[Chem. Pharm. Bull. 32(3) 877—886 (1984)]

Studies on Fused Indoles. II.[1] Structural Modifications and Analgesic Activity of 4-Aminomethyltetrahydrothiopyrano[2,3-*b*]indoles

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(Received June 18, 1983)

A series of 4-aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole derivatives was synthesized and evaluated for analgesic activity. Preliminary structure–activity relationship analysis showed that substitution on the benzene portion of the indole ring reduced the analgesic activity, whereas a short-chain N^b-alkyl substituent enhanced the potency, as exemplified by an N^b-methyl substituted analogue. This compound was equipotent to morphine in the acetic acid writhing assay using mice.

Keywords——thiopyrano[2,3-*b*]indole; rigid tryptamine; thio-Claisen rearrangement; analgesic activity; structure–activity relationship

The physiological activity of tryptamine and its derivatives has led to intense interest in the synthesis of tryptamines. In the preceding paper,[1] we reported a novel synthesis of 4-aminomethyltetrahydrothiopyrano[2,3-*b*]indoles, rigid analogues of tryptamine, which were found to have analgesic activity. The present paper describes structural modifications of the original active compound **1** (V, R = H) and the analgesic activities of the synthesized analogues. The structure–activity relationships are also discussed.

Chemistry

Chart 1 illustrates our methods employed for preparing most of the biologically tested compounds listed in Table I. Method A was used only at the early stage of this study, but appears to be useful for the construction of a nitrogen heterocycle[2] at position 4. Method B is more versatile and suitable for the introduction of substituents on the nitrogen of the side chain.

The experimental procedures were described in the preceding paper[1] for the synthesis of the original compounds **1**, **5** (VIII, $R^3 = Me$, $R^1 = R^2 = R^4 = H$) and **20** (VIII, $R^1 = R^2 = H$, $R^3 = R^4 = Me$). Similar procedures gave the corresponding elaborated analogues in good yields. It is particularly interesting that 9-phenyl analogues could be prepared by method B.

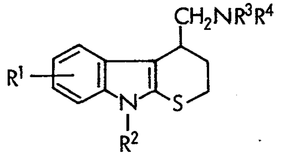
With regard to the amino portion, the preliminary assay suggested that the compound having a methyl group (compound **5**) was the most potent. Therefore, a variety of substituents were introduced on the indole nitrogen of **5** by method C.

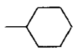
The S-dioxide of **5** (compound **43**) was derived from intermediate IX of method C by oxidation with *m*-chloroperbenzoic acid followed by deprotection, while the S-monooxide **42** was obtained by direct oxidation of **5** with HIO_4.

Pharmacological Methods

The acute toxicity was determined 72 h after oral administration in mice (DS strain, male, 4 weeks old). The LD_{50} was calculated by probit analysis. Analgesic activity was measured by the following methods: (1) the inhibition of phenyl-*p*-quinone induced writhing (PQW),[3]

TABLE I.[a)]



