Indian Journal of Chemistry
Vol. 20B, August 1981, pp. 672-679

Derivatives of 3-Mercaptoindole — Synthesis of a Potent Vasoconstrictor, 3-(2-Imidazolin-2-ylthio)indole (Tinazoline)†‡

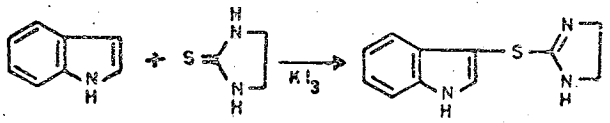
K. NAGARAJAN*, V. P. ARYA, T. N. PARTHASARATHY, S. J. SHENOY, R. K. SHAH & Y. S. KULKARNI
CIBA-GEIGY Research Centre, Goregaon East, Bombay 400 063

Received 24 *February* 1981; *accepted* 19 *March* 1981

Indoles are oxidatively coupled with various cyclic and acyclic thioureas using iodine to give rise to 3-(2-imidazolin-2-ylthio)indole, 1-30, 32 and 36-40. Similar products 33, 34 and 35 are respectively obtained from benz[g]-indole, 1, 6, 6-trimethyl-4,5,6,7-tetrahydroindole and 7-azaindole, while alkylation of 3-mercaptoindole 44 with chloromethyl imidazoline leads to 31. Among the products so obtained, 3-(2-imidazolin-2-ylthio)indole is a potent vasoconstrictor and the hydrochloride salt forms the active ingredient of Varsyl®. 3-Mercaptoindole (44) readily obtained by alkali treatment of S-(3-indolyl)isothiourea (36) is converted into amine derivatives 47 and 52 and to the acids 53-55. Acid-catalysed cyclisation of 55 affords the expected thiopyranone (57), as well as the interesting isomeric ketone (58). A mechanism is proposed for this novel rearrangement. 3-Mercaptoindole (44) is also converted to α-methyl-aminoacid (64) via the hydantoin (63). 3-Mercaptoindole-2-carboxylic acid (65) obtained from 10 is transformed to a variety of methylated derivatives 66-72. The amino acid 75 arising by the action of ethylenimine on 65 is esterified to 76 and cyclised to the condensed thiazepinone (77).

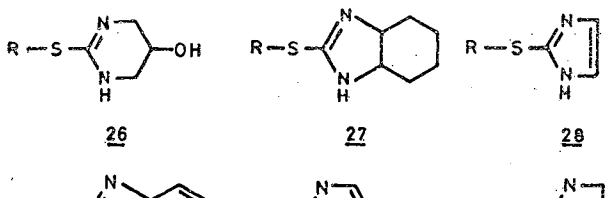
LITERATURE reports on the facile oxidative coupling of indole and thiourea to form S-(3-indolyl)isothiourea[1], the well-known pharmacological properties of indole derivatives and the profound cardiovascular effects of imidazolines (antihypertensives—clonidine, tolazoline; and vasoconstrictors—xylometazoline, oxymetazoline) prompted us to condense indole oxidatively with cyclic thioureas like ethylenethiourea and hexahydropyrimidinethione. The study led to the discovery of a potent vasoconstrictive agent. The ready availability of 3-mercaptoindoles from such condensation products by alkaline hydrolysis further provided an opportunity to explore their chemistry. The results of these endeavours are presented in this paper.

Oxidative coupling of indole and ethylenethiourea with iodine and potassium iodide afforded the hydriodide salt of **1** in 89% yield according to Scheme 1. The hydriodide salt was converted into the HCl salt on an ion exchange column or through the base. Other salts were also prepared. Since **1** showed considerable vasoconstrictive properties[2], structural changes were made on **1** by adding substituents at various positions. Further manipulations involved replacement of the imidazoline ring by tetrahydropyrimidine. One product **16** (Table 1) so obtained was found to have good antihypertensive activity in the renal rat. Hence further changes were caried out, replacing the imidazoline ring of **1** by tetrahydrodiazepine and hexahyrodiazocine residues. Compounds **1** to **25** thus prepared are listed in Table 1. A few other minor or major structural changes led to molecules **26** to **40** whose physical properties are shown in Table 2. Compounds **36** to **40** were prepared as acyclic analogues of **1** for structure-activity relationship studies. **31** was obtained by alkylating 3-mercaptoindole (**44**) with 2-chloromethylimidazoline. **41** which represented a considerable deviation from **1** was made using 2-chloroquinoline-4-carboxylic acid and ethylene thiourea but a similar reaction with 2-chlorobenzthiazole and 2-chlorobenzoxazole failed. An attempted esterification of **10** led to the tetracyclic lactam **42**. Efforts to convert **1** to a similar tetracyclic system by means of a Mannich-type reaction with formaldehyde did not succeed.

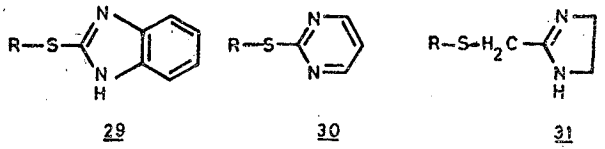


1 (HI)

Scheme 1



26 **27** **28**



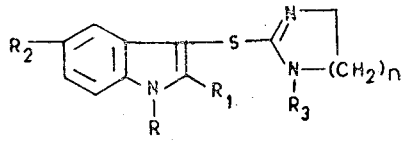
29 **30** **31**

R = (3-indolyl)

†Registered trade name of hydrochloride formulation, Varsyl®

‡Contribution No. 610 from CIBA-GEIGY Research Centre.

