SYNTHESES OF THIENO[3,2-f]MORPHAN, THIENO[4,3-f]MORPHAN AND 3-THIAMORPHINAN DERIVATIVES

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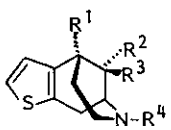
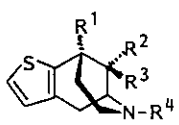
Abstract——Thieno[3,2-f]morphans (**4-7**), (**27**) and (**28**) were prepared by cyclization of 2-thenyl-4-hydroxypiperidines (**3**) or 2-thenyltetrahydropyridine (**26**) with hydrobromic acid. Thieno[4,3-f]morphans (**37**) and (**38**) and 3-thiamorphinan (**47**) were similarly prepared. Some kinds of N-substituents were introduced to the thienomorphans (**5 - 7**), (**29**) and (39) and a 3-thiamorphinan (**48**). Analgesic activities of the N-substituted compounds were investigated.

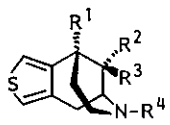
We are interested in the potential pharmacological activity of the sulfur-containing morphine derivatives. Recently we have reported the chemical modification of the phenolic hydroxyl group[1] and the ring system of opiates.[2] On the other hand, there are some reports on the synthesis of heteroaromatic derivatives of 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (6,7-benzomorphan) such as pyridomorphan,[3] pyrrolomorphan,[4] indolomorphan,[5] thiazolomorphan,[6] and thienomorphan.[7] We planned to synthesize thienomorphans and thiamorphinans in which the benzene ring of benzomorphans and morphinans is replaced by the thiophene ring in order to clarify the structure-activity relationship.[8] This paper describes the syntheses of the new thieno[3,2-f]morphans and thieno[4,3-f]morphans.



I

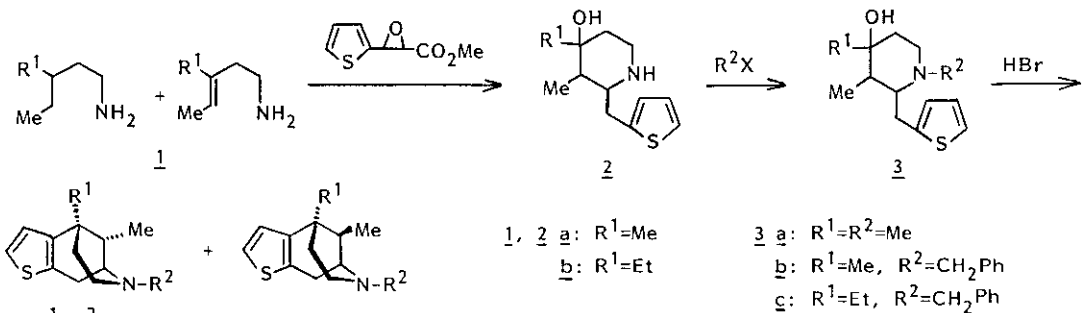


IIa: R^1=R^2=Me
b: R^1=Ph



III

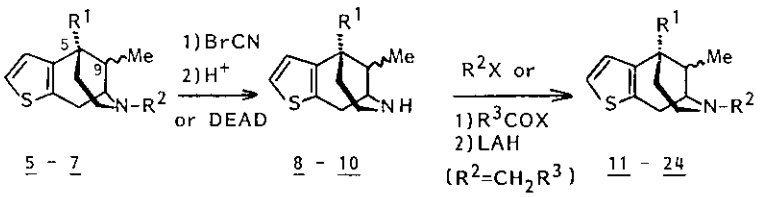
There are three constitutional isomers in thienomorphans, thieno[3,2-f]- (I), [2,3-f]- (II), and [4,3-f]morphans (III). 5,9-Dimethyl- (IIa) and 5-phenylthieno-[2,3-f]morphans (IIb) showed the high toxicity and the low analgesic activity, and were not antagonized against morphine.[7b,c] A few derivatives of thieno[3,2-f]-morphan (I) are known, but their pharmacology has not been studied in detail.[4] Therefore, we synthesized many kinds of derivatives substituted at 2-, 5- and 9-positions, and their synthetic routes are shown in Scheme 1.



1, 2 a: R^1=Me
b: R^1=Et

3 a: R^1=R^2=Me
b: R^1=Me, R^2=CH_2Ph
c: R^1=Et, R^2=CH_2Ph

4: R^1=R^2=Me
5: R^1=Me, R^2=CH_2Ph
6: R^1=Et, R^2=CH_2Ph 7: R^1=Et, R^2=CH_2Ph



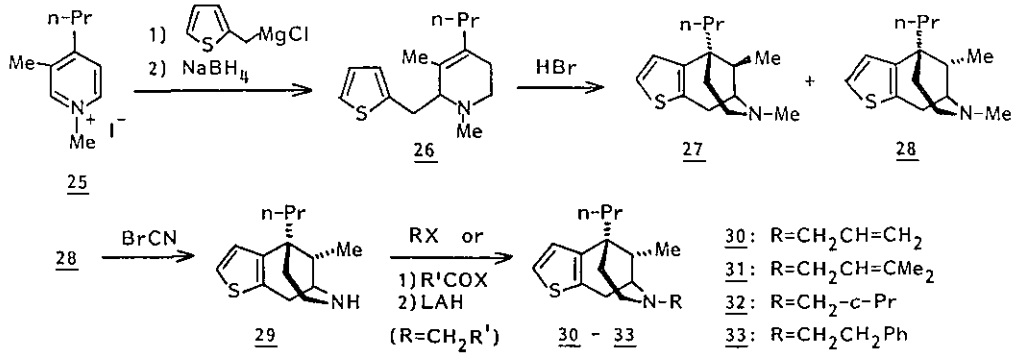
8: 9α-Me, R^1=Me
9: 9α-Me, R^1=Et
10: 9β-Me, R^1=Et

11: 9α-Me, R^1=Me, R^2=CH_2CH=CH_2
12: 9α-Me, R^1=Me, R^2=CH_2CH=CMe_2
13: 9α-Me, R^1=Me, R^2=CH_2CH_2Ph
14: 9α-Me, R^1=Me, R^2=CH_2-c-Pr
15: 9α-Me, R^1=Et, R^2=Me
16: 9β-Me, R^1=Et, R^2=Me
17: 9α-Me, R^1=Et, R^2=CH_2CH=CH_2
18: 9β-Me, R^1=Et, R^2=CH_2CH=CH_2
19: 9α-Me, R^1=Et, R^2=CH_2CH=CMe_2
20: 9β-Me, R^1=Et, R^2=CH_2CH=CMe_2
21: 9α-Me, R^1=Et, R^2=CH_2CH_2Ph
22: 9β-Me, R^1=Et, R^2=CH_2C≡CH
23: 9α-Me, R^1=Et, R^2=CH_2-c-Pr
24: 9β-Me, R^1=Et, R^2=CH_2-c-Pr

Scheme 1

A mixture of pentylamine and pentenylamine (1) was allowed to react with methyl β-(2-thienyl)glycidate to give 3-methyl-2-(2-thenyl)-4-hydroxypiperidine (2). Cyclization of the N-alkylated piperidines (3) with 47% hydrobromic acid gave a mixture of stereoisomers of 9-substituted thieno[3,2-f]morphans. Based on the knowledge of stereoisomers of benzomorphans,[9] configuration of 6 and 7 was assessed as the α- and β-diastereomers, respectively. Isomer ratio was 6/7=6 in the case

