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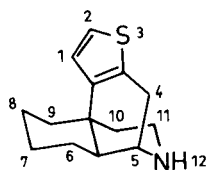
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The present paper deals with the synthesis of 5,5a,6,7,8,9-hexahydro-5,9a-iminoethano-4*H*-naphtho[2,1-*b*]thiophenes (I) as derivatives of the first of three novel isomeric *S*-heterocycles with morphinan-like structure ("thiamorphinans").

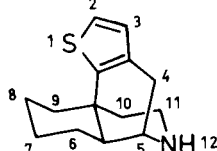
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As part of our continuing investigations in the field of annelated thiophenes and benzo[*b*]thiophenes we are particularly interested in the synthesis of heterocyclic systems with potential physiological, mainly pharmacological, activities. Within this scope we are now dealing with the chemistry of such fused thiophenes which act as narcotic or non-narcotic analgesics [1,2].

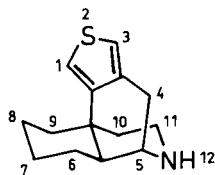
Since several research groups [3,4,5,6,7,8] synthesized thieno analogues of benzomorphan, it became a fascinating idea for us to open synthetic routes to the three isomeric systems which we, for convenience, would like to call thiamorphinans of the 1*S*-, 2*S*- and 3*S*-series, referring to the position of the sulphur atom.



I
5,5a,6,7,8,9-Hexahydro-5,9a-iminoethano-4*H*-naphtho[2,1-*b*]thiophene



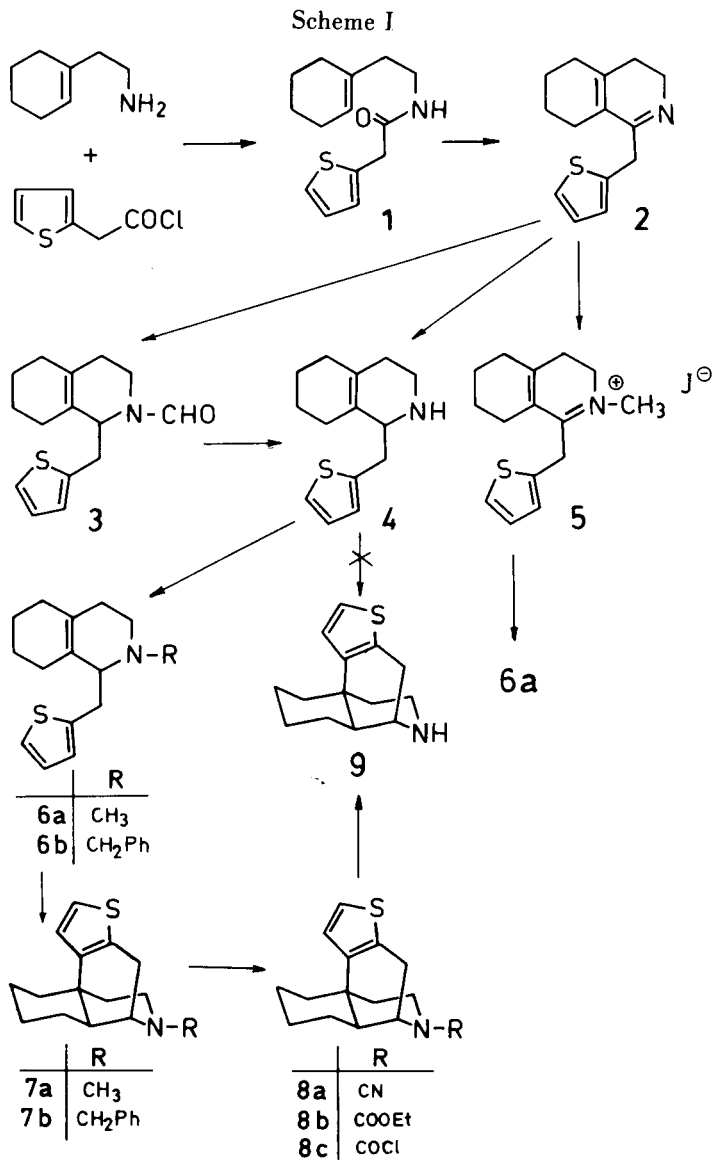
II
5,5a,6,7,8,9-Hexahydro-5,9a-iminoethano-4*H*-naphtho[1,2-*b*]thiophene



III
5,5a,6,7,8,9-Hexahydro-5,9a-iminoethano-4*H*-naphtho[1,2-*c*]thiophene

The present paper deals with the synthesis of the ring system I, *i.e.* with thiamorphinans of the 3*S*-series.

