Synthesis and Reactions of 4*H*-3,1-Benzothiazines

S. I. El-Desoky*, E. M. Kandeel and A. H. Abd-el-Rahman

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, A.R. Egypt

R. R. Schmidt

Fakulktät Chemie, Universität Konstanz, Fach M 725, D-78457 Konstanz, Germany

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This study is directed towards the synthesis of the pyrrolo[1,2-*a*]indole skeleton which is the essential ring system of the active antitumor miomycins. To this end a number of fused heterocycles such as benzothiazines, benzoxazines, indoles and quinolines were synthesized. The structures of the new compounds were assigned by ir, ^{1}H nmr and ms-data.

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The mitomycins **1** are an important class of chemotherapeutic compounds exhibiting potent antibiotic and antitumor properties [1]. For instance, three carcinostatic functional groups, quinone, carbamate, and aziridine are present in a specific arrangement in the pyrrolo[1,2-*a*]indole ring system. For instance, mitomycins also show activity against a variety of Gram positive organisms including tetracycline resistant species [2]. The great pharmacological interest in mitomycins encouraged the attempt to build its basic skeleton *via* a novel carbanionic route.

The investigation of this synthetic route required a number of related experiments which are divided into two parts: the first is to synthesize 4*H*-3,1-benzothiazines of structure **2** where Z and Y are leaving groups (nucleofuge), for example OR, SR, N^+R_3, which facilitate the construction of the target skeleton. The second part contains the application of a "Wittig rearrangement" analogous carbanionic reaction, which is performed by deprotonation of the heterocycles, thus treating these synthesized benzothiazines with lithium diisopropylamide in order to obtain the desired pyrroloindoles *via* ring contraction.

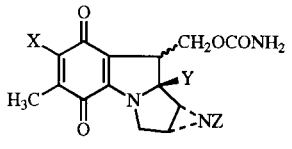
Fusion of *o*-aminobenzyl chloride hydrochloride **3** [3] with different thiocarboxamides afforded the 4*H*-3,1-benzothiazine derivatives **4a-e** in good yield. The ^{1}H nmr spectra of these compounds showed as expected, a singlet in the range δ = 3.92-4.03 for the CH_2 group of the benzothiazine ring. However, this method failed when **3** was fused with 3,4-*O*-isopropylidene-L-threonic acid thioamide. The latter compound was prepared by sulphurization of 3,4-*O*-isopropylidene-L-threonamide [4].

An alternative procedure which has hitherto not yet been reported was to react compound **3** with benzopyran-2-thione to give 2-[2-(2-hydroxyphenyl)vinyl]-4*H*-3,1-benzothiazine **4f** which on reaction with methyl iodide in basic medium gave 2-[2-(2-methoxyphenyl)-vinyl]-4*H*-3,1-benzothiazinium iodide **4g**. Compound **4g** exhibits strong uv absorption (λ_{max} = 420 nm), thus effecting a bathochromic shift [5]. The ^{1}H nmr spectra of compounds **4f** and **4g** have doublets at δ = 7.96 and 7.94, respectively, characteristic for the α-hydrogen atom of the substituted styryl group.

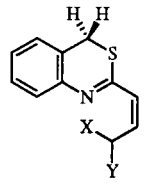
2-[(β-Substituted)vinyl]benzothiazines **4h-j** were obtained *via* an aldol condensation of compound **4a** with benzaldehyde, anisaldehyde, and isobutyraldehyde. The ^{1}H nmr spectra showed that the two α,β-vinylic hydrogen atoms of **4h-j** possess *trans* configuration ($J_{1',2'}$ = 16 Hz) thus preventing formation of the target skeleton. In order to overcome this problem, compound **4a** was reacted with bromoacetalaldehyde diethyl acetal using different bases, but unfortunately, the desired compound **4k** was not formed and instead compound **5** was obtained (see Scheme 1).

A further attempt to synthesize benzothiazine derivatives was to fuse compound **3** with tetrahydrofuran-2-thione. The desired 2-(3-hydroxypropyl)-4*H*-3,1-benazathiazine **4l** was not formed and instead, 1-(2-hydroxymethylphenyl)pyrrolidine-2-thione (**6**) was obtained. The ^{1}H nmr spectra of the product lacked the presence of the characteristic signal for the CH_2 group of the thiazine moiety (see Scheme 1).

1,4-Cycloaddition (Diels-Alder reaction) of **4e**, as a cisoid diene, with either dimethyl acetylenedicarboxylate or 2,3-dihydrofuran, as dienophiles, furnished the expected cycloadducts **7** and **8**, respectively (see Scheme 2).



