Studies on the Chemistry of Thienoannelated *O*,*N*- and *S*,*N*-Containing Heterocycles. 25 [1]. Synthesis of New Imidazolyl and Pyrazolyl Derivatives of Thiophene as Inhibitors of Nitric Oxide Synthase

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Some novel imidazolyl and pyrazolyl thiophene derivatives were synthesized. Different substituted *N*-containing heterocycles were chosen with the aim of enhancing the activity or selectivity of the products towards inhibition of one of the three isoforms of nitric oxide synthase. One series of substances was prepared by substitution reactions of 3-bromo-2-nitrothiophene with various heterocycles. In the other series introduction of a second heterocyclic substituent to pyrazolylthiophene compounds was attempted.

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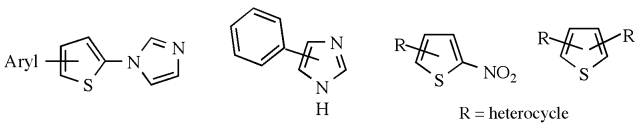
Phenylimidazole and other imidazole derivatives with aromatic residues are known to have moderate to good affinity towards hemoglobin containing enzymes. Nitric oxide synthase (NOS) is one of the enzymes with a hemoglobin group in its active center [2-4]. For example, some imidazole derivatives of the general formula **1** show selective NOS inhibiting activity [5]. Additionally, it is known that cytochrome P450, another Fe-containing enzyme is inhibited by simple compounds as shown in formula **2** [6] (Scheme 1).

Thus we planned to prepare a series of substituted thienylimidazoles and other *N*-containing thienylheterocycles of the general formula **3**. We expected that variation of the *N*-heterocycle may cause differentiated activity or selectivity to the inhibition of one of the three NOS-isoforms. Furthermore we considered, in the course of our studies on new substances with NOS-inhibiting activities, to synthesize some thienylimidazole derivatives with a second *N*-containing heterocycle attached to the thiophene ring as shown in formula **4** (Scheme 1).

The synthetic route to the target compounds **5a** - **5g** is outlined in Scheme 2. As starting material, 3-bromothiophene was chosen. Treatment of 3-bromothiophene with concentrated HNO_3 and acetic anhydride gave 3-bromo-2-nitrothiophene (**6**) [7] in good yield. Initial attempts to

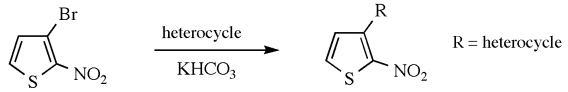
Scheme 1



1 **2** **3** **4**

introduce the pyrazole, imidazole or 4,5-dichloroimidazole moiety into the 3-position of substance **6** by heating with the corresponding heterocycle in *N*,*N*-dimethylformamide for several hours failed. These results suggested that a weak base, such as $KHCO_3$, could be an appropriate co-reactant. However, only a small amount of derivative **5c** was obtained from heating compound **6** with 4,5-dichloroimidazole and $KHCO_3$ without solvent at 75° while reaction of **6**, $KHCO_3$ and *N*-heterocycles in ethanol at 75° or *N*,*N*-dimethylformamide at 60° failed. Finally, compound **6** and various *N*-heterocycles were treated with $KHCO_3$ in *N*,*N*-dimethylformamide at 110° to afford the target compounds **5a** - **5g** in low yields. Surprisingly, only treatment with 1,2,4-triazole gave product **5b** in relatively good yield. Compounds **5c** and **5e** showed weak stability. The formation of two isomeric products by treatment of **6** with 4-methylimidazole is possible. In analogy to compound **10** only the preferred product **5f** was formed. The *N*-heterocyclic moieties, reaction conditions, melting points and yields are summarized in Table 1.