Out of the various routes leading to the classical morphinan-type structures the method devised by Schnider and Hellerbach [9] seemed to us to offer the best approach. Upon adapting the methodology for some steps in order to cope with the particular problems of thiophene chemistry, the reaction sequence as depicted below proved to be quite useful.

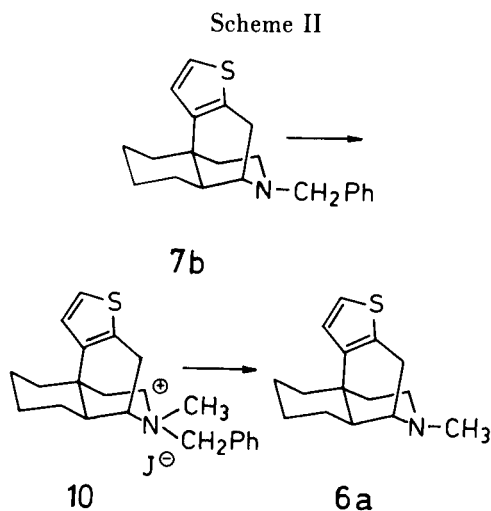


While the intermediate **1** was easily accessible from acylation of 2-(cyclohexen-1-yl) ethylamine [9] with 2-thiophene acetyl chloride [10], the product obtained from it by a subsequent Bischler-Napieralski cyclization (**2**) had to be handled rather carefully because of the instability of its

free base. It proved to be quite useful either to keep **2** in the resulting acidic solution or to react it as quick as possible to one of the following reaction products **3**, **4** or **5**. Reduction of **2** to **4** could be accomplished *via* the intermediacy of the formulated product **3** followed by hydrolysis, or, more advantageously, by direct sodium borohydride reduction of **2** in the acidic aqueous solution resulting from the above cyclization reaction.

In order to enhance the chance for the crucial cyclization step and to diminish the extent of side reactions, easily accessible alkylation products such as **6a** or **6b** were utilized. Nevertheless, some effort had to be made to minimize side reactions and to find optimal reaction conditions. Neither 80% sulphuric acid at room temperature nor various concentrations of phosphoric acid and polyphosphoric acid at varied elevated temperatures gave acceptable yields of the desired cyclization product. Only with 48% hydrobromic acid could the target compound **7** be obtained in reasonable yields (optimum conditions: 6 hours reflux), thus minimizing concomitant production of polymeric, resinous contaminations.

Seen from a pharmacological point of view, this direct cyclization could lead only to products belonging to a potential agonist type, since substituents of potential antagonists (such as allyl or cyclopropylmethyl) cannot be used applying the rather drastic reaction conditions of the cyclization, such as refluxing in hydrobromic acid. In order to accomplish such substitution patterns as well the corresponding NH-compound (**9**) was needed for later alkylation reactions. Since **9** could not be obtained by direct cyclization its synthesis was achieved by various dealkylations according to von Braun [9,11,12] and more modern variations [13,14,15,16] thereof *via* the intermediates **8a**, **8b** and **8c**. In order to introduce a broader variety of possible substituents a method described by Kikasawa [17] for various tertiary amines was tested as shown in Scheme 2 in order to be later applied also to acid-sensitive substituents.



EXPERIMENTAL

The ir spectra were recorded on a Perkin Elmer 377 spectrometer. The ¹H nmr spectra were obtained on Perkin Elmer R 12 A spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Elemental analyses were performed by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. Melting points were determined with a Kofler apparatus and are uncorrected.

N-[2-(Cyclohexen-1-yl)ethyl]thiophene-2-acetamide (**1**).

Dry potassium carbonate (80 g, 0.58 mole) was suspended in a solution of 2-(cyclohexen-1-yl)ethylamine (51.2 g, 0.41 mole) in dry benzene (200 ml). To the ice-cooled mixture a solution of thiophene-2-acetyl chloride (65.8 g, 0.41 mole) was added with stirring while the temperature was maintained below 10°. Stirring was continued for one hour at room temperature. After addition of water (200 ml), the organic layer was washed with 2*N* hydrochloric acid, aqueous sodium bicarbonate and water, dried (sodium sulfate), filtered and evaporated under reduced pressure to yield **1** (96 g, 94%). The crude product was sufficiently pure to be used for the next step. Crystallization from cyclohexane gave an analytical sample as colourless prisms, mp 42.5-43.5°; ¹H-nmr: δ 1.4-2.3 (m, 10H), 3.1-3.5 (m, 2H), 3.75 (s, 2H), 5.3 (m, 1H), 5.6 (s, broad, 1H), 6.85-7.1 (m, 2H), 7.15-7.35 ppm (m, 1H).

