Synthetic Approach to (±)-Vincamine *via* Cleavage of an α-Diketone Monothioacetal. Alternative Synthesis of (±)-Eburnamine, (±)-Isoeburnamine, and (±)-Eburnamenine [1]

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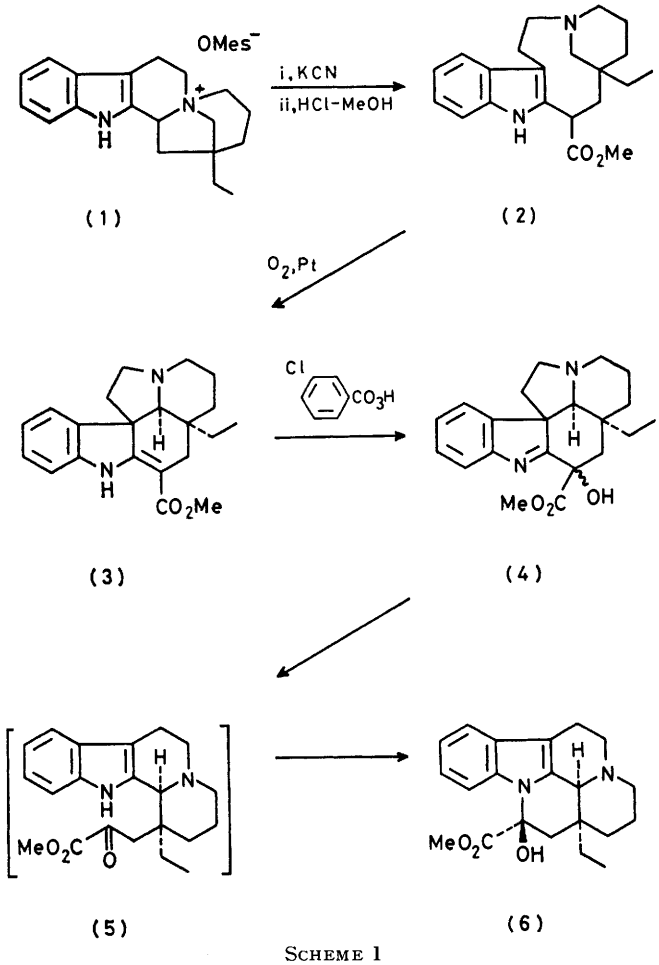
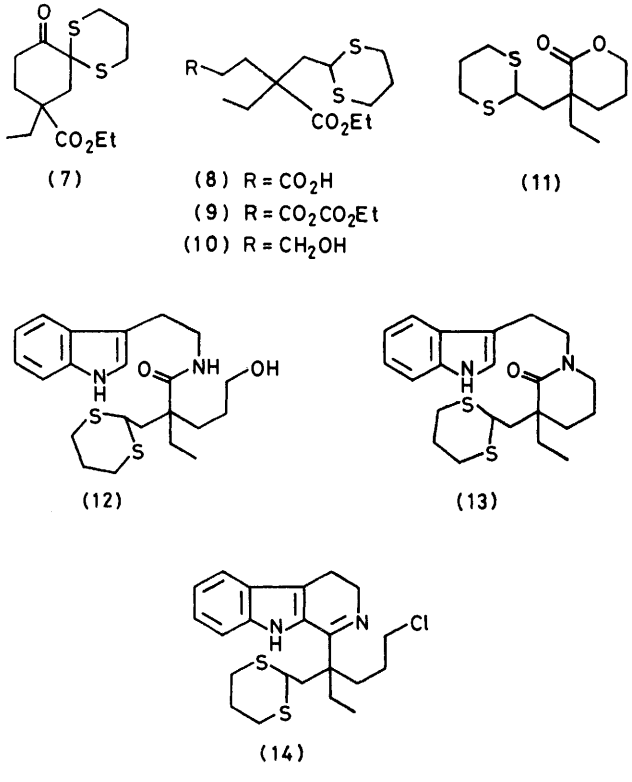
The half ester (8) prepared from cleavage of 2-(1,3-dithian-2-yl)-4-ethoxycarbonyl-4-ethylcyclohexanone (7) has been converted into (±)-eburnamine (20), (±)-isoeburnamine (21), and (±)-eburnamenine (22) by a stereospecific reaction sequence proceeding *via* the dithian intermediate (16). However an attempted conversion of (16) into (±)-vincamine (6) was unsuccessful.