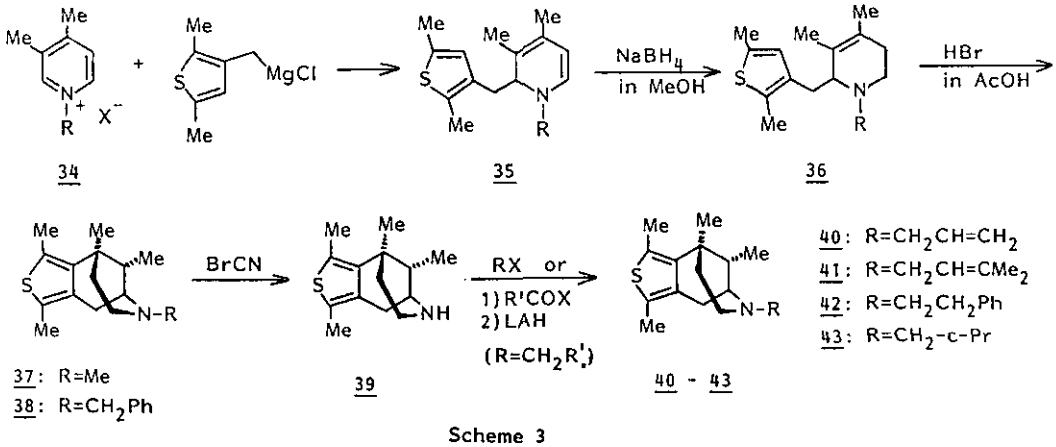
of R^1=Et. Each isomer was isolated by chromatographic separation of the mixture, but only α-isomers were purely obtained by vacuum distillation. N-Dealkylation of the thienomorphans (5 - 7) was performed with cyanogen bromide or diethyl azodicarboxylate (DEAD) in moderate yields. N-Substituted thienomorphans (11 - 24) were prepared by alkylation of 8 - 10 with alkyl halides or by acylation with acyl halides followed by reduction with lithium aluminum hydride (LAH). 5-n-Propyl derivatives were synthesized by the routes as shown in Scheme 2.



Scheme 2

Grignard reaction of pyridinium salt (25) with 2-thenylmagnesium chloride provided a dihydropyridine, which was reduced to 2-thenyltetrahydropyridine (26) by sodium borohydride without further purification. The tetrahydropyridine (26) was cyclized by 47% hydrobromic acid to give 2,9β-dimethyl-5-n-propylthienomorphan (27) and the α-isomer (28) in 6% and 50% yield, respectively. N-Substituted derivatives (30 - 33) were prepared in similar ways to thienomorphans (11 - 24).

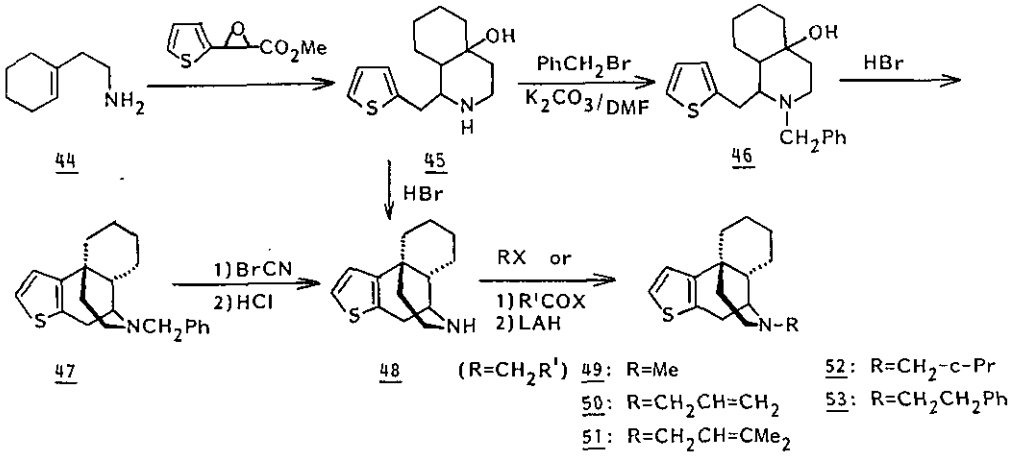
We also synthesized the thieno[4,3-f]morphan derivatives as shown in Scheme 3 since the thieno[4,3-f]morphan skeleton is unknown.



Scheme 3

Reaction of pyridinium salts (34) with 2,5-dimethyl-3-thenylmagnesium chloride gave unstable dihydropyridine derivatives (35), which were readily reduced to 2-thenyltetrahydropyridines (36) by sodium borohydride. The tetrahydropyridines (36) were treated with 47% hydrobromic acid to give cyclized products, thieno[4,3-f]morphans (37) and (38) in moderate yields. Stereochemistry of the 9-methyl groups of compounds (37) and (38) was determined to be α-configuration on the basis of the difference in the 9-methyl chemical shifts between α- and β-isomers.[9] The thienomorphans (37) and (38) were then dealkylated by cyanogen bromide to give compound (39). N-Substituted thienomorphans (40 - 43) were also provided by alkylation of 39 with alkyl halides or by acylation with acyl halides followed by reduction with LAH.

It is noted that levorphanol is four times stronger than morphine in terms of the analgesic activity,[10] and levallorphan and cyclorphan show the nalorphine-like activities.[11] Therefore we synthesized the 5,5a,6,7,8,9-hexahydro-5,9a-iminoethano-4H-naphtho-[2,1-b]thiophene (3-thiamorphinan) derivatives, in which the benzene ring of morphinan is replaced with the thiophene ring. Thiamorphinan skeleton was constructed by the procedures shown in Scheme 4.



44 45 46 47 48

(R=CH2R') 49: R=Me 50: R=CH2CH=CH2 51: R=CH2CH=CMe2 52: R=CH2-c-Pr 53: R=CH2CH2Ph

Scheme 4

Reaction of 2-(cyclohexen-1-yl)ethylamine (44) with methyl β-(2-thienyl)glycidate produced 1-(2-thenyl)-4a-hydroxyperhydroisoquinoline (45) in 29% yield. Cyclization of 45 with hydrobromic acid gave 3-thiamorphinan (48) in 30% yield. The thiamorphinan (48) was alternatively prepared by ways of benzylation of 45, cyclization of 46 and debenzylation of 47. Alkylation or acylation followed by reduction gave the alkylated 3-thiamorphinans (49 - 53).

Pharmacological activities of the thienomorphans and thiamorphinans were measured by the acetic acid-induced writhing inhibition in mice.[12] In thieno[3,2-f]morphans, 2-cyclopropyl-5-ethyl-9α-methyl derivative (**23**) has the same analgesic activity as morphine. Other thieno[3,2-f]morphans (**4**, **14**, **15**, **17**) were as active as codeine. Analgesic activity of thieno[4,3-f]morphans was weak. N-Methyl- (**49**) and N-cyclopropylmethylthiamorphinan (**52**) exhibited the strong activity. All analgesic compounds tested here showed the Straub tail reaction.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H-Nmr spectra were taken on a Hitachi R-20B or JEOL PMX-60S nuclear magnetic resonance instrument (60 MHz). Ir spectra were recorded in a JASCO IRA-100 or IR-810 spectrophotometer. In the ^{1}H-nmr spectra (60 MHz) of cyclic compounds, methylene and methine protons appeared as very broad multiplets and it is impossible to assign those peaks. Therefore, they were omitted from the ^{1}H-nmr data in the Experimental.

4-Hydroxy-3,4-dimethyl-2-(2-thenyl)piperidine (**2a**). A suspension of a mixture of 3-methylpentenylamine and 3-methylpentylamine (1:1)[13] (**1a**)(20 g, 0.23 mol) in water (2 l) was adjusted to pH 5.0 by adding 1 N hydrochloric acid. Methyl β-(2-thienyl)glycidate (37 g, 0.20 mol) was added to the solution thus prepared and the mixture was stirred for 30 h at 80 - 90°C, cooled and filtered. The filtrate was basified with 50% potassium carbonate and extracted with dichloromethane. The extracts were washed, dried (Na_2SO_4) and concentrated to dryness. The unreacted amines were removed by vacuum distillation. The residue was crystallized from ether and recrystallized from ethyl acetate to give colorless needles (12.5 g, 34%), mp 129 - 130°C. Ir (KBr) 3300 (OH), 3205 (NH) cm^{-1}. Anal. Calcd for $C_{12}H_{19}NOS$: C, 63.95; H, 8.50; N, 6.22. Found: C, 64.22; H, 8.53; N, 5.93.