1



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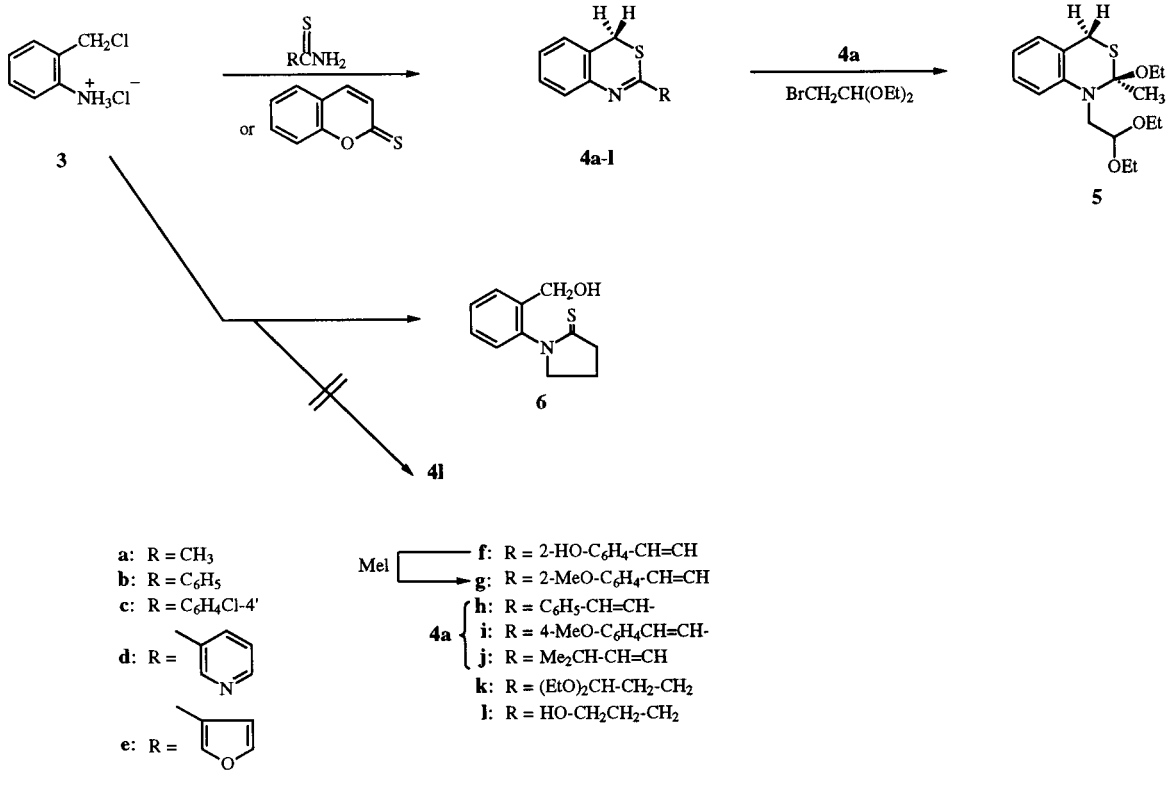
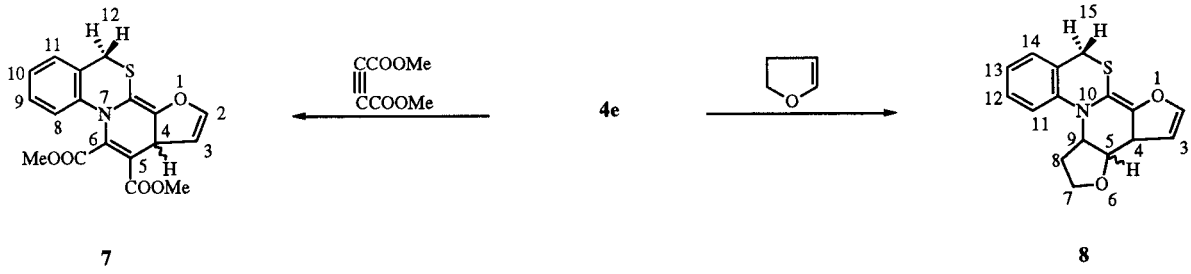
Scheme 1



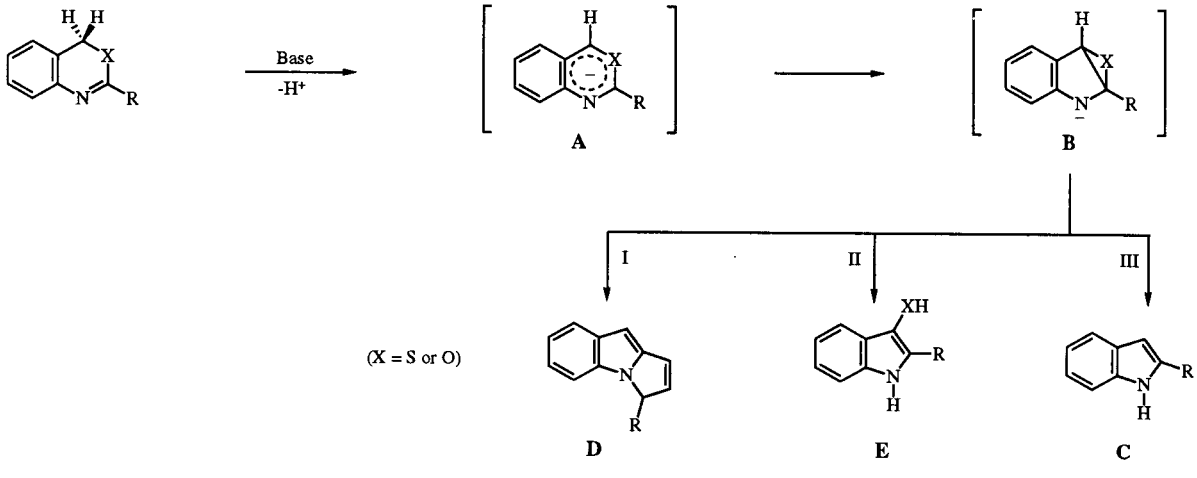
Scheme 2



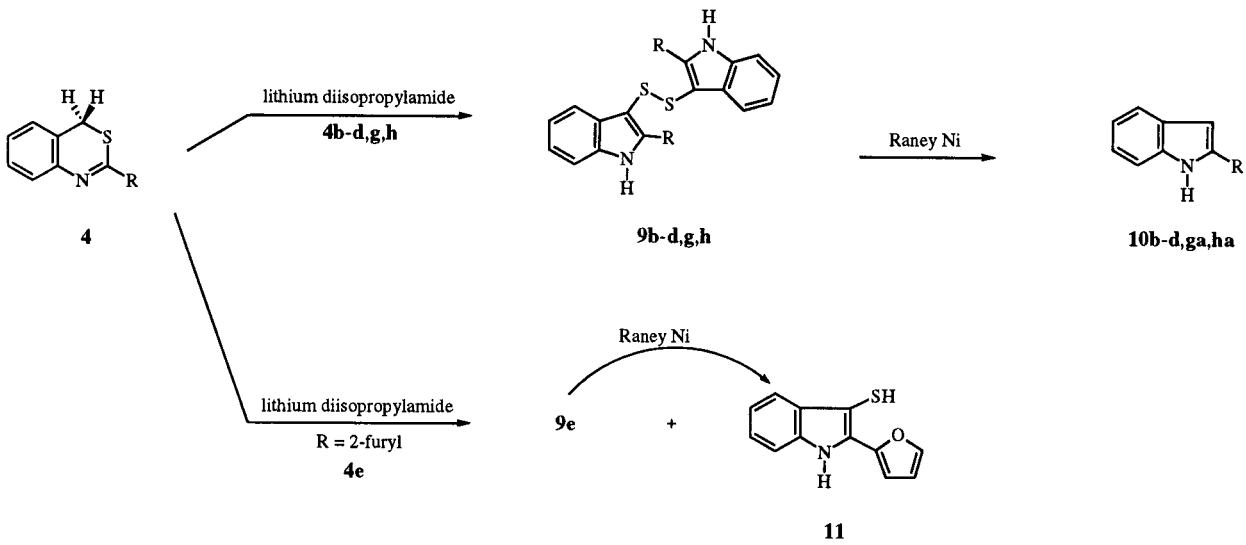
Intramolecular ring contraction of the benzothia or oxazine derivatives to the benzopyrrole sulphide (or oxide) anion **B** is favored: the high energy of anion **A** as a heterocyclic 8π system and the instability of the episulfide (or oxide) bond in anion **B** led finally to either fast and irreversible elimination of sulfur (or oxygen), thus giving **C** or **D** (routes I, III) or formation of the benzopyrrole-3-thiol (or 3-ol) derivative **E** (route II) (see Scheme 3) [6-8].