An interesting biogenetic-type transformation of the aspidosperma indole alkaloid, vincadifformine (3), into the eburnamine-vincamine indole alkaloid, vincamine (6), has previously been reported [2] (Scheme 1). An efficient synthesis of the quaternary base (1), a synthetic precursor of (3),[3] starting from the α-diketone monothioacetal [4] (7) would therefore constitute a formal synthesis of (±)-vincamine (6). However a more straightforward approach to this pharmacologically important compound [5] seemed to be available without passing through the quaternary base (1), provided that differentiation between the ethoxycarbonyl and the carboxy-groups of the nine-carbon half-ester (8) and the introduction of the one-carbon unit at the appropriate stage could be possible. Thus, a selective reduction of the carboxy-group under appropriate conditions should afford the lactone (11) which on condensation with tryptamine, followed by the Bischler–Napieralski cyclization and a stereospecific reduction should give the tetracyclic amine (16), the dithianyl group of which should allow introduction of a one-carbon unit leading to the equivalent (18) of the pyruvate (5) *via* the dianion intermediate (17).



Scheme 1

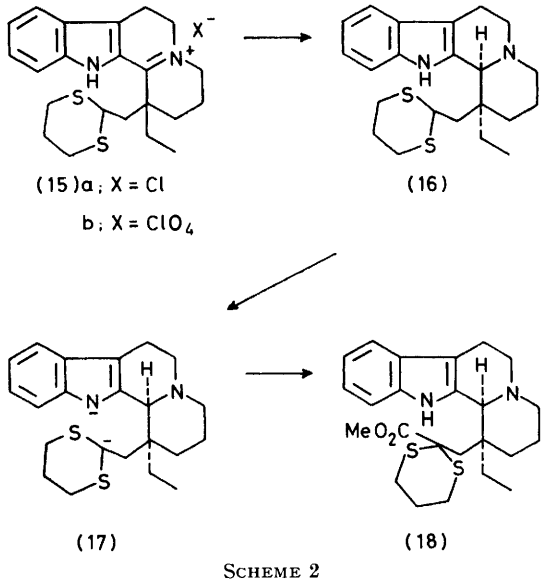
Treatment of the half-ester (8), which was prepared from the α-diketone monothioacetal [4] (7) almost quantitatively, with an excess of ethyl chloroformate in tetrahydrofuran in the presence of triethylamine gave the mixed anhydride (9) which, without further purification, was reduced with sodium borohydride [6] in aqueous tetrahydrofuran to form the primary alcohol (10). Lactonization of (10) yielding (11) was accomplished by reflux in benzene in the presence of a catalytic amount of



hydrochloric acid. The overall yield of (11) from the α-diketone monothioacetal (7) was 56%.

Fusion of the lactone (11) with tryptamine at 160 °C followed by chromatography on silica gel afforded the oily secondary amide (12) in 82% yield together with the crystalline lactam (13) (6%). Bischler–Napieralski cyclization of the amide (12) with phosphorus oxychloride gave a mixture, presumably consisting of the imine (14) and the iminium salt (15a), which upon reflux in methylene chloride, followed by treatment with lithium perchlorate,[7,8] yielded the iminium perchlorate (15b) quantitatively. The lactam (13) also afforded (15b) quantitatively by treatment with phosphorus oxychloride, followed by lithium perchlorate (Scheme 2).