4-Ethyl-4-hydroxy-3-methyl-2-(2-thenyl)piperidine (**2b**). A mixture of 3-ethylpentenylamine and 3-ethylpentylamine (9:1)[13] (**1b**)(40 g, 0.35 mol) was treated with methyl β-(2-thienyl)glycidate (57.7 g, 0.31 mol) in a similar way to the methyl derivative (**2a**). The product was recrystallized from ethyl acetate to give colorless needles (16.3 g, 21%), 149.5 - 150°C. ^{1}H-Nmr (CD_3OD) δ : 0.86 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 0.98 (3H, d, J=7 Hz, 3-CH_3), 6.80 - 7.00 (2H, m, thienyl β,β'-H), 7.15 - 7.30 (1H, m, thienyl α-H). Ir (KBr) 3300 (OH), 3265 (NH) cm^{-1}. Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.23; H, 8.84; N, 5.85. Found: C, 65.31; H, 8.98; N, 5.82.

4-Hydroxy-1,3,4-trimethyl-2-(2-thenyl)piperidine (**3a**). A mixture of 4-hydroxy-

3,4-dimethyl-2-(2-thenyl)piperidine (2a)(1 g, 4.0 mmol) and 37% formalin (4 ml, 49 mmol) in methanol (10 ml) was refluxed for 1 h and then cooled to room temperature. Sodium borohydride (0.5 g, 13 mmol) was added to the mixture and the whole was refluxed for 2 h. Solvent was evaporated under reduced pressure and the residue was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. Vacuum distillation of the residue gave an oil (0.32 g, 31%), bp 120 - 130°C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.92 (3H, s, 4-CH_3), 1.04 (3H, d, J=7 Hz, 3-CH_3), 2.30 (3H, s, N-CH_3), 2.96 - 3.10 (2H, m, CH_2-thienyl), 3.36 (1H, d, J=7 Hz, 3-H), 6.83 - 6.96 (2H, m, thienyl β,β'-H), 7.03 - 7.16 (1H, m, thienyl α-H). Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.01; H, 8.81; N, 5.84. Found: C, 65.10; H, 8.78; N, 5.91.

1-Benzyl-4-hydroxy-3,4-dimethyl-2-(2-thenyl)piperidine (3b). A mixture of 4-hydroxy-2-thenylpiperidine (2a) (3.5 g, 15.5 mmol), benzyl bromide (2.8 g, 16 mmol) and potassium carbonate (4.3 g, 31 mmol) in DMF (90 ml) was refluxed for 8 h with stirring. The cooled reaction mixture was poured into ice-water and extracted with ether. The extracts were washed with 10% hydrochloric acid. The aqueous solution was basified with 20% sodium hydroxide and extracted with ether. The ethereal extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The oily residue was purified by column chromatography on silica gel (ether). The hydrochloride was recrystallized from acetone to give colorless needles (4.48 g, 91%), mp 212 - 215°C(dec.). Anal. Calcd for $C_{19}H_{25}NS\cdot HCl$: C, 64.84; H, 7.45; N, 3.98. Found: C, 64.66; H, 7.62; N, 4.20.

1-Benzyl-4-ethyl-4-hydroxy-3-methyl-2-(2-thenyl)piperidine (3c). Compound (2b) (40 g, 0.17 mol) was treated with benzyl bromide (31.5 g, 0.18 mol) in a similar way to the methyl derivative (37a). The hydrochloride was recrystallized from acetone to give colorless needles (51.1 g, 84%), mp 197 - 199°C(dec.). ^{1}H-Nmr ($CDCl_3$) δ :0.80 (3H, t, J=8 Hz, $CH_2\underline{CH_3}$), 0.96 (3H, d, J=7 Hz, 3-CH_3), 3.48, 4.01 (2H, each d, J=12 Hz, CH_2Ph), 6.80 - 7.30 (3H, m, thienyl-H), 7.40 (5H, s, phenyl-H). Anal. Calcd for $C_{20}H_{27}NOS\cdot HCl$: C, 65.64; H, 7.71; N, 3.83. Found: C, 65.60; H, 7.79; N, 3.87.

2,5,9α-Trimethyl-6,7-thieno[3,2-f]morphan (4). A suspension of 1,3,4-trimethyl-2-(2-thenyl)-4-hydroxypiperidine (3a)(32 g, 0.13 mol) in 47% hydrobromic acid (100 ml) was heated at 130°C with stirring. The cooled reaction mixture was basified with sodium hydrogen carbonate and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (ether) and distilled *in vacuo* to give 9α-methyl derivative (10.4 g,

35%), bp 65 - 70°C/0.005 mmHg. The oil solidified gradually on standing, mp 59 - 62°C. ^{1}H-Nmr (CCl_4) δ : 0.82 (3H, d, J=6.6 Hz, 9-CH_3), 1.28 (3H, s, 5-CH_3), 2.26 (3H, s, N-CH_3), 6.69 (1H, d, J=4.8 Hz, thienyl β-H), 6.95 (1H, d, J=4.8 Hz, thienyl α-H). Anal. Calcd for $C_{13}H_{19}NS$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.53; H, 8.09; N, 6.28. The hydrobromide was recrystallized from acetone-ethanol, mp 257 - 259°C.

2-Benzyl-5,9α-dimethyl-6,7-thieno[3,2-f]morphan (5). A suspension of 1-bezyl-3,4-dimethyl-4-hydroxypiperidine (3b)(3 g, 10 mmol) in a mixture of 47% hydrobromic acid (100 ml) and acetic acid (20 ml) was heated at 140°C with stirring. The cooled mixture was poured into ice-water, basified with conc. aqueous ammmonia, and extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. Distillation of the residue gave an oil, bp 125 - 135°C/0.06 mmHg. The hydrochloride was recrystallized from acetone-ethanol to give colorless needles (1.3 g, 46%), mp 251 - 252°C(dec.). ^{1}H-Nmr (HCl salt, CD_3OD) δ: 1.44 (3H, d, J=7 Hz, 9-CH_3), 4.41 (2H, s, CH_2Ph), 6.96 (1H, d, J=5.4 Hz, thienyl β-H), 7.35 (1H, d, J=5.4 Hz, thienyl α-H), 7.50 - 7.80 (5H, m, phenyl-H). Anal. Calcd for $C_{19}H_{23}NS\cdot HCl$: C, 68.34; H, 7.24; N, 4.19. Found: C, 68.15; H, 7.25; N, 4.04.

2-Benzyl-5-ethyl-9-methyl-6,7-thieno[3,2-f]morphans (6, 7). Compound (3c) (2.0 g, 6 mmol) was cyclized in a similar way to compound (3b). The oily product was purified by vacuum distillation to furnish 9α-ethyl derivative (6), bp 120 - 130°C/0.01 mmHg, which was led to the hydrochloride (1.06 g, 56%) as colorless needles (from acetone-ether), mp 189 - 192°C(dec.). ^{1}H-Nmr (HCl salt, CD_3OD) δ: 0.74 (3H, d, J=6.5 Hz, 9-CH_3), 0.96 (3H, t, J=6 Hz, $CH_2\underline{CH_3}$), 4.38 (2H, br s, CH_2Ph), 6.90 (1H, d, J=5 Hz, thienyl β-H), 7.23 (1H, d, J=5 Hz, thienyl α-H), 7.30 - 7.50 (5H, m, phenyl-H). Anal. Calcd for $C_{20}H_{25}NS\cdot HCl$: C, 69.04; H, 7.53; N, 4.03. Found: C, 69.01; H, 7.62; N, 3.93.

When the oily raw product was purified by column chromatography on silica gel using ether, 9β-ethyl derivative (7), bp 105 - 110°C/0.01 mmHg, was obtained from the first fraction and led to the hydrochloride (9%), mp 234 - 236°C (from acetone-ether). ^{1}H-Nmr (HCl salt, $CDCl_3$) δ: 0.74 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.14 (3H, d, J=7 Hz, 9-CH_3). Anal. Calcd for $C_{13}H_{19}NS\cdot HCl$: C, 51.65; H, 6.67; N, 4.63. Found: C, 51.88; H, 6.68; N, 4.83.