In this work, when the benzothiazine derivatives **4b-d,g,h** were allowed to react with lithium diisopropylamide, the 2-substituted indoles **10** were not directly obtained *via* sulphur extrusion (route III, Scheme 3); bis[2-alkyl (or aryl)indolyl-3] disulfides **9b-d,g-h** were formed instead *via* oxidation of the thiol intermediate (route II, Scheme 3). Desulphurization of these disulfides using Raney nickel furnished indole derivatives **10b-d,ga,ha**; the styryl group in the case of the com-

Scheme 3



Scheme 4

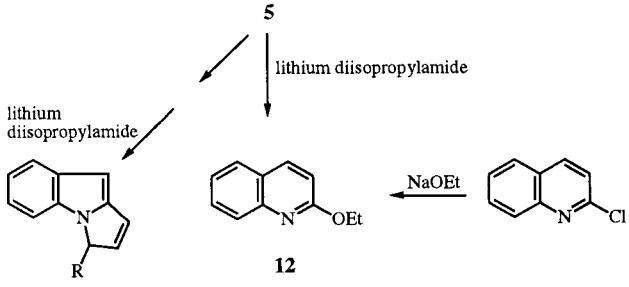


b: R = C_6H_5
c: R = C_6H_4Cl-4
d: R = 3'-pyridyl
e: R = 2'-furyl
g: R = $CH{=}CHC_6H_4OMe$-2
ga: R = $CH_2CH_2C_6H_4OMe$-2
h: R = $CH{=}CHC_6H_5$
ha: R = $CH_2CH_2C_6H_5$

pounds **4g,h** were also hydrogenated yielding the corresponding arylethyl group. Reaction of **4e** with lithium diisopropylamide under the same reaction conditions afforded an equimolar ratio of 2-(2-furyl)-3-mercaptoindole **11** and bis[2-(2-furyl)indol-3-yl] disulphide **9e**. The disulfide **9e** could be directly transformed into **11** upon treatment with Raney nickel. The formation of compounds **9** and **11**, instead of 2-furylindole **10**, may be attributed to localization of the negative charge at the nitrogen atom of **B** (Scheme 3) which leads to cleavage of the neighboring CS-bond.

Several attempts to generate the pyrrolo[1,2-*a*]indole skeleton in a one pot synthesis from the novel benzothiazine derivative **5** in a consecutive manner using lithium diisopropylamide as the base were unsuccessful but instead 2-ethoxyquinoline **12** was obtained (Scheme 5). This novel transformation seems to be based on loss of ethyl thioacetate and ethanol and ensuing electrocyclic ring closure. Both melting point and ^{1}H nmr spectral data of compound **12** and an authentic sample, prepared from 2-chloroquinoline, were identical [9].

Scheme 5

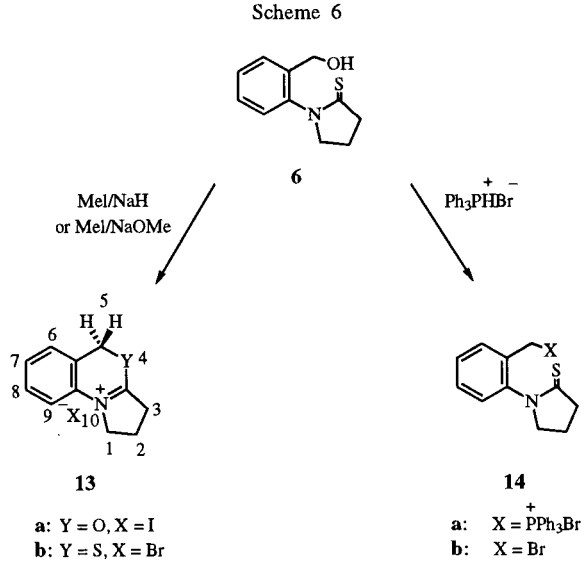


Several attempts were made to construct the pyrrolo-[1,2-*a*]benzothia or oxazinium salts **13**. This was accomplished by the reaction of **6** with methyl iodide in the presence of sodium hydride. Compound **13a** was also prepared in better yield *via* treatment of **6** with methyl iodide in a sodium methoxide/methanol mixture. Then an attempt was made to cyclize compound **6** *via* an intramolecular Wittig type reaction, a new modification of the Madelung indole synthesis. However, the desired salt **14a** could not be obtained. Also, nucleophilic replacement of the hydroxyl group by a bromine atom to give compound **14b** was not observed, instead 1,2-dihydro-3*H*,5*H*-pyrrolo[1,2-*a*][3,1]benzothiazinium bromide **13b** was isolated which is an analog of compound **13a**. Compound **13b** was also prepared *via* treatment of **6** with carbon tetrabromide and triphenylphosphine in toluene.

Attempts to prepare the pyrrolo[1,2-*a*]indole skeleton by treatment of **13a,b** with lithium diisopropylamide or *tert*-butyllithium were made but the desired product was not obtained.