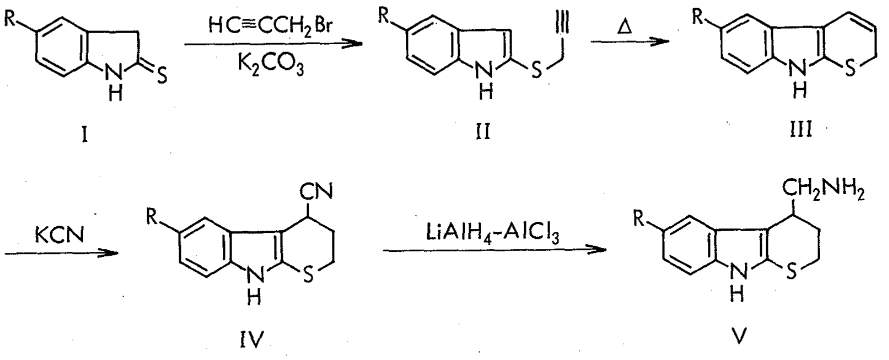
No.	R¹	R²	R³	R⁴	Salt[b)]	Acute toxicity LD_{50} mg/kg *p.o.*	PQW ED_{50} mg/kg *p.o.*	AAW ED_{50} mg/kg *p.o.*	Modified Haffner ED_{50} mg/kg *p.o.*	Foot licking ED_{50} mg/kg *p.o.*	Randall–Selitto ED_{50} mg/kg *p.o.*
1	H	H	H	H	—	481	30p	12.9	32.1	6.8	42.2
2	6-Cl	H	H	H	—	750p	200p	>50	>200	>25	>25
3	6-Me	H	H	H	—	750p	200p	35.4	>100	>25	>25
4	6-MeO	H	H	H	—	750p	200p	>50	>200	>25	>25
5	H	H	Me	H	A	330	5.6	4.2	5.9	2.0	4.9
6	H	H	Et	H	B	400p	20p	10.4	>100	2.6	38.4
7	H	H	*n*-Pr	H	A	400p	40p	>50	>100	3.5	>50
8	H	H	Iso-Pr	H	—	200p	75p	18.7	>50	25p	NT
9	H	H	*n*-Bu	H	C	750p	75p	>50	>200	14.2	35.9
10	H	H	$-CH_2CH=CH_2$	H	D	400p	75p	>50	>100	12.1	>50
11	H	H		H	C	400p	75p	>50	>100	11.4	42
12	H	H	$PhCH_2$	H	—	750p	400p	>50	>200	>25	NT
13	H	H	$Me_2NCH_2CH_2$	H	E	750p	>500	>50	>100	>25	>50
14	H	H	Ph	H	C	>1000	>1000	>50	>100	>25	>50
15	6-F	H	Me	H	C	175p	75p	30.3	51.9	>25	37.4
16	6-F	H	Et	H	C	375p	75p	23.4	>100	>25	>50
17	7-CF_3	H	Me	H	A	375p	175p	>50	>100	25p	>50
18	8-Et	H	Me	H	C	400p	37.5	20	>100	8.2	7.8
19	5,8-Di-Me	H	Me	H	A	375p	75p	21.3	47.3	3.3	14.5
20	H	H	Me	Me	—	200p	75p	21.4	>100	14.3	>25
21	H	H	*n*-Bu	*n*-Bu	—	NT	NT	>50	>100	32.5	>50

22	H	H	$-(CH_2)_5-$		C	750p	200p	>50	>100	>25	>50
23	H	H	$-(CH_2)_2-\overset{Me}{N}-(CH_2)_2$		—	400p	200p	>50	>100	>25	>50
24	H	Ph	H	H	F	>1000	400p	>50	>100	10.1	50p
25	H	Ph	Me	H	A	750	75p	>50	>100	2.3	>50
26	H	Ph	Et	H	A	>1000	400p	>50	>100	>25	>50
27	H	Ph	Me	Me	F	750p	400p	>50	>100	>25	>50
28	H	Me	Me	H	C	750p	20p	21.2	>100	0.54	17.8
29	H	Et	Me	H	—	750p	37.5p	12.2	>100	10.5	>50
30	H	*n*-Pr	Me	H	A	375p	37.5p	19.7	>100	14.8	50p
31	H	Iso-Bu	Me	H	A	175p	7.5p	2.5	80.6	1.7	4.7
32	H	Iso-Pr	Me	H	A	750p	75p	10.9	>100	12.8	45.4
33	H	$PhCH_2$	Me	H	A	>1000	175	>50	>100	>25	>50
34	H	$Me_2NCH_2CH_2$	Me	H	G	175p	>100p	>50	>50	>25	>50
35	H	Et_2NCOCH_2	Me	H	A	750p	400p	>50	>100	12.8	>50
36	H	COOMe	Me	H	A	175p	37.5	9.5	21.6	NT	>50
37	H	Ac	Me	H	A	175p	7.5p	5.1	4.7	0.74	4.7
38	H	COEt	Me	H	A	175p	17.5p	9.6	16.4	3.9	>50
39	H	COPh	Me	H	C	750p	17.5p	11.4	79.7	13.1	>50
40	H	COPhCl-*p*	Me	H	A	>1000p	17.5p	8.7	>100	17.3	>50
41	H	Ac	Me	Me	A	175p	17.5p	2.1	8.3	4.7	15.9
42 (S-Oxide)	H	H	Me	H	C	>1000	75p	>50	100p	25p	>50
43 (S-Dioxide)	H	H	Me	H	—	750p	75p	11.7	71.8	2.9	19.1
Aminopyrine						800	160	38	160	22	158

