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Studies of Heterocyclic Compounds. XVIII.[1] Synthesis of 1-(Substituted-phenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles

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1-(Substituted-phenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles (IV-2—IV-17) were synthesized from the correspoding 3-(substituted-phenyl)thiazolo[2,3-*b*]benzothiazolium perchlorates (III) by the reaction of 1-morpholino-1-cyclohexene, an enamine. On reaction with cuprous cyanide *p*-substituted bromobenzene (IV-2) furnished benzonitrile (IV-23), which was converted into the corresponding 1-phenyl derivatives (IV) with various aliphatic functional groups at the *para* position of the phenyl moiety. On reaction with methylmagnesium iodide and subsequent acid hydrolysis IV-23 was converted into acetophenone (IV-24), which reacted with methyltriphenylphosphylene to give 2-phenylpropylene (IV-38). Hydroboration of IV-38 afforded 2-phenylpropanol (IV-39), which was oxidized into the corresponding propionic acid (IV-43), the sulfur atom being oxidized at the same time into sulfoxide. Deoxygenation of the ester (IV-44) was successfully carried out with PBr_3 to obtain the desired α-phenyl substituted propionic acid ester (IV-45).

Keywords——3-(substituted-phenyl)thiazolo[2,3-*b*]benzothiazolium salts; 1-morpholino-1-cyclohexene; anti-inflammatory activity; 1-(substituted-phenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles; propionic acid ester; Rosenmund-von Braun reaction; Willgerodt-Kindler reaction; hydroboration; Jones oxidation; pyrrolo[2,1-*b*]benzothiazole 4-oxide

In the course of our studies on the synthesis and reactivity of pi deficient condensed thiazolium salts,[1,3-5] it was found that 1-morpholino-1-cyclohexene (enamine) attacked as nucleophile at the brigded $\gtrless C=N^+\lessgtr$ bond of 3-phenylthiazolo[2,3-*b*]benzothiazolium perchlorate (III-1) to furnish 1-phenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-1) and that some of the derivatives with pyrrolobenzothiazole system exhibited anti-inflammatory activity. In order to examine generality of this type of reaction mode as well as to search for physiologically more potent materials the thiazolium salts (III) have been treated with the enamine to obtain 1-(substituted-phenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles (IV), of which the phenyl substituents are shown in Table I, and besides, bromophenyl derivative (IV-2) has been converted into propionic acid ester, of which the α-position is substituted with this heteroaromatic system.

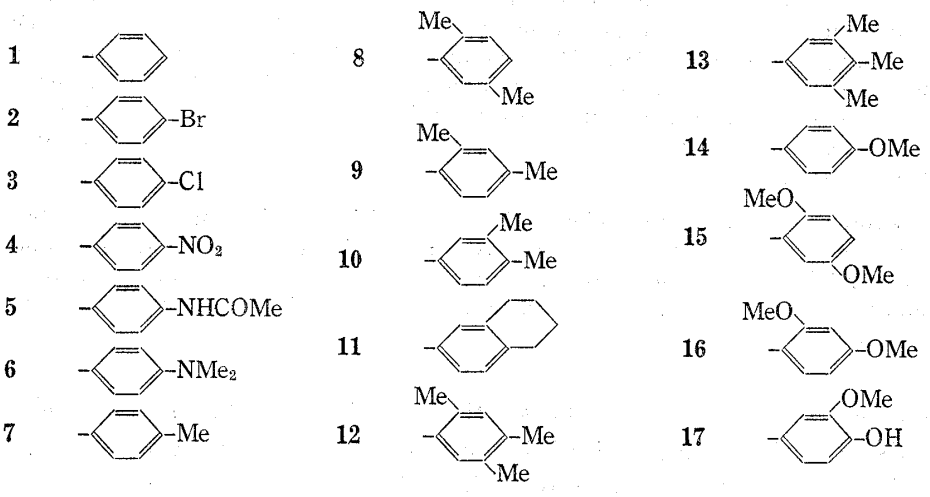
The quarternary ammonium salts (III) were synthesized as depicted in Chart 1:[1] substituted phenacyl halides (I), which were prepared by Friedel-Crafts reaction of substituted benzenes with chloroacetyl chloride or by halogenation of substituted acetophenones with bromine, was treated with sodium salt of 2-mercaptobenzothiazole to give 2-phenacylthiobenzothiazoles (II), and then cyclization of II by heating in perchloric acid or in conc.

1) Part XVII: S. Sawada, T. Miyasaka, and K. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 3370 (1977).
2) Location: *1-5-8, Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
3) *a*) S. Sawada, T. Miyasaka, and K. Arakawa, *Chem. Pharm. Bull.* (Tokyo), "submitted."
b) K. Arakawa, T. Miyasaka, and S. Sawada, *Chem. Pharm. Bull.* (Tokyo), "submitted."
4) *a*) H. Ohtsuka, H. Toyofuku, T. Miyasaka, and K. Arakawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 3234 (1975); *b*) H. Ohtsuka, T. Miyasaka, and K. Arakawa, *ibid.*, **23**, 3243 (1975); *c*) *Idem*, *ibid.*, **23**, 3254 (1975).
5) *a*) K. Arakawa, T. Miyasaka, and K. Satoh, *Chem. Pharm. Bull.* (Tokyo), **25**, 299 (1977); *b*) K. Satoh, T. Miyasaka, and K. Arakawa, *ibid.*, **25**, 307 (1977).

sulfuric acid furnished thiazolo[2,3-*b*]benzothiazolium salts (III). The reaction of III with the enamine proceeded slowly in warm N,N-dimethylformamide (DMF). After evaporation of the solvent the residue was taken up in chloroform and separated by silica gel chromatography into 1-(substituted-phenyl)pyrrolo[2,1-*b*]benzothiazoles (IV) and N-thioformylmorpholine as the eliminating group from the initially formed adduct (Chart 1). The physical properties are summarized in Table II.

Minor modification of the substituents of some of the compounds (IV) was carried out. 1-4′-Acetaminophenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-5) was hydrolyzed in 10%-hydrochloric acid to give *p*-aminophenyl derivative (IV-18). *p*-Anisyl compound (IV-14) was hydrolyzed by heating in molten pyridine-hydrochloride[6] to give *p*-hydroxyphenyl derivative (IV-19), which was transformed into ethyl α-phenoxypropionate (IV-20) and into ethyl α-phenoxyisobutyrate (IV-21) by alkylation with ethyl α-bromopropionate and with α-isobutyrate, respectively, in the presence of sodium hydride in DMF. 1-4′-Hydroxy-3′-

Table I. Substituents Y for Compounds II, III, and IV



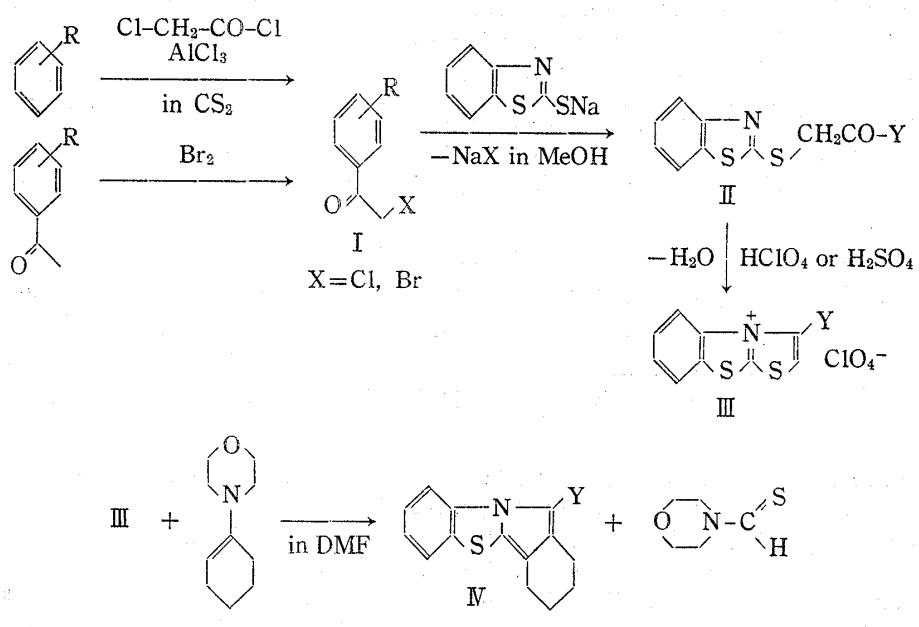


Chart 1

6) *cf.* V. Prey, *Ber.*, 74, 1219 (1941)