Although, pyrrolo[1,2-*a*]indole was not obtained, this work led to the synthesis of a number of novel heterocyclic moieties and afforded new methods for generating indole, benzothiazine, benzoaxazine and quinoline compounds.

Scheme 6



EXPERIMENTAL

Solvents were purified in the usual way. Petroleum ether had a boiling range of 35-60°. Melting pionts are uncorrected; ^{1}H nmr spectra Brucker WM 250 Cryospec, Jeol Jum FX 90; solvent deuteriochloroform unless otherwise noted. The internal standard was tetramethylsilane. Column chromatography was accomplished using Merck silica gel 60, 0.040-0.63 mm. Medium pressure liquid chromatography was accomplished using Merck silica gel LiChroprep Si 60, 15-25 μm. Thin layer chromatography was accomplished using Merck plates, silica gel 60 F_{254}, layer thickness 0.2 mm, detection by treatment with a solution of 20 g of ammonium molybdate and 0.4 g of Cerium(IV) sulfate in 400 ml of 10% sulfuric acid followed by heating at 120°. The eluent is the same in both thin layer and column chromatography.

General Procedure for the Preparation of 4*H*-3,1-Benzothiazine Derivatives.

4*H*-3,1-Benzothiazine Derivatives **4a-e**.

A mixture of 2-aminobenzyl chloride hydrochloride (**3**) [3] (17.8 g, 0.1 mole) and the appropriate thioamide {thionicotinamide was prepared by sulphurization of nicotinamide (vitamin pp) using the Lawesson reagent [10]} (0.12 mole) was fused in an oil bath at 100-110° for 30 minutes. The reaction mixture was made just alkaline with 20% sodium hydroxide solution and extracted with dichloromethane. The organic layer was dried (magnesium sulfate), filtered and the solvent evaporated *in vacuo*. The solids thus obtained were purified by chromatography to give **4a-1**.

2-Methyl-4*H*-3,1-benzothiazine (**4a**).

Column chromatography of the residue [petroleum ether/ethyl acetate (4:1)] gave **4a** (11.4 g, 70%) as yellow crystals, mp 42-45° (published [3]); ^{1}H nmr: δ 2.4 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 7.08-7.31 (m, 4H, Ar-H).

Anal. Calcd. for C_9H_9NS (163.24): C, 66.22; H, 5.56; N, 8.58. Found: C, 66.43; H, 5.34; N, 8.78.

2-Phenyl-4*H*-3,1-benzothiazine (**4b**).

Column chromatography of the residue [petroleum ether/ethyl acetate (4:1)] gave **4b** (17.12 g, 76% yield) as pale yellow crystals, mp 55-58°; ^{1}H nmr: δ 3.98 (s, 2H, CH_2), 7.13-8.16 (m, 9H, Ar-H).

Anal. Calcd. for $C_{14}H_{11}NS$ (225.31): C, 74.63; H, 4.92; N, 6.21. Found: C, 74.50; H, 4.98; N, 6.14.

2-(4-Chlorophenyl)-4*H*-3,1-benzothiazine (**4c**).

Column chromatography of the residue [petroleum ether/ethyl acetate (18:1)] gave **4c** (18.43 g, 71% yield) as pale yellow crystals, mp 122-125°; ^{1}H nmr: δ 4.01 (s, 2H, CH_2), 7.16-7.51 and 8.02-8.15 (m, 8H, Ar-H); ms: m/z 259.9 (M^+).

Anal. Calcd. for $C_{14}H_{10}NSCl$ (259.75): C, 64.74; H, 3.88; N, 5.39. Found: C, 64.60; H, 3.94; N, 5.22.

2-(3-Pyridyl)-4*H*-3,1-benzothiazine (**4d**).

Column chromatography of the residue [petroleum ether/ethyl acetate (3:2)] gave **4d** (19.23 g, 85% yield) as yellow crystals, mp 182°; ^{1}H nmr: δ 4.03 (s, 2H, CH_2), 7.16-7.48 (m, 5H, 5- to 8- and 4'-H), 8.39 (m, 1H, 5'-H), 8.72 (m, 1H, 6'-H), 9.32 (s, 1H, 2'-H); ms: m/z 226 (M^+).

Anal. Calcd. for $C_{13}H_{10}N_2S$ (226.3): C, 69.00; H, 4.45; N, 12.38. Found: C, 69.11; H, 4.54; N, 12.23.

2-(2-Furyl)-4*H*-3,1-benzothiazine (**4e**).

Column chromatography of the residue [petroleum ether/ethyl acetate] gave **4e** as yellow crystals (18.7 g, 87% yield), mp 54-56°; ^{1}H nmr: δ 3.95 (s, 2H, CH_2), 6.55 (dd, 1H, 4'-H), 7.13-7.15 (m, 2H, 8,3'-H), 7.25 (m, 1H, 7-H), 7.37 (m, 1H, 6-H), 7.47 (dd, 1H, 5-H), 7.55 (dd, 1H, 5'-H).

Anal. Calcd. for $C_{12}H_9NOS$ (215.27): C, 66.95; H, 4.21; N, 6.51. Found: C, 66.89; H, 4.22; N, 6.35.

Synthesis of 2-[2-(2-Hydroxyphenyl)vinyl]-4*H*-3,1-benzothiazine (**4f**).

(a) Synthesis of Benzopyran-2-thione.

A mixture of coumarin (14.6 g, 0.1 mole) and Lawesson's reagent (24.3 g, 0.06 mole) in dry toluene (200 ml) was refluxed for 4 hours. The reaction mixture was cooled, concentrated *in vacuo* and the product purified by column chromatography [petroleum ether/ethyl acetate (4:1)] to give benzopyran-2-thione (14.6 g, 90% yield) to be used directly in the synthesis of **4**.

(b) Compound **4**.

