Chemistry of Benzo[*b*]furan. V. (1). Synthesis of Substituted Thia-Analogs and Oxa-Analogs of Dihydrorutecarpine and Evodiamine

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Cycloaddition of 3,4-dihydrobenzo[*b*]thieno[2,3-*c*]pyridine (**6**) with the sulfinamide anhydride **9** (R = H) afforded the thia-analog of dihydrorutecarpine (**2a**). Condensation of the imine **6** with the sulfinamide anhydride **9** (R = CH_3) gave the thia-analog of evodiamine (**2b**). Starting from 1-methyl-3,4-dihydrobenzo[*b*]thieno[2,3-*c*]pyridine (**12**) and 1-methyl-3,4-dihydrobenzo[*b*]furo-[2,3-*c*]pyridine (**14**), a series of 3-methyl derivatives of thia-analogs of dihydrorutecarpine and evodiamine (**2c-2i**) and oxa-analogs of dihydrorutecarpine and evodiamine (**1a-1g**) were similarly prepared.

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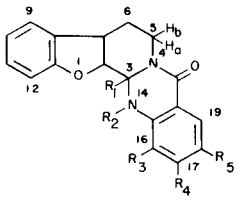
As a part of a continuing program designed to expand the chemistry of benzo[*b*]furan (2-5) and benzo[*b*]thiophene (6,7) toward the synthesis of analogs of indole alkaloids, it became necessary to synthesize oxa-analogs (**1a-1g**) and thia-analogs (**2a-2i**) of dihydrorutecarpine and evodiamine (8,9) for biological evaluation.