TABLE II. 1-(Substituted-phenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles (IV) from Thiazolium Salts (III) with 1-Morpholino-1-cyclohexene in DMF

Compound No.	Appearance mp (°C) from EtOH	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	IR ν_{max}^{KBr} cm^{-1}:	NMR (in $CDCl_3$) δ:
IV-1	Pale yellow needles 110.5—111.5	70.7	$C_{20}H_{17}NS$	79.16 (79.10)	5.46 (5.46)	4.61 (4.31)	3040, 2920, 1590, 1470	1.74 (4H, b), 2.62 (4H, b), 7.05—7.55 (9H, m)
IV-2	Colorless needles 118—120	63.7	$C_{20}H_{16}BrNS$	62.83 (62.62)	4.21 (4.16)	3.66 (3.67)	3020, 2930, 1585, 1470	1.75 (4H, b), 2.18 (4H, b), 7.04—7.64 (8H, m)
IV-3	Pale yellow needles 106—107	85.6	$C_{20}H_{16}ClNS$	71.09 (71.37)	4.77 (4.69)	4.14 (3.94)	3070, 2940, 1600, 1470	1.79 (4H, b), 2.60 (4H, b), 7.05—7.62 (4H, m), 7.50 (4H, bs)
IV-4	Orange flakes 165—167	16.1	$C_{20}H_{16}N_2O_2S$	68.94 (68.56)	4.62 (4.49)	8.04 (7.62)	3070, 2940, 1600, 1520, 1470, 1350	1.84 (4H, b), 2.67 (4H, b), 7.06—7.57 (4H, m), 7.60, 8.31 (2H, 2H, d, d J=4.0 Hz)
IV-5	Pale yellow flakes 236.5—238	70.8	$C_{22}H_{20}N_2OS$	73.30 (73.60)	5.59 (5.17)	7.77 (7.98)	3295, 3060, 2930, 1660, 1605, 1460	1.75 (4H, b), 2.18 (3H, s), 2.50 (4H, b), 7.00—7.85 (8H, m), 9.63 (1H, bs D_2O-exchange)
IV-6	Yellow needles 106—107	39.0	$C_{22}H_{22}N_2S$	76.25 (76.60)	6.40 (6.41)	8.08 (7.66)	3040, 2960, 2840, 1605, 1470	1.78 (4H, b), 2.26 (4H, b), 3.02 (6H, s), 6.75—7.47 (8H, m)
IV-7	Colorless prisms 116—117[a]	44.1	$C_{21}H_{19}NS$	79.45 (80.20)	6.03 (5.98)	4.41 (4.29)	3040, 2920, 1590, 1465	1.77 (4H, b), 2.41 (3H, s), 2.60 (4H, b), 6.95—7.80 (8H, m)
IV-8	Yellow needles 106.5—107.5	75.9	$C_{22}H_{21}NS$	79.71 (79.67)	6.38 (6.49)	4.22 (4.06)	3060[f], 2960, 1590, 1475	1.78 (4H, b), 2.07 (3H, s), 2.45 (3H, s), 2.52 (4H, b), 6.54—7.62 (7H, m)
IV-9	Pale yellow needles 117—118	52.7	$C_{22}H_{21}NS$	79.71 (79.39)	6.38 (6.34)	4.22 (4.24)	3060, 2940, 1590, 1470	1.80 (4H, b), 2.09 (3H, s), 2.43 (3H, s), 2.68 (4H, b), 6.55—7.56 (7H, m)
IV-10	Pale yellow prisms 134—135[b]	44.6	$C_{22}H_{21}NS$	79.71 (79.57)	6.38 (6.63)	4.22 (4.61)	3060, 2930, 1590, 1470	1.76 (4H, b), 2.34 (6H, bs), 2.60 (4H, b), 6.96—7.54 (7H, m)
IV-11	Yellow powders 70—71[c]	40.0	$C_{24}H_{23}NS$	80.63 (81.05)	6.48 (6.52)	3.91 (3.96)	3060, 2920, 1595, 1470	1.80 (8H, b), 2.20—3.04 (8H, b), 6.76—7.75 (7H, m)
IV-12	Yellow prisms 129—131	47.6	$C_{23}H_{23}NS$	79.96 (79.46)	6.69 (6.69)	4.05 (4.08)	3020, 2940, 1595, 1490	1.79 (4H, b), 2.20 (3H, s), 2.24 (3H, s), 2.42 (3H, s), 2.60 (4H, b), 6.83—7.87 (6H, m)
IV-13	Pale yellow prisms 134.5—136	62.5	$C_{23}H_{23}NS$	79.96 (80.03)	6.69 (6.73)	4.05 (3.99)	3060, 2920, 1605, 1475	1.76 (4H, b), 2.22 (3H, s), 2.30 (6H, s), 2.58 (4H, b), 6.91—7.85 (6H, m)
IV-14	Pale yellow prisms 91—93	77.7	$C_{21}H_{19}NOS$	75.64 (75.60)	5.74 (5.74)	4.19 (4.32)	3020, 2920, 2820, 1595, 1460	1.77 (4H, b), 2.69 (4H, b), 3.85 (3H, s), 6.84—7.63 (8H, m)
IV-15	Pale yellow flakes 150.5—151.5	58.9	$C_{22}H_{21}NO_2S$	72.69 (72.45)	5.82 (5.53)	3.85 (3.89)	3010, 2980, 2840, 1610, 1460	1.79 (4H, b), 2.62 (4H, b), 3.58 (3H, s), 3.74 (3H, s), 6.90—7.75 (7H, m)
IV-16	Colorless needles 119—120	51.8	$C_{22}H_{21}NO_2S$	72.69 (72.75)	5.82 (5.73)	3.85 (3.87)	3010, 2930, 2840, 1610, 1470	1.79 (4H, b), 2.62 (4H, b), 3.62 (3H, s), 3.84 (3H, s), 6.49—7.35 (7H, m)
IV-17	Pale yellow oil[d]	72.5	$C_{21}H_{19}NO_2S$[e]	—	—	—	3540[f], 3060, 2970, 2860, 1590, 1475	1.82 (4H, b), 2.66 (4H, b), 3.89 (3H, s), 5.80 (1H, s, D_2O-exchange), 7.69—7.70 (7H, m)

Recrystallized from *a*) *n*-hexane-ether, *b*) EtOH-$CHCl_3$, *c*) MeOH, *d*) Purified through silica gel column with 20% *n*-hexane-C_6H_6 as an eluent, *e*) The formula was determined by using high resolution mass spectroscopy MS (70 eV): *m/e* 349.1124 [M^+] for $C_{21}H_{19}NO_2S$=349.11, *f*) in $CHCl_3$.

methoxyphenyl compound (IV-17) was methylated with diazomethane into veratryl derivative (IV-22).

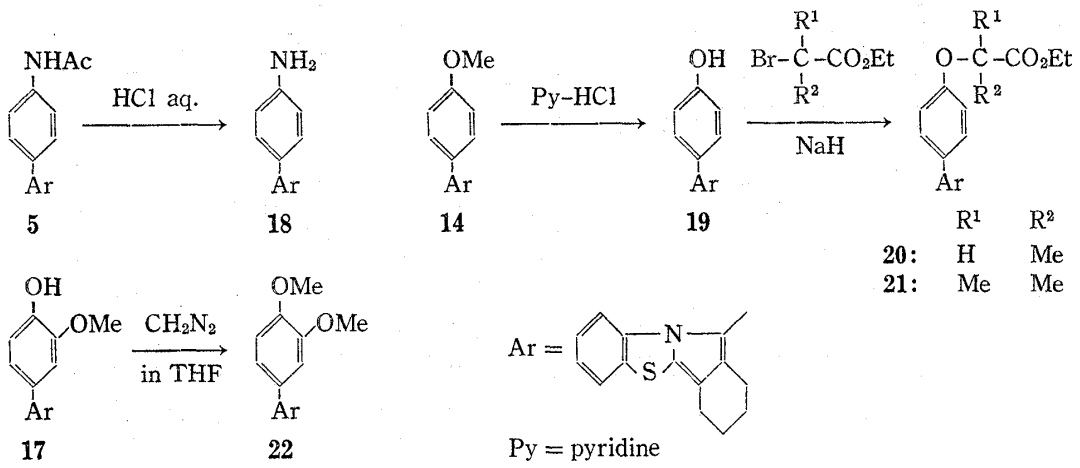


Chart 2

Now, introduction of various aliphatic functional groups into the pyrrolobenzothiazole system has attracted our attention because introduction of propionic acid side chain is often used as a technique to amplify the anti-inflammatory activity of some heteroaromatic system.[7]

Synthesis of α-phenylethanol (IV-25) was attempted from the bromobenzene (IV-2) through the corresponding phenyllithium or magnesium bromide. The metalation did not proceed and the starting material was recovered unchanged. The bromobenzene (IV-2) was, then, cyanated by stirring with cuprous cyanide in hot N-methylpyrrolidone according to the Boekelheide's modification of Rosenmund-von Braun reaction[8] to give 1-(cyanophenyl)-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-23) in 91% yield, which was chosen as a suitably functionalized starting material for the synthesis of the corresponding compounds with various carbon-substituents including acetic and propionic acid functions.