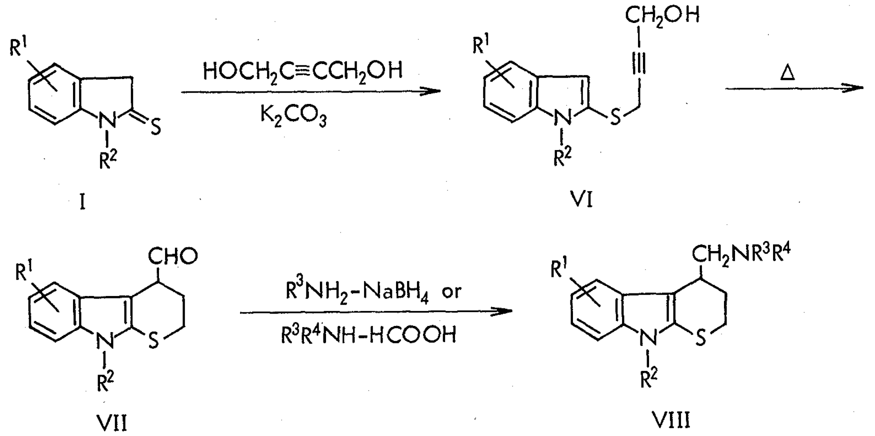
a) NT, not tested; p, value presumed when the number of doses was not enough for precise analysis.

b) A, HCl; B, HBr; C, oxalic acid; D, CH_3SO_3H; E, 2HBr; F, L-tartaric acid; G, 2HCl.

method A



method B



method C

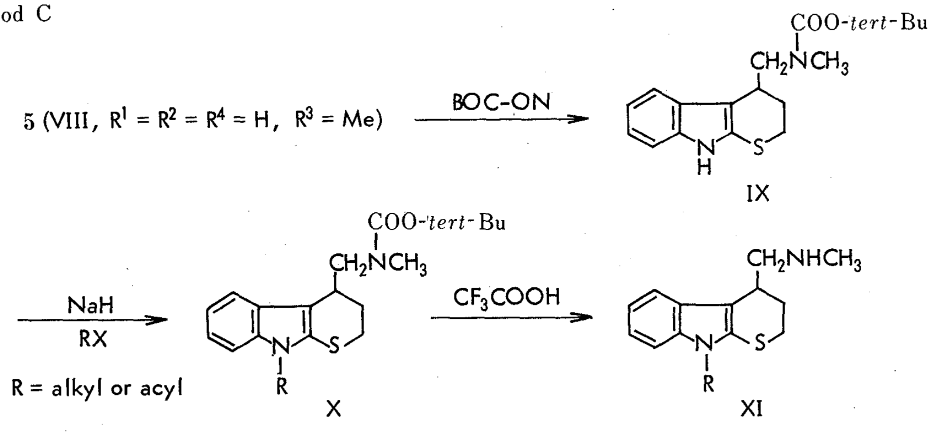


Chart 1

(2) the inhibition of acetic acid induced writhing (AAW),[4] (3) the modified Haffner method[5] (4), the foot licking method[6] and (5) the Randall–Selitto method.[7] The compounds were administered orally in all experiments. DS strain mice (male, 4 weeks old) were used for methods 1—3 and SLC-Wistar rats (female, 9 weeks old) for methods 4 and 5. The ED_{50}'s for analgesic activity were calculated by linear-regression analysis except for those in the PQW assay where the ED_{50}'s were obtained by probit analysis.

Results and Discussion

The structures and biological data of the parent compound **1** and its substituted analogues are given in Table I.

The data from the AAW screening led to the following structure–activity relationships. Clearly, substituents (R^1) on the benzene carbon of the indole ring reduced the analgesic activity of the unsubstituted analogues. Among compounds with substituents (R^3 and R^4) on the nitrogen of the side chain, compound **5** having a methyl group was three times more active than the parent compound **1**. Although an ethyl substituent slightly increased the potency of **1**, a higher alkyl or a bulky substituent weakened or eliminated the activity. Introduction of a second alkyl group on the nitrogen lowered the activity. The compounds possessing a phenyl (**12**, **14**), and amino (**13**) or a cyclic substituent (**22**, **23**) were all inactive.

The effect of substitution (R^2) on the indole nitrogen was rather complicated. The compound with an isopropyl group (**31**) exhibited greater activity than unsubstituted **5**, while other lower-alkyl substituents gave compounds which had half to one-fifth the potency of **5**. Acylation on the indole nitrogen of compound **5** caused a slight decrease in the activity. Interestingly, however, acetylation of compound **20** greatly enhanced its potency (compare **41** to **20**).

It is noteworthy that the S-oxide **42** had lost the activity of the parent compound **5**, while the S-dioxide **43** retained a fair degree of potency.

The above structure–activity relationships based on the AAW assay are reasonably consistent with the data from the four other assays with the exception of a few cases where the ED_{50} value in one of the assays greatly differed from those obtained by the other assays (for example, ED_{50} of 2.3 mg/kg in the foot-licking assay of **25**).