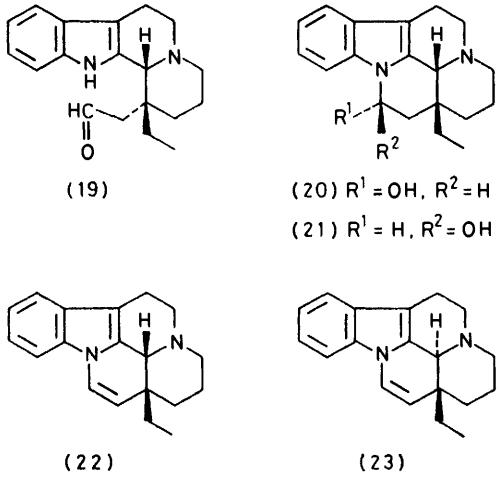
Reduction of (15b) with lithium tri-t-butoxyaluminium hydride in tetrahydrofuran at 0 °C, a procedure successfully employed in the stereospecific reduction of a related



SCHEME 2

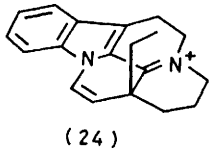
system by Schlessinger,[8] allowed a stereospecific hydrogenation to give the desired *cis* isomer (16) (Et and 12b-H *cis*) exclusively in yields of 72% from (12) and 79% from (13). Although its i.r. and n.m.r. spectra corresponded with those of Schlessinger's related compound indicating a '*cis*' configuration, its structure was confirmed by chemical conversion into known compounds as follows.

Exposure of the hydrochloride of (16) to an excess of methyl iodide in aqueous acetonitrile [9] at room temperature for 15 h effected hydrolysis without affecting the tertiary nitrogen to give a mixture of three compounds instead of the expected aldehyde (19). Preparative t.l.c. on silica gel yielded (±)-eburnamine [10] (20), (±)-isoeburnamine (21), and (±)-eburnamenine (22) in yields of 10, 3, and 34%, respectively. Of these compounds (20) and (22) were confirmed by direct comparison with authentic samples of natural origin, while (21) as well as (20) upon reflux with acetic acid [11] afforded (22) thus confirming its structure. Prolonged reaction time (30 h) allowed exclusive formation of (±)-eburnamenine (22) in 55% yield. In this conversion, protonation of the tertiary nitrogen in (16) prior to the hydrolysis was essential in order to suppress its nucleophilicity towards the alkylating agent. On the other hand the iminium perchlorate (15b) provided (±)-epieburnamenine (23) exclusively when the hydrolysis was carried out prior to the reduction with sodium borohydride. The structure



of (23) was confirmed by catalytic hydrogenation of platinum oxide giving (±)-dihydroepieburnamenine (23) (14,15-dihydro) which has been obtained through a different approach by Coffen.[12] The hydrolysis product (24) exists as a flat structure with an extruded ethyl group as shown, and hydrogenation apparently occurs therefore from the more accessible convex face resulting in (23) having *trans* configuration.

Having defined the stereochemistry of (16) to be *cis*, the introduction of a one-carbon unit into the required position leading to the penultimate intermediate (18) was attempted. Treatment of (16) with two equivalents of n-butyl-lithium in tetrahydrofuran [13] at −78 °C to give



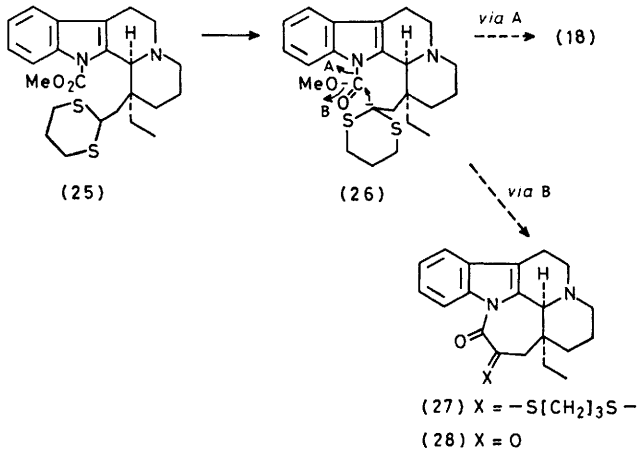
(24)