5,9α-Dimethyl-6,7-thieno[3,2-f]morphan (8). a) A solution of 2-benzyl-5,9α-dimethyl-6,7-thieno[3,2-f]morphan (5)(9.1 g, 31 mmol) in chloroform (300 ml) was added to a solution of cyanogen bromide (5.3 g, 50 mmol) in chloroform (100 ml). The whole

was stirred at room temperature for 1 h and then refluxed for 2 h. The solvent was removed under reduced pressure and ether was added to the residue. The ether solution was washed with water, dil. hydrochloric acid and dil. sodium carbonate successively, and dried. Evaporation of ether afforded an oily residue and 6% hydrochloric acid (250 ml) was added to the residue. The mixture was refluxed for 6 h, cooled, basified with conc. aqueous ammmonia, and extracted with chloroform. The extracts were washed with water, dried and concentrated. The residual oil was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 95 - 105°C/0.04 mmHg. ^{1}H-Nmr (CCl_4) δ : 0.79 (3H, d, J=7 Hz, 9-CH_3), 1.29 (3H, s, 5-CH_3), 6.66 (1H, d, J=5 Hz, thienyl β-H), 6.95 (1H, d, J=5 Hz, thienyl α-H). The hydrochloride was recrystallized from acetone-methanol to give colorless needles (2.6 g, 41%), mp 238 - 241°C(dec.). Anal. Calcd for $C_{12}H_{17}NS\cdot HBr$: C, 50.00; H, 6.29; N, 4.86. Found: C, 50.21; H, 6.37; N, 4.55.

b) Diethyl azodicarboxylate (0.3 g, 1.7 mmol) was added to a solution of 2,5,9α-trimethyl-6,7-thieno[3,2-f]morphan (**4**)(0.3 g, 1.4 mmol) in chloroform (100 ml). The whole was refluxed for 3 h and concentrated under reduced pressure. A solution of pyridine hydrochloride (0.2 g, 1.7 mmol) in a mixture of water (50 ml) and ethanol (100 ml) was added to the residue. The whole was stirred for 15 h at 25°C, basified with 10% sodium hydroxide and then extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was purified in the same way as method a) and led to the hydrobromide (0.12 g, 41%), which was identical with a sample prepared by method a).

5-Ethyl derivative (**9**) and (**10**) were prepared in a similar way to compound (**8**).

5-Ethyl-9α-methyl-6,7-thieno[3,2-f]morphan (**9**) bp 135 - 140°C/0.07 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.79 (3H, d, J=7 Hz, 9-CH_3), 1.02 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 6.87 (1H, d, J=5 Hz, thienyl β-H), 7.18 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from acetone-methanol to give colorless needles (69%), mp 245 - 248 °C(dec.).

5-Ethyl-9β-methyl-6,7-theino[3,2-f]morphan (**10**) bp 95 - 105°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.85 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.12 (3H, d, J=7 Hz, 5-CH_3), 6.77 (1H, s, thienyl β-H), 7.68 (1H, s, thienyl α-H). The hydrobromide was recrystallized from methanol-ethyl acetate to give colorless needles (63%), mp > 300°C. Anal. Calcd for $C_{13}H_{19}NS\cdot HBr$: C, 51.65; H, 6.67; N, 4.63. Found: C, 51.76; H, 6.55; N, 4.69.

2-Allyl-5,9α-dimethyl-6,7-thieno[3,2-f]morphan (**11**). A mixture of 5,9α-dimeth-

yl-6,7-thieno[3,2-f]morphan (**8**) hydrochloride (0.58 g, 2.4 mmol), allyl bromide (0.25 g, 2.1 mmol) and sodium carbonate (0.5 g, 4.7 mmol) in N,N-dimethylformamide (DMF) (100 ml) was refluxed for 5 h and concentrated under reduced pressure. Water was added to the residue and the whole was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (ether) and distilled in vacuo, bp 85 - 90°C/0.01 mmHg. ^{1}H-Nmr (CCl_4) δ: 0.79 (3H, d, J=6.8 Hz, 9-CH_3), 1.27 (3H, s, 5-CH_3), 4.00 - 6.00 (3H, m, vinyl H), 6.58 (1H, d, J=5.1 Hz, thienyl β-H), 6.85 (1H, d, J=5.1 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-ethanol to give colorless needles (0.47 g, 71%), mp 243 - 247 °C(dec.). Anal. Calcd for $C_{15}H_{21}NS\cdot HBr$: C, 54.87; H, 6.75; N, 4.27. Found: C, 54.61; H, 6.86; N, 4.01.

Other N-substituted thienomorphans (**12 - 13**), (**17 - 22**) were similarly prepared from thienomorphans (**8 - 10**) and alkyl halides.

5,9α-Dimethyl-2-(2-phenethyl)-6,7-thieno[3,2-f]morphan (**13**). Phenylacetyl chloride (0.3 g, 1.9 mmol) was added to a mixture of thienomorphan (**8**) (0.58 g, 2.8 mmol) and triethylamine (0.41 g, 4.1 mmol) in chloroform (100 ml). The whole was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was dissolved in dry THF (100 ml) and then lithium aluminum hydride (LAH)(2 g, 53 mmol) was added to the solution. The mixture was refluxed for 5 h, cooled, poured into ice-water and extracted with ether. The extracts were washed, dried (Na_2SO_4) and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 130 - 135°C/0.01 mmHg. The hydrobromide was recrystallized from 2-butanone-ethanol to give colorless needles (0.6 g, 77%), mp 285 - 288°C (dec.). ^{1}H-Nmr (CCl_4) δ: 0.78 (3H, d, J=7 Hz, 9-CH_3), 1.26 (3H, s, 5-CH_3), 6.58 (1H, d J=5 Hz, thenyl β-H), 6.82 (1H, d, J=5 Hz, thienyl α-H), 7.04 (5H, s, Ph). Anal. Calcd for $C_{20}H_{25}NS\cdot HBr$: C, 61.22; H, 6.68; N, 3.57. Found: C, 61.22; H, 6.77; N, 3.54. This compound was alternatively prepared by alkylation of **8** with phenethyl bromide in 54% yield.

Other N-substituted thienomorphans (**14, 23, 24**) were similarly prepared by acylation of thienomorphans (**8 - 10**) with acyl halides followed by reduction with LAH.

5-Ethyl-2,9α-dimethyl-6,7-thieno[3,2-f]morphan (**15**). Methyl iodide (3 g, 21 mmol) was added to a solution of 2-benzyl-5-ethyl-9α-methyl-6,7-thieno[3,2-f]morphan (**6**)(1.5 g, 4.8 mmol) in 2-butanone (10 ml). The whole was warmed at 60 - 70°C for 30 min and then stood overnight at room temperature. The precipitate was filtered

off and recrystallized from methanol-ether to give 2-benzyl-5-ethyl-2,9α-dimethyl-6,7-thieno[3,2-f]morphanium iodide as colorless needles (1.70 g, 90%), mp 192 - 193°C(dec.). A mixture of the thienomorphanium iodide (1.02 g) and 5% Pd-C (2 g) in ethanol (100 ml) was refluxed for 3 h under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give the residual oil, which was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 115°C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.86 (3H, d, J=7 Hz, 9-CH_3), 0.98 (3H, t, J=7.5 Hz, $CH_2\underline{CH_3}$), 2.47 (3H, s, N-CH_3), 7.05 (1H, d, J=7 Hz, thienyl β-H), 7.33 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from acetone-methanol to give colorless needles (0.66 g, 76%), mp 213 - 216°C(dec.). Anal. Calcd for $C_{14}H_{21}NS\cdot HBr$: C, 53.16; H, 7.01; N, 4.43. Found: C, 52.99; H, 7.07; N, 4.41.