According to Backmann's procedure[9] the benzonitrile (IV-23) was converted into the acetophenone (IV-24) by heating with methylmagnesium iodide in refluxing benzene and subsequent hydrolysis in hot hydrochloric acid in 82% yield. The acetophenone (IV-24) was reduced with sodium borohydride into α-phenylethanol (IV-25) in 82% yield, which could not, however, be converted into α-methylbenzyl chloride (IV-26) by heating in conc. hydrochloric acid, thionyl chloride, or phosphoryl chloride–pyridine–hydrogen chloride probably because of the instability of the product.

The benzonitrile (IV-23) was hydrolyzed with H_2O_2–NaOH into benzamide (IV-27) according to Wiberg's method[10] in 80% yield. Hydrolysis in 75% sulfuric acid afforded benzoic acid (IV-28) in 82% yield. Treatment of IV-23 with dry hydrogen chloride in absolute ethanol furnished imino ether (IV-29), the infrared (IR) spectrum of which indicated >C=N– bond at 1630 cm^{-1}. On subsequent hydrolysis of the imino ether in 10% hydrochloric acid at room temperature ethyl benzoate (IV-30) was obtained in 76% overall yield from the nitrile (IV-23).

7) *a*) T.H. Shen in "Nonsteroidal Anti-inflammatory Drugs," S. Garattini and H.N.G. Dukes, Ed., Excerpta Medica Foundation, Amsterdam, 1965, pp. 13—20; *b*) D.W. Dunwell, D. Evans, T.A. Hicks, C.H. Cashin, and A. Kitchen, *J. Med. Chem.*, **18**, 53 (1975).
8) *cf.* V. Boekelheide and J.B. Phillips, *J. Am. Chem. Soc.*, **89**, 1695 (1966).
9) *cf.* W.E. Backmann and C.H. Boatner, *J. Am. Chem. Soc.*, **58**, 2098 (1963).
10) *cf.* K.B. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953).

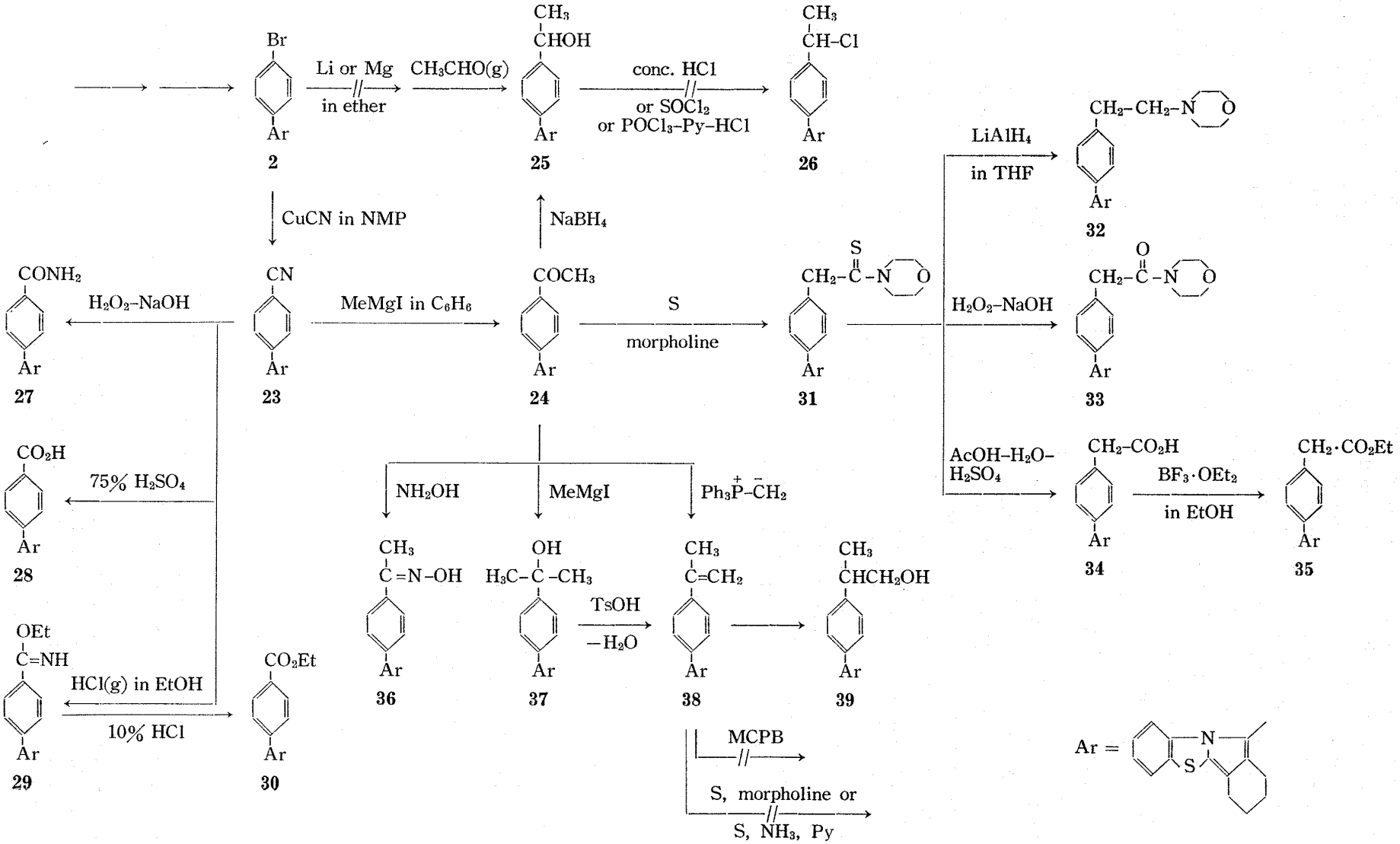


Chart 3

The acetophenone (IV-24) was converted into the phenylacetothiomorpholide (IV-31) in 71% yield by heating with sulfur-morpholine according to Newman's modification of Willgerodt reaction.[11] The thioamide band was observed at 1385 cm^{-1} (in KBr, strong) in the IR spectrum and the benzylic methylene was observed at 4.41 ppm (in $CDCl_3$, 2H, s) in the nuclear magnetic resonance (NMR) spectrum. Reduction of the thioamide (IV-31) with lithium aluminum hydride in refluxing THF gave N-phenethylmorpholine (IV-32), an aralkylamine. Partial hydrolysis of IV-31 with H_2O_2–NaOH gave phenylacetomorpholide (IV-33). Acidic hydrolysis, on the other hand, gave phenylacetic acid (IV-34), which was smoothly esterified to give ethylacetate (IV-35) in good yield by heating in ethanol in the presence of boron-trifluoride etherate.

The acetophenone (IV-24) reacted smoothly with hydroxylamine to furnish an oxime (IV-36). Grignard reaction of IV-24 with methylmagnesium iodide in C_6H_6 furnished α-phenylisopropanol (IV-37). On Wittig reaction of IV-24 with methyltriphenylphosphylene[12] 2-phenylpropylene (IV-38) was obtained in 65% yield, which was also obtained by dehydration of tertiary alcohol (IV-37) in refluxing benzene in the presence of catalytic amount of *p*-toluenesulfonic acid in 75% overall yield from acetophenone (IV-24). The NMR spectrum showed the signals of the terminal olefin at 5.15 and 5.50 ppm. Attempted oxidation of IV-38 into α-phenylpropionic acid derivatives was carried out using *m*-chloroperbenzoic acid and by Willgerodt reaction either with sulfur-morpholine or with sulfur-ammonia-pyridine in a sealed tube.[11] The desired oxidized material could not be isolated in either case.