Compound **5**, which had uniformly high potency in all the assays, was approximately 30 times more active in the PQW screening than aminopyrine and 9 times more active in the AAW assay. Moreover, when compared with morphine, this compound exhibited a similar order of activity in the AAW assay both by oral and subcutaneous administration (ED_{50}: 4.2 mg/kg *p.o.* and 0.55 mg/kg *s.c.* for **5**; 4.5 mg/kg *p.o.* and 0.66 mg/kg *s.c.* for morphine sulfate). Interestingly, in spite of its high analgesic potency, **5** exhibited neither opioid agonist nor antagonist activity by Kosterlitz's method.[8)]

These results suggest that the analogues in this series represent a novel class of analgesic agents with high activity. Detailed studies for further evaluation are continuing.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 instrument with tetramethylsilane as an internal standard. IR and NMR data are reported only for representative compounds, although all compounds exhibited spectra in accord with their assigned structures.

Unless otherwise noted, reactions were conducted under a nitrogen atmosphere and organic extracts were washed with water and dried over $MgSO_4$.

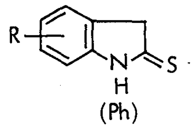
Preparation of Indoline-2-thione (I, R = H)——A Typical Procedure: The thiation procedure of Scheeren[9)] was applied to oxindole substrates. $NaHCO_3$ (16.8 g, 0.2 mol) was added in portions to a stirred solution of oxindole (13.3 g, 0.1 mol) and P_2S_5 (13.3 g, 0.06 mol) in tetrahydrofuran (THF) (150 ml) at room temperature. After being stirred for 3 h, the mixture was filtered and the filtrate was concentrated. The residue was taken up in ice water and extracted with $CHCl_3$. The extract was washed, dried and evaporated to give a yellow solid (13.7 g), which was recrystallized from MeOH, affording indoline-2-thione (11.7 g, 78%), mp 144—147 °C (lit.,[10)] 147—149 °C).

The thiones in Table II were prepared from the corresponding oxindoles in a similar manner.

Preparation of 4-Aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles V (Method A)——The detailed procedures for method A were described in the preceding paper[1)] for the preparation of compound **1** (V, R = H). 6-Substituted analogues were prepared by similar procedures. The yields and properties of the intermediates and final products are listed in Tables III and IV.

Preparation of 4-Aminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles VIII (Method B)——The detailed procedures of method B were described in the preceding paper[1)] for the preparation of compounds **5** (VIII, $R^1 = R^2 =$

TABLE II.



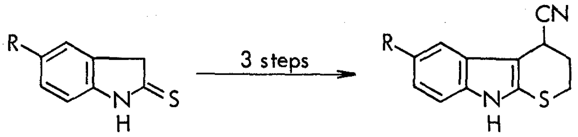
I

R	mp (°)	Recrystn. solvent	Yield (%)	Formula[b]
5-Cl	165—168	$CHCl_3$	78	C_8H_6ClNS
5-Me	158—162	EtOH	75	C_9H_9NS
5-OMe	179—182	EtOH	80	C_9H_9ClNSO
5-F	167—173	AcOEt	84	C_8H_6FNS
6-CF_3	180—183	AcOEt	86	$C_9H_6F_3NS$
7-Et	163—166	AcOEt	82	$C_{10}H_{11}NS$
4,7-Di-Me	208—212	AcOEt	86	$C_{10}H_{11}NS$
1-Ph	106—107	Et_2O–PB[a]	74	$C_{14}H_{11}NS$

[a] PB: petroleum benzin.

[b] All compounds were analyzed for C, H, N and S and gave analytical values within 0.4% of the theoretical ones.

TABLE III.

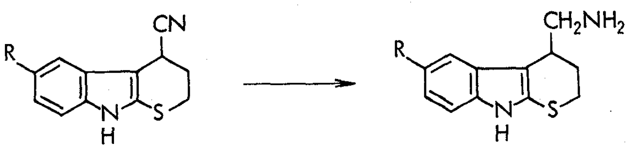


I IV

R	mp (°C)	Recrystn. solvent	Overall yield (%)	Formula[a]
6-Cl	190—192	EtOH	52	$C_{12}H_{19}ClN_2S$
6-Me	Oil	—	53	($C_{13}H_{12}N_2S$)
6-OMe	148—150	EtOH	54	$C_{13}H_{12}N_2OS$

[a] Crystalline compounds were analyzed for C, H, N and S and gave analytical values within 0.4% of the theoretical ones.

TABLE IV.



