-38106 Braunschweig, Germany

Summary. A five-step synthesis of both enantiomers of the marine alkaloid niphatesine D (**3**), starting from the readily available enantiomeric hydroxyalkylthiophenes **5** and *ent*-**5**, is described.

Keywords. Alkaloid; Niphatesine D; 3-Alkylpyridines; Reductive desulfurization.

3-Alkylpyridine, 3. Mitt. [1]. Totalsynthese von beiden Enantiomeren des antineoplastisch wirksamen marinen Alkaloids Niphatesin D

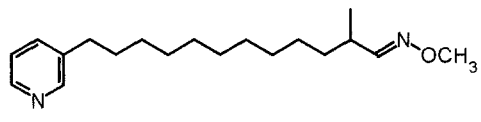
Zusammenfassung. Beide Enantiomere des marinen Pyridinalkaloids Niphatesin D (**3**) wurden, ausgehend von den gut zugänglichen Hydroxyalkylthiophenen **5** und *ent*-**5**, in jeweils fünf Schritten synthesisiert.

Introduction

In two previous publications, we described a convenient strategy for the preparation of biologically active marine 3-alkylpyridine alkaloids as (±)-ikimine A (**1**) [2] and niphatesine C (**2**) [1]. In this paper we wish to report on an extension of this methodology to the synthesis of both enantiomers of the related alkaloid niphatesine D (**3**). This natural product differs from **2** only in the position of the methyl branching. Niphatesine D was isolated from the sponge *Niphates* sp. and described to exhibit potent antineoplastic activity [3]. The absolute configuration of naturally occuring niphatesine D was established by a multistep total synthesis to be (*S*) by *Rama Rao et al.* [4].

For our synthesis of both enantiomers of **3**, we utilized the thiophene derivative **5** which is readily available in large quantities in both enantiomeric forms [5]. **5** has been shown to be a very useful chiral building block for the introduction of a C_7-chain containing a methyl branching at C-2 by other authors [5b, 6] and by us [1, 2]. Functionalization of **5** at both ends is conveniently achieved by regioselective *Friedel-Crafts* acylation at C-5 of the thiophene ring and by modification of the

[#] Dedicated to Prof. Dr. *E. Reimann* on the occasion of his 60th birthday



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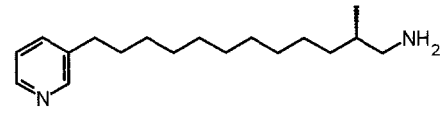

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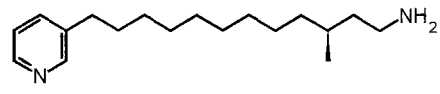

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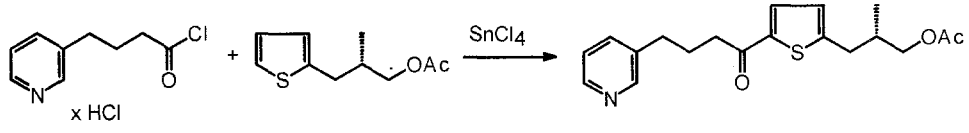
Scheme 1

terminal ester group, respectively. Finally, reductive desulfurization of the thiophene ring yields four methylene groups of the aliphatic chain.

Results and Discussion

4-(3-Pyridyl)butanoyl chloride hydrochloride (**4**) was easily prepared from known 4-(3-pyridyl)butyronitrile [7] by subsequent treatment with conc. hydrochloric acid



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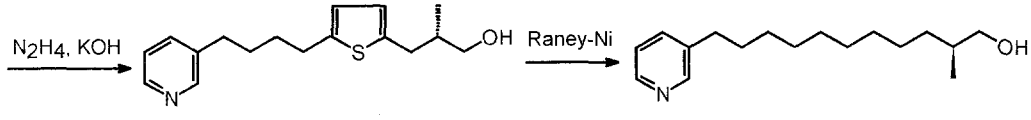

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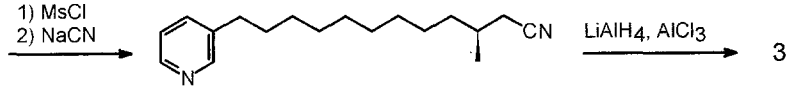

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Scheme 2

and oxalyl chloride. *Friedel-Crafts* acylation of the (*S*)-configurated thiophene **5** with the acid chloride **4** using $SnCl_4$ as the catalyst readily gave **6**.