5-Ethyl-2,9β-dimethyl-6,7-thieno[3,2-f]morphan (16). A mixture of compound (10) (0.896 g, 4.0 mmol), formic acid (0.921 g, 20 mmol) and 37% formalin (0.45 ml, 5.6 mmol) was warmed at 50°C and then at 90 - 100°C for 8 h. The cooled mixture was basified with dil. aqueous ammonia and extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The residual oil was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 90°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.75 (3H, t, J=7.5 Hz, 5-$CH_2\underline{CH_3}$), 1.17 (3H, d, J=7.6 Hz, 9-CH_3), 2.37 (3H, s, N-CH_3), 6.58 (1H, d, J=5 Hz, thienyl β-H), 7.18 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless needles (0.95 g, 74%), mp 244°C. Anal. Calcd for $C_{14}H_{25}NS\cdot HBr$: C, 53.16; H, 7.01; N, 4.43. Found: C, 53.09; H, 7.00; N, 4.50.

5,9α-Dimethyl-2-(3-methyl-2-butenyl)-6,7-thieno[3,2-f]morphan (12). bp 105 - 115 °C. ^{1}H-Nmr (CCl_4) δ : 0.85 (3H, d, J=7 Hz, 9-CH_3), 1.27 (3H, s, 5-CH_3), 1.62, 1.69 (each 3H, s, =$C(CH_3)_2$), 4.85 - 5.20 (1H, m, vinyl H), 6.50 (1H, d, J=5 Hz, thienyl β-H), 6.75 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (61%), mp 282 - 285°C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{17}H_{25}NS\cdot HBr$: C, 57.29; H, 7.35; N, 3.92. Found: C, 57.15; H, 7.52; N, 3.82.

2-Cyclopropylmethyl-5,9α-dimethyl-6,7-thieno[3,2-f]morphan (14). bp 110 - 115 °C/0.06 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0 - 0.65 (5H, m, J=7 Hz, cyclopropyl H), 0.82 (3H, d, J=6.4 Hz, 9-CH_3), 1.28 (3H, s, 5-CH_3), 6.50 (1H, d, J=4.9 Hz, thienyl β-H), 6.82 (1H, d, J=4.9 Hz, thienyl α-H). HBr salt: colorless needles (83%), mp 276 - 280 °C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{16}H_{25}NS\cdot HBr$: C, 56.13; H, 7.07; N, 4.09. Found: C, 56.05; H, 7.16; N, 4.07.

2-Allyl-5-ethyl-9α-methyl-6,7-thieno[3,2-f]morphan (17). bp 120°C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.88 (3H, d, J=6.5 Hz, 9-CH_3), 1.00 (3H, t, J=7 Hz, 5-CH_2CH_3), 5.10 - 6.10 (3H, m, $CH=CH_2$), 6.95 (1H, d, J=5.5 Hz, thienyl β-H), 7.23 (1H, d, J=5.5 Hz, thienyl α-H). HBr salt: colorless needles (61%), mp 240 - 243°C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{16}H_{22}NS\cdot HBr$: C, 56.13; H, 7.07; N, 4.09. Found: C, 56.41; H, 7.17; N, 4.18.

2-Allyl-5-ethyl-9β-methyl-6,7-thieno[3,2-f]morphan (18). bp 90 - 110°C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.72 (3H, t, J=7 Hz, 5-CH_2CH_3), 1.11 (3H, d, J=6.6 Hz, 9-CH_3), 4.68 - 5.20 (2H, m, $CH=CH_2$), 6.53 (1H, d, J=5 Hz, thienyl β-H), 6.83 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (84%), mp 218°C from ethyl acetate-methanol. Anal. Calcd for $C_{16}H_{23}NS\cdot HBr$: C, 56.13; H, 7.07; N, 4.09. Found: C, 56.26; H, 6.96; N, 4.10.

5-Ethyl-9α-methyl-2-(3-methyl-2-butenyl)-6,7-thieno[3,2-f]morphan (19). bp 120 °C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.90 (3H, d, J=7.5 Hz, 9-CH_3), 1.05 (3H, t, J=7 Hz, 5-CH_2CH_3), 1.81, 1.86 (each 3H, s, $=C(CH_3)_2$), 5.20 - 5.40 (1H, br s, $-CH=CH_2$), 6.91 (1H, d, J=5 Hz, thienyl β-H), 7.30 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (91%), mp 224 - 227°C (dec.) from 2-butanone-methanol. Anal. Calcd for $C_{18}H_{27}NS\cdot HBr$: C, 58.37; H, 7.62; N, 3.78. Found: C, 58.62; H, 7.71; N, 3.78.

5-Ethyl-9β-methyl-2-(3-methyl-2-butenyl)-6,7-thieno[3,2-f]morphan (20). bp 110 - 120°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.72 (3H, t, J=7 Hz, 5-CH_2CH_3), 1.10 (3H, d, J=7 Hz, 9-CH_3), 1.60, 1.68 (each 3H, s, $=C(CH_3)_2$), 4.80 - 5.20 (1H, br s, CH=C), 6.57 (1H, d, J=5 Hz, thienyl β-H), 6.87 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (74%), mp 221°C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{18}H_{27}NS\cdot HBr$: C, 58.37; H, 7.62; N, 3.78. Found: C, 58.16; H, 7.34; N, 3.62.

5-Ethyl-9α-methyl-2-phenethyl-6,7-thieno[3,2-f]morphan (21). bp 115°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.78 (3H, d, J=7.5 Hz, 9-CH_3), 1.00 (3H, t, J=7 Hz, 5-CH_2CH_3), 6.85 (1H, d, J=5 Hz, thienyl β-H), 7.10 (1H, d, J=5 Hz, thienyl α-H), 7.29 (5H, s, phenyl-H). HBr salt: colorless needles (53%), mp 239 - 244°C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{12}H_{27}NS\cdot HBr$: C, 62.06; H, 6.94; N, 3.45. Found: C, 62.09; H, 7.02; N, 3.38.

5-Ethyl-9β-methyl-2-propargyl-6,7-thieno[3,2-f]morphan (22). bp 105 - 112°C/0.03 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.74 (3H, t, J=7 Hz, 5-CH_2CH_3), 1.14 (3H, d, J=7 Hz, 9-CH_3), 6.72 (1H, d, J=5 Hz, thienyl β-H), 7.03 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (85%), mp 236.5°C from ethyl acetate-methanol. Anal. Calcd for $C_{16}H_{21}NS\cdot HBr$: C, 56.47; H, 6.52; N, 4.12. Found: C, 56.34; H, 6.54; N, 4.30.

2-Cyclopropylmethyl-5-ethyl-9α-methyl-6,7-thieno[3,2-f]morphan (23). bp 115°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0 - 0.70 (5H, m, cyclopropyl H), 0.80 (3H, d, J=7.5 Hz, 9-CH_3), 1.02 (3H, t, J=6.5 Hz, 5-CH_2CH_3), 6.70 (1H, d, J=5.5 Hz, thienyl β-H), 7.13 (1H, d, J=5.5 Hz, thienyl α-H). HBr salt: colorless needles (89%), mp 252 - 257 °C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{17}H_{25}NS\cdot HBr$: C, 57.29; H, 7.35; N, 3.93. Found: C, 57.26; H, 7.39; N, 3.88.

2-Cyclopropylmethyl-5-ethyl-9β-methyl-6,7-thieno[3,2-f]morphan (24). bp 95 - 110 °C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0 - 0.60 (5H, m, cyclopropyl H), 0.73 (3H, t, J=7 Hz, 5-CH_2CH_3), 1.13 (3H, d, J=6.6 Hz, 9-CH_3), 6.56 (1H, d, J=5 Hz, thienyl β-H), 6.68 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (84%), mp 230°C from ethyl acetate-methanol. Anal. Calcd for $C_{17}H_{25}NS\cdot HBr$: C, 57.29; H, 7.35; N, 3.93. Found: C, 57.35; H, 7.27; N, 3.93.