Anal. Calcd. for C₁₄H₁₉NOS: C, 67.43; H, 7.68; N, 5.62. Found: C, 67.66; H, 7.54; N, 5.63.

1,2,3,4,5,6,7,8-Octahydro-1-(2-thenyl)isoquinoline (**4**).

a) From **1** *via* **2**.

A solution of **1** (45 g, 0.18 mole) in dry benzene (220 ml) was refluxed 70 minutes after addition of phosphorus pentoxide (128 g, 0.9 mole). The cooled reaction mixture was poured on ice (300 g), the water layer was separated, extracted with benzene and decolorized with Norit. This acidic solution of **2** is stable for weeks in contrast to the free base which decomposes within a few hours. Ethanol (500 ml) was added to the stirred solution and after cooling treated dropwise with a solution of sodium borohydride (20 g, 0.53 mole) in water (40 ml) while maintaining the temperature below 3°. Stirring was continued for 1 hour at room temperature, then poured into water (1 l). Upon extraction with ether the aqueous layer was made alkaline with ammonia and extracted with 4 portions (200 ml) of ether. The combined ethereal extracts were dried over potassium carbonate and evaporated: 33.9 g (80%) of yellow oil was obtained sufficiently pure for the next step. The 3,5-dinitrobenzamide was obtained as yellow crystals, mp 114-116° (from methanol).

Anal. Calcd. for C₂₁H₂₁N₃O₅S: C, 59.01; H, 4.95; N, 9.83. Found: C, 59.29; H, 4.89; N, 9.88.

b) From **2** *via* **3**.

The cooled acidic solution of **2** obtained from **1** (32 mmoles) as described under a) was treated with potassium hydroxide, the liberated base extracted with benzene, dried over potassium carbonate and the solvent evaporated. The oil **2** so obtained was dissolved in formamide (125 ml), treated with 98% formic acid and heated under reflux for 3 hours. After cooling the reaction mixture was filtered through a hyflo-bed, diluted with water (150 ml) and extracted with 3 portions of chloroform (100 ml each). The combined organic extracts were washed with 2*N* hydrochloric acid and with water, dried (sodium sulfate) and evaporated to give 4.6 g (55%) of **3** as a brownish oil. The formamide **3** so obtained was hydrolyzed by heating 45 hours under reflux in ethanolic potassium hydroxide (2.4 g, 43 mmoles of potassium hydroxide, 30 ml of ethanol). The reaction mixture was poured into 50 ml of water, acidified with 4*N* hydrochloric acid, extracted with methylene chloride, the aqueous layer made alkaline with ammonia and extracted again with methylene chloride. Evaporation of the dried extracts yielded **4** (0.82 g, 20%), identified as the 3,5-dinitrobenzamide, mp 114-116°.

1,2,3,4,5,6,7,8-Octahydro-2-methyl-1-(2-thenyl)isoquinoline (**6a**).

a) From **4**.

Compound **4** (92 g, 0.39 mole) was dissolved in 85% formic acid (60 g, 1.1 mole), treated with aqueous 30% formaldehyde (50 g, 0.58 mole) and refluxed for 2 hours. The cooled mixture was diluted with water (500 ml), made alkaline with ammonia, then the oil which separated was extracted with methylene chloride. The combined extracts were dried (potassium carbonate) and evaporated to dryness yielding 82 g (84%) of a yellow oil (tlc-pure). A small amount was purified by vacuum distillation giving a colourless viscous oil, bp_{0.1} 130-132°; ¹H-nmr: δ = 1.3-2.0 (m, 10H), 2.35 (s, 3H), 2.5-3.3 (m, 5H), 6.7-7.1 ppm (m, 3H).

Anal. Calcd. for C₁₅H₂₁NS: C, 72.82; H, 8.56; N, 5.66. Found: C, 73.09; H, 8.26; N, 5.71.

The picrate was obtained as yellow prisms from ethanol, mp 125-129°.

b) From **2** via **5**.