rise to the dianion (17), followed by one equivalent of methyl chloroformate, did not provide the expected product (18), but in all attempts only the isomeric carbamate (25). However this carbamate (25) still seemed useful, since isomerization to (18) or the seven-membered ring lactam (27) [whose oxo equivalent (28) has been previously converted to (6) [8]] could occur by an internal nucleophilic reaction of the anion (26). However, no desired product could be detected after treatment with lithium di-isopropylamide under various conditions (Scheme 3).

A further attempt at introducing a one-carbon unit into the lactam (13) *via* the dianion (29) by treatment with n-butyl-lithium followed by methyl chloroformate

did not afford the expected product (31) but gave instead a degradation product (30). This arose probably through a retrograde Michael reaction followed by acylation (Scheme 4).

In conclusion, although a synthesis of (±)-vincamine



SCHEME 3

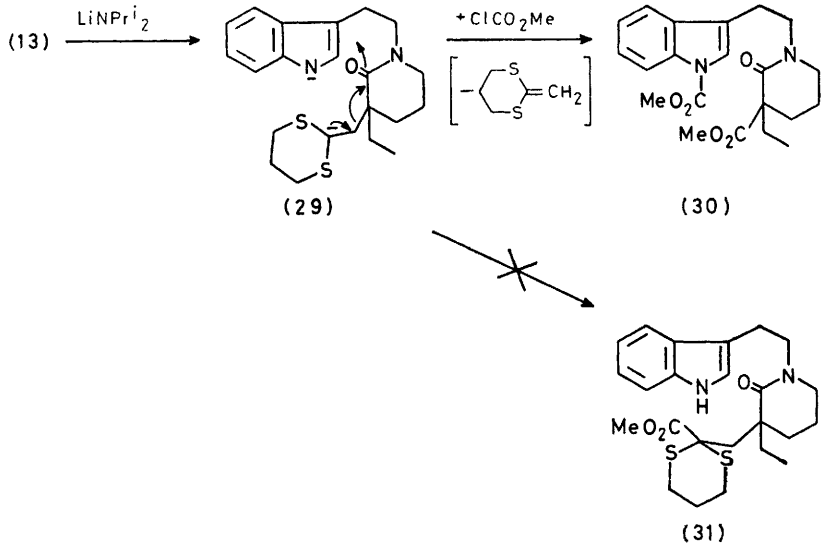
(6) was not achieved, the present study indicates the utility of the nine-carbon compound (8), obtained from cleavage of the α-diketone monothioacetal (7), for the construction of the non-tryptamine moiety of the eburnamine type of indole alkaloids.

EXPERIMENTAL

Melting points were determined on a Yanagimoto MP-S2 apparatus. I.r. spectra were recorded on a Shimadzu IR 400 instrument, and ^{1}H n.m.r. spectra were measured for solutions in deuteriochloroform on JEOL PS 100 and PMX 60 spectrometers with tetramethylsilane as internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer.

α-Ethyl-α-(1,3-dithian-2-ylmethyl)-δ-valerolactone (11).—To an ice-cooled solution of the crude half ester (8) (10 g), prepared from the α-diketone monothioacetal [4] (7) (10 g, 33 mmol), and triethylamine (6.9 ml, 50 mmol) in anhydrous tetrahydrofuran (THF) (100 ml) under nitrogen, was added ethyl chloroformate (4.8 ml, 50 mmol). After stirring at 0 °C for 3 h, the precipitated triethylamine hydrochloride was filtered off and washed with anhydrous THF (20 ml). The combined filtrate was added dropwise, over 30 min, to aqueous sodium borohydride (2.5M; 40 ml, 100 mmol) with cooling in an ice-bath. The reaction mixture was stirred at room temperature for a further 1.5 h and then acidified with concentrated HCl.The aqueous layer was separated off and then extracted with methylene chloride. The combined organic layers were washed with 5% w/v NaOH–water and saturated aqueous NaCl, and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the primary alcohol (10) (8.57 g) as a yellow oil, which was used without further purification.