A mixture of **3** (1.7 g, 0.01 mole) and benzopyran-2-thione (1.94 g, 0.012 mole) was fused in an oil bath at 120° for 30 minutes. The reaction mixture was worked up as described for **4a-c** and purified by column chromatography [petroleum ether/ethyl acetate (4:1)] to give **4f** (2.5 g, 94% yield) as golden yellow crystals, mp 174-176°; ^{1}H nmr: δ 3.92 (s, 2H, CH_2), 6.82-7.53 (m, 9H, Ar-H and β-H), 7.96 (d, 1H, α-H, styryl, $J_{\alpha,\beta}$ = 16.2 Hz), 9.43 (s, 1H, OH).

Anal. Calcd. for $C_{16}H_{13}NOS$ (267.34): C, 71.88; H, 4.90; N, 5.24. Found: C, 71.86; H, 4.90; N, 5.19.

2-[2(2-Methoxyphenyl)vinyl]-4*H*-3,1-benzothiazonium Iodide (**4g**).

Compound **4f** (1 g, 3.74 mmoles) was dissolved in dry tetrahydrofuran (20 ml), sodium hydride (0.2 g, 8.23 mmoles) was added and the reaction mixture stirred at room temperature. Iodomethane (1.4 g, 0.6 ml, 10 mmoles) was added dropwise and stirring continued for an additional 1 hour. Then water (10 ml) was carefully added. The reaction mixture was extracted with dichloromethane, washed with water (2 x 20 ml), dried (magnesium sulfate) and evaporated *in vacuo*. Short column chromatography [petroleum ether/ethyl acetate (4:1)] afforded **4g** (1.2 g, 79% yield) as golden crystals, mp 220-222; ^{1}H nmr: δ 3.88 (s, 3H, OMe), 3.94 (s, 2H, CH_2), 6.94-7.60 (m, 9H, Ar-H and β-H), 7.94 (d, 1H, α-H, $J_{\alpha,\beta}$ = 16.2 Hz).

Anal. Calcd. for $C_{17}H_{16}NOSI$ (409.28): C, 49.89; H, 3.94; N, 3.42. Found: C, 49 91; H, 3 99; N, 347.

Synthesis of Chalcones **4h-j**.

General Procedure.

To a solution of **4a** (1.63 g, 10 mmoles) in ethanol (20 ml) was added the corresponding aldehyde (benzaldehyde, anisaldehyde or isobutyraldehyde) (12 mmoles) then sodium hydroxide solution (15 ml, 30%) was added dropwise. The reaction mixture was stirred for 3 hours at room temperature, then refluxed for 3 hours. The reaction mixture was cooled, poured into crushed ice (200 ml), extracted with dichloromethane. The organic layer was dried (magnesium sulfate), evaporated *in vacuo* and the solid obtained were purified to give:

2-[(2-Phenyl)vinyl)]-4*H*-3,1-benzothiazine (**4h**).

Column chromatography [petroleum ether/ethyl acetate (9:1)] gave **4-h** (2.26 g, 90% yield) as yellow crystals, mp 150-152°; ^{1}H nmr: δ 3.94 (s, 2H, CH_2), 7.10-7.60 (m, 11H, α,β-styryl and Ar-H); ms: m/z 251 $[M]^+$, 250 $[M-H]^+$, 217 $[M-H_2S]$ and 121.1 [M-(H + quinoline)].

Anal. Calcd. for $C_{16}H_{13}NS$ (251.35): C, 76.46; H, 5.21; N, 5.57. Found: C, 76.23; H, 5.38; N, 5.41.

2-[2-(4-Methoxyphenyl)vinyl]-4*H*-3,1-benzothiazine (**4-i**).

Column chromatography [petroleum ether/ethyl acetate (4:1)] gave **4i** (2.36 g, 84% yield) as yellow crystals, mp 145-148°; ^{1}H nmr: δ 3.48 (s, 3H, OMe), 3.92 (s, 2H, CH_2), 6.92 (d, 1H, β-H styryl), 7.03 (d, 1H, α-H styryl, $J_{\alpha,\beta}$ = 16.7 Hz), 7.13-7.56 (m, 8H, Ar-H).

Anal. Calcd. for $C_{17}H_{15}NOS$ (281.37): C, 72.57; H, 5.37; N, 4.98. Found: C, 72.67; H, 5.69; N, 4.75.

2-[2-(Isopropyl)vinyl]-4*H*-3,1-benzothiazine (**4-j**).

Column chromatography [petroleum ether/ethyl acetate (8:1)] gave **4-j** (0.65 g, 30% yield) as yellow viscous material; ^{1}H nmr: δ 1.15 (d, 6H, 2 CH_3), 2.52 (m, 1H, 3'-H), 3.80 (s, 2H, CH_2), 6.41 (d, 1H, 1'-H, $J_{1'2}$ = 15.8 Hz), 6.78 (dd, 1H, 2'-H, $J_{1',2'}$ = 15.6 Hz, $J_{2',3'}$ = 6.4 Hz), 7.10-7.37 (m, 4H, Ar-H).

Anal. Calcd. for $C_{13}H_{15}NS$ (217.33): C, 71.85; H, 6.96; N, 6.44. Found: C, 71.73; H, 7.12; N, 6.60.

2-Ethoxy-1-(2,2-diethoxyethyl)-2-methyl-4*H*-3,1-benzothiazine (**5**).

To a stirred solution of **4a** (1.63 g, 10 mmoles) and bromoacetaldehyde diethyl acetal (2.97 g, 10 mmoles) in dry ethanol (30 ml) was added sodium ethoxide solution (0.5 mg of sodium/10 ml of dry ethanol) within 30 minutes. The reaction

mixture was refluxed for 10 hours, poured into ice-water and extracted with ether. The organic layer was dried (magnesium sulfate) evaporated *in vacuo* and purified by medium pressure chromatography [petroleum ether/ethyl acetate (14:1)] to give **5** as yellow viscous material (2.7 g, 83% yield); ^{1}H nmr: δ 1.21 (t, 6H, 2 CH_2CH_3), 1.35 (t, 3H, CH_2CH_3), 1.61 (s, 3H, CH_3), 2.62 (d, 2H, 1'-H), 3.46-3.67 (m, 4H, 2 OCH_2), 3.69 (s, 2H, 4-H), 4.26 (q, 2H, OCH_2), 4.54 (t, 1H, 2'-H), 6.63-7.28 (m, 4H, 5- to 8-H); ms: m/z = 325 [M^+], 279 [$M-C_2H_5OH]^+$.