IV V

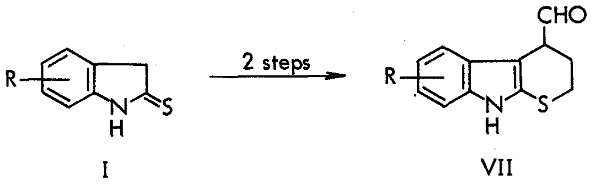
No.	R	mp (°C)	Recrystn. solvent	Yield (%)	Formula[a]
2	6-Cl	156—158	EtOH	70	$C_{12}H_{13}ClN_2S$
3	6-Me	125—127	AcOEt	46	$C_{13}H_{16}N_2S$
4	6-OMe	164—166	AcOEt	63	$C_{13}H_{16}N_2OS$

[a] See footnote *b*) in Table II.

$R^4=H$, $R^3=Me$) and **20** (VIII, $R^1=R^2=H$, $R^3=R^4=Me$). The following analogues were prepared by similar procedures. The yields and properties of the intermediate aldehydes and final products are listed in Tables V and VI.

4-Hydroxybut-2-ynyl 1-Phenylindol-2-yl Sulfide (VI, $R^1=H$, $R^2=Ph$)——The title compound was prepared from 1-phenylindolenine-2-thione in a similar manner to that described in the preceding paper[1)] for the preparation of 4-hydroxybut-2-ynyl indol-2-yl sulfide. Oil: yield 95% (after chromatography on silica gel). IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3600. NMR ($CDCl_3$) δ: 1.64 (1H, br, OH), 3.27 (2H, t, $J=2$ Hz), 4.09 (2H, br s, $W_{1/2}=8$), 6.87 (1H, s), 7.0—7.6 (9H, m).

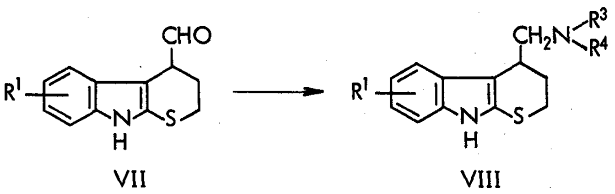
Table V.



R	mp (°C)	Recrystn. solvent	Overall yield (%)	Formula[b)]
6-F	94.5—96 (dec.)	PE[a)]-ether	76	$C_{12}H_{10}FNOS$
7-CF_3	139—141 (dec.)	Benzene-PE[a)]	75	$C_{13}H_{10}F_3NOS$
8-Et	154—157 (dec.)	Benzene	74	$C_{14}H_{15}NOS$
5,8-Di-Me	190.5—192 (dec.)	AcOEt	81	$C_{14}H_{15}NOS$

a) PE: petroleum ether.
b) See footnote b) in Table II.

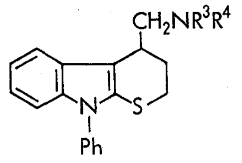
Table VI.



No.	R^1	R^3	R^4	Salt[a)]	mp (°C)	Yield (%)	Formula[b)]
6	H	Et	H	HBr	209—211 (dec.)	64	$C_{14}H_{19}BrN_2S$
7	H	*n*-Pr	H	HCl	245—250 (dec.)	70	$C_{15}H_{21}ClN_2S$
8	H	Iso-Pr	H	—	106—108	70	$C_{15}H_{20}N_2S$
9	H	*n*-Bu	H	o	219—222 (dec.)	68	$C_{16}H_{22}N_2S$
10	H	$-CH_2CH=CH_2$	H	CH_3SO_3H	245—248 (dec.)	72	$C_{16}H_{22}N_2O_3S_2$
11	H	Cyclohexyl	H	o	230—232 (dec.)	75	$C_{20}H_{26}N_2O_4S$
12	H	$-CH_2Ph$	H	—	117.5—118	80	$C_{19}H_{20}N_2S$
13	H	$-CH_2CH_2NMe_2$	H	2HBr	148—150 (dec.)	85	$C_{16}H_{25}BrN_3S$
14	H	Ph	H	o	173—175 (dec.)	20 (59)[c)]	$C_{20}H_{20}N_2O_4S$
15	6-F	Me	H	o	217—223 (dec.)	74	$C_{15}H_{17}FN_2O_4S$
16	6-F	Et	H	o	203—205 (dec.)	61	$C_{16}H_{19}FN_2O_4S$
17	7-CF_3	Me	H	HCl	183—187 (dec.)	79	$C_{14}H_{16}ClF_3N_2S$
18	8-Et	Me	H	o	225—229 (dec.)	78	$C_{17}H_{22}N_2O_4S$
19	5,8-Di-Me	Me	H	HCl	277.5—280 (dec.)	85	$C_{15}H_{21}ClN_2S$
21	H	*n*-Bu	*n*-Bu	o	175—178 (dec.)	83	$C_{22}H_{32}N_2O_4S$
22	H	$-(CH_2)_5-$		o	226—228 (dec.)	84	$C_{19}H_{24}N_2O_4S$
23	H	$-CH_2-CH_2\underset{\underset{Me}{\mid}}{N}-CH_2CH_2-$		—	153—5	60	$C_{17}H_{23}N_3S\cdot 2H_2O$