Scheme 2

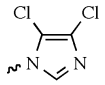
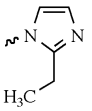
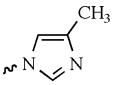
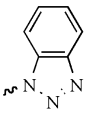


6 **5a - g**

The intermediates for synthesizing the target compounds of general formula **4** were prepared as shown in Scheme 3. Treatment of 5-acetyl-2-chloro-3-nitrothiophene **7** [8] with an excess of pyrazole, imidazole or 4-methylimidazole under heating gave compounds **8**, **9**, and **10** in good yields. Reduction of the acetyl group in **8** - **10** with trifluoroacetic acid and triethylsilane was expected to afford the ethyl derivatives. It is known that compounds with an alkyl group next to the sulfur atom of the thiophene ring can show increased biological activity [9]. Compound **8** was smoothly reduced to **11**, while reduction of **9** failed. From **10** was obtained only the alcohol **12**. A second attempt, to reduce the ketones in **9** and **10** to alkanes with lithium aluminium hydride and $AlCl_3$ also failed.

Reduction of the nitro groups in **9**, **10** and **11** to the amine compounds **13**, **14** and **15** was accomplished with iron powder in glacial acetic acid and water. Treatment of the

Table 1

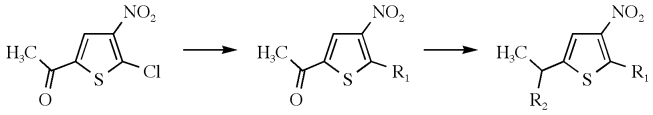
Compd.	R	React. temp. (°C)	React. time (h)	melting point (°C)	Yield
5a		110	4	98	167 mg (17%)
5b		110	20	146	744 mg (75%)
5c		110	4	92	355 mg (36%)
5d		110	16	168	175 mg (17%)
5e		110	16	102-104	145 mg (13%)
5f		110	20	142-144	300 mg (29%)
5g		110	4	147-151	349 mg (28%)

amines **13**, **14** and **15** with acetyl chloride gave the expected amides **16**, **17** and **18**. These amides were also prepared in one step with higher yields by heating **9**, **10** and **11** with iron powder in glacial acetic acid and water at 110°.

The reaction of **18** with potassium *tert*-butoxide and diethyl chlorophosphate followed by ethyl isocyanoacetate [10] gave compound **19** in an unsatisfactory low yield of less than 1% and therefore will be not discussed here.

The exact position of the methyl group in compound **10** could not undoubtedly be confirmed using ^{13}C, ^{1}H-COSY and ^{13}C, ^{1}H-HMBC nmr spectroscopy because of the lack of protons to obtain long-range ^{13}C,^{1}H correlations *via* ^{2}J (^{13}C, ^{1}H) and ^{3}J (^{13}C, ^{1}H). Therefore, **10** was treated with Raney-Ni to produce substance **20** *via* reductive desulfuration of the thiophene ring forming a CH_2 group at the imidazole nitrogen. The structure elucidation with ^{13}C,

