Benzomorphan Analogues: Synthesis of Some Thieno[2,3-*f*]morphans

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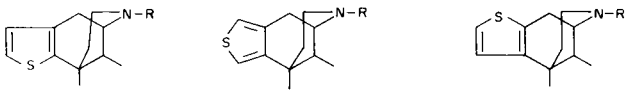
A series of *N*-substituted 5,9-dimethylthieno[2,3-*f*]morphans and 5-phenylthieno[2,3-*f*]-morphans has been prepared starting from 3,4-dimethylpyridine and 4-phenylpyridine and 3-thenylbromide by an application of the Grewe morphinan synthesis. The thieno[2,3-*f*]morphans were tested for analgetic activity, but only weak analgetic activity relative to toxicity and no morphine antagonism activity was observed.

Many benzomorphans are known to possess good analgetic activity and some are known to possess morphine antagonism activtiy (1). The present work was undertaken in our laboratories to investigate the structure activity effect of replacing the benzene ring in benzomorphans with a thiophene ring. This can be done in three ways as indicated in structures I, II, and III.



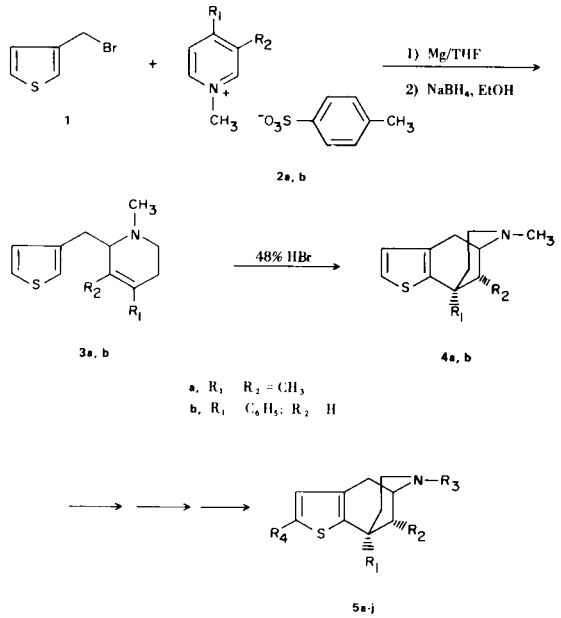
I II III

The relative ease of synthesis of compounds of structure I by well established synthetic routes (2) suggested their preparation (See Scheme I).

The reaction of the Grignard reagent, prepared from magnesium and 3-thenyl bromide **1**, with the pyridinium compounds **2a** and **2b** followed by sodium borohydride reduction gave the tetrahydropyridine compounds **3a** and **3b** respectively. Cyclization of these compounds was achieved with 48% hydrobromic acid to give the thieno-[2,3-*f*]morphans **4a** and **4b**. The configuration of the 9-methyl group in **4a** was determined by examination of its nmr spectrum in deuteriochloroform, The signal for the 9-methyl appears as a diamagnetically shifted doublet δ 0.8 (J = 6 Hz) due to its position over the aromatic ring (3). Therefore, **4a** is the α isomer (*cis* 5,9-dimethyl). Demethylation by the method of von Braun (4) gave **5a** and **5b**. These secondary amino compounds were converted to *N*-alkylated derivatives either by treatment with an allylic bromide to give **5c** and **5d**, or by acylation with the appropriate acyl chloride followed by lithium aluminum hydride reduction to give **5e**, **5f**, and **5g**.

In the benzomorphan series the most active compounds generally possess a hydroxy group in the 2′ position. We, therefore, attempted to functionalize the corresponding

Scheme I



5a-j

position in the thieno[2,3-*f*]morphan series. Bromination of the thiophene ring of **4a** gave the 2′-bromo derivative **5h**. Treatment of **4a** with acetic anhydride-polyphosphoric acid gave the 2′-acetyl derivative **5i**, which was converted to its oxime **5j** by treatment with hydroxylamine hydrochloride.

Conversion of **5i** into the 2′-hydroxy derivative was attempted *via* Bayer Villager oxidation followed by hydrolysis of the acetoxy intermediate, but only tars were obtained. Preparation of the 2′-amino derivative from **5j** was attempted *via* Beckmann rearrangement followed by hydrolysis of the acetamido intermediate, but again only tars were obtained. The inability to isolate either the the 2′-hydroxy or 2′-amino derivative can probably be explained by the known instability of 2-amino and 2-hydroxy thiophenes (5).