TABLE 1 — CYCLIC S-(3-INDOLYL)ISOTHIOUREAS

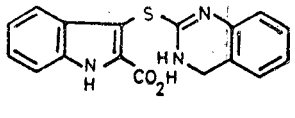


Compound No.	R	R_1	R_2	R_3	*n*	Yield (%)	Mol. formula	m.p. (°C)	N (%) Calc.	N (%) Found
1	H	H	H	H	1	89	$C_{11}H_{11}N_3S$	118–22	19.35	19.43
1 .HI							$C_{11}H_{11}N_3S.HI$	221–23	12.17	12.14
1 .HCl							$C_{11}H_{11}N_3S.HCl$	234–36	16.56	16.81
1 .Maleate.H_2O							$C_{11}H_{11}N_3S.C_4H_4O_4.H_2O$	122	11.96	11.88
1 .CH_3SO_3H							$C_{11}H_{11}N_3S.CH_3SO_3H$	234–35	13.42	13.39
1 .H_2SO_4							$C_{11}H_{11}N_3S.H_2SO_4$	178–80	13.33	13.32
1 .HNO_3							$C_{11}H_{11}N_3S.HNO_3$	188–90	19.99	20.02
2 .HI	H	Me	H	H	1	50	$C_{12}H_{13}N_3S.HI$	277–78(d)	11.69	11.99
3 .HI	H	H	H	Me	1	20	$C_{12}H_{15}N_3S.HI$	215–16	11.69	11.28
4 .HI	H	Ph	H	H	1	84	$C_{17}H_{17}N_3S.HI$	260–61	9.98	10.09
5	H	CO_2H	H	H	1		$C_{12}H_{11}N_3O_2S$	212(d)	16.09	15.72
5 .HI						90	$C_{12}H_{11}N_3O_2S.HI$	>310	10.79	10.44
5 .HCl.H_2O							$C_{12}H_{11}N_3O_2S.HCl.H_2O$	187–88	13.31	11.70
6 .HI	Me	Me	H	H	1	91	$C_{13}H_{15}N_3S.HI$	203–5	11.26	10.89
6 .HCl. 1/2 H_2O						60	$C_{13}H_{15}N_3S.HCl.1/2\,H_2O$	200–201	14.45	14.63
7 .HI	Me	Me	H	Me	1	58	$C_{14}H_{17}N_3S.HI$	250–51	10.86	11.13
8 .HI	H	H	H	H	2	66	$C_{12}H_{13}N_3S.HI$	250–51	11.69	11.85
8 .HCl .H_2O	H	H	H	H	2	70	$C_{12}H_{13}N_3S.HCl.H_2O$	122–23	14.70	14.35
9 .HI	H	Me	H	H	2	55	$C_{13}H_{15}N_3S.HI$	242	11.26	11.65
10 .HI	H	CO_2H	H	H	2	60	$C_{13}H_{13}N_3O_2S.HI$	250–52	10.42	10.18
11 .HI	H	H	Br	H	2	44	$C_{12}H_{12}BrN_3S.HI$	241–42	9.59	9.84
12 .HI	H	Ph	H	H	2	92	$C_{18}H_{17}N_3S.HI$	249–50(d)	9.65	9.86
13 .HI	H	H	H	Me	2	40	$C_{12}H_{15}N_3S.HI$	207	11.26	11.14
14 .HI	H	CO_2H	OMe	H	2	50	$C_{14}H_{15}N_3O_3S.HI$	239–40	9.70	9.97
15 .HI	Me	CO_2H	H	H	2	52	$C_{14}H_{15}N_3O_2S.HI$	227(d)	10.07	9.65
16 .HI	H	CO_2H	H	Me	2	60	$C_{14}H_{15}N_3O_2S.HI$	230–31	10.07	9.77
17 .HI	Me	Me	H	H	2	65	$C_{14}H_{17}N_3S.HI$	246 (d)	10.86	10.62
18 .HI	Me	Me	H	Me	2	38	$C_{15}H_{19}N_3S.HI$	239–40(d)	10.47	10.88
19 .HI	H	CO_2H	OMe	Me	2	44	$C_{15}H_{17}N_3O_3S.HI$	256 (d)	9.39	9.04
20 .HI	H	H	H	H	3	48	$C_{13}H_{15}N_3S.HI$	236 (d)	11.26	10.85
21 .HI	H	Me	H	H	3	47	$C_{14}H_{17}N_3S.HI$	237–38(d)	10.86	10.76
22 .HI	H	CO_2H	H	H	3	16	$C_{14}H_{15}N_3O_2S.HI$	242–43(d)	10.12	10.30
23 .HI	H	H	Br	H	3	54	$C_{13}H_{14}BrN_3S.HI$	243–47 (d)	9.30	9.31
24 .HI	Me	Me	H	H	3	56	$C_{15}H_{19}N_3S.HI$	244–45	10.47	10.57
25 .HI	Me	Me	H	H	4	63	$C_{16}H_{21}N_3S.HI$	243–45	10.12	10.30

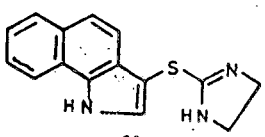
The oxidative coupling product of indole with ethylene-thiourea is formulated as **1** arising from an attack at the β-position of the indole nucleus, in analogy with the literature report[1] and also based on the chemical shift of 7.8 ppm for the indole proton. Further, while indoles carrying a substituent at position-2 like methyl, phenyl or carboxyl group (although not ethoxycarbonyl) underwent the oxidative coupling reaction with ethylene thiourea, 3-monosubstituted indoles, e.g. 3-methylindole and indole-3-acetic acid failed to couple with thioureas. Quite understandably, 3-(methylthiocarbamoyl)aminoethylindole (tryptamine derivative) failed to undergo intramolecular oxidative coupling; but a similar failure on the part of 2-(methylthiocarbamoyl)aminomethylindole (**43**) was unexpected and disappointing.

Out of all the compounds discussed so far, **1** (generic name : tinazoline) had the most outstanding vasoconstrictive activity and as the hydrochloride sal forms the active ingredient of Varsyl® which is being developed as a nasal decongestant. Structure-activity relationships in this series[3] and the detailed pharmacology of **1**[4] are being published elsewhere.