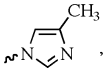
Scheme 3



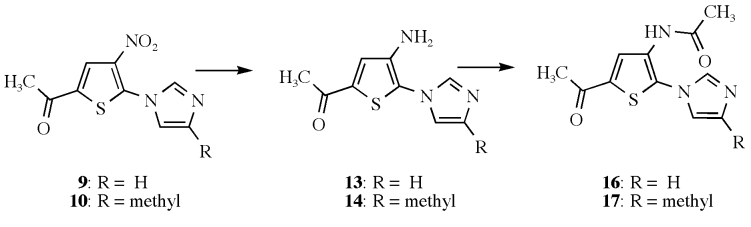
7 **8-10** **11, 12**

8, 11: R_1 =  , R_2 = H

9: R_1 = 

10, 12: R_1 =  , R_2 = OH

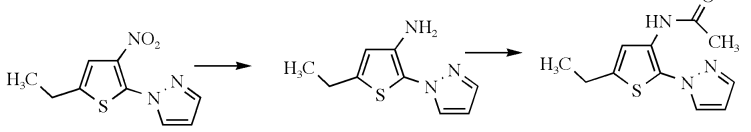
Scheme 4



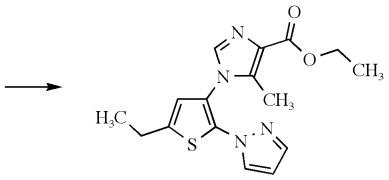
9: R = H
10: R = methyl

13: R = H
14: R = methyl

16: R = H
17: R = methyl



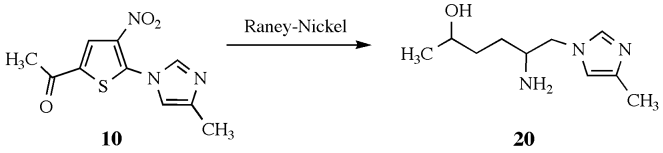
11 **15** **18**



19

^{1}H-HMBC nmr spectroscopy was accomplished using the shift correlation signals of the methylene protons and the tertiary imidazole carbons. We observed that the CH_2-$N_{imidazole}$ protons of **20** correlate with both tertiary imidazole carbons but not with the quaternary carbon that is bound to the methyl group. The lack of the latter shift correlation signal verifies the structure of compound **10**.

Scheme 5



10 **20**

Some of the compounds described herein have already been tested with respect to their NOS-inhibiting activity and show interesting pharmacological profiles. The results of the tests will be published elsewhere.

EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded on a Bruker Avance 200 (200 MHz), a Bruker Avance 400 DPX (400 MHz) or on a Varian Unity*Plus*-300 (300 MHz) spectrometer using deuteriochloroform as solvent, if not otherwise stated, and tetramethylsilane as internal standard. Mass spectra were obtained by using a Shimadzu GC/MS QP 1000 EX or a Hewlett Packard (GC: 5890; MS 5970) spectrometer. Column chromatography was performed using silica gel 60, 70 - 230 mesh ASTM (Merck). Solutions in organic solvents were dried over anhydrous sodium sulfate. All materials were commercially available unless otherwise noted.

1-(2-Nitro-3-thienyl)-1*H*-imidazole (**5a**).

A suspension of 1.03 g (5 mmoles) of **6**, 0.34 g (5 mmoles) of imidazole and 0.5 g (5 mmoles) of $KHCO_3$ in 12.5 ml of absolute *N*,*N*-dimethylformamide was stirred at 110 °C for 4 hours. The reaction mixture was concentrated and the residue diluted with ethyl acetate and washed with water. The organic layer was dried and evaporated *in vacuo*. The product was purified by recrystallisation from 15% ethanol; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.86 (s, 1H, imidazole H), 7.62 (d, J = 5.8 Hz, 1H, thiophene H), 7.09 (d, J = 5.8 Hz, 1H, thiophene H), 7.23 (s, 2H, imidazole H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 140.4, 133.7, 132.9, 128.9, 126.9, 120.6; ms: m/z 195 (5), 165 (50), 139 (52), 111 (56), 84 (45), 45 (100).

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.58; N, 21.53. Found: C, 42.81; H, 2.53; N, 21.29.

Compounds **5b** - **5g** were obtained by the same method to that used for **5a**. The *N*-heterocycle moieties, reaction temperatures and times, melting points and yields are listed in Table 1.

1-(2-Nitro-3-thienyl)-1*H*-1,2,4-triazole (**5b**).

The product was purified by recrystallisation from 70% ethanol; ^{1}H nmr (deuteriochloroform): δ 8.93 (s, 1H, triazole H), 8.14 (s, 1H, triazole H), 7.64 (d, J = 5.8 Hz, 1H, thiophene H), 7.46 (d, J = 5.8, 1H, thiophene H); ^{13}C nmr (deuteriochloroform): δ 152.4, 145.9, 132.6, 130.5, 126.5; ms: m/z 196 (22), 113 (23), 70 (26), 45 (100).

Anal. Calcd. for $C_6H_4N_4O_2S$: C, 36.73; H, 2.06; N, 28.56. Found: C, 36.86; H, 2.04; N, 28.26.