Hydroboration with diborane in THF[13] effected terminal hydroxylation of IV-38 to give 2-phenylpropanol (IV-39) in 85% yield. The IR spectrum showed hydroxyl band at 3600, and 3440 cm^{-1} (in $CHCl_3$) and NMR spectrum showed methyl, methylene, and methine signals at 1.37 (3H, d), 3.80 (2H, d), and 3.40 (1H, sextet) ppm, respectively.

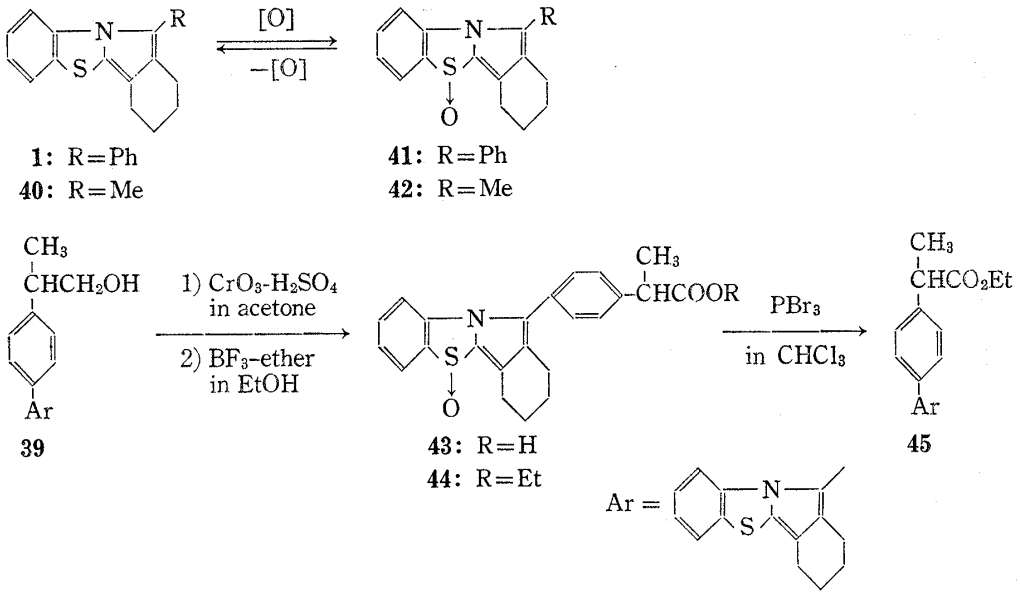


Chart 4

On oxidation of the primary alcohol (IV-39) with Jones reagent[14] an oily propionic acid derivative (IV-43) was isolated in 61% yield from the acidic fraction. The IR spectrum

11) *cf. a)* M.S. Newman, *J. Org. Chem.*, **9**, 521 (1944). and also *cf. b)* D.F. DeTar, M. Carmack, *J. Am. Chem. Soc.*, **68**, 2025 (1946); *idem*, *ibid.*, **68**, 2029 (1946); *idem*, *ibid.*, **68**, 2033.
12) *cf.* I.T. Harrison and B. Lythgoe, *J. Chem. Soc.*, **1958**, 843.
13) *cf.* G. Zweifel and H.C. Brown, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
14) K. Bowers, T.G. Halsall, E.R.H. Jones, and A.J. Lemin, *J. Chem. Soc.*, **1953**, 2555.

of this material indicated two very strong bands at 1720 cm^{-1} (–COOH) and 1660 cm^{-1}. The NMR spectrum showed methyl, methine, and carboxylic proton at 1.40 (3H, d), 3.69 (1H, q), and 9.03 (1H, D_2O-exchangeable) ppm, respectively, indicating the formation of α-substituted propionic acid. It also indicated the tetramethylene side chain at 2,3-position by the signals at 1.87 (4H, br), 2.50 (2H, br), and 2.76 (2H, br) ppm, respectively. By the high-resolution mass spectroscopy the molecular ion [M^+] was observed at *m/e* 391.1225, which was agreeable with the calculated value 391.12 for $C_{23}H_{21}NO_3S$. The ethyl ester (IV-44) of the propionic acid (IV-43) also showed an intense absorption at 1660 cm^{-1} in addition to the ester carbonyl band at 1730 cm^{-1} in the IR spectrum (in $CHCl_3$). The high-resolution mass spectroscopy exhibited [M^+]=*m/e* 419.1558, which was agreeable with the calculated value for $C_{25}H_{25}NO_3S$.

On reaction with CrO_3–H_2SO_4 in the same manner 1-phenylpyrrolobenzothiazole (IV-1) gave an oxidized product (IV-41), whose molecular formula was determined $C_{20}H_{17}NOS$ by elemental analysis and by high-resolution mass spectroscopy. The compound also showed an intense absorption at 1660 cm^{-1} (Fig. 1), and also exhibited signals of tetramethylene protons at 1.92 (4H, br), 2.50 (2H, br), and 2.77 (2H, br) ppm, respectively. The ultrariolet (UV) spectra of the compounds IV-41 and IV-44 were almost superimposable as shown in

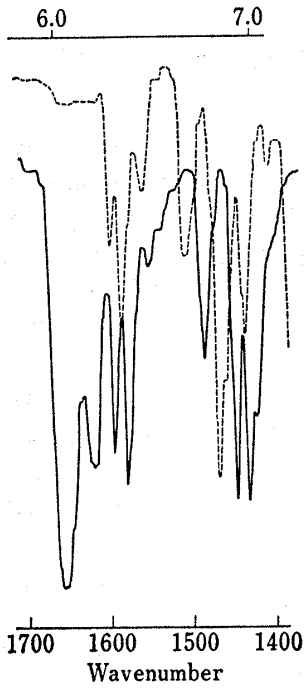


Fig. 1. IR Spectra of IV-1 and IV-41 (KBr)
------, IV-1; ——, IV-41.

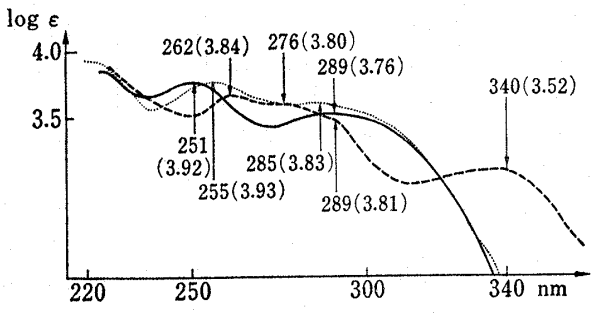


Fig. 2. UV Spectra of IV-1, IV-41 and IV-44
IV-1, ------; IV-41, ——; IV-44, ·····.

Fig. 2 and the fact suggested that the both compounds had nearly the same chromophoric grouping. The compound (IV-41) was also obtained by oxidation of IV-1 with *m*-chloroperbenzoic acid in chloroform or with sodium periodate in dioxane-water. On oxidation of 1-methyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-40) with *m*-chloroperbenzoic acid or with sodium periodate the same product, $C_{15}H_{15}NOS$ (IV-42) was obtained, the IR spectrum of which showed a strong band at 1690 cm^{-1}. The UV spectrum of this compound was similar to that of IV-41. The starting IV-1 and IV-40 were recovered on heating of IV-41 and IV-42 with PBr_3 in chloroform. The ^{13}C–NMR spectra of IV-1, IV-41, IV-40, and IV-42 showed the signals of the tetramethylene carbon as four distinct peaks of aliphatic sp^3-carbon and, therefore, the extra oxygen atom was not incorporated into the side chain carbon to form ketone. (Fig. 3, Table III).