The cooled acidic solution of **2** obtained from **1** (64 mmoles) as described previously was treated with potassium hydroxide, the liberated base extracted with benzene, dried (potassium hydroxide) and the solvent evaporated. The oil **2** so obtained was dissolved in acetonitrile (150 ml) and treated with methyl iodide (20 ml, 0.32 mole). After standing over night at room temperature the solvent was evaporated, the residue distributed between ether and water, the aqueous layer decolorized by Norit and concentrated to 200 ml. Upon diluting this solution of the quaternary salt **5** with ethanol (300 ml) a solution of sodium borohydride (6.4 g, 0.17 mole) in water (10 ml) was added with stirring at such a rate that the temperature could be maintained below 5°. After additional stirring at room temperature for 30 minutes the reaction mixture was acidified with 15 ml of concentrated hydrochloric acid, diluted with water (600 ml) and extracted with ether. The acidic aqueous layer was brought to pH 9 by addition of ammonia and extracted again with ether (3 × 150 ml). The product obtained after drying (potassium carbonate) and evaporating to dryness was a mixture of **6a** and **4** (3:1), which was methylated by the Eschweiler-Clarke procedure to yield **6a** (4.6 g, 29%). The picrate was obtained as yellow prisms from ethanol, mp 125-129°.

2-Benzyl-1,2,3,4,5,6,7,8-octahydro-1-(2-thenyl)isoquinoline (**6b**).

Dry potassium carbonate (55 g, 0.4 mole) was suspended in a solution of **4** (67.8 g, 0.29 mole) in dry benzene (600 ml). This mixture was stirred at 80° and treated dropwise with a solution of benzyl bromide (54.4 g, 0.32 mole) in benzene (50 ml) over a period of 2 hours. After refluxing and stirring for an additional 7 hours the precipitate was dissolved by additional water (600 ml), the organic layer separated, washed with water, dried over potassium carbonate and evaporated to dryness. The residue solidified upon treatment with a small amount of methanol, the crystals were filtered and washed with cold methanol to yield **6b** (77.8 g, 83%). An analytical sample was prepared by recrystallization from ethanol, colourless crystals, mp 54-55°; ¹H-nmr: δ = 1.5-2.0 (m, 10H), 2.2-3.2 (m, 5H), AB-System, δ_A = 7.5, δ_B = 7.8, J_{AB} = 14 Hz, 6.7-7.4 ppm (m, 8H).

Anal. Calcd. for C₂₁H₂₅NS: C, 77.97; H, 7.79; N, 4.33. Found: C, 77.86; H, 7.76; N, 4.24.

5,5a,6,7,8,9-Hexahydro-12-methyl-5,9a-iminoethano-4H-naphtho[2,1-b]thiophene (**7a**).

A solution of **6a** (92.4 g, 0.37 mole) in 48% hydrobromic acid (1.5 l) was heated under reflux for 6 hours. The mixture was then concentrated to 500 ml, cooled to room temperature and poured into 1 l of ice-water, brought to pH 9 by addition of ammonia and extracted with methylene chloride (3 × 500 ml). Drying over potassium carbonate, treatment with Norit, evaporating to dryness and distillation under reduced pressure yielded **7a** (40.2 g, 43.5%) as a yellowish viscous oil, bp_{0.03} 95-97°, which solidified after some time, mp 63-64°; ¹H-nmr: δ = 1.1-3.2 (m, 16H), 2.4 (s, 3H), AB-System, δ_A = 6.8, δ_B = 7.1 ppm, J_{AB} = 5.3 Hz.

Anal. Calcd. for C₁₅H₂₁NS: C, 72.82; H, 8.56; N, 5.66. Found: C, 73.12; H, 8.47; N, 5.63.

The picrate was obtained as yellow needles from ethanol, mp 186-189°.

Anal. Calcd. for C₂₁H₂₄N₄O₇S: C, 52.93; H, 5.07; N, 11.77. Found: C, 52.95; H, 5.16; N, 11.75.

12-Benzyl-5,5a,6,7,8,9-hexahydro-5,9a-iminoethano-4H-naphtho[2,1-b]thiophene (**7b**).

Compound **6b** (15.9 g, 49 mmoles) was dissolved in 48% hydrobromic acid (300 ml) and heated under reflux for 15 hours. After cooling the reaction mixture was poured into water (800 ml) and made alkaline by addition of ammonia. The oily precipitate was dissolved in methylene chloride, the aqueous layer extracted twice with the same solvent (100 ml portions), the combined extracts dried (potassium carbonate), evaporated and distilled under reduced pressure to give **7b** (6.9 g, 43%) as yellow viscous oil, bp_{0.03} 170°, which solidified with methanol. Recrystallization from ethanol yielded colourless crystals, mp 94-95°; ¹H-nmr: δ = 1.0-3.0 (m, 16H), AB-System: δ_A = 3.55, δ_B = 3.65, J_{AB} = 14 Hz, AB-System: δ_A = 6.65, δ_B = 7.08, J_{AB} = 5.35 Hz, 7.2-7.5 ppm (m, 5H).

Anal. Calcd. for C₂₁H₂₅NS: C, 77.97; H, 7.79; N, 4.33. Found: C, 78.15; H, 8.08; N, 4.22.