4,5-Dichloro-1-(2-nitro-3-thienyl)-1*H*-imidazole (**5c**).

The product was purified by recrystallisation from 50% ethanol; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.70 (d, J = 5.6 Hz, 1H, thiophene H), 7.13 (d, J = 5.6 Hz, 1H, thiophene H), 7.58 (s, 1H, imidazole H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 136.6, 133.0, 129.7, 128.2, 125.6, 113.4; ms: m/z 263 (2), 233 (2), 207 (32), 82 (71), 45 (100).

Anal. Calcd. for $C_7H_3Cl_2N_3O_2S$: C, 31.84; H, 1.15; N, 15.91. Found: C, 31.68; H, 1.23; N, 15.58.

2-Methyl-1-(2-nitro-3-thienyl)-1*H*-imidazole (**5d**).

The product was purified by column chromatography (ethyl acetate/methanol 9/1); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.63 (d, J = 5.8 Hz, 1H, thiophene H), 7.10 (d, J = 1.5 Hz, 1 H, imidazole H), 7.06 (d, J = 5.8 Hz, 1H, thiophene H), 6.95 (d, J = 1.5 Hz, 1H, imidazole H), 2.30 (s, 3H, CH_3); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 145.5, 144.1, 134,1, 129.7, 128.6, 127.5, 119.9, 13.3; ms: m/z 209 (5), 153 (5), 137 (4), 69 (6), 43 (100).

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.93; H, 3.37; N, 20.08. Found: C, 45.68; H, 3.11; N, 19.89.

2-Ethyl-1-(2-nitro-3-thienyl)-1*H*-imidazole (**5e**).

The product was purified by column chromatography (ethyl acetate/methanol 9/1); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.22 (d, J = 5.8 Hz, 1H, thiophene H), 7.47 (d, J = 5.8 Hz, 1H, thiophene H), 7.35 (d, J = 1.3 Hz, 1H, imidazole H), 7.03 (d, J = 1.3 Hz, 1H, imidazole H), 2.56 (q, J = 7.5 Hz, 2H, CH_2), 1.17 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 148.8, 139.9, 134.3, 132.6, 128.2, 127.4, 120.8, 19.8, 11.8; ms: m/z 223 (3), 167 (6), 137 (6), 11 (4), 57 (100), 45 (45).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.17; H, 3.76; N, 18.55.

4-Methyl-1-(2-nitro-3-thienyl)-1*H*-imidazole (**5f**).

The product was purified by recrystallisation from 40% ethanol; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 8.17 (d, J = 5.8 Hz, 1H, thiophene H), 8.09-8.05 (m, 1H, imidazole H), 7.42 (d, J = 5.8 Hz, 1H, thiophene H), 7.35-7.29 (m, 1H, imidazole H), 2.22 (d, J = 8.7 Hz, 3H, CH_3); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 139.8, 137.4, 133.9, 132.9, 126.6 (2C), 116.4, 13.4; ms: m/z 209 (5), 179 (17), 139 (38), 111 (34), 42 (100).

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.93; H, 3.37; N, 20.08. Found: C, 45.74; H, 3.36; N, 19.76.

1-(2-Nitro-3-thienyl)-1*H*-1, 2, 3-benzotriazole (**5g**).

The product was purified by column chromatography (toluene/ethyl acetate 8/2); ^{1}H nmr (deuteriochloroform): δ 8.19 (d, J = 8.3 Hz, 1H, benzotriazole-H), 7.74 (d, J = 5.8 Hz, 1H, thiophene H), 7.41 (d, J = 5.8 HZ, 1H, thiophene H), 7.61-7.56 (m, 1H, benzotriazole H), 7.51-7.46 (m, 1H, benzotriazole H), 7.31 (d, J = 8.3 Hz, 1H, benzotriazole H); ^{13}C nmr (deuteriochloroform): δ 145.7, 144.4, 132.9, 131.9, 130.9, 128.9, 127.0, 124.8, 120.6, 110.6; ms: m/z 246 (18), 172 (49), 128 (31), 92 (100), 64 (86), 45 (92).