A solution of the crude (10) (8.57 g) in benzene (50 ml) was refluxed in the presence of a catalytic amount of concentrated HCl (5 drops) for 30 min. Removal of the solvent under reduced pressure afforded a yellow oil (8.32 g) which was purified by chromatography on silica gel (150 g). Elution with benzene gave the *lactone* (11) [4.84 g, 56.3% from (7)] as an oil: $\nu_{max.}$ (neat) 1 710 cm^{-1}; δ ($CDCl_3$) 0.93 (3 H, t, *J* 7.0 Hz), 3.90 (1 H, dd, *J* 7.0 and 6.0 Hz), and 4.29 (2 H, m); *m/e* 260 (M^+), 133, 119, and 113 (Found: C, 55.6; H, 7.85; S, 24.6. $C_{12}H_{20}O_2S_2$ requires C, 55.35; H, 7.75; S, 24.6%).



SCHEME 4

Fusion of the Lactone (11) *with Tryptamine*.—A mixture of the lactone (11) (3.0 g, 11.5 mmol) and tryptamine (2.0 g, 12.5 mmol) was heated at 160 °C for 3 h under nitrogen to give yellow viscous oil (4.9 g), which was purified by chromatography on silica gel (50 g). Elution with chloroform afforded the lactam (13) (0.27 g, 5.8%) and then the amide (12) (3.93 g, 82.2%). 2-(1,3-*Dithian-2-ylmethyl*)-2-*ethyl-5-hydroxy-*N-(*indol-3-ylethyl*)*pentamide* (12), a viscous oil, showed $\nu_{max.}$ (neat), 3 300 and 1 620 cm^{-1}; δ ($CDCl_3$) 0.75 (3 H, t, *J* 7.0 Hz), 1.00—2.20 (10 H, m), 2.30—3.20 (7 H, m, 1 H, exch. with D_2O), 3.25—4.10 (5 H, m), 6.05br (1 H, t, *J* 5.0 Hz, exch. with D_2O), 6.76—7.80 (5 H, m), and 8.83br

(1 H, s, exch. with D_2O); *m/e* 420 (M^+), 288, 243, 144, 143, 131, 130, and 119 (Found: C, 62.75; H, 7.75; N, 6.55; S, 14.9. $C_{22}H_{32}N_2O_2S_2$ requires C, 62.8; H, 7.65; N, 6.65; S, 15.25%). 3-(1,3-*Dithian*-2-*ylmethyl*)-3-*ethyl*-1-(*indol*-3-*yl*-*ethyl*)-2-*piperidone* (13), needles (from ethyl acetate), had m.p. 153—154 °C; $\nu_{max.}$ (Nujol) 3 250 and 1 602 cm^{-1}; δ ($CDCl_3$) 0.80 (3 H, t, *J* 7.0 Hz), 4.13 (1 H, dd, *J* 5.8 and 6.0 Hz), 6.80—7.76 (5 H, m), 8.73br (1 H, s, exch. with D_2O); *m/e* 402 (M^+), 294, 270, 251, 143, 140, 130, and 119 (Found: C, 65.35; H, 7.5; N, 6.5; S, 16.4. $C_{22}H_{30}N_2OS_2$ requires C, 65.6; H, 7.5; N, 6.95; S, 15.95%).