a) o: oxalic acid. b) See footnote b) in Table II.
c) Yield obtained by reduction of the imine with $LiAlH_4$ in Et_2O.

TABLE VII.



VIII

	R^3	R^4	Salt	mp (°C)	Yield (%)	Formula[a]
25	Me	H	HCl	*ca.* 253 (dec.)	76	$C_{19}H_{21}ClN_2S$
26	Et	H	HCl	232—238 (dec.)	58	$C_{20}H_{23}ClN_2S$
27	Me	Me	L-Tartaric acid	172—177	70	$C_{24}H_{28}N_2O_6S$

[a] See footnote *b*) in Table II.

4-Formyl-9-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (VII, R^1=H, R^2=Ph)——A solution of VI (R^1=H, R^2=Ph) (200 mg) in toluene (2 ml) and pyridine (0.1 ml) was refluxed for 30 min. Evaporation of the solvent gave an oil which was used for further reactions without purification. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720. NMR ($CDCl_3$) δ: 1.8—3.2 (4H, m), 3.97 (1H, m), 7.0—7.5 (9H, m), 9.84 (1H, d, J=2 Hz).

4-Aminomethyl-9-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (24)——A solution of VI (R^1=H, R^2=Ph) (3.71 g, 0.013 mol) in pyridine (75 ml) was heated at 110 °C for 70 min then cooled, and MeOH (25 ml) and $NH_2OH \cdot HCl$ (2.2 g, 2.5 eq) were added. After the mixture had been stirred at room temperature, the solvent was evaporated off and the residue was taken up in cold 3 N HCl and extracted with $CHCl_3$. The extract was washed, dried and evaporated, giving an oil (5 g), which was passed through silica gel (10 g, benzene eluent) to afford the crude oxime (3.28 g). A mixture of the oxime and $LiAlH_4$ (1.4 g, 0.037 mol) in THF (55 ml) was refluxed with stirring for 1 h. Usual work-up gave an oil (*ca.* 3 g), which was converted into an L-tartrate by treatment with a solution of L-tartaric acid in MeOH–EtOAc (3.0 g, 52% from VI), mp 196—198 °C (dec.). *Anal.* Calcd for $C_{22}H_{24}N_2O_6S$: C, 59.45; H, 5.44; N, 6.30; S, 7.21. Found: C, 59.37; H, 5.72; N, 6.28; S, 7.03.

4-(*N*-Alkylaminomethyl)-9-phenyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indoles VIII (R^1=H, R^2=Ph)——The compounds in Table VII were prepared from VI (R^1=H, R^2=Ph) in a similar manner to that described in the preceding paper[1] for the preparation of 9-unsubstituted analogues.

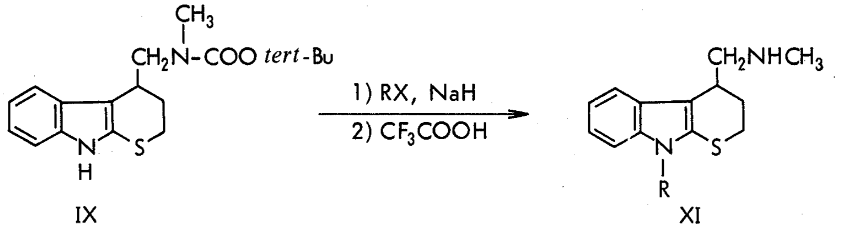
9-Methyl-4-(*N*-methylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (28)——A solution of **5** (free base; 1.63 g, 7 mmol) in THF (5 ml) was added to a solution of $NaNH_2$ (prepared from 198 mg of Na) in liq. NH_3 (100 ml) at −33 °C. The mixture was stirred for 5 min, a solution of CH_3I (1.20 g, 1.2 eq) in THF (5 ml) was added, and then stirring was continued for 1 h. NH_4Cl (150 mg) was added and the NH_3 was removed. The residue was taken up in H_2O and extracted with Et_2O. After the extract had been washed, dried and evaporated, the residue was treated with a solution of oxalic acid in MeOH to give the oxalate of **28** as crystals (2.10 g, 89%), mp 251—254 °C (dec.). *Anal.* Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33; S, 9.53. Found: C, 57.08; H, 6.04; N, 8.04; S, 9.77.