Anal. Calcd. for $C_{10}H_6N_4O_2S$: C, 48.78; H, 2.46; N, 22.75. Found: C, 49.01; H, 2.51; N, 22.51.

1-[4-Nitro-5-(1*H*-1-pyrazolyl)-2-thienyl]-1-ethanone (**8**).

A solution of 6.00 g (29.2 mmoles) of **7** and 10.40 g (150 mmoles) of pyrazole in 100 ml of absolute acetonitrile was refluxed for 27 hours, followed by addition of 5.00 g (72.1 mmoles) of pyrazole. After refluxing for further 43 hours the solvent was removed under vacuum and the residue crystallized from ethanol to yield 5.92 g of **8** (86%), mp 155°; ^{1}H nmr (deuteriochloroform): δ 8.38 (d, J = 2.8 Hz, 1H, pyrazole H), 8.06 (s, 1H, thiophene H), 7.80 (d, J = 1.8 Hz, 1H, pyrazole H), 6.58 (dd, J = 1.8 Hz, J = 2.8 Hz,1H, pyrazole H), 2.59 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 189.7, 149.2, 144.1, 135.8, 133.4, 132.9, 127.7, 110.1, 25.8; ms: m/z 237 (100), 222 (62), 148 (49), 105 (45), 69 (80), 52 (54).

Anal. Calcd. for $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71. Found: C, 45.67; H, 2.91; N, 17.58.

1-[5-(1*H*-1-Imidazolyl)-4-nitro-2-thienyl]-1-ethanone (**9**).

A solution of 6.00 g (29.2 mmoles) of **7**, 3.97 g (58.4 mmoles) of imidazole and 100 ml of absolute ethanol was refluxed for 22 hours. After concentrating the reaction mixture the residue was crystallized from ethanol to yield 4.93 g of **9** (71%), mp 176°; ^{1}H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): δ 8.61 (s, 1H, thiophene H), 8.21 (s, 1H, imidazole H), 7.70 (s, 1H, imidazole H), 7.20 (s, 1H, imidazole H), 2.68 (s, 3H, CH_3); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 190.6, 143.4, 138.4, 137.1, 130.0, 128.5, 121.9, 25.9; ms: m/z 237 (84), 209 (45), 179 (73), 94 (83), 84 (100), 69 (81), 52 (100).

Anal. Calcd. for $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71. Found: C, 45.79; H, 3.11; N, 17.61.

1-[5-(4-Methyl-1*H*-1-imidazolyl)-4-nitro-2-thienyl]-1-ethanone (**10**).

A solution of 206 mg (1 mmol) of **7** and 164 mg (2 mmoles) of 4-methylimidazole in 5 ml of absolute *N*,*N*-dimethylformamide was stirred at 70° for 3 hours. The reaction mixture was poured onto ice water and the precipitate was collected by filtration and crystallized from ethanol to yield 189 mg of **10** (75%), mp 114-115°; ^{1}H nmr (deuteriochloroform): δ 8.11 (s, 1H, thiophene H), 7.79 (s,1H, imidazole H), 6.95 (s, 1H, imidazole H), 2.61 (s, 3H, $COCH_3$), 2.29 (s, 3H, imidazole H); ^{13}C nmr (deuteriochloroform): δ 189.8, 144.7, 141.2, 138.2, 137.9, 137.5, 127.8, 118.1, 26.2, 13.9; ms: m/z 251 (38), 223 (16), 19 (59), 181 (100), 153 (53), 107 (36), 84 (67), 69 (41).

Anal. Calcd. for $C_{10}H_9N_3O_3S$: C, 47.80; H, 3.61; N, 16.72. Found: C, 47.46; H, 3.71; N, 16.39.

General Procedure for the Reduction of compounds **8** and **10** (Preparation of **11** and **12**).