Anal. Calcd. for $C_{17}H_{27}NSO_3$ (325.47): C, 62.74; H, 8.36; N, 4.30. Found: C, 62.54; H, 8.25; N, 4.25.

1-(2-Hydroxymethylphenyl)-2-thiopyrrolidine (**6**).

(A) Synthesis of Tetrahydrofuran-2-thione.

A mixture of γ-butyrolactone (8.6 g, 0.1 mole) and Lawesson's reagent (24.2 g, 0.06 mole) in toluene (100 ml) was refluxed for 3 hours. The solvent was evaporated *in vacuo* and the residue was purified using column chromatography [petroleum ether/ethyl acetate (5:1)] to give tetrahydrofuran-2-thione as a yellow viscous material which was used directly in the second step.

(B) Compound **6**.

A mixture of **3** (17.8 g, 0.1 mole) and tetrahydrofuran-2-thione (12.3 g, 0.12 mole) was fused for 30 minutes at 110° then sodium hydroxide solution (30 ml, 30%) was added to form a white emulsion which was heated at 60° for 10 minutes. Dichloromethane (30 ml) was added with stirring at room temperature and the medium was neutralized by adding diluted hydrochloric acid. The organic layer was separated, dried (magnesium sulfate), evaporated *in vacuo* and the residue which was formed, purified using column chromatography [petroleum ether/ethyl acetate (1:1)] to give **6** (13.1 g, 63% yield) as white crystals, mp 51-53°; ^{1}H nmr: δ 1.86 (s, br, 1H, OH), 2.28 (quintet, 2H, 4'-H), 2.61 (t, 2H, 5'-H), 3.71 (d, 2H, CH_2OH, J = 7.6 Hz), 3.86 (t, 2H, 3'-H, J = 7 Hz), 7.14-7.44 (m, 4H, Ar-H).

Anal. Calcd. for $C_{11}H_{13}NOS$ (207.29): C, 63.74; H, 6.32; N, 6.76. Found: C, 63.55; H, 6.40; N, 6.82.

Reaction of **10e** with Dimethylacetylene Dicarboxylate and Dihydrofuran. Preparation of Compound **7** and **8**.

A mixture of **10e** (0.22 g, 1 mmole) and dimethylacetylene dicarboxylate or (dihydrofuran) (1.2 mmoles) in dry toluene (10 ml) was refluxed for 8 hours in the presence of molecular sieves (0.3 g, 4 Å). The reaction mixture was evaporated *in vacuo* then purified by flash chromatography [petroleum ether/ethyl acetate (5:1)].

Compound **7** (0.24 g, 67% yield) was obtained as a yellow viscous substance; ^{1}H nmr: δ 3.81 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.99 (d, 2H, 12-H), 5.83 (d, 1H, 4-H, J = 1.9 Hz), 7.10-7.47 (m, 6H, Ar-H).

Anal. Calcd. for $C_{18}H_{15}NO_5S$ (357.38): C, 60.50; H, 4.23; N, 3.92. Found: C, 60.68; H, 4.41; N, 3.74.

Compound **8** (0.2 g, 70% yield) was obtained as a yellow viscous substance; ^{1}H nmr: δ 1.83 (m, 2H, 8-H), 2.14 (m, 2H, 7-H), 3.82-4.03 (m, 3H, 5-H and 15-H), 5.55 (dd, 1H, 4H), 6.50 (dd, 1H, 3-H), 6.94-7.48 (m, 4H, Ar-H), 7.62 (d, 1H, 2-H). Upon tlc, compound **15** appeared as a two isomers and could not be isolated.

Anal. Calcd. for $C_{16}H_{15}NO_2S$ (285.36): C, 67.34; H, 5.30; N, 4.91. Found: C, 67.19; H, 4.98; N, 5.00.

Bis-[2-(substituted)indol-3-yl] Disulphides **9b-d,g,h**.

General procedure.

To a solution of lithium diisopropylamide [prepared from diisopropylamine and *n*-butyllithium (5.55 ml, 1.8 *M*) in dry tetrahydrofuran (20 ml)] was added dropwise the appropriate benzotiazine derivatives **4** (5.5 mmoles) in dry tetrahydrofuran (10 ml) at -60° within 10 minutes. The reaction mixture was sitrred for 1 hour at -60°, for an additional 1 hour at -10°, then warmed to room temperature. The solution was quenched with ammonium chloride solution, extracted with ether, dried (magnesium sulfate) and the filtrate evaporated *in vacuo*. The residue which was formed was purified by column chromatography to give **9b-d,g,h**.

Compound **9b**.

Column chromatography [petroleum ether/ethyl acetate (9:1)] gave **9b** as pale yellow crystals (1.1 g, 89% yield), mp 87-90°; ^{1}H nmr: δ 6.92-7.64 (m, 18H, Ar-H), 8.03 (s, 2H, 2 NH); ms: M^+ at m/z = 448.6 "base peak at m/z = 224 is generated by homogeneous cleavage of the bond between the two sulfur atoms".

Anal. Calcd. for $C_{28}H_{20}N_2S_2$ (448.60): C, 74.97; H, 4.49; N, 6.24. Found: C, 74.85; H, 4.46; N, 5.98.

Compound **9c**.

Column chromatography [petroleum ether/ethyl acetate (5:1)] gave **9c** as yellow crystals (1.14 g, 80% yield), mp 188-190°; ^{1}H nmr: δ 6.92-7.64 (m, 16H, Ar-H), 8.06 (s, 2H, 2 NH); ms: M^+ at m/z 516.7 also homogeneous cleavage peak at m/z = 259.

Anal. Calcd. for $C_{28}H_{18}N_2S_2Cl_2$ (517.49): C, 65.00; H, 3.51; N, 5.41. Found: C, 65.17; H, 3.83; N, 5.81.

Compound **9d**.