4-(*N*-*tert*-Butoxycarbonyl-*N*-methylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (IX)——A solution of **5** (free base; 4.41 g, 18 mmol) and 2-*tert*-butoxycarbonyloxyimino-2-phenylacetonitrile (BOC-ON) (4.87 g, 1.1 eq) in THF (50 ml) and Et_3N (4 ml) was stirred at room temperature for 1 h, then the solvent was evaporated off to leave a solid, which, when washed with Et_2O, afforded a crude product. This was recrystallized from acetone to provide IX (5.57 g, 93%), mp 221—223 °C (dec.). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3460, 1675. NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.1—3.2 (5H, m), 3.02 (3H, s), 3.57 (2H, m), 7.0—7.6 (4H, m), 7.95 (1H, br, NH). *Anal.* Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43; S, 9.64. Found: C, 64.94; H, 7.28; N, 8.32; S, 9.65.

Method C: Compounds **29**—**40** were prepared by method C in the yields shown in Table VIII. The procedures were similar to those for preparing **31** and **37**.

4-(*N*-Methylaminomethyl)-9-isopropyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (31)——NaH (50% in oil, 432 mg, 1.5 eq) was added to a solution of IX (1.998 g, 6 mmol) in dimethylformamide (DMF) (40 ml), and the mixture was stirred at room temperature for 1 h. Then a solution of iso-PrBr (1.20 g, 1.5 eq) in DMF (10 ml) was added and stirring was continued at 40 °C for 4 h. The mixture was taken up in cold 10% aq. NH_4Cl and extracted with $CHCl_3$. After the extract had been washed, dried and evaporated, the resulting residue was dissolved in CH_2Cl_2 (10 ml) and treated with CF_3COOH (5 ml) at ice-bath temperature for 2 h. The solvent was evaporated off and the residue was dissolved in $CHCl_3$. The solution was washed (excess aq. K_2CO_3, H_2O), dried and evaporated to leave an oil, which was converted into an oxalate by treatment with a solution of oxalic acid in acetone. The oxalate was basified (aq. K_2CO_3) and extracted with $CHCl_3$, giving fairly pure **31** as an oil (1.50 g, 91%). NMR ($CDCl_3$) δ: 1.58

Table VIII.



No.	Reagent	R	Salt[a]	mp (°C)	Overall yield (%)	Formula[b]
29	ROTs	Et	HCl	247—251 (dec.)	67	$C_{15}H_{21}ClN_2S$
30	ROTs	*n*-Pr	HCl	239—246 (dec.)	64	$C_{16}H_{23}ClN_2S$
32	RBr	Iso-Bu	HCl	241—245 (dec.)	66	$C_{17}H_{25}ClN_2S$
33	RCl	$PhCH_2$–	HCl	265—270 (dec.)	72	$C_{20}H_{23}ClN_2S$
34	RCl·HCl	$Me_2NCH_2CH_2$–	2HCl	252—260 (dec.)	89	$C_{17}H_{27}Cl_2N_3S$
35	RCl	Et_2NCOCH_2–	HCl	265—269 (dec.)	93	$C_{19}H_{23}ClN_3OS$
36	RCl	-COOMe	HCl	202—204 (dec.)	40	$C_{15}H_{19}ClN_2O_2S$
38	RCl	-COEt	HCl	250—260 (dec.)	65	$C_{16}H_{21}ClN_2OS$
39	RCl	-COPh	o	236—238 (dec.)	91	$C_{22}H_{22}N_2O_5S$
40	RCl	-COPh-Cl-*p*	HCl	252—255 (dec.)	81	$C_{20}H_{20}Cl_2N_2OS$

a) o: oxalic acid. *b*) See footnote *b*) in Table II.

(6H, d, $J=7$ Hz), 2.0—3.5 (7H, m), 2.45 (3H, s), 4.58 (1H, septet, $J=7$ Hz), 6.9—7.6 (4H, m). Treatment of this base with HCl–EtOH afforded a hydrochloride (1.44 g, 77% from IX), mp 243—247 °C (dec.). *Anal.* Calcd for $C_{16}H_{23}ClN_2S$: C, 61.82; H, 7.46; N, 9.01; S, 10.31. Found: C, 61.65; H, 7.58; N, 8.74; S, 10.21.