To a solution of **8** or **10** in trifluoroacetic acid, triethylsilane was added dropwise and the mixture was stirred at room temperature or at 40°. The reaction mixture was cooled, poured onto ice water and neutralized with solid sodium bicarbonate. The product was either extracted with ethyl acetate or collected by filtration in case of a precipitate and purified.

1-(5-Ethyl-3-nitro-2-thienyl)-1*H*-pyrazole (**11**).

The reagents used were: 5.92 g (25 mmoles) of **8** in 25 ml of trifluoroacetic acid and 37.5 ml of triethylsilane. Reaction time: 72 hours at 40°. Purification: after extraction with ethyl acetate the organic layer was dried, concentrated and triethylsilane removed by kugelrohr distillation. Yield: 4.96 g (89%) of **11** as an oil; ^{1}H nmr (deuteriochloroform): δ 8.17 (d, J = 2.8 Hz, 1H, pyrazole H), 7.74 (d, J = 1.7 Hz, 1H, pyrazole H), 7.26-7.24 (m, 1H, thiophene H), 6.51 (dd, J = 1.7 Hz, J = 2.8 Hz, 1H, pyrazole H), 2.80 (dq, J = 1.1Hz, J = 7.5 Hz, 2H, CH_2), 1.34 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 142.8, 141.7, 140.8, 134.8, 132.9, 119.1, 108.5, 23.4, 14.9; ms: m/z 223 (75), 208 (30), 91 (28), 69 (64), 45 (100).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.29; H, 4.16; N, 18.44.

1-[5-(4-Methyl-1*H*-1-imidazolyl)-4-nitro-2-thienyl]-ethanol (**12**).

The reagents used were: 251 mg (1 mmol) of **10** in 3 ml of trifluoroacetic acid and 0.8 ml of triethylsilane. Reaction time: 96 hours. Purification: the precipitate was dried and crystallized from water. Yield: 120 mg of **12** (47%), mp 126-128°; ^{1}H nmr (deuteriochloroform): δ 7.62 (s, 1H, thiophene H), 7.35 (s, 1H, imidazole H), 6.86 (s, 1H, imidazole H), 5.08 (q, J = 6.4 Hz, 1H, CH), 4.37 (broad s, 1H, COH), 2.24 (s, 3H, imidazole CH_3), 1.60 (d, J = 6.4 Hz, 3H, COH-CH_3); ^{13}C nmr (deuteriochloroform): δ 147.6, 139.1, 138.3, 136.2, 118.1, 117.7, 65.3, 25.0, 13.2; ms: m/z 253 (25), 183 (100), 137 (78), 110 (46), 96 (54), 84 (50), 78 (74), 69 (48).

Anal. Calcd. for $C_{10}H_{11}N_3O_3S$: C, 47.42; H, 4.38; N, 16.60. Found: C, 47.72; H, 4.30; N, 16.57.

General Procedure for the Preparation of **13**, **14** and **15**.

To a solution of **9**, **10** or **11** in a mixture of glacial acetic acid and water, iron powder was added portion-wise. After heating at 50° or 70° the mixture was filtered, concentrated and the product purified.

1-[4-Amino-5-(1*H*-1-imidazolyl)-2-thienyl]-1-ethanone (**13**).

The reagents used were: 3.31 g (14 mmoles) of **9**, 5.12 g of iron powder, 70 ml of glacial acetic acid and 7 ml of water. Reaction temperature: 70°. Reaction time: 90 minutes. Purification: extraction with water/ethyl acetate, drying, evaporating the organic layer and recrystallizing from toluene. Yield: 1.21 g of **13** (41%), mp 145-148°. ^{1}H nmr (deuteriochloroform): δ 7.69 (s, 1H, aromatic H), 7.22 (s, 2H, aromatic H), 7.14 (s, 1H, aromatic H), 3.77 (s, 2H, NH_2), 2.52 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 190.1, 139.9, 138.5, 130.5, 123.9, 120.8, 119.1, 26.2; ms: m/z 207 (63), 188 (50), 164 (18), 137 (35), 110 (38), 84 (48), 43 (100).