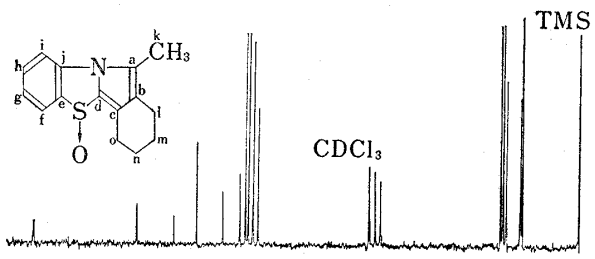


Fig. 3. ^{13}C-NMR Spectrum of 1-Methyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole 4-Oxide (IV-42)

Table III. Carbon-13 Spectrum of IV-42

Position[a]	Assignments[c]
206.2 (s)[b]	C-d
167.1 (s)	C-j
153.0 (s)	C-e
144.6 (s)	C-a
134.7 (s)	C-b or c
128.2 (s)	C-b or c
126.1 (d)	C-h
125.0 (d)	C-g
123.2 (d)	C-i
121.3 (d)	C-f
29.4 (q)	C-k
28.6 (t)	C-l,m,n,and o
27.4 (t)	C-l,m,n,and o
22.0 (t)	C-l,m,n,and o
21.5 (t)	C-l,m,n,and o

a) ppm from TMS in $CDCl_3$.
b) off-resonance experiment.
c) *cf.* J. Perregaard and S.S. Lawesson, *Acta Chem. Scand.*, **B 31**, 203 (1977).

These data suggested that the oxidized products were 1-phenyl and 1-methyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole 4-oxides and that the strong IR absorption in the carbonyl region was to be assigned as the polarized C=C bond in the pyrrole nucleus, where the conjugation effect of nitrogen lone pair was amplified by the sulfoxide function. The oxidation of sulfide with chromic acid is precedented,[16] however it is of interest that the sulfur atom as a part of aromatic resonance was easily oxidized to form sulfoxide with chromic acid, organic peracid, and periodate.

Now that the structure of the oxidized compound (IV-43) was elucidated, the ethyl ester (IV-44) was deoxygenated with PBr_3 in chloroform to give the desired ethyl α-(4-2′,3′-tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropionate (IV-45). The molecular ion was observed at *m/e* 403.1612, which was agreeable with the calculated value 403.16 for $C_{25}H_{25}NO_2S$. In the NMR spectrum the tetramethylene signals were observed at 1.76 (4H, br), 2.61 (4H, br) ppm and the UV spectrum was almost superimposable with that of the compound (IV-1).

Detailed discussion with respect to anti-inflammatory activity of these compounds vs. carrageenin estimated in terms of inhibition (%) and P.B. index will be published in the near future.

Experimental[17]

General Procedure for Synthesis of 1-Substituted-phenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazoles (IV) by Reaction of Thiazolium Salts (III) with 1-Morpholino-1-cyclohexene——Into a solution of thiazolium salt (III) in abs. DMF there was added 1-morpholino-1-cyclohexene (1.4 eq.) dropwise with stirring at room temperature. After stirring for 20 hours, the mixture was heated at 60—70° for 4 hours. The DMF was

16) D. Edwars and J.B. Stenlake, *J. Chem. Soc.*, **1954**, 3272. and *loc. cit.*
17) All extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. All melting points were measured in a capillary tube and were uncorrected. The ^{1}H-NMR spectra were measured by Hitachi R-20 60MC and R-22 90MC NMR spectrophotometer, using TMS as an internal reference. The ^{13}C-NMR spectra were measued by JEOL-JNM FX60 (2500 Hz) and JNM- FX100 (4167 Hz) spectrometer. The IR and UV spectra were measured by JASCO IRA-I spectrophotometer and on a Hitachi EPS-3 spectrophotometer, respectively. The mass spectra were recorded on a JEOL JMS-01SG high-resolution mass spectrometer with a direct inlet system.

evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was washed with H_2O. The $CHCl_3$ extract was dried and evaporated to dryness. The residue was purified by column chromatography on silica gel with C_6H_6 as an eluent. The detail data are shown in Table II.

1-4′-Aminophenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-18)——A suspension of IV-5 (1.70 g) in 10% HCl (80 ml) was refluxed for 2 hours. After cooling the mixture was washed with ether (30 ml), made alkaline with 10% NaOH, and extracted with $CHCl_3$ (100 ml) and the $CHCl_3$ extract was dried and evaporated to dryness. The residue was recrystallized from *n*-hexane–C_6H_6 to give 1.36 g (91.8% yield) of pale yellow needles, mp 144.5—146°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3370, 3040, 2950, 1625, 1475. NMR δ (in $CDCl_3$): 1.76 (4H, br), 2.58 (4H, br), 3.61 (2H, br s, D_2O-exchangeable), 6.60—7.65 (8H, m). *Anal.* Calcd. for $C_{20}H_{18}N_2S$: C, 75.43; H, 5.69; N, 8.79. Found: C, 75.10; H, 5.70; N, 8.88.

1-4′-Hydroxyphenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-19)——A mixture of IV-14 (3.12 g) and freshly prepared pyridine-HCl[6] (21.60 g) was heated at 200—210° for 6 hours under fusion. After cooling the mixture was dissolved in $CHCl_3$ (200 ml), the extract was washed with H_2O. The $CHCl_3$ solution was dried and evaporated to dryness. The residue was decolorized by active carbon and recrystallized from H_2O–MeOH to give 1.49 g (60.0% yield) of colorless needles, mp 160.5—163°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 3040, 2920, 1610, 1475. NMR δ ($CDCl_3$) 1.77 (4H, br), 2.60 (4H, br), 5.15 (1H, br s, D_2O-exchangeable), 6.75—7.70 (8H, m). *Anal.* Calcd. for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.38. Found: C, 74.88; H, 5.26; N.4.41.

Ethyl α-4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenoxypropionate (IV-20)——50% Oily NaH (0.18 g) was added to a stirred solution of IV-19 (1.03 g) in abs. DMF (30 ml) and the resulting suspension was stirred for 20 min at room temperature. Ethyl α-bromopropionate (0.72 g) was then added dropwise with stirring to the suspension. After stirring for additional 16 hours at room temperature, the mixture was heated at 70—80° for 2 hours. The DMF was evaporated *in vacuo*. The residue was dissolved in ether (50 ml) and the solution was washed with H_2O. The ether solution was dried and evaporated to dryness. The residue was purified by column chromatography through silica gel. The fractions which were eluted with $CHCl_3$ were collected to give 1.21 g (93.7% yield) of pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3060, 2960, 1700, 1595, 1465, 1250. NMR δ (in $CDCl_3$): 1.35 (3H, t, J=8 Hz), 1.64 (3H, d, J=8 Hz), 1.78 (4H, br), 2.58 (4H, br), 4.26 (2H, q, J=8 Hz), 4.82 (1H, q, J=8 Hz), 6.84—7.60 (8H, m). MS (70 eV) *m/e*: 419.1548 [M^+] for $C_{25}H_{25}NO_3S$=419.15.

Ethyl α-Methyl-α-4-(2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenoxypropionate (IV-21)——50-% Oily NaH (0.19 g) was added to a stirred solution of IV-19 (1.20 g) in abs. DMF (30 ml) and the resulting suspension was stirred for 20 min at room temperature. Ethyl α-bromoisobutyrate (1.00 g) was then added with stirring to the suspension. After the reaction mixture was stirred at room temperature for 4 hours. and it was heated at 70—80° for 18 hours. The mixture was worked up as described above to give 1.35 g (83.7% yield) of pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3060, 2940, 1710, 1610, 1475, 1215. MS (70 eV) *m/e*: 433.1704 [M^+] for $C_{26}H_{27}NO_3S$=433.1711.

1-3′,4′-Dimethoxyphenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-22)——Into a solution of IV-17 (1.20 g) in abs. ether (50 ml) there was added an etheral solution of diazomethane, freshly prepared from *p*-tosyl-N-methyl-N-nitrosoamide (3.25 g) and KOH (0.85 g) by general procedure, with stirring at room temperature. After the mixture was stirred for additional 60 hours, a small amount of AcOH was added to the mixture. The solution was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to give 0.80 g (65.0% yield) of pale yellow needles, mp 118—119°. IR ν_{max}^{KBr} cm^{-1}: 3020, 2960, 2840, 1610, 1460. NMR δ (in $CDCl_3$): 1.74 (4H, br), 2.60 (4H, br), 3.79 (3H, s), 3.89 (3H, s), 6.75—7.64 (7H, m). *Anal.* Calcd. for $C_{22}H_{21}NO_2S$: C, 72.69; H, 5.82; N, 3.85. Found: C, 72.60; H, 5.63; N, 4.10.