1,3-Dimethyl-4-n-propyl-2-thenyl-1,2,5,6-tetrahydropyridine (26). A solution of 2-thenyl chloride (42 g, 0.32 mol) in dry ether (200 ml) was added dropwise over 2 h to a suspension of 1,3-dimethyl-4-n-propylpyridinium iodide[14] (25)(65 g, 0.23 mol) and magnesium (12 g, 0.50 mol) in dry ether (1 l). The mixture was refluxed for another 2 h and then cooled. Aqueous ammonium chloride was added to the mixture and the whole was extracted with ether. The extracts were washed with dil. hydrochloric acid for several times. The washings were basified with conc. aqueous ammonia and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in methanol (300 ml) and sodium borohydride (10 g, 0.26 mol) was added portionwise to the solution. The mixture was refluxed for 5 h, cooled, poured into water, and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 115°C/0.06 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.78 (3H, t, J=6 Hz, CH_2CH_3), 1.58 (3H, s, 3-CH_3), 2.37 (3H, s, 1-CH_3). The oxalate was recrystallized from 2-butanone-methanol to give colorless needles (28 g, 32%), mp 110 - 111°C. Anal. Calcd for $C_{15}H_{23}NS\cdot(CO_2H)_2$: C, 60.05; H, 7.42; N, 4.13. Found: C, 60.42; H, 7.47; N, 4.26.

2,9-Dimethyl-5-n-propyl-6,7-thieno[3,2-f]morphinans (27, 28). A suspension of tetrahydropyridine (26) oxalate (5 g, 15 mmol) in 47% hydrobromic acid (150 ml) was heated at 140°C for 6 h with stirring, cooled and poured into ice-water. The mixture was basified with conc. aqueous ammonia and extracted with ether. The extracts were washed with water, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel (ether). β-Stereoisomer (27)

was obtained from the first fraction and α-isomer (**28**) was given from the second fraction. The thienomorphans (**27**) and (**28**) were led to the hydrobromides. β-Isomer (**27**): bp 85 - 90°C/0.05 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.80 - 1.05 (3H, m, $CH_2\underline{CH_3}$), 1.13 (3H, d, J=7 Hz, 9-CH_3), 2.30 (3H, s, N-CH_3), 6.68 (1H, d, J=5 Hz, thienyl β-H), 6.98 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless plates (0.29 g, 6%), mp 212 - 214°C from 2-butanone. Anal. Calcd for $C_{15}H_{23}NS\cdot HBr$: C, 54.54; H, 7.32; N, 4.24. Found: C, 54.69; H, 7.12; N, 4.00. α-Isomer (**28**): bp 110°C/0.06 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0.79 (3H, d, J=7 Hz, 9-CH_3), 2.35 (3H, s, N-CH_3), 6.77 (1H, d, J=4.4 Hz, thienyl β-H), 7.02 (1H, d, J=4.4 Hz, thienyl α-H). HBr salt: colorless prisms (2.9 g, 50%), mp 153.5 - 154.5°C from 2-butanone. Anal. Calcd for $C_{15}H_{23}NS\cdot HBr$: C, 54.54; H, 7.32; N, 4.24. Found: C, 54.52; H, 7.62; N, 4.00.

9α-Methyl-5-n-propyl-6,7-thieno[3,2-f]morphan (**29**) was prepared by demethylation of **28** with cyanogen bromide in a similar way to compound (**8**). bp 105°C/0.05 mmHg. HBr salt: colorless plates (51%), mp 241 - 244.5°C(dec.) from 2-butanone-methanol. ^{1}H-Nmr ($CDCl_3$) δ : 0.75 (3H, d, J=7.5 Hz, 9-CH_3), 6.68 (1H, d, J=4.7 Hz, thienyl β-H), 6.91 (1H, 1H, d, J=4.7Hz, thienyl α-H). Anal. Calcd for $C_{14}H_{21}NS\cdot HBr$: C, 53.16; H, 7.01; N, 4.43. Found: C, 53.13; H, 6.88; N, 4.53.

2-Allyl-9α-methyl-5-n-propyl-6,7-thieno[3,2-f]morphan (**30**) was prepared by alkylation of thienomorphan (**29**) in a similar way to compound (**11**). bp 115°C/0.05 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.74 (3H, d, J=7 Hz, 9-CH_3), 4.75 - 6.00 (3H, m, $CH{=}CH_2$), 6.71 (1H, d, J=5 Hz, thienyl β-H), 6.84 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless plates (88%), mp 265 - 267°C (dec.) from 2-butanone. Anal. Calcd for $C_{17}H_{25}NS$ HBr: C, 57.29; H, 7.35; N, 3.93. Found: C, 57.55; H, 7.45; N, 3.81.

9α-Methyl-2-(3-methyl-2-butenyl)-5-n-propyl-6,7-thieno[3,2-f]morphan (**31**) was prepared by alkylation of thienomorphan (**29**) in a similar way to compound (**11**). bp 125°C/ 0.05 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.74 (3H, d, J=7 Hz, 9-CH_3), 1.59, 1.63 (each 3H, s, $=C(CH_3)_2$), 6.59 (1H, d, J=5 Hz, thienyl β-H), 6.81 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless prisms (62%), mp 205 - 206°C(dec.) from 2-butanone. Anal. Calcd for $C_{19}H_{29}NS\cdot HBr$: C, 58.00; H, 7.94; N, 3.56. Found: C, 58.09; H, 7.82; N, 3.62.

2-Cyclopropylmethyl-9α-methyl-5-n-propyl-6,7-thieno[3,2-f]morphan (**32**) was prepared by acylation of thienomorphan (**29**) followed by reduction with LAH in a similar way to compound (**13**). bp 120°C/0.04 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0 - 0.60 (5H, m, cyclopropyl H), 0.75 (3H, d, J=7 Hz, 9-CH_3), 6.62 (1H, d, J=5 Hz, thienyl β-H), 6.83 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless prisms (74%), mp 248.5 - 250°C(dec.)

from 2-butanone. Anal. Calcd for $C_{17}H_{27}NS \cdot HBr$: C, 57.30; H, 7.35; N, 3.93. Found: C, 57.45; H, 7.40; N, 3.91.

9α-Methyl-2-phenethyl-5-n-propyl-6,7-thieno[3,2-f]morphan (33) was prepared by acylation of thienomorphan (**29**) followed by reduction with LAH in a similar way to compound (**13**). bp 145 - 150°C/0.05 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 0.72 (3H, d, J=7 Hz, 9-CH_3), 6.60 (1H, d, J=5 Hz, thienyl β-H), 6.82 (1H, d, J=5 Hz, thienyl α-H), 7.00 (5H, s, Ph). HBr salt: colorless prisms (48%), mp 206 - 208°C from 2-butanone. Anal. Calcd for $C_{22}H_{29}NS \cdot HBr$: C, 62.84; H, 7.19; N, 3.33. Found: C, 63.04; H, 7.38; N, 3.29.

2-(2,5-Dimethyl-3-thenyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (36a). A solution of 2,5-dimethyl-3-thenyl chloride[15] (4.72 g, 29 mmol) in dry THF (20 ml) was added dropwise to a boiling suspension of magnesium (1.52 g, 63 mmol) in THF (70 ml) under nitrogen. The mixture was refluxed for 40 min and cooled. The Grignard reagent thus prepared was added dropwise over 30 min to a suspension of 1,3,4-trimethylpyridinium iodide[16] (**34a**)(4.94 g, 20 mmol) in dry THF (50 ml) The whole was stirred for 3 h at room temperature, decomposed with 20% aqueous ammonia and extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated to dryness. The oily product was led to the oxalate, which was recrystallized from ethanol to give colorless needles (2.77 g, 36%), mp 144 - 146°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.55, 1.63 (each 3H, br s, 3,4-CH_3), 2.37 (3H, s, NCH_3), 2.30, 2.37 (each 3H, s, thienyl-CH_3). Anal. Calcd for $C_{15}H_{23}NS \cdot (CO_2H)_2$: C, 60.15; H, 7.42; N, 4.13. Found: C, 59.89; H, 7.42; N, 4.97.