1

a) $R_1=CH_3$, $R_2=R_3=R_4=R_5=H$

b) $R_1=R_2=CH_3$, $R_3=R_4=R_5=H$

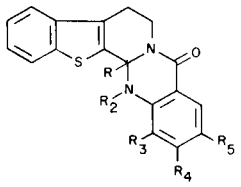
c) $R_1=R_3=CH_3$, $R_2=R_4=R_5=H$

d) $R_1=R_4=CH_3$, $R_2=R_3=R_5=H$

e) $R_1=R_5=CH_3$, $R_2=R_3=R_4=H$

f) $R_1=CH_3$, $R_2=R_3=R_5=H$, $R_4=Cl$

g) $R_1=CH_3$, $R_2=R_3=R_4=H$, $R_5=Cl$



2

a) $R_1=R_2=R_3=R_4=R_5=H$

b) $R_1=R_3=R_4=R_5=H$, $R_2=CH_3$

c) $R_1=CH_3$, $R_2=R_3=R_4=R_5=H$

d) $R_1=R_2=CH_3$, $R_3=R_4=R_5=H$

e) $R_1=R_3=CH_3$, $R_2=R_4=R_5=H$

f) $R_1=R_4=CH_3$, $R_2=R_3=R_5=H$

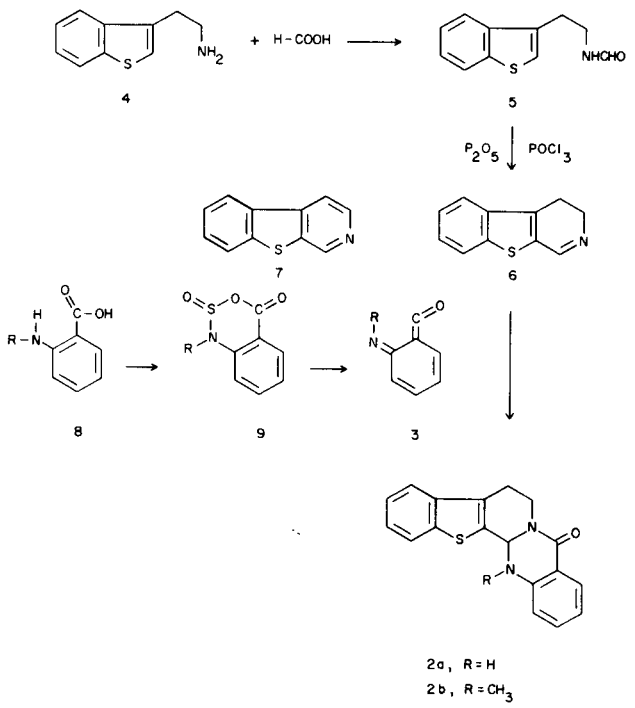
g) $R_1=R_5=CH_3$, $R_2=R_3=R_4=H$

h) $R_1=CH_3$, $R_2=R_3=R_5=H$, $R_4=Cl$

i) $R_1=CH_3$, $R_2=R_3=R_4=H$, $R_5=Cl$

Evodiamine (9) and dihydrorutecarping (8), the indoloquinazoline alkaloids found in *Evodia rutaecarpa* and *Zanthoxylum flavum*, respectively, have been synthesized by many authors (10-13). The cycloaddition of the keteneimine **3** (R = CH_3), which was prepared through the reaction of *N*-methylanthranilic acid with thionyl chloride, has been recently used for the synthesis of evodiamine (14). In this work, the syntheses of oxa-analogs and thia-analogs of dihydrorutecarpine and evodiamine through the application of this method are described. The feasibility of the cycloaddition reaction was demonstrated as shown in Scheme I.

Scheme I



Reaction of 2-(3-benzo[*b*]thienyl)ethylamine (**4**) (15) with formic acid afforded 3-(2-formamidoethyl)benzo[*b*]thiophene (**5**) which was cyclized with phosphorous oxychloride and phosphorous pentoxide to 3,4-dihydrobenzo-[*b*]thieno[2,3-*c*]pyridine (**6**) (16) and benzo[*b*]thieno[2,3-*c*]-pyridine (**7**) (17). Heating anthranilic acid (**8**, R = H) with thionyl chloride in dry benzene under reflux gave the unstable sulfinamide anhydride **9** (R = H). The reaction of the latter with **6** in dry benzene at room temperature afforded the thia-analog of dihydrorutecarpine (**2a**). The lat-

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ter was formed through the cycloaddition of the imine **6** either with sulfinamide anhydride **9** (R = H), with simultaneous loss of sulfur dioxide, or with keteneimine **3** (R = H) (14).

It is reported that dihydrorutecarpine is unstable under the above experimental conditions and by a spontaneous dehydrogenation it gives rutecarpine (14b). However, in our case, the thia-analog of dihydrorutecarpine was stable. The structure was determined by ir [ν max 3260 (NH), 1635 cm^{-1} (amide)], nmr [δ 6.29 ppm (s, 1H, H_3)] and mass [retro-Diels-Alder type fragmentation afforded two characteristic ions **10** (*m/e* 186) and **11** (*m/e* 119)] spectroscopy (Scheme II).

The thia-analog of evodiamine (**2b**) was obtained starting from *N*-methylanthranilic acid (**8**, R = CH_3) (Scheme II).

Heating *N*-methylanthranilic acid with thionyl chloride in dry benzene gave an unstable sulfinamide anhydride **9** (R = CH_3), which on treatment with **6** evolved sulfur dioxide to give the thia-analog of evodiamine (**2b**) in good yield. In a similar manner a series of 3-methyl derivatives of thia-analogs of dihydrorutecarpine and evodiamine were prepared through the reaction of 1-methyl-3,4-dihydrobenzo[*b*]thieno[2,3-*c*]pyridine (**12**) (7,15) with derivatives of anthranilic acid (**13**, R_1 = H) or *N*-methyl-