1-(1,3-*Dithian*-2-*ylmethyl*)-1-*ethyl*-1,2,3,4,6,7,12,12b-*octahydroindolo*[2,3-a]*quinolizine* (16).—(*a*) *From the amide* (12). A solution of the amide (12) (2.85 g, 6.8 mmol) in phosphorus oxychloride (30 ml) was refluxed under nitrogen for 6 h. Most of the phosphorus oxychloride was removed under reduced pressure and the residue was treated with saturated aqueous $NaHCO_3$ and extracted with methylene chloride. The extract was dried over anhydrous K_2CO_3, concentrated to 50 ml under reduced pressure, and then refluxed for 1 h. After cooling in an ice-bath, aqueous $LiClO_4$ (1M; 20 ml) was added and the mixture was stirred at room temperature for 1 h. The organic layer was separated, washed twice with aqueous $LiClO_4$ (0.1M; 20 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded the iminium perchlorate (15b) (3.30 g) as a yellow powder, which was used without further purification; $\nu_{max.}$ (Nujol) 3 400 cm^{-1}; δ ($CDCl_3$ + CD_3OD) 0.97 (3 H, t, *J* 7.0 Hz), 4.10 (4 H, m), and 7.00—7.90 (4 H, m).

The crude iminium perchlorate (15b) (3.30 g) was added to an ice-cooled solution of lithium tri-t-butoxyaluminium hydride, prepared from lithium aluminium hydride (1.29 g, 34 mmol) and t-butyl alcohol (10 ml, 105 mmol) in anhydrous THF (100 ml) under nitrogen. After stirring at 0 °C for 3 h, the mixture was treated with 10% w/v NH_4OH–water and the resulting sludge was filtered through Celite. The filtrate was separated and the aqueous layer extracted with methylene chloride. The combined organic layers were washed with saturated aqueous NaCl and dried over anhydrous K_2CO_3. Removal of the solvent under reduced pressure afforded a pale yellow crystalline residue (2.66 g), which was recrystallized from ethanol to give (16) [1.85 g, 71.7% from (12)] as *needles*, m.p. 185—186 °C; $\nu_{max.}$ (Nujol) 3 420 cm^{-1}; δ ($CDCl_3$) 1.20 (3 H, t, *J* 7.0 Hz), 3.33 (1 H, s), 3.80 (1 H, t, *J* 5.0 Hz), 7.00—7.40 (4 H, m), and 7.82br (1 H, s, exch. with D_2O); *m/e* 386 (M^+), 267, 197, 185, 171, 170, 169, and 124 (Found: C, 68.15; H, 7.85; N, 6.95; S, 16.8. $C_{22}H_{30}N_2S_2$ requires C, 68.35; H, 7.8; N, 7.25; S, 16.6%).

(*b*) *From the lactam* (13). A mixture of the lactam (13) (80 mg, 0.2 mmol) and phosphorus oxychloride (0.55 ml, 6.0 mmol) in anhydrous acetonitrile (5.0 ml) was refluxed under nitrogen for 6.5 h. Most of the excess of phosphorus oxychloride and the solvent were removed under reduced pressure. The residue was dissolved in methylene chloride (10 ml) and treated with aqueous $LiClO_4$ (1M; 1.0 ml), as above, to give the iminium perchlorate (15b) (102 mg) as a yellow powder, which was used without further purification.

The crude iminium perchlorate (15b) was reduced with lithium tri-t-butoxyaluminium hydride under the same conditions as above to give (16) [60 mg, 78.5% from (13)] as needles.

Formation of (±)-*Eburnamine* (20), (±)-*Isoeburnamine* (21), *and* (±)-*Eburnamenine* (22) *from the Dithianyl Amine* (16).—(*a*) A mixture of the hydrochloride of (16) (215 mg) [prepared from (16) (200 mg, 0.51 mmol), methyl iodide (2.20 ml, 35.2 mmol), and water (0.44 ml, 24.4 mmol)] in acetonitrile (22 ml) was stirred under nitrogen at room temperature for 15 h. Most of the excess of methyl iodide and the solvent were removed under reduced pressure below 40 °C. The residue was treated with saturated aqueous $NaHCO_3$ and extracted with methylene chloride. The extract was washed with water, 1% w/v $Na_2S_2O_3$–water, and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated under reduced pressure to give a dark brown viscous oil (150 mg). Preparative t.l.c. on silica gel developed with methanol–chloroform (7 : 100) afforded (±)-eburnamine (20) (42 mg, 34.0%), (±)-isoeburnamine (21) (4 mg, 2.9%), and (±)-eburnamenine (22) (13 mg, 9.5%).