9-Acetyl-4-(*N*-methylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (37)——NaH (50% in oil, 432 mg, 1.5 eq) was added to a solution of IX (1.998 g, 6 mol) in DMF (40 ml), and the mixture was stirred at room temperature for 1 h, then cooled to ice-bath temperature. A solution of AcCl (707 mg, 1.5 eq) in DMF (5 ml) was added, and then the whole was stirred at room temperature for 1.5 h. Work-up and treatment with CF_3COOH, as described above, yielded the hydrochloride of **37** (1.36 g, 73%) mp 254—257 °C (dec.). *Anal.* Calcd for $C_{15}H_{19}ClN_2OS$: C, 57.96; H, 6.16; N, 9.01; S, 10.32. Found: C, 57.86; H, 6.25; N, 9.00; S, 10.52. IR (free base) $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1695. NMR (free base) ($CDCl_3$) δ: 2.0—3.4 (7H, m), 2.46 (3H, s), 2.75 (3H, s), 7.0—8.0 (4H, m).

9-Acetyl-4-(*N*,*N*-dimethylaminomethyl)-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (41)——NaH (50% in oil, 72 mg, 1.5 eq) was added to a solution of **20** (free base; 246 mg, 1 mmol) in DMF (4 ml), and the mixture was stirred at room temperature for 2 h. Next, a solution of AcCl (95 mg, 1.2 eq) in DMF (1 ml) at ice-bath temperature was added and the mixture was warmed to room temperature. Stirring was continued for 1 h, then cold aq. NH_4Cl was added at ice-bath temperature, followed by extraction with $CHCl_3$. The extract was washed, dried and evaporated to give a solid, which was recrystallized from MeOH, affording **41** as crystals (244 mg, 84%) mp 131—133 °C. Treatment with ethanolic HCl gave a hydrochloride, mp 225—232 °C (dec.). *Anal.* Calcd for $C_{16}H_{21}ClN_2OS$: C, 59.15; H, 6.52; N, 8.62; S, 9.87. Found: C, 58.94; H, 6.74; N, 8.59; S, 9.81.

4-(*N*-Methylaminomethyl)-1-oxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (42)——A solution of $NaIO_4$ (1.32 g, 1.2 eq) in H_2O (20 ml) was added to a solution of **5** (free base, 1.26 g, 5.14 mmol) in MeOH (40 ml) at room temperature, and the mixture was stirred for 4 h. The resulting solid was filtered off and the filtrate was concentrated. The residue was taken up in aq. K_2CO_3 and extracted with $CHCl_3$. The extract was washed, dried and concentrated, giving an oil which was converted into an oxalate. Recrystallization from H_2O afforded pure crystals (1.49 g, 83%, mp 194—198 °C (dec.)). *Anal.* Calcd for $C_{15}H_{18}N_2O_5S \cdot 1/2H_2O$: C, 51.89; H, 5.51; N, 8.07; S, 9.23. Found: C, 51.69; H, 5.61; N, 7.96; S, 9.29. IR (free base) $\nu_{\max}^{CHCl_3}$: 3440, *ca.* 3150, 1010. NMR (free base) ($CDCl_3$) δ: 2.48 (3H, s), 2.2—3.5 (7H, m), 7.0—7.8 (4H, m).

4-(*N*-Methylaminomethyl)-1,1-dioxo-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (43)——*m*-Chloroperbenzoic acid (93.5% purity, 2.33 g, 2.1 eq) was added in portions to a solution of IX (1.99 g, 6 mmol) in $CHCl_3$ (240 ml) at ice-bath temperature, and the mixture was stirred at room temperature for 3 h. This mixture was diluted with $CHCl_3$ (250 ml), washed (5% NaOH, H_2O, sat. NaCl) and dried. Evaporation of the solvent left a solid (2.4 g). The solid was dissolved in CH_2Cl_2 (10 ml) and then CF_3COOH (10 ml) was added at ice-bath temperature. After the mixture had been stirred at room temperature for 2 h, the solvent was removed, giving a solid (3.65 g) which was taken up in 5% NaOH (10 ml) and extracted with $CHCl_3$. The extract was washed, dried and evaporated, leaving crude **43**. Recrystallization from EtOH afforded pure **43** (1.35 g, 85%), mp 165—167 °C. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 3450, *ca.* 3320, 1295, 1140, 1120. NMR (acetone-d_6) δ: 2.47 (3H, s), 2.4—3.7 (7H, m), 7.0—7.9 (4H, m). *Anal.* Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.05; H, 6.28; N, 10.32; S, 11.91.

References and Notes

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