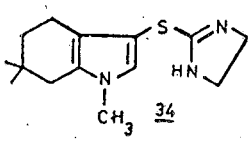
Alkaline hydrolysis of the thiourea condensation product **36** of indole is reported to give a good yield of 3-mercaptoindole (**44**)[1]. In our hands, **44** was accompanied by significant amounts of the disulphide (**45**) (Scheme 2). Attempts to transform **44** into **46** or **47** by alkylation with ethylenimine or propyleni mine respectively were unsuccessful. **47** however became available by alkylation of **44** with chloracetone to form **49**, transformation to the oxime (**50**) and subsequent LAH reduction. One bid to cyclise the acetyl derivative (**48**) of **47** to an indolothiazepine a also another one on **50** under Beckmann transforma tion conditions using PCl_5 were unsuccessful. The



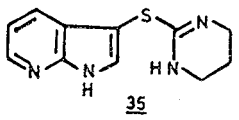
32



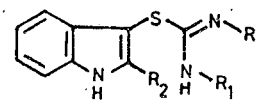
33



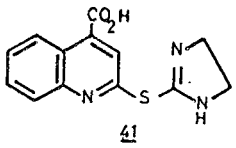
34



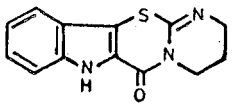
35



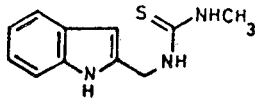
36. R = R_1 = R_2 = H
37. R = Ph, R_1 = R_2 = H
38. R = Et, R_1 = R_2 = H
39. R = R_1 = Me, R_2 = H
40. R = R_1 = H, R_2 = Me



41



42

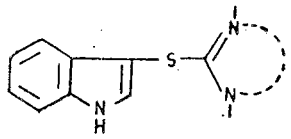


43

ring system could be, however, synthesised by another route (*vide infra*). Addition of **44** to acrylonitrile, followed by LAH reduction of the product (**51**) afforded the propyl amine derivative **52**. Zinc chloride treatment of **51** under Hoesch conditions failed to convert it to the ketone (**57**), which was obtained by a different route shown in Scheme 3.

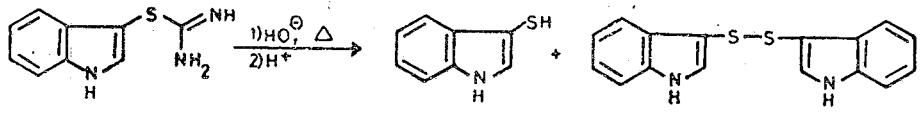
Alkylation of 3-mercaptoindole (**44**) with ethyl chloracetate and subsequent hydrolysis gave rise to **53** as the major and **54** as the minor products. Propionic acid (**55**), the higher homologue of **53** was prepared from **44** using acrylic acid. Cyclisation of **55** with PPA at 80° gave in low yield a mixture of **57** and **58** in which the latter predominated. The use of P_2O_5 on the other hand led to the same mixture of ketones again in low yield, but with **57** predominating. The ketones were isomeric (mass spectra, elemental analyses). PMR spectra helped to assign

TABLE 2 — MISCELLANEOUS CYCLIC AND ACYCLIC S-(3-INDOLYL)-ISOTHIOUREAS



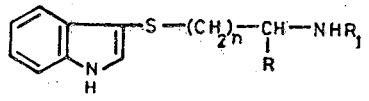
Compound No.	Yield (%)	Mol. formula	m.p. (°C)	N(%) Calc.	N(%) Found
26. HI	16	$C_{12}H_{13}N_3OS.HI$	228-29	11.20	11.13
27. Picrate	26	$C_{15}H_{17}N_3S.C_6H_3N_3O_7$	207-8		
28 .HI	24	$C_{11}H_9N_3S$ .HI	199-201	12.25	12.33
29 .HCl .H_2O	92	$C_{15}H_{11}N_3S.HCl.H_2O$	218-20	13.14	12.82
30	60	$C_{12}H_9N_3S$	275	18.49	18.29
32 .HI	55	$C_{17}H_{13}N_3O_2S.HI$	245(d)	9.31	9.13
33 .HI[a]	46	$C_{15}H_{13}N_3S.HI$	242-44	10.63	10.42
34 .HI[b]	80	$C_{14}H_{21}N_3S.HI$	174-76	10.74	10.56
35 .HI[c]	27	$C_{11}H_{12}N_4S.HI$	302-3	10.56	15.30
36 .HI	95	$C_9H_9N_3S.HI$	219-22(d)	13.17	13.13
37 .HI	90	$C_{15}H_{13}N_3S.HI$	225-26	10.63	10.46
38 .HI	20	$C_{11}H_{13}N_3S.HI$	185-86	12.11	12.00
39 .HCl	60	$C_{11}H_{13}N_3S.HCl$	224-26	16.44	16.43
40 .HI	45	$C_{10}H_{11}N_3S.HI$	195-200	12.61	12.39

(a) From 1*H*-benz[*g*]indole[11]
(b) The starting material, 1,6,6-trimentyl-4,5,6,7-tetrahydroindole was a liquid obtained by Wolff-Kischner reduction of the corresponding 4-keto compound[12].
(c) From 7-azaindole[13].