(±)-Eburnamine (20), needles (from ethanol), had m.p. 133—136 °C (lit.,[10] 136—140 °C); $\nu_{max.}$ (Nujol) 3 270 cm^{-1}; δ ($CDCl_3$) 0.87 (3 H, t, 7.0 Hz), 2.93br (1 H, s, exch. with D_2O), 3.62 (1 H, s), 5.43 (1 H, dd, *J* 10.0 and 5.5 Hz), and 6.90—7.80 (4 H, m); *m/e* 296 (M^+), 295, 267, 249, 208, 206, and 193. The spectral data (n.m.r. and mass) and R_F value (silica gel) were identical with those of natural eburnamine.

(±)-Isoeburnamine (21), a pale yellow semi-solid, whose mass spectrum was identical with that of (±)-eburnamine (20), was converted into (±)-eburnamenine (22) quantitatively by refluxing with acetic acid for 30 min.

(±)-Eburnamenine (22), a pale yellow semi-solid, showed the following characteristics: $\nu_{max.}$ (neat) 1 622 cm^{-1}; δ ($CDCl_3$) 1.00 (3 H, t, *J* 7.0 Hz), 4.23 (1 H, s), 5.07 (1 H, d, *J* 7.5 Hz), 6.90 (1 H, d, *J* 7.5 Hz), and 6.95—7.60 (4 H, m); *m/e* 278 (M^+), 249, 208, 206, 193, and 151. The spectral data (n.m.r. and mass) and R_F value (silica gel) were identical with those of natural eburnamenine.

(*b*) A mixture of the hydrochloride of (16) (110 mg) [from (16) (100 mg, 0.26 mmol), methyl iodide (1.0 ml, 16 mmol), and water (0.2 ml, 11 mmol)] in acetonitrile (10 ml) was stirred under nitrogen at room temperature for 30 h. Work-up and purification as above gave (±)-eburnamenine (22) (39 mg, 54.7%) as a pale yellow semi-solid.

(±)-*Epieburnamenine* (23).—A mixture of the crude iminium perchlorate (15b) [from the amide (12) (138 mg, 0.33 mmol), methyl iodide (1.2 ml, 19.2 mmol), and water 0.24 ml, 13.3 mmol)] in acetonitrile (12 ml) was stirred under nitrogen at room temperature. After 24 h, the mixture was concentrated under reduced pressure. The residue was dissolved in methanol (10 ml) and sodium borohydride (125 mg, 3.30 mmol) was added with cooling in an ice-bath. After stirring at 0 °C for 1.5 h, most of the methanol was removed under reduced pressure and the residue was treated with water and extracted with methylene chloride. The extract was washed with water and saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated under reduced pressure to leave a dark yellow gum (65 mg). Preparative t.l.c. on silica gel using methanol–chloroform (7 : 100) as eluant gave (±)-epieburnamenine (23) [45 mg, 49.0% from the amide (12)] as a pale yellow semi-solid: $\nu_{max.}$ (neat) 2 800—2 750 and 1 642 cm^{-1}; δ ($CDCl_3$) 0.68 (3 H, t, *J* 7.0 Hz), 5.13 (1 H, d, *J* 7.5 Hz), 6.87 (1 H, d, *J* 7.5 Hz), and 6.90—7.60 (4 H, m); the mass spectrum was similar to that displayed by (±)-eburnamenine (22).