1-4′-Cyanophenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-23)——A suspension of IV-2 (16.10 g) and CuCN (6.80 g) in N-methylpyrrolidone (15 ml)[8] was heated at 195—200° for 6 hours with srirring. Addition of H_2O (500 ml) to the hot mixture deposited brown solid, which was collected by filtration and was heated under reflux in $CHCl_3$ (300 ml) for 20 min. The insoluble material was filtered off and the filtrate was dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was decolorized by active carbon and recrystallized from *n*-hexane–C_6H_6 to give 13.00 g (91.0% yield) of pale yellow prisms, mp 147—149°. IR ν_{max}^{KBr} cm^{-1}: 3020, 2940, 2205, 1590, 1460, NMR δ (in $CDCl_3$): 1.77 (4H, br), 2.60 (4H, br), 7.05—7.85 (7H, m).

1-4′-Acetylphenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole (IV-24)——Into a solution of MeMgI in abs. ether (20 ml), freshly prepared from Mg (1.42 g) and MeI (8.00 g) by general procedure, there was added IV-23 (13.00 g) in abs. C_6H_6 (200 ml) dropwise with stirring.[9] The mixture was refluxed for 22 hours with stirring. After cooling, aqueous solution of NH_4Cl (15 g/100 ml) was added to the mixture and it was stirred for 15 min at room temperature. The organic layer was separated and was shaken with 15% HCl (200 ml) to give reddish brown precipitate. The solid was collected by filtration and was dissolved in $CHCl_3$ (100 ml). The acidic aqueous solution was separated and heated under reflux for 15 min. After cooling, the hydrolyzed mixture was extracted with $CHCl_3$ (100 ml). The organic extracts were all combined, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give brown solid, which was decolorized with active carbon and was purified by recrystallization from *n*-hexane–C_6H_6. 11.00 g (82.1% yield) of pale yellow prisms, mp 167—169° were obtained. IR ν_{max}^{KBr} cm^{-1}: 3010, 2970, 1680, 1605, 1475. NMR δ (in

$CDCl_3$): **1.71** (4H, br) 2.66 (4H, br), 2.68 (3H, s), 7.00—8.20 (8H, m). *Anal.* Calcd. for $C_{22}H_{19}NOS$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.89; H, 5.60; N, 4.05.

α-4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylethanol (IV-25)——THF (30 ml) was added to a suspension of IV-24 (1.00 g) in 90% EtOH (10 ml) until IV-24 was dissolved in. Into the solution there was added $NaBH_4$ (0.10 g) in small portions with stirring. The stirring was continued for additional 45 min at room temperature. The solution was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and the extract was dried, and evaporated to dryness. The residue was recrystallized from *n*-hexane–C_6H_6 to give 0.83 g (83.0% yield) of pale yellow prisms, mp 114.5—116°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610, 3420, 3020, 2920, 1595, 1475. NMR δ (in $CDCl_3$): 1.58 (3H, d, J=7 Hz), 1.77 (4H, br), 2.60 (4H, br), 4.96 (1H, q, J=7 Hz), 6.95—7.70 (8H, m). *Anal.* Calcd. for $C_{22}H_{21}NOS$: C, 76.04; H, 6.09; N, 4.02. Found: C, 75.65; H, 6.31; N, 4.40.

4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)benzamide (IV-27)——C_6H_6 (10 ml) was added to a suspension of IV-23 (1.00 g) in ethanolic NaOH (0.12 g/10 ml) until IV-23 was dissolved in. Into the ice-cold solution there was added dropwise with stirring 30% H_2O_2 (1.5 ml).[10] The stirring was continued for additional 20 min in an ice bath, and then the mixture was heated at 60° for 3 hours with stirring. After cooling, the pale yellow precipitate was collected by filtration and recrystallized from MeOH. 1.05 g (80.0% yield) of pale yellow needles, mp 241.5—242° were obtained. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 3160, 3020, 2960, 1650, 1610, 1470. NMR δ (in $CDCl_3$): 1.74 (4H, br), 2.62 (4H, br), 6.66 (2H, br s, D_2O-exchangeable), 7.07—7.85 (8H, m). *Anal.* Calcd. for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.23; N, 8.08. Found: C, 72.93: H, 5.37; N, 8.42.

4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)benzoic Acid (IV-28)——A suspension of IV-23 (1.50 g) in 75% H_2SO_4 (15 ml) was heated at 150—155° for 2.5 hours, and then at 190—195° for further 2 hours. After cooling, the mixture was made alkaline with 10% NaOH and then washed with ether. The aqueous layer separated was acidified with 10% HCl and the resulting solution was extracted with $CHCl_3$. The extract was dried and evaporated to give yellow crystals which were recrystallized from *n*-hexane–C_6H_6. 1.30 g (82.2% yield) of pale yellow needles, mp 223°-dec., was obtained. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000—2500, 2940, 1690, 1605, 1475, NMR δ (in $CDCl_3$): 1.82 (4H, br), 2.67 (4H, br), 7.00—8.41 (8H, m), 10.56 (1H, D_2O-exchangeable). *Anal.* Calcd. for $C_{21}H_{17}NO_2S$: C, 72.59; H, 4.93; N, 4.02. Found: C, 72.46; H, 4.68; N, 3.77.

Ethyl 4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)benzoate (IV-30)——Into a solution of IV-23 (1.50 g), in EtOH, there was induced dry HCl gas (*ca.* 4.5 g) with stirring, and the stirring was continued for further 1.5 hour at room temperature. The resulting mixture was poured into H_2O (300 ml) and the precipitated mixture was extracted with $CHCl_3$ (50 ml × 2). The combined $CHCl_3$ extracts were dried and evaporated to give yellow crystals, (imino ether IV-29, 1.61 g, crude mp 134—135.5°), whose IR spectrum displayed $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (C=N–H), 3000, 2960, 1630 (C=N), 1595, 1480. and NMR spectrum displayed δ (in $CDCl_3$): 1.35 (3H, t, J=7 Hz), 1.80 (4H, br), 2.61 (4H, br), 4.37 (2H, q, J=7 Hz). The crystals were dissolved in 10% HCl (50 ml)–$CHCl_3$ (10 ml) and the mixture was stirred at room temperature for 20 hours. The $CHCl_3$ layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 ml × 2). The combined extracts were dried and evaporated to dryness. The residue was recrystallized from EtOH to give pale yellow needles 1.30 g (overall 76.2% yield from IV-23), mp 88—90°. IR ν_{max}^{KBr} cm^{-1}: 3000, 2960, 1720, 1610, 1480, NMR δ (in $CDCl_3$): 1.38 (3H, t, J=7 Hz), 1.74 (4H, br), 2.59 (4H, br), 4.29 (2H, q, J=7 Hz), 7.07—7.95 (8H, m). *Anal.* Calcd. for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.63; N, 3.72. Found: C, 73.47; H, 5.45; N, 3.54.

4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylacetothiomorpholide (IV-31)——A mixture of IV-24 (8.30 g) and sulfur (2.70 g) in morpholine (7.31 g) was refluxed for 18 hours with stirring.[11] The hot reaction mixture was poured into warm EtOH (500 ml), and the precipitated crystals were collected by filtration. The crystals were decolorized by active carbon and recrystallized from MeOH–$CHCl_3$ to give colorless needles (7.25 g, 71.0% yield), mp 211—212°. IR ν_{max}^{KBr} cm^{-1}: 3020, 2920, 2845, 1585, 1470, 1385. NMR δ (in $CDCl_3$): 1.76 (4H, br), 2.60 (4H, br), 3.27—3.94 (6H, br), 4.40 (2H, m), 4.41 (2H, s), 7.00—7.70 (8H, m). *Anal.* Calcd. for $C_{26}H_{26}N_2OS_2$: C, 69.91; H, 5.86; N, 6.27. Found: C, 69.47; H, 6.02; N, 6.17.

N-2-4′-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylethylmorpholine (IV-32)——Into a slurry of $LiAlH_4$ (0.10 g) in abs. THF (20 ml), there was added dropwise IV-31 (1.50 g) in abs. THF (20 ml) and the mixture was heated under reflux for 20 hours with stirring. After excess hydride was decomposed with a small amount of H_2O, the solution was evaporated to dryness *in vacuo*. The residue was dissolved in 10% HCl (50 ml) and the mixture was washed with ether (50 ml). The aqueous layer was made alkaline with 10% NaOH and extracted with $CHCl_3$ (30 ml × 2). The combined extracts were dried and evaporated to dryness. The residue was recrystallized from MeOH to give 1.06 g (72.6% yield) of pale yellow needles, mp 104—105°. IR ν_{max}^{KBr} cm^{-1}: 3020, 2920, 2840, 1585, 1465. NMR δ (in $CDCl_3$): 1.74 (4H, br), 2.34—2.95 (12H, br), 3.75 (4H, br), 6.97—7.60 (8H, m). *Anal.* Calcd. for $C_{26}H_{28}N_2OS$: C, 74.96; H, 6.77; N, 6.72. Found: C, 74.59; H, 6.98; N, 6.62.