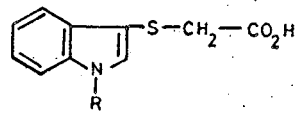


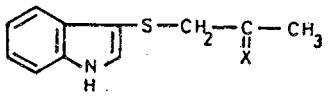
36 44 45

Scheme 2

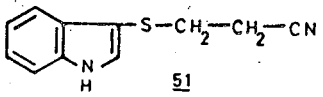


46 R = R_1 = H, n = 1
47 R = Me, R_1 = H, n = 1
48 R = Me, R_1 = Ac, n = 1
52 R = R_1 = H, n = 2



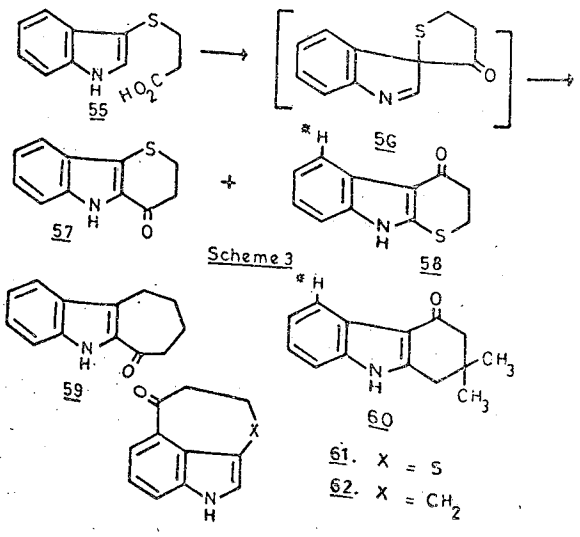


49 X = O
50 X = NOH



51

53 R = H
54 R = CH_2CO_2H



Scheme 3

the correct structures. Thus the pattern of the aromatic protons in **57** was similar to that in the reference compound **59**[5], while the aromatic region of **58** corresponded to that of **60**[6], especially the chemical shift of the starred proton (8.14 ppm in **58**; 8.17 ppm in **60**). The similarity in the UV spectra of the pairs **57** and **59** and **58** and **60** (Fig. 1) (allowing for bathochromic shifts due to the sulphur atom) was even more striking and clinched the issue. Another possible structure **61** could be readily ruled out by comparison of IR and PMR spectral data of **61** with those of a known model compound **62**[7]. We believe that a rational explanation for the formation of **57** and **58** from **55** would require the postulation of a spiroketone intermediate **56**. Tryptamine derivatives are known to form such spirocyclic intermediates which then rearrange to carbolines[8]. Some fruitless efforts were spent on locating **56** in the mixture of cyclisation products. Ketone **49** was finally converted into the hydantoin **63**, which was then hydrolysed to the α-methyl-DOPA analogue **64**.

Alkaline hydrolysis of **10** (HI salt) followed by acidification afforded in high yield, 3-mercaptoindole-2-carboxylic acid (**65**) (Scheme 4) which by virtue of its bifunctional substitution at positions 2 and 3 of the indole nucleus, was considered to be a suitable candidate for chemical manipulation. Methylation using excess methyl iodide and potassium carbonate in acetone led to the formation of ester (**66**) which was hydrolysed to the acid (**67**). Oxidation using alkaline hydrogen peroxide transformed **67** into the sulphoxide (**68**). The IR spectrum of the latter exhibited νC = O as a broad band at an inordinately high frequency (1880 cm^{-1}) suggesting that it may perhaps exist as the lactal (**70**), since the methyl ester (**69**) had the C = O band in the normal position (1720 cm^{-1}). Reaction of **65** with diazomethane led to the expected ester (**71**), the disulphide (**73**) appearing as a byproduct in one experiment. Presumably, the carboxyl group in **65** was rapidly and preferentially esterified and the resultant sulphydryl derivative dimerised before alkylation took place. Hydrolysis of **71** gave the acid (**72**), while heating with pyrrolidine gave the pyrrolidide (**74**) Interaction of **65** with ethylenimine in alcohol solution led to the

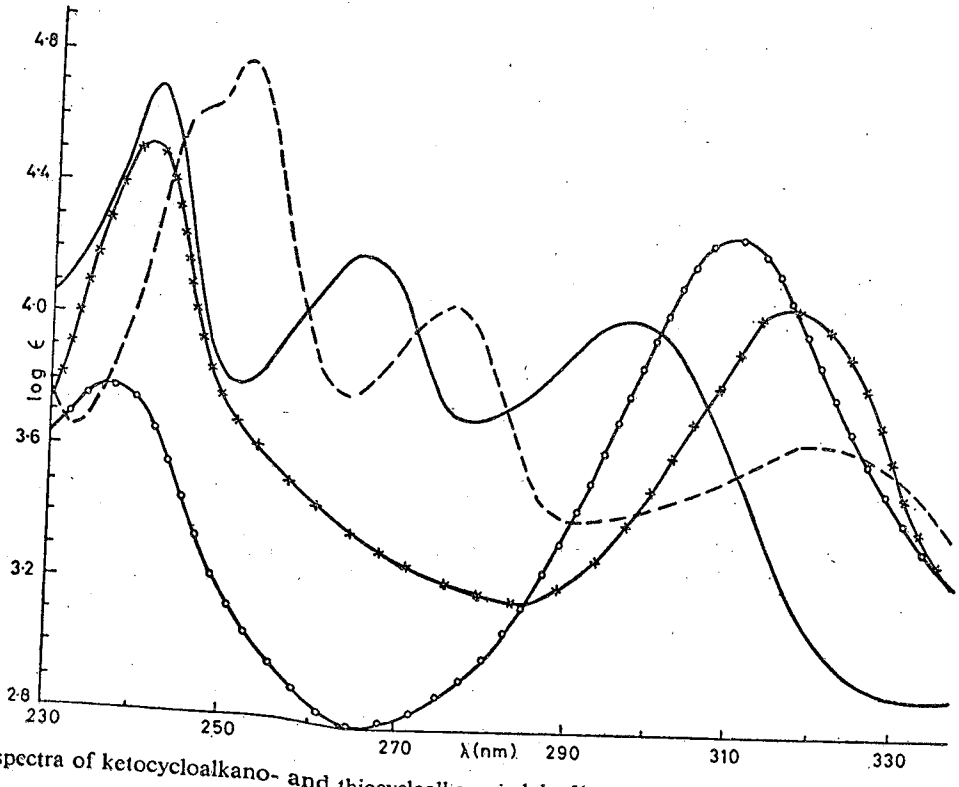
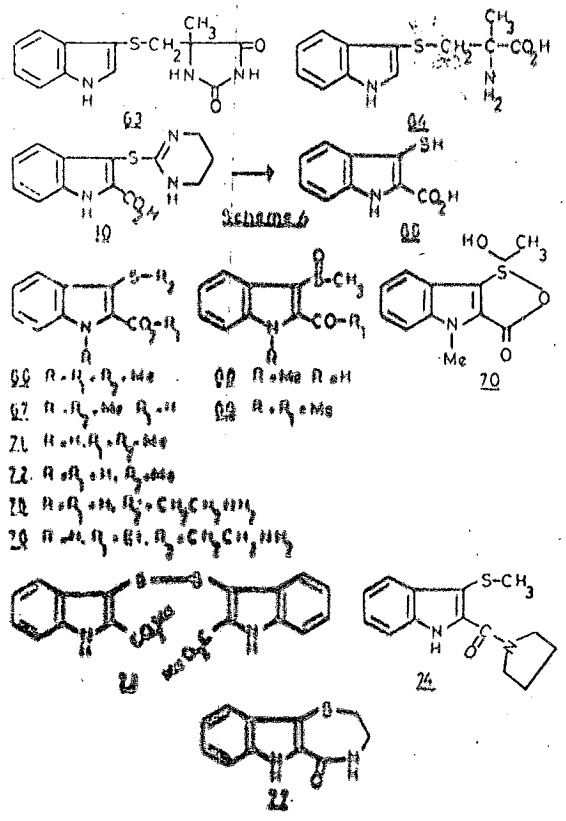