1-Benzyl-2-(2,5-dimethyl-3-thenyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine (36b) was prepared by reaction of **34b** with thenylmagnesium chloride followed by reduction with sodium borohydride in a similar way to **36a**. The oxalate was recrystallized from ethanol to give colorless columns (46%), mp 168 - 170°C. ^{1}H-Nmr ($CDCl_3$) δ: 1.55, 1.63 (each 3H, br s, 3,4-CH_3), 2.20, 2.33 (each 3H, s, thienyl-CH_3). Anal. Calcd for $C_{21}H_{27}NS \cdot (CO_2H)_2$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.46; H, 7.04; N, 3.24.

1',2,3',5,9α-Pentamethyl-6,7-thieno[4,3-f]morphan (37). A mixture of compound (**36a**) (1.33 g, 5.3 mmol), 48% hydrogen bromide (10 ml) and methanol (5 ml) was refluxed for 24 h. The cooled mixture was basified with conc. aqueous ammonia and extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography on silica gel (ether) gave an oil (0.75 g, 57%). ^{1}H-Nmr ($CDCl_3$) δ: 0.85 (3H, d, J=7

Hz, 9-CH_3), 1.43 (3H, s, 5-CH_3), 2.38 (6H, s, N- and 1' or 3'-CH_3), 2.74 (3H, s, 1' or 3'-CH_3). HBr salt: colorless prisms, mp 272 - 274°C(dec.) from ethanol-acetone. Anal. Calcd for $C_{15}H_{23}NS \cdot HBr \cdot 1/2H_2O$: C, 54.69; H, 7.17; N, 3.99. Found: C, 54.70; H, 7.32; N, 4.11.

2-Benzyl-1',3',5,9α-tetramethyl-6,7-thieno[4,3-f]morphan (38) was prepared in a similar way to compound (37). A colorless oil (60%). ^{1}H-Nmr ($CDCl_3$) δ: 0.79 (3H, d, J=7.0 Hz, 9-CH_3), 1.41 (3H, s, 5-CH_3), 2.25, 2.35 (each 3H, s, 1', 3'-CH_3), 3.53, 3.68 (each 1H, d, J=14.0 Hz, NCH_2Ph). HBr salt: colorless prisms, mp 240 - 243 °C(dec.) from ethanol-acetone. Anal. Calcd for $C_{21}H_{27}NS \cdot HBr \cdot 1/2H_2O$: C, 61.81; H, 6.84; N, 3.28. Found: C, 62.22; H, 6.94; N, 3.31.

1',3',5,9α-Tetramethyl-6,7-thieno[4,3-f]morphan (39). A solution of N-methyl-thienomorphan (37) (2.98 g, 12 mmol) in chloroform (50 ml) was added dropwise over 10 min to an ice-cold solution of cyanogen bromide (1.5 g, 14 mmol) in chloroform (20 ml) under nitrogen. The mixture was stirred at that temperature for 1 h and then refluxed for 3 h. After being cooled to room temperature, it was washed with 1 N hydrochloric acid, 0.5 N sodium hydroxide, and water, successively, and dried (Na_2SO_4). The solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel (ether) and led to the hydrobromide (1.6 g, 51%). ^{1}H-Nmr (free base, $CDCl_3$) δ: 0.83 (3H, d, J=7.0 Hz, 9-CH_3), 1.43 (3H, s, 5-CH_3), 2.24, 2.40 (each 3H, s, 1', 3'-CH_3). Colorless prisms, mp > 300°C (dec.) from methanol. Anal. Calcd for $C_{14}H_{21}NS \cdot HBr$: C, 53.16; H, 7.01; N, 4.43. Found: C, 53.25; H, 7.12; N, 4.28.

2-Allyl-1',3',5,9α-tetramethyl-6,7-thieno[4,3-f]morphan (40). Allyl bromide (0.42 g, 3.5 mmol) was added to a suspension of thienomorphan 39 hydrobromide (1 g, 3.2 mmol) and sodium hydrogen carbonate (0.6 g, 7.1 mmol) in DMF (50 ml), and the whole was refluxed for 5 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (ether) and led to the hydrobromide. ^{1}H-Nmr (free base, $CDCl_3$) δ: 0.81 (3H, d, J=7.0 Hz, 9-CH_3), 1.43 (3H, s, 5-CH_3), 2.23, 2.37 (each 3H, s, 1', 3'-CH_3), 4.90- 5.40(3H, m, vinyl H). Colorless prisms (0.69 g, 81%), mp 253 - 255°C(dec.) from ethanol. Anal. Calcd for $C_{17}H_{25}NS \cdot HBr$: C, 57.30; H, 7.35; N, 3.93. Found: C, 57.41; H, 7.39; N, 3.72.

2-(3-Methyl-2-butenyl)-1',3',5,9α-tetramethyl-6,7-thieno[4,3-f]morphan (41) was prepared in a similar way to compound (40). ^{1}H-Nmr ($CDCl_3$) δ: 0.83 (3H, d, J=7 Hz,

9-CH_3), 1.43 (3H, s, 5-CH_3), 1.68, 1.75 (each 3H, s, =$C(CH_3)_2$), 2.26, 2.38 (each 3H, s, 1', 3'-CH_3), 3.10 (2H, br d, J=6 Hz, NCH_2), 5.30 (1H, br t, J=6 Hz, CH_2=C). HBr salt: colorless prisms (40%), mp 210 - 213°C(dec.) from ethanol. Anal. Calcd for $C_{19}H_{29}NS \cdot HBr$: C, 59.36; H, 7.87; N, 3.64. Found: C, 59.49; H, 7.65; N, 3.51.

1',3',5,9α-Tetramethyl-2-phenethyl-6,7-thieno[4,3-f]morphan (42). Phenylacetyl chloride (0.59 g, 3.8 mmol) was added dropwise over 30 min to a mixture of thienomorphan (39) hydrobromide (1 g, 3.2 mmol) and triethylamine (1.1 ml, 7.9 mmol) in chloroform (50 ml). The whole was stirred for 1 h at room temperature and concentrated to dryness. The residue was dissolved in dry THF and LAH (2 g, 53 mmol) was added to the solution and the whole was refluxed with stirring for 5 h. The cooled mixture was poured into ice-water and extracted with ether. The extracts were dried (Na_2SO_4) and concentrated to dryness. The residual oil was purified by column chromatography on silica gel (ether). ^{1}H-Nmr ($CDCl_3$) δ: 0.83 (3H, d, J=7 Hz, 9-CH_3), 1.43 (3H, s, 5-CH_3), 2.20, 2.37 (each 3H, s, 1', 3'-CH_3), 7.24 (5H, s, phenyl H). HBr salt: colorless prisms (1.16 g, 87%), mp 244 - 247°C(dec.) from ethanol. Anal. Calcd for $C_{22}H_{29}NS \cdot HBr$: C, 62.85; H, 7.19; N, 3.33. Found: C, 62.65; H, 7.25; N, 3.21.

2-Cyclopropyl-1',3',5,9α-tetramethyl-6,7-thieno[4,3-f]morphan (43) was prepared in a similar way to compound (42). ^{1}H-Nmr ($CDCl_3$) δ: 0 - 0.55 (5H, m, cyclopropyl H), 0.83 (3H, d, J=7 Hz, 9-CH_3), 1.45 (3H, s, 5-CH_3), 2.24, 2.40 (each 3H, s, 1', 3'-CH_3). HBr salt: colorless prisms (88%), mp 250 - 265°C(dec.) from ethanol. Anal. Calcd for $C_{18}H_{27}NS \cdot HBr$: C, 58.37; H, 7.62; N, 3.78. Found: C, 58.25; H, 7.52; N, 3.52.