4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylacetomorpholide (IV-33)——C_6H_6 (10 ml) was added to a suspension of IV-31 (1.50 g) in ethanolic NaOH (0.26 g/40 ml) until IV-31 was dissolved in. There was added dropwise with stirring 30% H_2O_2 (2.2 ml) to the cooled solution in an ice bath. After stirring for 2 hours at room temperature the solution was heated at 55—60° with stirring for 1.5 hour. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$ (30 ml) and the solution

was washed with H_2O, dried and evaporated to dryness. The residue was recrystallized from *n*-hexane–C_6H_6 to give 0.92 g (63.8% yield) of pale yellow prisms, mp 161—162.5°. IR ν_{max}^{KBr} cm^{-1}: 3000, 2940, 2840, 1635, 1610, 1470. NMR δ (in $CDCl_3$): 1.75 (4H, br), 2.60 (4H, br), 3.52 (4H, br), 3.58 (4H, br), 3.78 (2H, s), 6.95—7.79 (8H, m). *Anal.* Calcd. for $C_{26}H_{26}N_2O_2S$: C, 72.52; H, 6.08; N, 6.50. Found: C, 72.48; H, 6.28; N, 6.39.

4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylacetic Acid (IV-34)——A solution of IV-31 (4.00 g) in AcOH (8 ml)-H_2O (2 ml)–conc. H_2SO_4 (1.2 ml) was heated under reflux for 3 hours. After cooling, the mixture was extracted with $CHCl_3$ (30 ml ×2). The combined extracts were washed with H_2O, dried, and evaporated to dryness. The residue was recrystallized from *n*-hexane–C_6H_6. 2.60 g (70.0% yield) of pale yellow needles, mp 160.5—162° were obtained. IR ν_{max}^{Nujol} cm^{-1}: 3010, 3000—2500, 1715, 1590, 1470. NMR δ (in $CDCl_3$): 1.79 (4H, br), 2.62 (4H, br), 3.76 (2H, s), 7.50—7.70 (8H, m). *Anal.* Calcd. for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.29; N, 3.87. Found: C. 73.20; H, 5.34; N, 3.75.

Ethyl 4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylacetate (IV-35)——A solution of IV-34 (1.37 g) in EtOH (50 ml) was refluxed for an hour in the presence of BF_3-ether (0.80 g). The EtOH solution was evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ (50 ml), and the extract was washed with H_2O, dried, and then evaporated to dryness. The residue was recrystallized from *n*-hexane–ether to give 0.97 g (79.5% yield) of pale yellow prisms, mp 110—111°. IR ν_{max}^{KBr} cm^{-1}: 3005, 2960, 1735, 1470, 1275. NMR δ (in $CDCl_3$): 1.28 (3H, t, J=7 Hz), 1.78 (4H, br), 2.61 (4H, br), 3.68 (2H, q, J=7 Hz), 4.20 (2H, s), 6.93—7.70 (8H, m). *Anal.* Calcd. for $C_{24}H_{23}NO_2S$: C, 74.00; H, 5.95; N, 3.59. Found: C, 73.73; H, 6.32; N, 3.39.

{1-4′-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylethylidene}azanol (IV-36)——Into a suspension of IV-42 (0.10 g) in EtOH (10 ml), there were added $NH_2OH \cdot HCl$ (26 mg) and $AcONa \cdot 3H_2O$ (30 mg). Then the mixture was heated under reflux for 2 hours. After cooling, the precipitated crystals were collected by filtration and were purified by recrystallization from EtOH to give 46 mg (44.2% yield) of yellow needles, mp 210—212°. IR ν_{max}^{KBr} cm^{-1}: 3640—3320, 1590, 1475. NMR δ (in DMSO-d_6): 1.75 (4H, br), 2.22 (3H, s), 2.54 (4H, br), 7.07—7.96 (8H, m), 11.20 (1H, s, D_2O-exchangeable). *Anal.* Calcd. for $C_{22}H_{20}N_2OS$: C, 73.31; H, 5.60; N, 7.80. Found: C, 73.34; H, 5.66; N, 7.82.

α-4-(2,3-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1-yl)phenylisopropyl Alcohol (IV-37)——Into a solution of MeMgI in abs. ether (20 ml), freshly prepared from Mg (0.18 g) and MeI (1.00 g) by general procedure, there was added IV-24 (1.00 g) in abs. C_6H_6 (40 ml) with stirring at room temperature. After the mixture was stirred for additional 2 hours, 5% HCl (15 ml) was added to the mixture and the stirring was continued for 15 min at room temperature. The C_6H_6 layer was separated and the aqueous layer was extracted with $CHCl_3$ (30 ml×2). The $CHCl_3$ extracts were combined with the C_6H_6 extract, dried, and evaporated to dryness. The residual oil was purified by column chromatography on silica gel with $CHCl_3$ as an eluent. 1.30 g (82.7% yield) of yellow oil was obtained. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3590, 3400, 3080, 2960, 1585, 1470. NMR δ (in $CDCl_3$): 1.62 (6H, s), 1.72 (4H, br), 2.62 (4H, br), 6.95—7.80 (8H, m).

2-(4-2′,3′-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropene (IV-38)——Method i: A solution of IV-37 (1.30 g) in C_6H_6 (30 ml) was refluxed for an hour in the presence of *p*-toluenesulfonic acid (50 mg). After cooling, the solution was washed with H_2O, dried, and evaporated to dryness. The residue was recrystallized from MeOH–$CHCl_3$ to give 1.12 g (91.0% yield) of pale yellow needles, mp 111—112°. IR ν_{max}^{KBr} cm^{-1}: 3020, 2930, 1605, 1465, 895. NMR δ (in $CDCl_3$): 1.78 (4H, br), 2.23 (3H, br s), 2.62 (4H, br), 5.15 (1H, m), 5.50 (1H, br s), 6.64—7.73 (8H, m), *Anal.* Calcd. for $C_{23}H_{21}NS$: C, 80.42; H, 6.16; N, 4.07. Found: C, 80.22; H, 6.16; N, 3.86.

Method ii: Into a solution of methyltriphenylphosphylene in abs. THF (30 ml), freshly prepared from methyltriphenylphosphonium bromide (2.70 g) and *n*-BuLi (15% *n*-hexane solution, 4.7 ml) by general procedure,[12] there was added dropwise with stirring IV-24 (2.70 g) in abs. THF (30 ml) at room temperature. The stirring was continued for further 16 hours. The mixture was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel with C_6H_6 as an eluent to give IV-38 as pale yellow needles after recrystallization from MeOH–$CHCl_3$, mp 111—112°, identical with the sample described in the Method i by comparing the melting points and IR spectra.

2-(4-2′,3′-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropanol (IV-39)——Into a solution of IV-38 (1.00 g) in abs. THF (30 ml), there was induced B_2H_6, freshly prepared from $NaBH_4$ (0.18 g) and BF_3-ether (0.96 g) in diglyme by general procedure,[13] with stirring at room temperature. The stirring was continued for additional 5.5 hours. After excess of borane was decomposed with a small amount of H_2O, 3N NaOH (1.5 ml) and 30% H_2O_2 (2 ml) were added to the solution with stirring. The mixture was heated at 50—60° with stirring for 1.5 hour. After cooling, the mixture was extracted with ether (30 ml×3). The combined extracts were dried, and evaporated to dryness. The residue was recrystallized from MeOH to give 0.90 g (85.7% yield) of pale yellow needles, mp 130.5—132°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3440, 3020, 2950, 1595, 1475. NMR δ (in $CDCl_3$): 1.37 (3H, t, J=7 Hz), 1.83 (4H, br), 2.64 (4H, br), 3.04 (1H, sextet, J=7 Hz), 3.80 (2H, d, J=7 Hz), 7.00—8.00 (8H, m). *Anal.* Calcd. for $C_{23}H_{23}NOS$: C, 76.41; H, 6.41; N, 3.87. Found: C, 76.76; H, 6.56; N, 3.98.