Scheme 2

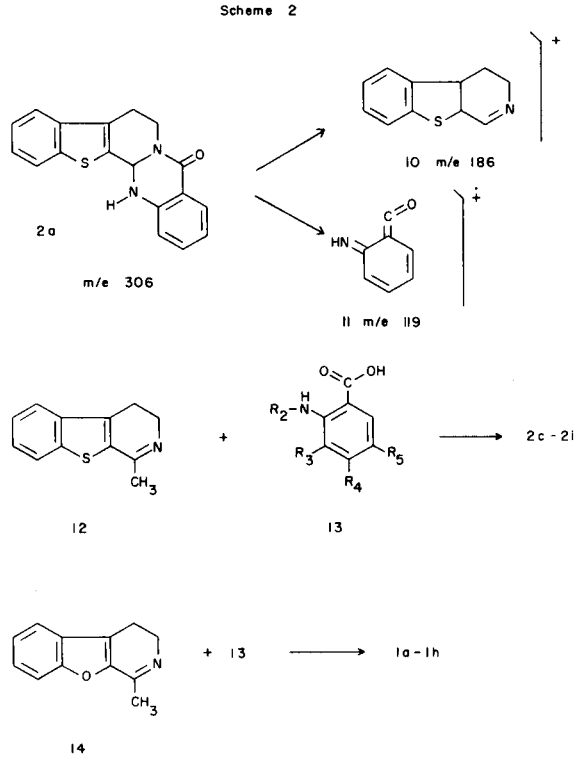

Table I

Proton Magnetic Resonance of Derivatives of Thia-Analogs of Dihydrorutecarpine and Evodiamine

Compound No.	3	5a	14 (a)	16 (b)	17	18	19
2a	6.29 (s, 1H)	4.62-4.95 (m, 1H)	4.42 (s, 1H)		8.20-7.0 (m, 4H, aromatic)		
2b	6.0 (s, 1H)	4.79-5.13 (m, 1H)	2.92 (s, 3H)		6.90-8.0 (m, 3H, aromatic)		8.10 (q, 1H, $J_{18,19}$ = 8.5 Hz, $J_{17,19}$ = 1.8 Hz
2c	1.82 (s, 3H)	5.03-5.36 (m, 1H)	4.59 (s, 1H)		6.72-8.16 (m, 4H, aromatic)		
2d	1.69 (s, 3H)	5.03-5.36 (m, 1H)	2.46 (s, 3H)		8.27-7.06 (m, 4H, aromatic)		
2e	1.75 (s, 3H)	5.0 -5.33 (m, 1H)	4.13 (s, 1H)	2.21 (s 3H)	6.73-8.0 (m, 4H, aromatic)		
2f	1.79 (s, 3H)	5.03-5.33 (m, 1H)	4.42 (s, 1H)	6.62 (d, 1H $J_{16,18}$ = 2 Hz)	2.29 (s, 3H)	6.69 (q, 1H, $J_{18,19}$ = 8.5 Hz $J_{16,18}$ = 2 Hz	7.92 (d, 1H, $J_{18,19}$ = 8.5 Hz
2g	1.75 (s, 3H)	5.03-5.29 (m, 1H)	4.33 (s, 1H)	6.73 (d, 1H, $J_{16,17}$ = 8.5 Hz)	7.20 (q, 1H, $J_{16,17}$ = 8.5 Hz, $J_{17,19}$ = 2 Hz	2.29 (s, 3H)	7.90 (d, 1H) $J_{17,19}$ = 2 Hz
2h	1.79 (s, 3H)	5.05-5.33 (m, 1H)	4.74 (s, 1H)	6.82 (d, 1H, $J_{16,18}$ = 2 Hz)		6.89 (q, 1H, $J_{18,19}$ = 8.5 Hz $J_{16,18}$ = 2 Hz	7.92 (d, 1H, $J_{18,19}$ = 8.5 Hz
2i	1.79 (s, 3H)	5.03-5.29 (m, 1H)	4.56 (s, 1H)	6.8 (d, 1H, $J_{16,17}$ = 8.5 Hz)	7.26-7.93 (m, 1H)		8.0 (d, 1H, $J_{17,19}$ = 2 Hz

(a) In all compounds, one of the hydrogens at carbon 5 and two hydrogens at carbon 6 appeared as a multiplet at 2.56-3.34 ppm. (b) In all compounds, H_9-H_{12} appeared as a 4 hydrogen multiplet in the aromatic region (7.0-8.0 ppm).