Table I

Thieno[2,3-*f*]morphans

No	R_1	R_2	R_3	R_4	Method(a)	Mp, °C (Solvent) (b)	Yield %	Formula	Analyses					
									C	Calcd. H	N	C	Found H	N
4a	CH_3	CH_3	CH_3	H	-	169-179 (E)	81	$C_{13}H_{19}NS\cdot C_4H_4O_4$	60.53	6.87	4.15	60.28	7.15	4.35
4b	C_6H_5	H	CH_3	H	-	202-206 (E)	41(c)	$C_{17}H_{19}NS\cdot 1/2C_4H_4O_4$	69.81	6.47	4.28	70.09	6.68	4.15
5a	CH_3	CH_3	H	H	A	181-186 (E)	71	$C_{12}H_{17}NS\cdot C_2H_2O_4$	56.54	6.44	4.71	56.63	6.76	4.60
5b	C_6H_5	H	H	H	A	217-224 (E-W)	25	$C_{16}H_{17}NS\cdot C_2H_2O_4$	62.58	5.54	4.06	62.75	5.78	4.07
5c	CH_3	CH_3	$-CH_2CH=CH_2$	H	B	225-230 (P)	67	$C_{15}H_{21}NS\cdot HCl$	63.46	7.81	4.93	63.40	7.92	4.91
5d	CH_3	CH_3	$-CH_2CH=C(CH_3)_2$	H	B	205-207 (P)	35	$C_{17}H_{25}NS\cdot HCl$	65.46	8.40	4.49	65.13	8.41	4.43
5e	CH_3	CH_3	$-CH_2$-c-C_3H_5	H	C	230-240 (P)	87	$C_{16}H_{23}NS\cdot HCl$	64.51	8.12	4.70	64.49	7.98	4.65
5f	CH_3	CH_3	$-CH_2CH_2$-C_6H_5	H	C	222-229 (E)	54	$C_{20}H_{25}NS\cdot HCl$	69.04	7.53	4.04	69.22	7.79	3.99
5g	C_6H_5	H	$-CH_2CH_2$-C_6H_5	H	C	230 dec (M-W)	55	$C_{24}H_{25}NS\cdot HCl$	72.79	6.62	3.54	72.49	6.82	3.32
5h	CH_3	CH_3	CH_3	Br	-	265 dec (E)	56	$C_{13}H_{18}BrNS\cdot HBr$	40.96	5.02	3.68	41.29	5.17	3.93
5i	CH_3	CH_3	CH_3	$-COCH_3$	-	91-95 (E)	87	$C_{15}H_{21}NOS\cdot C_2H_2O_4$	57.77	6.56	3.96	57.50	6.84	3.85
5j	CH_3	CH_3	CH_3	$-C(NOH)CH_3$	-	218-228 (F)	52	$C_{15}H_{22}N_2OS\cdot HCl$	57.21	7.36	8.90	57.33	7.60	9.01

(a) Method refers to experimental section. (b) Solvents: E = ethanol; W = water; P = 2-propanol; M = methanol; F = 95% ethanol. (c) Overall yield from **2b**.

The compounds were evaluated for analgetic activity by the mouse hot plate test (6). As a class of compounds, the thieno[2,3-*f*]morphans showed a high degree of toxicity. Only compounds **4a** MED 40 mg./kg. and **5e** MED 20 mg./kg. showed any analgetic activity. None of the compounds possessed any morphine antagonism activity. Thus, it appears that this mode of substitution of a thiophene ring for a benzene ring has not produced any compounds of significant analgetic interest.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Nmr and ir spectra were recorded for all compounds and are consistent with assigned structures.

1,3,4-Trimethylpyridinium-*p*-toluenesulfonate (**2a**).

Methyl *p*-toluenesulfonate (372 g., 2 moles) and 3,4-lutidine (214 g., 2 moles) were placed together in 500 ml. of acetone and 500 ml. of benzene and stored at 5° for 18 hours. Collection of the crystals gave 560 g. (95%), m.p. 118-119°.

Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.68; H, 6.99; N, 4.47.

1-Methyl-4-phenylpyridinium-*p*-toluenesulfonate (**2b**).

Compound **2b** was prepared in a similar manner from 4-phenylpyridine and methyl *p*-toluenesulfonate (86%), m.p. 152-153°.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.85; H, 5.93; N, 4.10.

2-(3-Thenyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (**3a**).

To a vigorously stirred refluxing suspension of 90 g. (45 g. of powder and 45 g. of chips) of magnesium in 1.5 l. of tetrahydrofuran was added a solution of 133 g. (0.75 mole) of 3-thenyl bromide (7) in 400 ml. of tetrahydrofuran over a period of 1.5 hours. Refluxing was continued for 0.5 hour, then the excess magnesium was removed by filtration.

This Grignard reagent was added to a stirred suspension of 147 g. (0.5 mole) of **2a** in 500 ml. of tetrahydrofuran over a period of 0.5 hour. The reaction mixture was stirred at ambient temperature for 2 hours and then treated with 600 ml. of an aqueous solution of 120 g. of ammonium chloride. The organic layer was separated and the aqueous layer was extracted further with ether. The extracts were acidified with 1*N* hydrochloric acid and the layers separated. Neutralization of the aqueous layer with potassium hydroxide, followed by ether extraction, drying (magnesium sulfate), and concentration gave 88 g. of the crude unstable dihydropyridine.