Fig. 1 — UV spectra of ketocycloalkano- and thiocycloalkano-indoles [(×——×) **57**; (- - - - -) **58**; (—·—·—·—) **59**; and (————) **60**]



Scheme 6

ethyl amine derivative (75) which resisted ring closure to thiazepinone (77) thermally or by hot acetic anhydride. The ethyl ester (76) also did not afford 77 under pyrrolytic conditions, but was coaxed to do so by ethanolic sodium ethoxide.

Experimental Procedure

Melting points are uncorrected. UV spectra were run for 95% ethanol solutions on a Beckman DK 2A spectrophotometer, IR spectra (ν_{max} in cm^{-1}) for nujol mulls on a Perkin-Elmer infracord spectrometer and PMR spectra on Varian A-60 or Bruker WH 90 spectrometer; chemical shifts (δ) are quoted in ppm downfield from TMS as internal reference. Compounds listed in Tables 1 and 2 had correct C, H analyses and only nitrogen analyses are given for brevity (C,H analyses can be had from the authors on demand).

Condensation of indoles with cyclic and acyclic thioureas : General method — A solution of indole (35.1 g) and ethylenethiourea (30.6 g) in methanol (750 ml) was stirred at room temperature and treated with a solution of iodine (76.6 g) and potassium iodide (150 g) in water (250 ml) during 30 min. The mixture was stirred for 2 hr more and the solution concentrated *in vacuo* to remove most of the methanol. The crystalline product was filtered off and washed with water and ether to give **1** hydriodide as brownish yellow crystals (92.5 g, 89%); m.p. 223° (from EtOH-ether).

An aqueous suspension of the hydriodide was covered with methylene chloride and shaken with a slight excess of 10% aq. NaOH to give the free base, which was filtered off and recrystallised from ethyl alcohol; m.p. 118-22°.

The above base was suspended in ethyl alcohol and treated with HCl gas in the same solvent. The hydrochloride salt was precipitated by the addition of ether and recrystallised from ethyl alcohol-ether; m.p. 228-29° (d). Alternatively, the HCl salt could also be obtained by passing a MeOH solution of the hydriodide through a column of Amberlite IRA 400 (Cl^- form). It could also be prepared as follows :

A mixture of 3-mercaptoindole (**44**) (1.5 g) and NaOMe (0.7 g Na in 40 ml MeOH) was stirred at room temperature for 30 min. The mixture was then cooled to 10° and 2-chloro-2-imidazoline[9] in methanol (20 ml) added dropwise. After the addition was over, the mixture was stirred at room temperature for 2 hr. The solvent was evaporated off, the residue treated with water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried (Na_2SO_4), evaporated *in vacuo* and the residue converted into HCl salt which on recrystallisation from MeOH-ether gave **1**. HCl (0.5 g), m.p. 228-9°.

Other salts like maleate, methanesulphonate, sulphate and nitrate are reported in Table 1 as also several analogues of **1** in Tables 1 and 2 prepared by the procedure for **1** HI. These were generally crystallised from methanol or ethanol alone or in combination with ether.

2-(3-*Indolylmercapto*) *methylimidazoline* (**31**) — A solution of 3-mercaptoindole (**44**) (7 g) in methanol (50 ml) was mixed with sodium methoxide (from 2g Na in 50 ml methanol) and treated with 2-chloromethylimidazoline (from 7.8 g HCl salt and 50 mmol sodium methoxide in 100 ml methanol). The mixture was stirred at 25° for 16 hr, filtered, the filtrate evaporated to dryness *in vacuo*, the residue extracted with CH_2Cl_2 and the solution filtered from insoluble sodium chloride. The filtrate was treated with HCl gas in isopropanol, the solution evaporated and the residue crystallised from MeOH-ether to afford **31** HCl salt (4.5 g); m.p. 172-74° (Found : C, 53.89; H, 5.42; N, 15.31. $C_{12}H_{13}N_3S$. HCl requires C, 53.83; H, 5.27; N, 15.69%; PMR (DMSO-d_6) : 12.00 (NH, *s*), 10.25 (NH, *s*), 7.08-7.65 (Ar-H, 4H, *m*), 7.67 (C_2-H, *s*), 3.65 (2N-CH_2, S-CH_2, 6H, *s*): M^+ at m/z 231.

2-(2-*Imidazolin*-2-*ylthio*) *quinoline*-4-*carboxylic acid* (**41**) — To a hot solution of ethylenethiourea (10.2 g) in absolute ethanol (250 ml) was added a hot solution of 2-chloroquinoline-4-carboxylic acid (20.7 g)[10] in absolute ethanol (250 ml) and the mixture refluxed for 20 hr. The solution on cooling gave a yellow solid which was filtered off and recrystallised from methanol-ether to give **41** hydrochloride (22.5 g); m.p. 241° (Found : C, 50.45; H, 4.20; N, 13.54. $C_{13}H_{11}N_3O_2S$. HCl requires C, 50.40; H, 3.91; N, 13.56%); IR : 3300 (NH), 1700 (C = O).

Tetracyclic lactam (**42**) — Pyrimidylmercapto acid (**10**) hydriodide (13 g) was left in ethanol (250 ml) saturated previously with HCl gas, at 25° for 16 hr and the solution refluxed for 2 hr. It was concentrated to a small volume and poured into water. Basification with ammonia gave a white solid which was

filtered off and crystallised from ethanol to give **42** (6.6 g); m.p. 297° (d) (Found : C, 61.17; H, 4.41; N, 16.88. $C_{12}H_{11}N_3OS$ requires C, 60.69; H, 4.31; N, 16.34%); M^+ at m/z 257; IR : 3320 (NH), 1620 (C=O); PMR ($CDCl_3$ + DMSO-d_6) : 7.0-7.58 (Ar-H, 4H, *m*), 3.53 (N-CH_2, *t*), 3.37 (N-CH_2, *t*), 1.95 (CH_2, *q*).