Huang-Minlon reduction of the ketone **6** was accompanied by hydrolysis of the terminal ester group and gave compound **7** in 80% yield. Reductive desulfurization of the thiophene ring to yield the saturated side chain of the alkaloid was accomplished by hydrogenation with *Raney* nickel under medium pressure. The resulting primary alcohol **8** was converted to the nitrile **9** by mesilation and subsequent substitution with cyanide. Pd/C-catalyzed hydrogenation of **9** did not give satisfactory yields of the desired primary amine **3**. These problems may be due to traces of sulfur compounds, originating from incomplete reductive desulfurization of the thiophene ring, which are potent catalyst poisons. Finally, the reduction of the cyano group could be performed with $LiAlH_4/AlCl_3$ to give the alkaloid niphatesine D (**3**) in 68% yield. The spectroscopic data of this compound are in full agreement with the values published in the literature [3].

In an analogous manner, the unnatural *R*-enantiomer *ent*-**3** was prepared starting from *ent*-**5** [5].

In conclusion, we could demonstrate another attractive application of the chiral building blocks **5** and *ent*-**5** in natural product synthesis. The biological activities of the products **3** and *ent*-**3** are under investigation.

Experimental

NMR spectra: Bruker AM 400; internal standard: *TMS*. Mass spectra: Finnigan MAT 8430. IR spectra: Pye-Unicam PU-9800. Analytical data (C, H, N): C–H–N–O Elemental Analyzer 1106, Carlo Erba. Flash column chromatography: Kieselgel 60 (230–400 mesh), Merck. HPLC: Merck Hitachi L 6200A.

(S)-2-Methyl-3-(5-(4-(3-pyridyl)butanoyl)-2-thienyl)propyl acetate (**6**)

a) *4-(3-Pyridyl)butanoic acid hydrochloride*

A solution of 4-(3-pyridyl)butyronitrile [7] (3.6 g, 24.6 mmol) in conc. hydrochloric acid (50 ml) was refluxed for 8 h. Then the solution was evaporated *in vacuo* and the residue dissolved in ethanol. Addition of acetone caused precipitation of a white solid. The precipitate was collected, washed with cold acetone, and dried *in vacuo* to give 3.7 g (89%) of the hydrochloride of the known 4-(3-pyridyl)butanoic acid [7], m.p. 115–120 °C.

b) *4-(3-Pyridyl)butanoyl chloride hydrochloride* (**4**)

The carboxylic acid hydrochloride described above (1.0 g, 5.9 mmol) was dissolved in anhydrous dichloromethane (20 ml) under a nitrogen atmosphere. After addition of one drop of *DMF*, oxalyl chloride (1.8 g, 14.0 mmol) was added dropwise and the mixture was stirred at room temperature for 4 h. Then the mixture was evaporated *in vacuo* and the crude acid chloride (1.3 g) was used immediately for the next step.

c) *Friedel-Crafts acylation*

$SnCl_4$ (2.74 g, 10.5 mmol) was added slowly with stirring to an ice-cooled solution of crude **4** (1.3 g) and (*S*)-2-methyl-3-(2-thienyl)propyl acetate (**5**; ee = 94% [5a]; 694 mg, 3.5 mmol) in anhydrous dichloromethane (30 ml). After 1 h, 6 *M* HCl was added with stirring until the precipitate was dissolved

and then the mixture was made alkaline with satd. KOH and extracted with ethyl acetate (3 × 70 ml). The combined organic layers were dried and evaporated. Purification of the residue by flash column chromatography gave 790 mg (65%) **6** as a colourless oil. IR (KBr, film): $\nu = 3443, 2961, 2936, 1738, 1659, 1456, 1242, 1040, 716\ cm^{-1}$; MS (70 eV): $m/e = 345$ (M^+; 18), 272 (22), 180 (20), 148 (20), 106 (100), 92 (20); ^1H NMR ($CDCl_3$): $\delta = 8.46$ (d, $J = 2$ Hz, 1H, 2-H), 8.44 (dd, $J = 5$ Hz, $J = 1$ Hz, 1H, 6-H), 7.53 (ddd, $J = 8$ Hz, $J = 2$ Hz, $J = 1$Hz, 1H, 4-H), 7.50 (d, $J = 4$ Hz, 1H, Ar–H), 7.22 (m, 1H, 5-H), 6.81 (d, $J = 4$ Hz, 1H, Ar–H), 3.95 (d, $J = 6$ Hz, 2H, OCH_2), 2.95 (dd, $J = 15$ Hz, $J = 6$ Hz, 1H, thiophene-C**H**H), 2.88 (t, $J = 7$ Hz, 2H, pyridine-CH_2), 2.72 (m, 3H, CH_2-CO and thiophene-CH**H**), 2.15 (m, 1H, CH), 2.09 (m, 2H, CH_2), 2.07 (s, 3H, CO–CH_3), 0.98 (d, $J = 7$ Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 192.2, 171.1, 152.3, 150.0, 147.6, 142.4, 136.9, 135.9, 132.1, 126.9, 123.4, 68.0, 37.7, 34.8, 34.4, 32.3, 25.7, 20.9, 16.6$ ppm; $C_{19}H_{23}NO_3S$ (345); calcd.: C 66.06, H 6.71, N 4.05; found: C 65.46, H 6.57, N 3.86; $[\alpha]_D^{20} = +6.9$ ($c = 1.0$, $CHCl_3$).