Column chromatography [petroleum ether/ethyl acetate (1:2)] gave **9d** as yellow needless (1.13 g, 92% yield), mp 250-252°; ^{1}H nmr: δ 6.43-9.10 (m, 16H, Ar-H), 12.7 (s, 2H, 2 NH).

Anal. Calcd. for $C_{26}H_{18}N_4S_2$ (450.58): C, 69.31; H, 4.03; N, 12.43. Found: C, 69.18; H, 4.20: N, 12.33.

Compound **9g**.

Column chromatography [petroleum ether/ethyl acetate (3:2)] gave **9g** as yellow crystals (1.23 g, 80% yield), mp 235-238°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.77 (s, 6H, 2 OMe), 6.24-7.90 (m, 16H, Ar-H), 7.30-7.35 (2 douplets, 4H, α-H and β-H, $J_{\alpha,\beta}$ = 16.8 Hz), 10.46 (s, 2H, 2 NH).

Anal. Calcd. for $C_{34}H_{28}N_2O_2S_2$ (560.73): C, 72 83; H, 5.03; N, 5.00. Found: C, 72.60; H, 4.87; N, 5.14.

Compound **9h**.

Column chromatography [petroleum ether/ethyl acetate (3:2)] gave **9h** as yellow crystals (1.31 g, 85% yield), mp 117-119°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 3.19 (s, 6H, 2 OMe), 6.07-6.88 (two douplets, 4H, α-H and β-H, $J_{\alpha,\beta}$ = 16.8 Hz), 6.51-7.85 (m, 16H, Ar-H), 11.21 (s, 2H, 2 NH).

Anal. Calcd. for $C_{34}H_{28}N_2O_2S_2$ (560.73): C, 72 83; H, 5.03; N, 5.00. Found: C, 73.01; H, 5.16; N, 4.87.

2-Substituted Indoles. Preparation of Compounds **10b-d, ga** and **ha**.

General Procedure.

The appropriate bis[2-(substituted)indol-3-yl] disulphide **9b-d,g,h** (1 mmole) was dissolved in dry tetrahydrofuran (20 ml)

and stirred vigorously with Raney nickel (2 g) at room temperature for 3-6 hours, monitored by tlc. The reaction mixture was filtered and washed with ethyl acetate. The filtrate was evaporated *in vacuo* and purified by column chromatography to provide the following 2-substituted-indoles.

2-Phenylindole (**10b**).

Column chromatography [petroleum ether/ethyl acetate (17:3)] gave **10b** as white crystals (0.38 g, 98% yield), mp 271 -274° (published 275°); ^{1}H nmr spectrum showed the N-H shift at δ 8.37 and 3-H at δ 6.83 which was in complete agreement with the published values [11].

Anal. Calcd. for $C_{14}H_{11}N$ (193.24): C, 87.01; H, 5.74; N, 7.25. Found: C, 87.26; H, 6.01; N, 7.51.

2-(4-Chlorophenyl)indole (**10c**).

Column chromatography [petroleum ether/ethyl acetate (12:1)] gave **10c** as yellow crystals (0.34 g, 75% yield), mp 208-211°; the ^{1}H nmr and mp agreed with the published values [12].

Anal. Calcd. for $C_{14}H_{10}NCl$ (227.69): C, 72.85; H, 4.42; N, 6.15. Found: C, 73.79; H, 4.24; N, 6.02.

2-(Pyrid-3-yl)indole (**10d**).

Column chromatography [petroleum ether/ethyl acetate (1:2)] gave **10d** as yellow crystals (0.33 g, 85% yield), mp 176-178°; ^{1}H nmr: δ 6.9 (s, 1H, 3-H), 8.56 (s, 2H, 1H and NH), 7.12-8.97 (m, 8H, Ar-H); ms: m/z = 194 [M$^+$]; the mp and ^{1}H nmr are in agreement with the published values [13].

Anal. Calcd. for $C_{13}H_{10}N_2$ (194.24): C, 80.39; H, 5.19; N, 14.92. Found: C, 80.27; H, 5.19; N, 14.62.

2-[2-(2-Methoxyphenyl)ethyl]indole (**10ga**).

Column chromatography [petroleum ether/ethyl acetate (8:1)] gave **10ga** as brown crystals, mp 140-143°; ^{1}H nmr: δ 3.0 (m, 4H, CH_2CH_2), 3.8 (s, 3H, OMe), 6.20 (s, 1H, 3-H), 6.81-7.54 (m, 8H, Ar-H), 7.74 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{17}NO$ (251.33): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.09; H, 6.78; N, 5.37.

2-[2-(4-Methoxyphenyl)ethyl]indole (**10ha**).

Column chromatography [petroleum ether/ethyl acetate (9:1)] gave **10ha** as pale brown crystals (0.42 g, 84% yield), mp 112-114°; the ^{1}H nmr exhibits nearly the same chemical shift as for **10ga**; ms: m/z = 251.8 [M$^+$].

Anal. Calcd. for $C_{17}H_{17}NO$ (251.33): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.33; H, 6.97; N, 5.32.

Bis[2-(2-furyl)indol-3-yl] Disulphide (**9e**) and 2-(2-furyl)-3-mercaptoindole (**11**).

Reaction of compound **4e** with lithium diisopropylamide was carried out and worked up according to the previously described procedure. The products were separated using column chromatography to give compound **9e** and **11** in a ratio (1:1) and with a total yield of 70%.

Compound **9e**.

This compound was obtained as yellow crystals, mp 185-187°; ^{1}H nmr: δ 6.14 (dd, 2H, 4'-H), 6.75 (dd, 2H, 3'-H), 7.08-7.26 (m, 8H, Ar-H), 7.53 (dd, 2H, 5'-H, $J_{4',5'}$ = 7.9 Hz), 8.45 (s, br, 2H, 2 NH).

Anal. Calcd. for $C_{24}H_{16}N_2O_2S_2$ (428.52): C, 67.27; H, 3.76; N, 6.54. Found: C, 67.11; H, 3.83; N, 6.50.

Compound **11**.