N-2-Indolylmethyl-N'-methylthiourea (**43**) — A mixture of 2-aminomethylindole (2.8 g) and methyl isothiocyanate (1.44 g) in benzene (30 ml) was refluxed for 3 hr. Evaporation of the solvent and crystallisation of the residue from ethanol gave **43** (0.35 g); m.p. 220-21° (Found : C, 59.97; H, 6.39; N, 18.96. $C_{11}H_{13}N_3S$ requires C, 60.26; H, 5.98; N, 19.15%); M^+ at *m/z* 219.

3-Mercaptoindole (**44**) — S-(3-Indolyl) isothiouronium iodide (**36**) (16 g) was mixed with 10% aq. NaOH (40 ml) and heated at 80° for 30 min under nitrogen. The solution was filtered from insolubles and the filtrate acidified with dil. HCl to give **44** (8 g); m.p. 102-3° (from hot water) (Found : C, 64.8; H, 4.99; N, 9.66. C_8H_7NS requires C, 64.42; H, 4.73; N, 9.39%).

The insoluble part (1 g) was S, S'-bis-(3-indolyl) disulphide (**45**), m.p. 228-30° (from MeOH), (Found : C, 65.10; H, 3.83; N, 9.68. $C_{16}H_{12}N_2S_2$ requires C, 64.86; H, 4.08; N, 9.46%). The yield of the disulphide could be improved by prolonging the heating of the aqueous alkaline solution.

S-(3-Indolyl) (2-amino-1-propyl) sulphide (**47**) — **44** (10 g) was dissolved in aq. NaOH (2.7 g in 50 ml water) and treated with chloroacetone (6.2 g). The solution was stirred overnight, extracted with ether, the ether layer washed with 10% aq. NaOH, dried and evaporated to give (3-indolyl) mercaptoacetone (**49**) as a syrup (11.5 g), which was slightly contaminated with the disulphide (**45**). The syrup (5.2 g) in ethanol (40 ml) was refluxed for 4 hr with hydroxylamine hydrochloride (2.1 g) and KOH (1.5 g) in 15 ml water. The solution was concentrated to 15 ml, poured onto crushed ice, the resultant solid filtered and crystallised from water to give the oxime (**50**); m.p. 106-8° (Found : C, 60.39; H, 5.67; N, 12.48. $C_{11}H_{12}N_2OS$ requires C, 59.99; H, 5.49; N, 12.72%).

A slurry of **50** (15 g) in dry ether (100 ml) was added to lithium aluminium hydride (8 g) in ether (150 ml). The mixture was stirred at 25° for 16 hr, excess lithium aluminium hydride decomposed with moist ether and water, the ether layer was separated and the basic product extracted with 10% aq. HCl. The HCl extract was neutralized with Na_2CO_3 and the poduct recovered with ether. Crystallisation from benzene-hexane afforded the **47** (7.4 g); m.p. 111-12° (Found : C, 63.78; H, 6.73; N, 13.59. $C_{11}H_{14}N_2S$ requires C, 64.06; H, 6.84; N, 13.58%); acetyl derivative, m.p. 142-43° (from water) (Found : C, 63.14; H, 6.80; N, 11.16. $C_{13}H_{16}N_2OS$ requires C, 62.89; H, 6.50; N, 11.28%).

S-(3-Indolyl)(3-amino-1-propyl) sulphide (**52**) — **44** (5 g) and acrylonitrile (3 ml) were heated together under reflux with triethyl amine (25 ml) for 6 hr. The solution was concentrated *in vacuo*, the residue treated with 10% aq. NaOH, extracted with ether and the ether layer evaporated to give the propionitrile (**51**) (6 g) as a homogenous liquid. The nitrile (6 g) in ether (150 ml) was reduced with lithium aluminium hydride (2 g) in ether (100 ml) overnight, decomposed with water, the ether layer separated, concentrated and treated with alc. HCl to give **52** HCl salt (**59**), which after crystallisation from ethanol-ether afforded **52**. HCl salt (3g), m.p. 242-4° (Found : C, 54.44; H, 6.40; N, 11.65. $C_{11}H_{14}N_2S$. HCl requires C, 54.43; H, 6.23; N, 11.54%).

3-Indolylmercaptoacetic acid (**53**) — A mixture of **44** (2.25 g), ethyl chloroacetate (2.1 g) anhydrous potassium carbonate (6.3 g) and acetone (20 ml) was refluxed for 8 hr and then filtered. The filtrate was evaporated, the residue taken up in ether, the ether layer successively washed with 10% aq. NaOH and water and dried. Evaporation left an oil (2.3 g) which was subjected to hydrolysis on a water-bath with 10% aqueous NaOH (23 ml) for 3 hr. The solution was filtered and acidified with dil. HCl. The product was extracted into chloroform and the extract treated with hexane to give a solid (0.5g) which was recrystallised from ether-hexane to afford **53** (0.3 g); m.p. 115-17° (Found : C, 58.39; H, 4.34; N, 6.98. $C_{10}H_9NO_2S$ requires C, 57.97; H, 4.38; N, 6.76%); IR : 3380 (NH), 1720 (C=O).

In one larger run, a byproduct was obtained which was separated from the above acid using the insolubility of the former in benzene. This was crystallised from ether-hexane and identified as the bis-acetic acid (**54**); m.p. 162-66° (Found : C, 54.57; H, 4.50; N, 5.28. $C_{12}H_{11}NO_4S$ requires C, 54.34; H, 4.18; N, 5.28%).