(*R*)-Enantiomer *ent*-**6** (prepared from *ent*-**5** (yee ⩾96%) [5a]): $[\alpha]_D^{20} = -8.4$ ($c = 1.1$, $CHCl_3$).

(S)-2-Methyl-3-(5-(4-(3-pyridyl)-1-butyl)-2-thienyl)-1-propanol (**7**)

A solution of **6** (710 mg, 2.05 mmol), powdered KOH (750 mg, 13.4 mmol), and 80% hydrazine hydrate (0.75 ml) in diethylene glycol (10 ml) was stirred at 120 °C for 8 h. Then the temperature was raised to 210 °C and kept at this temperature for 4 h. After cooling to ambient temperature, water (50 ml) was added and the mixture was extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with water, dried, and evaporated. The residue was purified by flash column chromatography to give 475 mg (80%) **7** as a colourless oil. IR (KBr, film): $\nu = 3316, 2932, 1578, 1423, 1043, 795, 714\ cm^{-1}$; MS (70 eV): $m/e = 289$ (M^+, 20), 260 (20), 259 (90), 258 (100), 244 (50), 111 (20), 97 (20), 92 (22); ^1H NMR ($CDCl_3$): $\delta = 8.40$ (m, 2H, 2-H and 6-H), 7.47 (ddd, $J = 8$ Hz, $J = 2$ Hz, $J = 2$ Hz, 1H, 4-H), 7.19 (dd, $J = 8$ Hz, $J = 5$ Hz, 1H, 5-H), 6.56 (d, $J = 3$ Hz, 1H, Ar–H), 6.54 (d, $J = 3$ Hz, 1H, Ar–H), 3.52 (m, 2H, OCH_2), 3.07 (br s, 1H, OH), 2.88 (dd, $J = 15$ Hz, $J = 6$ Hz, 1H, thiophene-C**H**H), 2.77 (t, $J = 7$ Hz, 2H, CH_2), 2.62 (t, $J = 8$ Hz, 2H, CH_2), 2.58 (dd, $J = 15$ Hz, $J = 7$ Hz, 1H, thiophene-CH**H**), 1.92 (m, 1H, CH), 1.67 (m, 4H, 2 CH_2), 0.96 (d, $J = 7$ Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 149.7, 147.0, 142.9, 141.1, 137.6, 136.0, 124.7, 123.7, 123.3, 67.0, 38.1, 33.8, 32.6, 30.9, 30.3, 29.8, 16.6$ ppm; $C_{17}H_{23}NOS$ (289); calcd.: C 70.55, H 8.01, N 4.84; found: C 70.24, H 7.96, N 4.70; $[\alpha]_D^{20} = -3.6$ ($c = 1.1$, $CHCl_3$).

(*R*)-Enantiomer *ent*-**7**: $[\alpha]_D^{20} = +3.8$ ($c = 1.1$, $CHCl_3$).

(S)-2-Methyl-11-(3-pyridyl)-1-undecanol (**8**)

Freshly prepared *Raney* nickel (7.5 g), suspended in methanol (20 ml), was stirred under a hydrogen atmosphere for 30 min. Then a solution of **7** (741 mg, 2.56 mmol) in methanol (5 ml) was added and the suspension was stirred under a hydrogen atmosphere (10 at) at 80 °C for 2 h. After cooling to room temperature, the catalyst was removed by filtration and extracted thoroughly with methanol. The combined methanolic layers were evaporated and the residue was purified by flash column chromatography to give 510 mg (76%) **8** as a colourless oil. IR (KBr, film): $\nu = 3397, 2926, 2855, 1682, 1466, 1221, 1170, 719\ cm^{-1}$; MS (70 eV): $m/e = 263$ (M^+, 12), 262 ($M^+ - 1$, 20; high resolution: $C_{17}H_{28}NO$ requires 262.2171; found: 262.2170), 233 (25), 232 (50), 204 (30), 190 (26), 106 (100), 93 (78), 92 (38); ^1H NMR ($CDCl_3/CF_3COOD$): $\delta = 8.64$ (d, $J = 6$ Hz, 1H, 6-H), 8.61 (s, 1H, 2-H), 8.38 (d, $J = 8$ Hz, 1H, 4-H), 7.95 (dd, $J = 8$ Hz, $J = 6$ Hz, 1H, 5-H), 4.25 (dd, $J = 10$ Hz, $J = 6$ Hz, 1H, C**H**H–O), 4.16 (dd, $J = 10$ Hz, $J = 7$ Hz, 1H, CH**H**–O), 2.88 (t, $J = 8$ Hz, 2H, Ar–CH_2), 1.90 (m, 1H, CH), 1.72 (m, 1H), 1.36–1.21 (m, 15H), 0.97 (d, $J = 7$ Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3/CF_3COOD$): $\delta = 147.2, 144.5, 140.9, 139.1, 127.3, 73.5, 33.0, 32.9, 32.5, 30.5, 29.7, 29.5, 29.4, 29.3, 29.1, 26.8, 16.5$ ppm; $[\alpha]_D^{20} = -2.8$ ($c = 1.1$, $CHCl_3$).