Anal. Calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.13; H, 4.22; N, 20.03.

1-[4-Amino-5-(4-methyl-1*H*-1-imidazolyl)-2-thienyl]-1-ethanone (**14**).

The reagents used were: 502 mg (2 mmoles) of **10**, 784 mg of iron powder, 20 ml of glacial acetic acid 1.5 ml of water and 1.5 ml of methanol. Reaction temperature: 50°. Reaction time: 2 hours. Purification: extraction with water/ethyl acetate, drying and evaporating the organic layer and recrystallizing from isobutyl methyl ketone. Yield: 370 mg of **14** (84%), mp 165-166°. ^{1}H nmr (deuteriochloroform): δ 7.54 (s, 1H, thiophene H), 7.18 (s, 1H, imidazole H), 6.81 (s, 1H, imidazole H), 3.79 (s, 2H, NH_2), 2.48 (s, 3H, CO-CH_3), 2.25 (s, 3H, imidazole CH_3); ^{13}C nmr (deuteriochloroform): δ 190.1, 139.7, 139.6, 138.1, 137.3, 124.0, 119.7, 117.0, 26.1, 13.5; ms: m/z 221 (85), 181 (14), 179 (100), 153 (29), 137 (16), 120 (16), 110 (56), 84 (24).

Anal. Calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.52; H, 4.78; N, 18.73.

5-Ethyl-2-(1*H*-1-pyrazolyl)-3-thienylamine (**15**).

The reagents used were: 454 mg (2 mmoles) of **11**, 784 mg of iron powder, 10 ml of glacial acetic acid and 1 ml of water. Reaction temperature: 70°. Reaction time: 45 minutes. Purification: column chromatography (toluene/ethyl acetate 8/2). Yield: 281 mg (51%) of **15** as an oil; ^{1}H nmr (deuteriochloroform): δ 7.67 (s, 1H, pyrazole H), 7.58 (d, J = 2.3 Hz, 1H, pyrazole H), 6.39-6.35 (m, 1H, pyrazole H), 6.32-6.29 (m, 1H, thiophene H), 4.11 (s, 2H, NH_2), 2.72 (q, J = 7.7 Hz, 2H, CH_2), 1.27 (t, J = 7.7 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 141.3, 140.4, 136.4, 130.0, 117.4, 112.7, 106.2, 23.6, 15.4; ms: m/z 193 (99), 178 (62), 164 (57), 59 (55), 53 (100).

Anal. Calcd. for $C_9H_{11}N_3S$: C, 55.93; H, 5.74; N, 21.74 Found: C, 56.21; H, 5.53; N, 21.37.

General Procedure for the Preparation of **16**, **17** and **18**.

To a solution of **9**, **10** or **11** in glacial acetic acid, iron powder was added portion-wise. After heating at 110° the mixture was filtered, concentrated, diluted with water and neutralized with sodium hydrogen carbonate or made alkaline with NaOH in case of **17**. After extraction with ethyl acetate, drying and evaporating the organic layer the products were purified by column chromatography or by recrystallizing the residue.

N-[5-Acetyl-2-(1*H*-1-imidazolyl)-3-thienyl]acetamide (**16**).

The reagents used were: 4.93 g (21.8 mmoles) of **9**, 8.66 g of iron powder and 150 ml of glacial acetic acid. Reaction time: 21 hours. Purification: crystallisation from ethanol. Yield: 1.42 g of **16** (26%), mp 288-291°. ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 9.93 (s, 1H, NH), 8.14 (s 1H, thiophene H), 8.10-8.05 (m, 1H, imidazole H), 7.60-7.55 (m, 1H, imidazole H), 7.23-7.18 (m, 1H, imidazole H), 2.60 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 190.7, 168.9, 136.8, 132.6, 131.2, 129.8, 129.3, 121.0, 26.0, 22.8; ms: m/z 249 (19), 207 (46), 192 (17), 84 (19), 43 (100).

Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.87. Found: C, 52.92; H, 4.28; N, 16.58.

N-[5-Acetyl-2-(4-methyl-1*H*-1-imidazolyl)-3-thienyl]acetamide (**17**).

The reagents used were: 502 mg (2 mmoles) of **10**, 784 mg of iron powder and 20 ml of glacial acetic acid. Reaction time: 48 hours. Purification: crystallisation from ethyl acetate/ethanol. Yield: 401 mg of **17** (76%), mp 202-204°. ^{1}H nmr (deuteriochloroform): δ 10.41 (s, 1H, NH), 8.45 (s, 1H, thiophene H), 6.72 (s, 1H, imidazole H), 2.57 (s, 3H, NH-CO-CH_3), 2.24 (s, 3H, CO-CH_3), 2.07 (s, 3H, imidazole H); ^{13}C nmr (deuteriochloroform): δ 190.9, 169.3, 139.7, 138.8, 137.1, 133.0, 128.0, 127.0, 117.6, 26.1, 23.5, 13.1; ms: m/z 263 (93), 248 (19), 221 (76), 206 (28), 179 (100), 153 (28), 110 (26), 84 (33).

Anal. Calcd. for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.77; H, 4,89; N, 15.67.

N-[5-Ethyl-2-(1*H*-1-pyrazolyl)-3-thienyl]acetamide (**18**).

The reagents used were: 2.37 g (10.63 mmoles) of **11**, 4.15 g of iron powder and 80 ml of glacial acetic acid. Reaction time: 14 hours. Purification: column chromatography (toluene/ethyl acetate 6/4). Yield: 615 mg of **18** (25%), mp 87-91°. ^{1}H nmr (deuteriochloroform): δ 9.81 (s, 1H, NH), 7.71 (d, J = 1.9 Hz, 1H, thiophene H), 7.64 (d, J = 2.3 Hz, 2H, pyrazole H), 6.43-6.40 (dd, J = 4.3 Hz, J = 4.9 Hz, 1H, pyrazole H), 2.79 (dq, J = 1.9 Hz, J = 7.5 Hz, 2H, CH_2), 2.16 (s, 3H, CH_3CO), 1.31 (t, J = 7.5 Hz, 3H, CH_3CH_2); ^{13}C nmr (deuteriochloroform): δ 167.3, 140.5, 139.3, 129.1, 126.6, 120.3, 119.3, 106.6, 24.4, 23.7, 15.5; ms: m/z 235 (67), 193 (42), 178 (50), 164 (38), 43 (100).

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86. Found: C, 56.04; H, 5.82; N, 17.64.

5-Amino-6-(4-methyl-1*H*-1-imidazolyl)-2-hexanol (**20**).

To a refluxing suspension of 1.004 g (4 mmoles) of **10** and 2 g of Raney-Nickel (W2) in 50 ml of ethanol, a further 2 g of Raney-Ni was added after 30 and again after 60 minutes. The reaction was completed after 90 minutes (thin layer chromatography control) at which time the catalyst was removed by filtration and washed with ethanol three times. The solvent was removed under vacuum and the residue diluted with methylene chloride and washed with water. The organic layer was dried, evaporated and purified by kugelrohr distillation ($1.4x10^{-2}$ mbar, 100°) to yield 39 mg (3.9%) of **12** as an oil; ^{1}H nmr (deuteriochloroform): δ 7.36 (s, 1H, imidazole H), 6.64 (s, 1H, imidazole H), 3.93-3.59 (m, 2H, CH_2), 3.05-2.85 (m, 1H, CH), 2.85-2.81 (m, 3H, CH, CH_2), 2.19 (s, 3H, CH_3), 1.83-1.60 (m, 2H, CH_2), 1.10-0.97 (m, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 137.7, 136.7, 116.2, 63.5, 59.5, 52.4, 46.2, 32.1, 27.7, 20.8, 13.6, 12.6. Exact mass Calcd. for $C_{10}H_{19}N_3O$: 197.1528. Found 197.1541.

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