β-(3-Indolyl)mercaptopropionic acid (**55**) — A mixture of 3-mercaptoindole (**44**) (4.5 g), acrylic acid (2.5 g) and triethylamine (25 ml) was refluxed for 8 hr. Triethylamine was removed *in vacuo*, the residue treated with saturated aq. sodium bicarbonate and filtered. Acidification of the filtrate gave **55** which crystallised from benzene(4.7 g), m.p. 176° (Found : C, 59.59; H, 5.30; N, 6.08. $C_{11}H_{11}NO_2S$ requires C, 59.72; H, 5.01; N, 6.33%); IR : 3350 (NH), 1680 (C = O); PMR ($CDCl_3$ + DMSO-d_6) : 10.08 (NH, *s*), 7.73 (Ar-H, 1H, *m*), 7.11-7.46 (Ar-H, 3H, *m*), 7.34 (C_2-H, *d*), 2.90 (S-CH_2, *m*), 2.50 (C-CH_2, *m*).

Cyclisation of propionic acid (**55**) — (i) A mixture of **55** (1 g) and PPA (15 g) was heated at 80° for 4 hr and then poured onto crushed ice. Extraction with chloroform gave tarry material from which a crystalline material was extracted by ether and recrystallised from ether-hexane to give the ketone (**58**). (50 mg); m.p. 228° (Found : C, 65.19; H, 4.61; N, 7.12. $C_{11}H_9NOS$ requires C, 65.02; H, 4.46; N, 6.89%); M^+ at m/z 203; IR : 3400 (NH), 1620 (C = O); PMR ($CDCl_3$ + DMSO-d_6) : 11.59 (NH, *s*), 8.14 (Ar-H, 1H, *m*), 7.09-7.36 (Ar-H, 3H, *m*), 3.39 (S-CH_2 or CO-CH_2, *m*), 2.81 (CO-CH_2 or SCH_2, m). TLC of the mother liquor showed the presence of the ketone (**57**).

(ii) A mixture of **55** (2 g) and phosphorous pentoxide (5 g) was heated in benzene (50 ml) under reflux for 2 hr. The benzene layer was decanted off, the residue neutralised with aq. sodium bicarbonate and extracted with chloroform. The organic layers were

mixed, evaporated *in vacuo* and the residue crystallised from benzene-hexane to 57 (0.1 g), m.p. 147° (Found : C, 64.61; H, 4.64; N, 7.00. $C_{11}H_9NOS$ requires C, 65.02; H, 4.46; N, 6.89%); M^+ at *m/z* 203; IR : 3450 (NH), 3260, 1640 (C = O); NMR ($CDCl_3$ + DMSO-d_6) : 11.15 (NH, *s*), 7.00-7.60 (Ar-H, 4H, *m*), 3.38 (S-CH_2 or CO-CH_2, *m*), 2.91 (CO-CH_2 or S-CH_2, *m*).

Hydantoin (63) — (3-Indolyl)mercaptoacetone (49) (10.2 g), potassium cyanide (5.2 g), ammonium carbamate (50 g), ethanol (145 ml) and water (145 ml) were heated together with stirring at 80° for 12 hr. The mixture was set aside for 12 hr at 25° and filtered. The precipitate was washed with water and re-crystallized from ethanol to give 63 (9 g), m.p. 183-85° (Found : C, 56.60; H, 4.81; N, 14.87. $C_{13}H_{13}N_3O_2S$ requires C, 56.72; H, 4.76; N, 15.27%), M^+ at *m/z* 275); IR : 3420 (NH), 3380, 1760 (C = O), 1760, 1710 cm^{-1}; PMR (DMSO-d_6); 11.33, 10.73; 7.88 (3 NH, broad *s*), 7.11-7.66 (ArH, 4H, *m*), 7.4 (C_2-H, *d*), 2.98 (CH_2, *s*), 1.29 (CH_2, *s*).

Amino acid (64) — The above hydantoin (63) (4 g) and barium hydroxide (20 g) were refluxed together in water (100 ml) for 4 days. The solution was cooled and treated with dil. sulphuric acid till barium was completely precipitated. The mixture was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was crystallized from water to give 64 (0.5 g); m.p. 236-38° (Found : C, 53.87; H, 6.53; N, 10.64. $C_{12}H_{14}N_2O_2S.H_2O$ requires C, 53.74; H, 6.01; N, 10.44%); M^+ at *m/z* 250; IR : 3240 (NH), 3120 ; 1600 (C = O); PMR (DMSO-d_6): 7.0-7.7 (Ar-H, 4H, *m*), 7.56 (C_2-H, *d*), 3.06 (S-CH_2 centre of *ABq*, *J* = 6Hz), 1.30 (CH_3, *s*).

3-*Mercaptoindole-2-carboxylic acid* (65) — Tetrahydropyrimidinylmercapto acid (10) (13 g) was heated with 10% aq. NaOH (130 ml) under N_2 atmosphere for 1 hr. The resultant solution was acidified with conc. HCl and the precipitate recrystallized from aq. ethanol to give 65 (6.5 g); m.p. 168-69° (Found : C, 56.26; H, 3.89; N, 7.51. $C_9H_7NO_2S$ requires C, 55.96; H, 3.65; N, 7.25%); IR : 3430 (NH) ,1680 (C = O).

1-*Methyl*-3-*mercaptomethylindole-2-carboxylic acid* (67) — The above acid (65) (6 g), methyl iodide (26.6 g), anhydrous K_2CO_3 (13 g) and acetone (50 ml) were heated overnight under reflux. The mixture was filtered and the filtrate evaporated to give the methyl ester (66) of the desired acid (67) as a thick oil (4.3 g). The ester (3 g) was hydrolysed by heating in methanol (5 ml) and 10% aq. NaOH (10 ml) for 1 hr. Removal of methanol *in vacuo*, dilution with water and acidification with conc. HCl gave 67 which crystallised from methanol (2.5 g); m.p. 126-27° (Found : C, 59.53; H, 5.10; N, 6.65. $C_{11}H_{11}NO_2S$ requires C, 59.72; H, 5.00; N, 6.33%); IR : 1700 (C = O).

1-*Methyl*-2-*methylsulphoxidoindole-2-carboxylic acid* (68) — The methylmercapto acid (67) (1.1 g) was dissolved in 1*N* aq. NaOH (6 ml) and the solution heated under reflux with 30% aq. H_2O_2 (2 ml) for 12 hr. It was filtered and acidified with HCl and the product crystallised from ethanol to give 68, (0.85 g); m.p. 182-83° (Found : C, 55.45; H, 4.99; N, 5.92. $C_{11}H_{11}NO_3S$ requires C, 55.69; H, 4.67; N, 5.91%); M^+ at *m/z* 237; IR : 1880 (C = O).