(*R*)-Enantiomer *ent*-**8**: $[\alpha]_D^{20} = +5.0$ ($c = 1.2$, $CHCl_3$).

(S)-3-Methyl-12-(3-pyridyl)dodecanenitrile (**9**)

An ice-cooled solution of **8** (300 mg, 1.14 mmol) and pyridine (135 mg, 1.7 mmol) in anhydrous dichloromethane (2 ml) was treated dropwise, stirring with mesyl chloride (157 mg, 1.4 mmol). The mixture was stirred at 0 °C for 4 h, then water (10 ml) was added and the mixture was extracted with dichloromethane (3 × 15 ml). The combined organic layers were washed with water, dried, and evaporated *in vacuo*. The crude mesilate was dissolved in anhydrous *DMF* (5 ml) and NaCN (300 mg, 6.1 mmol) was added. The solution was stirred under a nitrogen atmosphere at 60 °C for 12 h, then diluted with water (20 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic layers were washed with water, dried, and evaporated. The residue was purified by flash column chromatography to give 202 mg (65%) of the nitrile **9** as a colourless oil. IR (KBr, film): ν = 2988, 2855, 2245, 1636, 1576, 1478, 1464, 1421, 1026, 716 cm^{-1}; MS (70 eV): m/e = 272 (M^+, 5; high resolution: $C_{18}H_{28}N_2$ requires 272.2252; found: 272.2252), 233 (15), 232 (97), 204 (20), 107 (20), 106 (100), 93 (45), 92 (30); ^{1}H NMR ($CDCl_3$): δ = 8.44 (d, J = 2 Hz, 1H, 2-H), 8.42 (dd, J = 5 Hz, J = 2 Hz, 1H, 6-H), 7.48 (ddd, J = 8 Hz, J = 2 Hz, J = 2 Hz, 1H, 4-H), 7.20 (dd, J = 8 Hz, J = 5 Hz, 1H, 5-H), 2.60 (t, J = 8 Hz, 2H, Ar–CH_2), 2.25 (m, 2H, CH_2–CN), 1.82 (m, 1H, CH), 1.61 (m, 2H, CH_2), 1.40–1.27 (m, 14H, 7 CH_2), 1.05 (d, J = 7 Hz, 3H, CH_3) ppm; ^{13}C NMR ($CDCl_3$): δ = 150.0, 147.2, 137.9, 135.8, 123.2, 119.0, 35.9, 33.0, 31.1, 30.5, 29.5, 29.4, 29.4, 29.3, 29.1, 26.8, 24.5, 19.5 ppm; $[\alpha]_D^{20}$ = +1.4 (c = 1.2, $CHCl_3$).

(*R*)-Enantiomer *ent*-**9**: $[\alpha]_D^{20}$ = −1.5 (c = 1.2, $CHCl_3$).

Niphatesine D (**3**)

A solution of anhydrous $AlCl_3$ (25 mg, 0.19 mmol) in anhydrous diethyl ether (0.5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (7 mg, 0.18 mmol) in anhydrous diethyl ether (0.5 ml). Stirring was continued for 10 min and then a solution of the nitrile **9** (20 mg, 0.073 mmol) in anhydrous *THF* (1 ml) was added dropwise and the mixture was stirred at room temperature for 3 h. Then water (2 ml) was added slowly, followed by addition of sodium hydroxide solution to dissolve the aluminum salts. The mixture was extracted with dichloromethane (5 × 10 ml), the combined organic layers were dried and evaporated *in vacuo*. The oily residue was purified by reversed phase HPLC (RP 18) to give 14 mg (69%) pure **3** as a colourless oil. $[\alpha]_D^{20}$ = +1.7 (c = 0.5, MeOH; Ref. [3]: $[\alpha]_D^{25}$ = +4.4 (c = 0.045, MeOH). The spectroscopic data of the product are in full agreement with the values published for the alkaloid niphatesine D [3].

(*R*)-Enantiomer *ent*-**3**: $[\alpha]_D^{20}$ = −1.9 (c = 0.8, MeOH).

Acknowledgement

This work was supported by the *Fonds der Chemischen Industrie*.

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Received June 19, 1995. Accepted August 1, 1995