12-Cyano-5,5a,6,7,8,9-hexahydro-5,9a-iminoethano-4H-naphtho[2,1-b]thiophene (**8a**).

A solution of **7a** (8.7 g, 35.2 mmole) in dry chloroform (80 ml) was treated with cyanogen bromide (7.5 g, 70.8 mmoles) and stirred under reflux for 2 hours. The reaction mixture was evaporated and the oily residue distributed between water and ether. The etheral layer was washed with 2N hydrochloric acid, aqueous sodium bicarbonate and water, dried over sodium sulfate and evaporated to yield **8a** (8.0 g, 88%) as a yellowish tlc-pure oil, which solidified with ether, colourless crystals, mp 124-126°.

Anal. Calcd. for C₁₅H₁₈N₂S: C, 69.73; H, 7.02; N, 10.84. Found: C, 69.68; H, 7.05; N, 10.84.

5,5a,6,7,8,9-Hexahydro-5,9a-iminoethano-4H-naphtho[2,1-b]thiophene (**9**).

a) From **8a**.
A suspension of **8a** (6.3 g, 24.4 mmoles) in 1N hydrochloric acid (300 ml) was refluxed with stirring for 5 hours. The clear brown solution was brought to pH 9 with ammonia, extracted with ether, dried (sodium sulfate) and evaporated to dryness, yielding **9** (4.5 g, 79%) as a yellow, tlc-pure oil. The picrate was obtained as yellow crystals from ethanol, mp 213-219° dec.

Anal. Calcd. for C₂₀H₂₂N₄O₇S: C, 51.94; H, 4.79; N, 12.11. Found: C, 51.83; H, 4.71; N, 12.07.

b) From **7b** via **8b**.

A solution of **7b** (0.5 g, 1.55 mmoles) in dry benzene (6 ml) was added dropwise with stirring at 70° over a period of 30 minutes to the solution of ethyl chloroformate (0.5 g, 4.65 mmoles) in dry benzene (3 ml) and refluxed for additional 5 hours. The cooled solution was evaporated to yield crude **8b** which was hydrolyzed immediately by refluxing with ethanolic potassium hydroxide (0.5 g potassium hydroxide, 0.7 ml ethanol) for 4 hours. The reaction mixture was poured into water, extracted with benzene and the combined extracts were extracted with 2N hydrochloric acid. The free base of **9** was liberated by making these acidic extracts alkaline with ammonia, extracting it with ether, drying (sodium sulfate) and evaporation of the solvent yielded **9** (0.26 g, 72%) as a yellowish tlc-pure oil. The picrate was obtained as yellow crystals from ethanol, mp 211-219° dec; ¹H-nmr: δ = 1.0-2.0 (m, 9H), 2.0-3.2 (m, 8H), AB-System: δ_A = 6.77, δ_B = 7.08, J_{AB} = 5.3 Hz.

Anal. Calcd. for C₂₀H₂₂N₄O₇S: C, 51.91; H, 4.79; N, 12.11. Found: C, 51.85; H, 4.89; N, 12.16.

c) From **7a** via **8c**.

A solution of phosgene (1.0 g, 10.1 mmoles) in dry toluene (2 ml) was added to a solution of **7a** in dry toluene (10 ml) and kept for 3 days at room temperature. The solid was filtered off, the filtrate evaporated to dryness, treated with water (20 ml) and stirred for 3 hours at 40°. Making alkaline with ammonia, extracting with ether, drying over sodium sulfate and evaporation yielded **9** (1.02 g, 57%), mp of the picrate and spectral data are consistent with the desired structure and the products obtained under a) and b).

12-Methyl-5,5a,6,7,8,9-hexahydro-5,9a-iminoethano-4H-naphtho[2,1-b]thiophene (**7a**) (From **7b** via **10**).

A solution of **7b** (3.0 g, 9.27 mmoles) and methyl iodide (26 g, 0.18 mole) in dry benzene (15 ml) was stirred at 45° for 60 hours. The reaction mixture was evaporated to dryness and the residue treated with 20% sodium hydroxide (14 ml) and thiophenole (7.6 ml). After stirring for 5 hours at 90° the solution was poured into water and extracted with benzene. The organic layer was extracted several times with 2*N* hydrochloric acid, the acidic solution made alkaline with ammonia and the free base extracted again with benzene. The dried (sodium sulfate) solution was evaporated to dryness to yield **7a** (1.9 g, 83%) as a yellow, tlc-pure oil. The ¹H nmr, tlc data and mp of the picrate are consistent with the product obtained by cyclization of **6a**.

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