This material without purification was reduced with 15 g. of sodium borohydride in 500 ml. of ethanol at a water bath temperature of 55-60°. After stirring for 1.5 hours, the reaction mixture was treated with dilute hydrochloric acid and concentrated. The residue was treated with dilute sodium carbonate and extracted with ether. After drying over magnesium sulfate and concentration, 67 g. of crude oily product was obtained. Treatment with oxalic acid in acetone gave 49 g. (32%) of crystalline product. Recrystallization from ethanol gave an analytical sample m.p. 136-137°.

Anal. Calcd. for $C_{13}H_{19}NS\cdot C_2H_2O_4$: C, 57.86; H, 6.80, N, 4.50. Found: C, 57.68; H, 6.99; N, 4.47.

2,5,9-Trimethylthieno[2,3-*f*]morphan (**4a**).

The free base of **3a** (23.7 g., 0.107 mole) was treated with 237 ml. of 48% hydrobromic acid and heated at 90-100° for 24 hours. The reaction mixture was concentrated, neutralized with ammonium hydroxide, and extracted with methylene chloride. After drying (magnesium sulfate) and concentration 23.7 g. of crude product was obtained. Purification was achieved by chromatography on alumina (Woelm neutral, grade I). Elution with benzene gave 19.1 g. (81%) of **4a** as an oil. Treatment with fumaric acid in acetone followed by recrystallization from ethanol gave the pure hydrogen fumarate salt of **4a**.

2-Methyl-5-phenylthieno[2,3-*f*]morphan (**4b**).

Compound **4b** was prepared in a similar manner as **4a** from 88.5 g. (0.5 mole) of **1** and 109.5 g. (0.35 mole) of **2b**. The tetrahydropyridine **3b**, 90 g. was not isolated as it was probably a mixture of isomers.

Cyclization of 70 g. of **3b** with 48% hydrobromic acid gave 70 g. of crude product. Chromatography on alumina (Woelm neutral, grade I), and elution with 1:1 benzene-ethyl ether afforded 30 g. of crystalline **4b** (43%). This was converted to its crystalline fumarate salt by treatment with fumaric acid in ethanol.

N-Substituted 5,9-Dimethyl- and 5-Phenylthieno[2,3-*f*]morphans (**5a-g**).

Method A.

Equimolar amounts of cyanogen bromide and **4a** or **4b** were refluxed in chloroform for 4 hours. The resultant cyanamide was hydrolized by refluxing with 2*N* hydrochloric acid for 20 hours. The crude demethylated product was isolated by neutralization with sodium hydroxide and extraction with methylene chloride. Purification was achieved by recrystallization of the appropriate salt.

Method B.

Equimolar amounts of an allylic bromide and **5a** were refluxed for 3 hours in dimethylformamide in the presence of sodium carbonate. After removal of solvent the residue was diluted with water and the product isolated by extraction with ethyl acetate. Purification was achieved by recrystallization of the hydrochloride salt.

Method C.

Compound **5a** or **5b** was dissolved in a mixture of triethylamine and chloroform and treated with a 10% excess of acyl chloride. After stirring for 2 hours the amide was isolated in the usual manner. It was reduced with excess lithium aluminum hydride in tetrahydrofuran by refluxing for 2 hours. Purification was achieved by crystallization of the hydrochloride salt.

2′-Bromo-2,5,9-trimethylthieno[2,3-*f*]morphan (**5h**).

To a stirred solution of 4.4 g. (0.02 mole) of **4a** in 40 ml. of acetic acid was added 6.4 g. (0.02 mole) of pyridinium bromide perbromide. Stirring was continued for 16 hours. After removal of solvent and crystallization from 2-propanol-water, 4.0 g. (56%) of the hydrobromide salt was obtained, which was recrystallized from ethanol.

2′-Methylcarbonyl-2,5,9-trimethylthieno[2,3-*f*]morphan (**5i**).

Compound **4a** (6.5 g., 0.029 mole) was placed together with 3 g. of acetic anhydride and 65 g. of polyphosphoric acid and heated on a steam bath for 1 hour. The reaction mixture was diluted with ice water, neutralized with potassium carbonate, and extracted with methylene chloride. Removal of solvent gave 7.9 g. of crude product. Formation of the oxalate salt in ethanol gave 9.2 g. of **5i** which was recrystallized from 95% ethanol.

2′-Methylcarbonyl-2,5,9-trimethylthieno[2,3-*f*]morphan Oxime (**5j**).

A mixture of **5i** (5.3 g., 0.02 mole) and hydroxylamine hydrochloride (1.4 g., 0.02 mole) in 70 ml. of 95% ethanol was refluxed with stirring for 3 hours. After cooling 3.3 g. of crystals were obtained. Recrystallization from 95% ethanol gave an analytical sample.

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