Formation of 1-Phenyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole 4-Oxide (IV-41)——a) Oxidation with CrO_3: Into a chilled solution of IV-1 (1.00 g) in acetone (10 ml), there was added dropwise a solution

of CrO_3 (0.17 g) in 29% H_2SO_4 (0.7 ml)[14] with stirring during 5 min. After the mixture was stirred at room temperature for 45 min, MeOH (5 ml) was added to the mixture and the stirring was continued for additional 5 min. The solution was evaporated *in vacuo*. The residue was extracted with $CHCl_3$ (30 ml×3). The combined extracts were washed with H_2O, dried, and evaporated to dryness. The residual crystals were purified by recrystallization from ether–*n*-hexane to give 0.66 g (62.8% yield) of colorless prisms, mp 101.5—102.5°. IR ν_{max}^{KBr} cm^{-1}: 3060, 2940, 1655, 1595. NMR δ (in $CDCl_3$): 1.92 (4H, br), 2.50 (2H, br), 2.77 (2H, br), 7.06—7.99 (9H, m). *Anal.* Calcd. for $C_{20}H_{17}NOS$: C, 75.20; H, 5.37; N, 4.38. Found: C, 75.45; H, 5.46; N, 4.44. MS *m/e*: 319.1030 [M+] for $C_{20}H_{17}NOS$=319.10.

b) Oxidation with Periodate: Dioxane (*ca.* 10 ml) was added to a suspension of IV-1 (0.10 g) in H_2O (3 ml) until IV-1 was dissolved in. $NaIO_4$ (0.20 g) was added to the solution and the mixture was heated at 60—70° for 3 hours. After cooling, the reaction mixture was extracted with $CHCl_3$ (30 ml×3), and washed with saturated aq. NaCl. The extracts were all combined, and then the $CHCl_3$ solution was dried, and evaporated to dryness. The residue was recrystallized from ether–*n*-hexane to give 50 mg (47.6% yield) of IV-41 as colorless prisms, mp 101.5—102.5°.

c) Oxidation with Peracid: Into a solution of IV-1 (0.50 g) in $CHCl_3$ (10 ml), there was added *m*-chloroperbenzoic acid (0.4 g) in small portions with stirring. After the reaction mixture was stirred at room temperature for 3 hours, the mixture was shaken with aqueous Na_2SO_3 solution. The separated $CHCl_3$ layer was dried, and evaporated to dryness. The residue was recrystallized from ether–*n*-hexane. 0.26 g (49% yield) of IV-41 was obtained as colorless prisms, mp 101.5—102.5°.

Formation of 1-Methyl-2,3-tetramethylenepyrrolo[2,1-*b*]benzothiazole 4-Oxide (IV-42)——a) Oxidation with Periodate: To a solution of IV-40 (0.10 g) in dioxane (14 ml)–H_2O (4 ml), 0.30 g of $NaIO_4$ was added and the mixture was heated at 60—70° for 1.5 hours. The reaction mixture was worked up as described in the procedure for oxidation of IV-1 to give 56 mg (52.9% yield) of pale yellow needles, mp 60—61° [from *n*-hexane]. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2960, 1690, 1435. NMR δ (in $CDCl_3$): 1.78 (4H, br), 2.19 (3H, s), 2.10—2.76 (4H, br), 7.24—8.07 (4H, m). MS *m/e*: 257.0940 [M+] for $C_{15}H_{15}NOS$=257.08. UV λ_{max}^{EtOH} nm (log ε): 239 (3.77), 245 (sh, 3.76), 295 (3.83).

b) Oxidation with Peracid: Into a solution of IV-40 (0.50 g) in $CHCl_3$ (10 ml) there was added *m*-chloroperbenzoic acid (0.58 g) in small portions with stirring. After the reaction mixture was stirred at room temperature for 20 min, the mixture was worked up as described in the procedure for oxidation of IV-1 to give 0.36 g (71.4% yield) of IV-42 as pale yellow needles, mp 60—61°, after recrystallization from *n*-hexane.

Deoxygenation of IV-41——A mixture of IV-41 (0.42 g) and PBr_3 (0.55 g) in $CHCl_3$ (5 ml) was heated under reflux for 1.5 hours. After cooling, H_2O (50 ml) was added to the solution and the $CHCl_3$ layer was separated. Aqueous layer was extracted with $CHCl_3$ (20 ml×2). The $CHCl_3$ extracts were all combined, dried and evaporated to dryness. The residue was recrystallized from EtOH to give 0.22 g (99.0% yield of pale yellow needles, mp 102—104°.

The product was identical with IV-1 by comparing with the melting points and the IR spectra.

Deoxygenation of IV-42——A mixture of IV-42 (80 mg) and PBr_3 (0.12 g) in $CHCl_3$ (5 ml) was stirred for 1.5 hours at room temperature and then it was heated under reflux for 30 min. After cooling, the reaction mixture was worked up as described above to give 40 mg (crude, 53.3% yield) of pale yellow crystals, mp 87—90°.

The product was identical with IV-40 by comparing with the melting points and the IR spectra.

α-(4-4′-Oxido-2′,3′-tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropionic Acid (IV-43)——Into a chilled solution of IV-39 (2.50 g) in acetone (20 ml), there was added dropwise a solution of CrO_3 (2.86 g) in 29% H_2SO_4[14] (13 ml) with stirring. After the mixture was stirred at room temperature for 40 min, the solution was diluted with MeOH (10 ml), and was evaporated under reduced pressure. The residue was dissolved in 10% NaOH and the alkaline solution was washed with ether (50 ml). The aqueous solution was acidified with 10% HCl and extracted with $CHCl_3$ (75 ml×2). The combined extracts were dried, and evaporated to dryness. The residue was purified by column chromatography through silica gel with $CHCl_3$ to give 1.45 g (61.0% yield) of IV-43 as a pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000—2500, 1720, 1660, 1615, 1460. NMR δ (in $CDCl_3$): 1.41 (3H, d, J=7 Hz), 1.86 (4H, br), 2.40 (2H, br), 2.77 (2H, br), 3.69 (1H, q, J=7 Hz), 7.03—8.24 (8H, m), 9.03 (1H, br s, D_2O-exchangeable). MS *m/e*: 391.1225 [M+] for $C_{23}H_{21}NO_3S$=391.12.

Ethyl α-(4-4′-Oxido-2′,3′-tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropionate (IV-44)——A suspension of IV-43 (0.30 g) in EtOH (10 ml) was refluxed in the presence of BF_3-ethar (0.10 g) for an hour. The reaction mixture was worked up as described in the procedure for the ester IV-35. IV-44 (0.24 g, 74.5% yield) was obtained as pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2950, 1730, 1660, 1440, 1250. NMR δ (in $CDCl_3$): 1.10 (3H, t, J=7 Hz), 1.38 (3H, d, J=7 Hz), 1.87 (4H, br), 2.50 (2H, br), 2.76 (2H, br), 3.66 (1H, q, J=7 Hz), 4.07 (2H, q, J=7 Hz), 6.95—7.95 (8H, m). MS *m/e*: 419.1558 [M+] for $C_{25}H_{25}NO_3S$=419.15. UV λ_{max}^{EtOH} nm (log ε): 255 (3.93), 285 (3.83).

Ethyl α-(4-2′,3′-Tetramethylenepyrrolo[2,1-*b*]benzothiazol-1′-yl)phenylpropionate (IV-45)——A mixture of crude ester (IV-44) (0.22 g) and PBr_3 (0.44 g) in $CHCl_3$ (10 ml) was heated under reflux for an hour. The reaction mixture was worked up as described in the procedure for IV-41 to give 0.30 g of brown oil, from

which 47 mg of IV-45 was isolated as a pale yellow oil by column chromatography through silica gel with $CHCl_3$ as an eluent. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3000, 2960, 2860, 1735, 1595, 1475. NMR δ (in $CDCl_3$): 1.24 (3H, t, $J=7$ Hz), 1.56 (3H, d, $J=7$ Hz), 1.76 (4H, br), 2.61 (4H, br), 3.79 (1H, q, $J=7$ Hz), 4.18 (2H, q, $J=7$ Hz), 7.00—7.75 (8H, m). MS m/e: 403.1612 [M^+] for $C_{25}H_{25}NO_2S=403.16$. UV λ_{max}^{EtOH} nm (log ε): 264 (3.84), 279 (3.80), 291 (3.81), 340 (3.57).

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