A solution of 68 (50 mg) in methanol was left overnight at room temperature with diazomethane (from 1.5 g nitrosomethylurea) in ether (30 ml). The solution was evaporated *in vacuo* to give the ester (69); M^+ at *m/z* 251; IR : 1720 (C = O).

3-*Mercaptomethylindole-2-carboxylic acid*(72) — A solution of 65 (10 g) in methanol (50 ml) was left overnight at room temperature with diazomethane (from 33.6 g nitrosomethylurea) in ether (300 ml). The solution was evaporated *in vacuo* and the residue crystallised from ether-hexane to give ester 71 (8 g), m.p. 103-4° (Found : C, 59.75; H, 5.58; N, 6.37. $C_{11}H_{11}NO_2S$ requires C, 59.72; H, 5.01; N, 6.33%); IR : 3340 (NH), 1690 (C = O).

In one experiment, a byproduct sparingly soluble in ether was obtained and identified as 73; m.p. 239–41° (from ethanol) (Found : C, 58.35; H, 4.14; N, 6.28. $C_{25}H_{16}N_2O_4S_2$ requires C, 58.25; H, 3.91; N, 6.79%) IR : 3250 (NH), 1720 (C = O); M^+ at *m/z* 412. Ester 71 (5.5 g) in methanol (50 ml) was mixed with 10% aq. NaOH (50 ml) and heated on the water-bath to get a clear solution. This was left overnight at 25°, diluted with water and acidified with conc. HCl. The precipitate (3.5 g) was filtered to give acid 72 (2.8 g) (aq. MeOH) m.p. 132-33° (Found : C, 58.07; H, 4.64; N, 7.05. $C_{11}H_9NO_2S$ requires C, 57.97; H, 4.38; N, 6.76%). In one experiment, the product had a different crystalline form, m.p. 155-56°. Heating of 71 (1.1 g) with pyrrolidine (0.36 g) at 90-100° for 16 hr gave the pyrrolidide 74 (0.5 g) m.p. 172° (from ethanol) (Found : C, 64.51; H, 6.47; N, 10.95. $C_{14}H_{16}N_2OS$ requires C, 64.60; H, 6.20; N, 10.76%).

3-(2-*Amino*-1-*ethyl*) *mercaptoindole-2-carboxylic acid* (75) — 65 (2.9 g) and ethyleneimine (0.7 g) were stirred together in ethanol for 16 hr at 25°. The precipitate was filtered off, triturated with hot ethanol and crystallised from acetic acid to give 75 (2.5 g), m.p. 292-93° (Found : C, 55.99; H, 5.40; N, 11.57. $C_{11}H_{12}N_2O_2S$ requires C, 55.92; H, 5.12; N, 11.87%).

Esterification of 75 (0.2 g) with alcoholic HCl (10 ml) at 25° for 16 hr gave the ethyl ester 76 (0.15 g), m.p. 141-42° (Found C, 59.09; H, 6.32; N, 10.60. $C_{13}H_{16}N_2O_2S$ requires C, 59.08; H, 6.10; N, 10.60%); IR : 1700 (C = O).

1,2,3,4-*Tetrahydro*-1-*oxothiazepino*[6,7-*b*]*indole* (77) — The above ester (76) (1 g) was refluxed with ethanolic sodium ethoxide (2 g Na in 50 ml ethanol) for 4 hr. The solvent was evaporated off, the residue treated with water and extracted with ether. The ether layer was washed with 2*N* HCl and then with water and dried. This was then decolourised with Norit and concentrated to give the thiazepinone (77), m.p. 175-76° (Found : C, 60.76; H, 5.06; N, 12.87. $C_{11}H_{10}N_2OS$ requires C, 60.54; H, 4.62; N, 12.84%); 3420 (NH), 3380; 1650 (C = O) cm^{-1}; M^+ at *m/z* 218; PMR ($CDCl_3$ + DMSO-d_6) : 11.5 (NH, *s*) 8.13 (CO-NH, *t*), 6.90-7.7 (Ar-H, 4H, *m*), 3.75 (N-CH_2, *m*),3.17 (S-CH_2, *t*).

Acknowledgement

We are thankful to Prof. T. R. Govindachari and Dr R. S. Grewal for thier interest and encouragement and to Dr S. Selvavinayakam and his associates for analytical and spectroscopic data.

References

1. HARRIS, R. C. N., *Tetrahedron Lett.*, (1969), 4465.
2. ARYA, V. P. & NAGARAJAN, K., *Ger. Offen.*, 2, 427, 207 (to CIBA-GEIGY); *Chem. Abstr.*, **82** (1975), 156360 w.
3. NAGARAJAN, K., ARYA, V. P., KAUL, C. L., DAVID, J. & GREWAL, R. S., *Indian J. exptl Biol.* (communicated).
4. GREWAL, R. S., KAUL, C. L. & DAVID, J., *Indian J. exptl Biol.* (communicated).
5. NAGARAJAN, K., MADHAVAN PILLAI, P. & KULKARNI, C. L., *Indian J. Chem.*, **7** (1969), 319.
6. BORCH, R. R. & NEWELL, R. G., *J. org. Chem.*, **38** (1973), 2729.
7. NAGASAKA, T. & OHKI, S., *Chem. pharm. Bull. Japan*, **25** (1977), 3031.
8. VAN TAMELEN, H. E., YARDLEY, J. P. & MIYANO, M., *Tetrahedron Lett.*, (1963), 1011; WOODWARD, R. B., *Tetrahedron*, **19** (1963), 247.
9. TRANI, A. & BELLASIO, E., *J. heterocycl. Chem.*, **11** (1974), 260.
10. AESCHLIMANN, J. A., *J. chem. Soc.*, (1926), 2909.
11. PENNINGTON, F. C., JELLINEK, M. & THURN, R. D., *J. org. Chem.*, **24** (1959), 565.
12. BOBITT, J. M. & DUTTA, C. P., *Chem. Commun.*, (1968), 1429.
13. CLEMO, G. R. & SWAN, G. A., *J. chem. Soc.*, (1945), 603.