This compound was obtained as yellow crystals, mp 140°; ^{1}H nmr: δ 2.87 (s, 1H, SH), 6.44 (dd, 1H, 4'-H, $J_{4',5'}$ = 1.9 Hz, $J_{4',3'}$ = 3.4 Hz), 7.10-7.18 (m, 4H, Ar-H), 7.33 (dd, 1H, 3'-H), 7.61 (dd, 1H, 5'-H, $J_{5',4'}$ = 3.4 Hz), 8.41 (s, br, 1H, NH).

Anal. Calcd. for $C_{12}H_9NOS$ (215.27); C, 66.95; H, 4.21; N, 6.51. Found: C, 66.79; H, 3.98; N, 6.62.

2-Ethoxyquinoline (**12**).

A solution of **5** (6.65 g, 2 mmoles) in tetrahydrofuran (10 ml) was slowly injected under nitrogen at -80° to a solution of lithium diisopropylamide [prepared from diisopropylamine (1.01 g, 10 mmoles) and *n*-butyllithium (5.55 ml, 1.8 moles) in 20 ml dry tetrahydrofuran]. The reaction was completed as described previously in the preparation of the compounds **9**. The product was purified by flash chromatography [petroleum ether/ethyl acetate (12:1)] to give **12** (0.24 g, 69% yield) as a colourless oil; ^{1}H nmr: δ 1.44 (t, 3H, CH_3CH_2), 4.53 (q, 2H, CH_3CH_2), 7.31-7.84 (m, 4H, 5- to 8-H), 7.87-7.93 (two douplets, 2H, 3-, 4-H, $J_{3,4}$ = 8.8 Hz).

An authentic sample of 2-ethoxyquinoline was prepared as described in the literature [9] by boiling 2-chloroquinoline in sodium ethoxide solution.

1,2-Dihydro-3*H*,5*H*-pyrrolo[1,2-*a*][3,1]benzoxazinium Iodide (**13a**).

To a solution of **6** (0.41 g, 2 mmoles) in dry tetrahydrofuran (10 ml) was added sodium hydride (0.15 g, 6 mmoles) portionwise, then iodomethane (1.42 g, 10 mmoles) was added within 10 minutes. The reaction mixture was stirred for 30 minutes at room temperature, then quenched with water (20 ml), extracted with dirchloromethane, dried (magnesium sulfate) and purified using medium pressure chromatography [petroleum ether/ethyl acetate (1:1)] to give **13a** (0.31 g, 53% yield) as a buff viscous substance; ^{1}H nmr: δ 2.35 (dd, 2H, 9-H), 2.60 (t, 2H, 10-H), 3.90 (t, 2H, 8-H), 4.50 (s, 2H, 2-H), 7.13-7.48 (m, 4H, Ar-H); ms: m/z = 301 [M$^+$], 174 [M-I]$^+$.

Anal. Calcd. for $C_{11}H_{12}NOI$ (301.13): C, 43.88; H, 4.02; N, 4.65. Found: C, 44.08; H, 4.18; N, 4.65.

1,2-Dihydro-3*H*,5*H*-pyrrolo[1,2-*a*][3,1]benzothiazinium Bromide (**13b**).

Method A.

A mixture of **6** (2.07 g, 10 mmoles) and triphenylphosphonium bromide (4.12 g, 12 mmoles) in tetrahydrofuran (50 ml) was stirred under reflux for 4 hours. A white preciptate was formed, filtered, and washed with tetrahydrofuran to give **13b** (2.57 g, 95% yield) as colourless crystals, mp 178-179°; ^{1}H nmr: δ 2.47 (dd, 2H, 9-H), 3.46 (t, 2H, 10-H, $J_{9,10}$ = 7.9 Hz), 4.42 (s, 2H, 2-H), 4.61 (t, 2H, 8-H, $J_{8,9}$ = 7.6 Hz), 7.40-7.60 (m, 4H, 3- to 6-H); ms: m/z = 190 [M-Br]$^+$.

Anal. Calcd. for $C_{11}H_{12}NSBr$ (270.19): C, 48.90; H, 4.48; N, 5.18. Found: C, 48.83; H, 4.34; N, 5.03.

Method B.

Compound **13b** was also obtained in the same yield when a molar ratio of compound **11**, carbon tetrabromide and triphenylphosphine in dry toluene was boiled for 2 hours. The white crystals were filtered and washed with hot petroleum ether to give the same compound; the mp and ^{1}H nmr are identical.

REFERENCES AND NOTES

[1] A. P. Kozikowski and B. B. Mugrage, *J. Chem. Soc., Chem. Commun.*, 198 (1988).

[2] G. R. Allen and J. F. Poletto, *J. Am. Chem. Soc.*, **86**, 3877 (1964).

[3] B. Beilenson and F. M. Hamer, *J. Chem. Soc.*, 98 (1942).

[4] C. C. Wei, S. De Bernardo, J. P. Tengi, J. Borgesa and M. Weigele, *J. Org. Chem.*, **50**, 3402 (1985).

[5] B. Beilenson, F. M. Hamer and R. J. Rotghbone, *J. Chem. Soc.*, 222 (1945).

[6] R. R. Schmidt, *Angew. Chem.*, **87**, 603 (1975); *Angew. Chem., Int. Ed. Engl.*, **14**, 581 (1975), and references therein.

[7] R. R. Schmidt and M. Dimmler, *Chem. Ber.*, **107**, 3800 (1974).

[8] R. R. Schmidt, W. J. W. Mayer and H. U. Wagner, *Liebigs Ann. Chem.*, 2010 (1973).

[9] N. Al-Wadi and R. Taylor, *J. Chem. Soc., Perkin Trans II*, 98 (1942).

[10] M. P. Cava and M. I. Levinson, *Tetrahedron*, **41**, 5061 (1985).

[11] H. M. Kissman, D. W. Farnsworth and B. Witkop, *J. Am. Chem. Soc.*, **74**, 3948 (1952).

[12] C. E. Blades and A. L. Wilds, *J. Org. Chem.*, **21**, 1013 (1956).

[13] S. S. Tiuwari and R. K. Satsangi, *Pharmazie*, **35**, 742 (1988).