Table II

Proton Magnetic Resonance of Derivatives of Oxa-Analogs of Dihydrorutecarpine and Evodiamine

Compound No.	3	5a	14 (a)	16 (b)	17	18	19
1a	1.79 (s, 3H)	5.03-5.36 (m, 1H)	4.90 (s, 1H)		6.66-8.16 (m, 4H, aromatic)		
1b	1.69 (s, 3H)	5.03-5.36 (m, 1H)	2.66 (s, 3H)		7.0-7.72 (m, 3H, aromatic)		8.14 (q, 1H, $J_{18,19}$ = 8.5 Hz, $J_{17,19}$ = 1.8 Hz
1c	1.79 (s, 3H)	4.95-5.36 (m, 1H)	4.62 (s, 1H)	2.19 (s, 3H)	6.53-7.63 (m, 2H, aromatic)		8.0 (q, 1H, $J_{18,19}$ = 8.5 Hz, $J_{17,19}$ = 1.8 Hz
1d	1.75 (s, 3H)	5.0-5.33 (m, 1H)	4.82 (s, 1H)	6.56 (d, 1H, $J_{16,18}$ = 1.8 Hz)	2.29 (s, 3H)	6.70 (q, 1H, $J_{16,18}$ = 1.8 Hz)	$J_{18,19}$ = 8.5 Hz, 8.0 (d, 1H, $J_{18,19}$ = 8.5 Hz
1e	1.79 (s, 3H)	5.0-5.36 (m, 1H)	4.72 (s, 1H)	6.73 (d, 1H, $J_{16,17}$ = 8 Hz)	7.13-7.8 (m, 1H)	2.29 (s, 3H)	7.90 (d, 1H, $J_{17,19}$ = 2 Hz)
1f	1.79 (s, 3H)	5.0-5.46 (m, 1H)	5.42 (s, 1H)	6.85 (d, 1H $J_{16,18}$ = 2 Hz)		6.78 (q, 1H, $J_{18,19}$ = 9 Hz $J_{16,18}$ = 2 Hz	7.98 (d, 1H, $J_{18,19}$ = 9 Hz)
1g	1.79 (s, 3H)	5.03-5.33 (m, 1H)	4.89 (s, 1H)	6.73 (d, 1H, $J_{16,17}$ = 8.5 Hz)	7.23-7.7 (m, 1H)		8.05 (d, 1H, $J_{17,19}$ = 2.5 Hz)

(a) In all compounds, one of the hydrogens at carbon 5 and two hydrogens at carbon 6 appeared as a multiplet at 2.56-3.36 ppm. (b) In all compounds, H_9-H_{12} appeared as a 4 hydrogen multiplet in the aromatic region (7.0-8.10 ppm).

Table III

Physical Data of Derivatives of Oxa-Analogs and Thia-Analogs of Dihydrorutecarpine and Evodiamine

Compound No.	M.P., °C (a)	Yield %	Formula	C%		H%		N%	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
1a	93-95	60	$C_{19}H_{16}N_2O_2$	75.00	74.82	5.26	5.08	9.21	9.35
1b	oil	52	$C_{20}H_{18}N_2O_2$	75.47	75.64	5.66	5.84	8.80	8.96
1c	oil	70	$C_{20}H_{18}N_2O_2$	75.47	75.36	5.66	5.82	8.80	8.94
1d	234-236	82	$C_{20}H_{18}N_2O_2$	75.47	75.29	5.66	5.49	8.80	8.69
1e	220-222	63	$C_{20}H_{18}N_2O_2$	75.47	75.32	5.66	5.51	8.80	8.96
1f	230-232	86	$C_{19}H_{15}ClN_2O_2$	67.36	67.18	4.43	4.58	8.27	8.15
1g	228-230	77	$C_{19}H_{15}ClN_2O_2$	67.36	67.49	4.43	4.61	8.27	8.42
2a	217-219	60	$C_{18}H_{14}N_2OS$	70.59	70.78	4.57	4.75	9.15	9.34
2b	203-204	75	$C_{19}H_{16}N_2OS$	71.25	71.07	5.00	5.15	8.75	8.58
2c	173-175	54	$C_{19}H_{16}N_2OS$	71.25	71.44	5.00	4.85	8.75	8.91
2d	oil	68	$C_{20}H_{18}N_2OS$	71.86	71.98	5.39	5.51	8.38	8.21
2e	148-150	90	$C_{20}H_{18}N_2OS$	71.86	71.69	5.39	5.45	8.38	8.46
2f	199-201	80	$C_{20}H_{18}N_2OS$	71.86	71.98	5.39	5.48	8.38	8.56
2g	205-207	65	$C_{20}H_{18}N_2OS$	71.86	71.69	5.39	5.24	8.38	8.19
2h	214-216	95	$C_{19}H_{15}ClN_2OS$	64.32	64.17	4.23	4.41	7.90	7.76
2i	180-182	84	$C_{19}H_{15}ClN_2OS$	64.32	64.19	4.23	4.18	7.90	8.04