4a-Hydroxy-1-(2-thenyl)perhydroisoquinoline (45). Water (1.8 l) was added with stirring vigorously to a solution of 2-(cyclohexen-1-yl)ethylamine (44)(37.5 g, 0.30 mol) in 1 N hydrochloric acid (300 ml). The mixture was warmed to 50°C and then 90°C, and stirred for 24 h at that temperature. Methyl β-(2-thienyl)glycidate (25.5 g, 0.30 mol) was added to it at that temperature with stirring. The cooled reaction mixture was basified with conc. aqueous ammonia and extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residue was recrystallized from methanol-ethyl acetate to give colorless prisms (21.5 g, 29%), mp 175 - 175.5°C. Anal. Calcd for $C_{14}H_{21}NOS$: C, 66.89; H, 8.42; N, 5.57. Found: C, 66.82; H, 7.45; N, 5.44.

2-Benzyl-4a-hydroxy-1-(2-thenyl)perhydroisoquinoline (46). A mixture of perhydroisoquinoline (45) (10 g, 40 mmol), benzyl bromide (7.5 g, 44 mmol) and potassium

carbonate (11 g, 80 mmol) in DMF (250 ml) was refluxed for 3 h. Water was added to the cooled mixture and the whole was extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 180°C/0.1 mmHg. The hydrochloride was recrystallized from 2-butanone-methanol to give colorless prisms (7.7 g, 51%), mp 196 - 199°C. ^{1}H-Nmr (CD_3OD) δ: 3.63 (2H, s, NCH_2Ph), 7.15.(3H, s, ArH). Anal. Calcd for $C_{21}H_{27}NOS\cdot HCl$: C, 66.73; H, 7.47; N, 3.71. Found: C, 66.84; H, 7.40; N, 3.55.

12-Benzyl-3-thiamorphinan (47). A solution of perhydroisoquinoline (46) hydrochloride (5.0 g, 13 mmol) in 48% hydrobromic acid (400 ml) was heated at 140°C for 15 h. The cooled mixture was basified conc. aqueous ammonia and extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (ether) and vacuum distillation, bp 125°C/0.02 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 3.52 (2H, s, NCH_2Ph), 6.58 (1H, d, J=5 Hz, thienyl β-H), 6.83 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless prisms (2.3 g, 42%), mp 273 - 275°C(dec.). Anal. Calcd for $C_{21}H_{25}NOS\cdot HBr$: C, 62.37; H, 6.48; N, 3.46. Found: C, 62.58; H, 6.48; N, 3.56.

3-Thiamorphinan (48). A solution of cyanogen bromide (1.59 g, 15 mmol) in chloroform (25 ml) was added to a solution of N-benzylthiamorphinan (47) (2.8 g, 8.2 mmol) in chloroform (100 ml). The mixture was stirred for 2 h at room temperature and then refluxed for 2 h. Chloroform was evaporated and the residue was extracted with ether. The extracts were washed with dil. hydrochloric acid and dil. sodium carbonate, successively, dried (Na_2SO_4) and concentrated. A solution of the residue in 6% hydrochloric acid (300 ml) was refluxed for 6 h and then cooled. The mixture was basified with conc. aqueous ammonia and extracted with dichloromethane. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on alumina (ether) and vacuum distillation, bp 110°C/0.005 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 6.58 (1H, d, J=5 Hz, thienyl β-H), 6.91 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless needles (1.85 g, 71.5%), mp 257 - 258.5°C (dec.). Anal. Calcd for $C_{14}H_{19}NS\cdot HBr$: C, 53.50; H, 6.41; N, 4.46. Found: C, 53.67; H, 6.38; N, 4.31. Compound (48) was alternatively prepared by cyclization of perhydroisoquinoline (45) with 48% hydrobromic acid in 30% yield.

12-Methyl-3-thiamorphinan (49). A mixture of thiamorphinan (48) (1.96 g, 8.4

mmol), formic acid (3.0 g, 65 mmol) and 27% formalin (1.1 ml, 10 mmol) was heated at 90 - 100°C for 8 h. The cooled mixture was poured into water (200 ml), basified with conc. aqueous ammonia and extracted with ether. The extracts were washed with water, dried (Na_2SO_4) and concentrated. The residual oil was purified in a similar way to compound (**47**). bp 125 - 130°C/0.15 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 2.42 (3H, s, NCH_3), 6.68 (1H, d, J=5 Hz, thienyl β-H), 7.20 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless needles (1.18 g, 57%), mp 223 - 228°C. Anal. Calcd for $C_{15}H_{21}NS\cdot HBr$: C, 54.87; H, 6.75; N, 4.27. Found: C, 55.07; H, 6.76; N, 4.27.

12-Allyl-3-thiamorphinan (**50**). A mixture of thiamorphinan (**48**) hydrobromide (1.26 g, 4.1 mmol), sodium hydrogen carbonate (0.7 g, 8.3 mmol), allyl bromide (0.49 g, 4.1 mmol) in DMF (80 ml) was refluxed for 5 h with stirring. The cooled mixture was poured into water and extracted with ether. The extracts were washed with water, dried and concentrated. The residual oil was purified in a similar way to compound (**47**). bp 110°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 4.80 - 6.00 (3H, m, vinyl H), 6.65 (1H, d, J=5 Hz, thienyl β-H), 6.96 (1H, d, J=5 Hz, thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless needles (1.26 g, 87%), mp 269 - 271°C. Anal. Calcd for $C_{17}H_{23}NS\cdot HBr$: C, 57.62; H, 6.83; N, 3.95. Found: C, 57.85; H, 6.91; N, 3.95.

12-(3-Methyl-2-butenyl)-3-thiamorphinan (**51**) was prepared in a similar way to compound (**48**). bp 110°C/0.01 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 1.56, 1.62 (each 3H, s, $=C(CH_3)_2$), 4.85 - 5.20 (1H, m, vinyl H), 6.51 (1H, d, J=5 Hz, thienyl β-H), 6.83 (1H, d, J=5 Hz, thienyl α-H). HBr salt: colorless needles (72%), mp 265 - 267°C (dec.) from 2-butanone-ethanol. Anal. Calcd for $C_{19}H_{27}NS\cdot HBr$: C, 59.67; H, 7.38; N, 3.66. Found: C, 59.74; H, 7.40; N, 3.40.

12-Cyclopropylmethyl-3-thiamorphinan (**52**). Cyclopropanecarbonyl chloride (0.42 g, 4.0 mmol) was added dropwise over 30 min to a mixture of thiamorphinan (**48**) hydrobromide (1.26 g, 4.1 mmol) and triethylamine (0.82 g, 8.1 mmol) in chloroform (100 ml) and the whole was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in dry THF (50 ml). LAH (1.5 g, 40 mmol) was added to the solution and the mixture was refluxed for 5 h. The cooled mixture was decomposed with ice-water and extracted with ether. The extracts were washed with water, dried and concentrated. The residue was purified in a similar way to compound (**47**). bp 120 °C/0.005 mmHg. ^{1}H-Nmr ($CDCl_3$) δ : 0 - 1.00 (5H, m, cyclopropyl H), 6.57 (1H, d, J=5 Hz, thienyl β-H), 6.88 (1H, d, J=5 Hz,

thienyl α-H). The hydrobromide was recrystallized from 2-butanone-methanol to give colorless needles (1.2 g, 82%), mp 268 - 271°C(dec.). Anal. Calcd for $C_{18}H_{25}NS$·HBr: C, 58.69; H, 7.11; N, 3.80. Found: C, 58.88; H, 7.02; N, 3.50.

12-Phenethyl-3-thiamorphinan (53) was prepared in a similar way to compound (52). bp 140 C/0.005 mmHg. ^{1}H-Nmr ($CDCl_3$) δ: 6.57 (1H, d, J=5 Hz, thienyl β-H), 6.88 (1H, d, J=5 Hz, thienyl α-H), 7.03 (5H, s, Ph). HBr salt: colorless needles (50%), mp 190 - 191°C(dec.) from 2-butanone-methanol. Anal. Calcd for $C_{22}H_{27}NS$·HBr: C, 63.15; H, 6.74; N, 3.35. Found: C, 62.97; H, 6.79; N, 3.29.

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Received, 7th December, 1990