(a) Unless otherwise mentioned, the compound was crystallized from absolute ethanol.

anthranilic acid (**13**, R_1 = CH_3) and thionyl chloride, respectively (Scheme II). Finally, starting from 1-methyl-3,4-dihydrobenzo[*b*]furo[2,3-*c*]pyridine (**14**) (3,18), a series of 3-methyl derivatives of oxa-analogs of dihydrorutecarpine and evodiamine were similarly prepared (Scheme II).

The structures of all compounds prepared were confirmed by spectroscopic methods (ir, nmr, ms) and chemical analysis. The nmr spectral data for the compounds prepared are summarized in Tables I and II.

The physical data for the compounds prepared are summarized in Table III.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 267 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT MS-311 spectrometer at 70 eV.

3-(2-Formamidoethyl)benzo[*b*]thiophene (5).

A solution of 1.77 g. (0.01 mole) of 2-(3-benzo[*b*]thienyl)ethylamine (**4**) (15) and 6 ml. of formic acid was refluxed in an oil bath at 140-160° for 1.5 hours. The solvent was evaporated. To the residue, water (20 ml.) was added and the solution was extracted with ether. The ether was evaporated and the residue was crystallized from ether to give 1.11 g. (54%) of **5**, m.p. 72-74°; ir (potassium bromide): 3300 (NH), 1650 cm^{-1} (amide); ms: *m/e* (relative intensity) 205 (M^+, 22), 160 (100), 147 (64), 115 (8).

Anal. Calcd. for $C_{11}H_{11}NOS$: C, 64.39; H, 5.37; N, 6.83. Found: C, 64.52; H, 5.18; N, 6.98.

3,4-Dihydrobenzo[*b*]thieno[2,3-*c*]pyridine (**6**).

A stirring suspension of **5** (2.05 g., 0.01 mole), phosphorous oxychloride (3.5 ml.) and phosphorous pentoxide (4 g.) in 60 ml. of dry xylene was refluxed for 5 hours. After cooling, ice water was added and the mixture was stirred for 24 hours. The aqueous layer was made alkaline with a concentrated solution of sodium hydroxide and extracted with chloroform. The organic layer was dried and evaporated. The residue was purified by tlc (silica gel, chloroform). The fast moving fraction was crystallized from ether to give benzo[*b*]thieno[2,3-*c*]pyridine (**7**) (0.37 g., 20%), m.p. 96-98° [lit. (17) m.p. 96-98°]; nmr (deuteriochloroform): 9.16 (s, 1H, Pyridine α-H), 8.65 (d, 1H, pyridine α-H, J = 6.5 Hz), 7.2-8.3 ppm (m, 5H, aromatic).

The slow moving fraction was crystallized from ether to give 0.97 g. (52%) of **6**, m.p. 104-106°; nmr (deuteriochloroform): 7.13-7.92 (m, 4H, aromatic), 5.35 (t, 1H, H_1), 3.84 (sextet, 2H, CH_2N) and 2.76 ppm (t, 2H, CH_2); *m/e* (relative intensity): 187 (M^+, 100), 186 (92), 160 (58), 115 (74), 89 (14), 69 (28), 63 (24).

Anal. Calcd. for $C_{11}H_9NS$: C, 70.59; H, 4.81; N, 7.49. Found: C, 70.75; H, 4.67; N, 7.65.

Thia-Analog of Dihydrorutecarpine (**2a**).

A solution of 548 mg. (4 mmoles) of anthranilic acid (**8**, R = H) and 6 ml. of thionyl chloride in 60 ml. of dry benzene was refluxed for 2 hours in a current of nitrogen, then an excess of reagent and solvent was evaporated under the reduced pressure to leave the sulfinamide anhydride **9** (R = H). To the latter was added a solution of 374 mg. (2 mmoles) of **6** in 20 ml. of dry benzene. The mixture was allowed to stand at room temperature overnight. After evaporation of benzene, the residue was dissolved in chloroform. The chloroform was washed with 10% sodium hydroxide and water, and then dried. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform) to give 370 mg. (60%) of **2a**, m.p. 217-219° (ethanol); ir (potassium bromide): 3260 (NH), 1635 cm^{-1} (amide); nmr (deuteriochloroform): 7.0-8.2 (m, 8H, aromatic), 6.29 (s, 1H, H_3), 4.62-4.95 (m, 1H, H_{5a}), 4.42 (s, 1H, H_{14}), and 2.66-3.33 ppm (m, 3H, $H_{6,5b}$); ms: *m/e* (relative intensity): 306 (M^+, 83), 305 (100), 304 (67), 303 (74), 186 (7), 119 (12), 115 (7).

Anal. Calcd. for $C_{18}H_{14}N_2OS$: C, 70.59; H, 4.57; N, 9.15. Found: C, 70.78; H, 4.75; N, 9.34.

Thia-Analog of Evodiamine (**2b**).

A solution of 187 mg. (1 mmole) of **6** in 30 ml. of dry benzene was added to the sulfinamide anhydride (**9**, R = CH_3) [prepared from 302 mg. (2 mmoles) of *N*-methylanthranilic acid] and the mixture was worked up as above to give 240 mg. (75%) of **2b**; m.p. 203-204° (ethanol); ir (potassium bromide): 1650 cm^{-1} (amide); nmr (deuteriochloroform): 8.10 (q, 1H, H_{19}, $J_{18,19}$ = 8.5 Hz, $J_{17,19}$ = 1.8 Hz), 6.90-8.0 (m, 7H, aromatic), 6.0 (s, 1H, H_3), 4.79-5.13 (m, 1H, H_{5a}) 2.95-3.62 (m, 3H, $H_{6,5b}$), and 2.92 ppm (s, 3H, CH_3N); ms: *m/e* (relative intensity): 320 (M^+, 94), 319 (100), 105 (20).

Anal. Calcd. for $C_{19}H_{16}N_2OS$: C, 71.25; H, 5.0; N, 8.75. Found: C, 71.07; H, 5.15; N, 8.58.

Oxa-Analog of 3-Methyldihydrorutecarpine (**1a**).

A solution of 608 mg. (2 mmoles) of 1-methyl-3,4-dihydrobenzo[*b*]furo-[2,3-*c*]pyridine (**14**) (3,18) in 40 ml. of dry benzene was added to the sulfinamide anhydride **9** (R = H) [prepared from 548 mg. of anthranilic acid (**8**, R = H)] and the mixture was worked up as above to give 365 mg. (60%) of **1a**, m.p. 193-195° (ethanol); ir (potassium bromide): 3325 (NH), 1635 cm^{-1} (amide); nmr (deuteriochloroform): 6.66-8.16 (m, 8H, aromatic), 5.03-5.36 (m, 1H, H_{5a}), 4.90 (s, 1H, NH), 2.59-3.39 (m, 3H, $H_{6,5b}$), and 1.79 (s, 3H, CH_3); ms: *m/e* (relative intensity): 304 (M^+, 3), 289 ($M-CH_3$, 100), 144 (7), 115 (5).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.26; N, 9.21. Found: C, 74.82; H, 5.08; N, 9.35.

Starting from derivatives of anthranilic acid (**13**), compound **12** or **14** and thionyl chloride, other derivatives of oxa-analogs and thia-analogs of dihydrorutecarpine and evodiamine were similarly prepared (See Tables I, II & III).

Acknowledgement.

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