(±)-*Epidihydroeburnamenine* (23) (14,15-*Dihydro*).—A solution of (±)-epieburnamenine (23) (65 mg, 0.23 mmol) in methanol (5 ml) was stirred under hydrogen in the presence of platinum oxide (40 mg) at room temperature. After hydrogen uptake had ceased, the mixture was filtered and

the filtrate concentrated under reduced pressure to leave a pale yellow gum (70 mg). Preparative t.l.c. on silica gel developed with 7% methanol–chloroform (7 : 100) followed by recrystallization from methylene chloride–ether gave (±)-epidihydroeburnamenine (23) (14,15-dihydro) (35 mg, 54.3%) as needles, m.p. 183—184 °C (lit.,[12] 183—184 °C); $\nu_{max.}$ (Nujol) 1 625 cm^{-1}, δ ($CDCl_3$) 0.76 (3 H, unsym. t, *J* 5.0 Hz), 3.47—4.30 (2 H, m), and 6.90—7.60 (4 H, m); *m/e* 280 (M^+), 279, 251, 223, 210, and 195. The spectral data of this material were identical with the reported data.[12]

Methoxycarbonylation of the Dithianyl Amine (16).—To a stirred solution of (16) (193 mg, 0.5 mmol) in anhydrous THF (5.0 ml) under nitrogen at −40 °C was added 10% w/v n-butyl-lithium–n-hexane (0.7 ml, 1.1 mmol). After stirring at −25 °C for 2 h, methyl chloroformate (0.04 ml, 0.55 mmol) was added and the mixture was stirred at the same temperature for 4 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with methylene chloride The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to leave a yellow viscous oil (230 mg). Preparative t.l.c. on silica gel developed with methanol–chloroform (1 : 200) gave (25) (100 mg, 45.0%) along with recovered starting material (16) (40 mg, 20.7%). 1-(1,3-*Dithian*-2-*ylmethyl*)-1-*ethyl*-1,2,3,4,-6,7,12,12b-*octahydro*-12-*methoxycarbonylindolo*[2,3-a]*quinolizine* (25), needles (from methanol), had m.p. 164—165 °C; $\nu_{max.}$ (Nujol) 1 720 cm^{-1}; δ ($CDCl_3$) 0.90 (3 H, t, *J* 7.0 Hz), 3.97 (3 H, s), 7.00—7.55 (4 H, m), and 8.00 (1 H, m); *m/e* 444 (M^+), 325, 255, 229, 228, 227, 169, 168, 156, 155, 154, 144, 143, and 142 (Found: C, 64.75; H, 7.55; N, 5.85; S, 14.3. $C_{24}H_{32}N_2O_2S_2$ requires C, 64.85; H, 7.25; N, 6.3; S, 14.4%).

Fragmentation of the Lactam (13).—To a stirred solution of the lactam (13) (100 mg, 0.25 mmol) in anhydrous tetrahydrofuran (5.0 ml) under nitrogen with cooling in an ice–salt-bath was added a solution of lithium di-isopropylamide in tetrahydrofuran (5 ml), prepared di-isopropylamine (150 mg, 1.5 mmol), and 10% (w/v) n-buthyl-lithium in n-hexane (1.0 ml, 1.5 mmol). After stirring at the same temperature for 3 h, the mixture was cooled to −78 °C and methyl chloroformate (0.2 ml, 2.5 mmol) added. Stirring was continued at −78 °C for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with methylene chloride. The extract was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to leave a yellow viscous oil (155 mg). Preparative t.l.c. on silica gel developed with methanol–chloroform (1 : 50) gave the degradation product (30) (90 mg, 93.7%) as a pale yellow viscous oil, $\nu_{max.}$ (neat) 1 710 and 1 620 cm^{-1}; δ ($CDCl_3$) 0.95 (3 H, t, *J* 7.0 Hz), 1.50—2.40 (6 H, m), 2.80—3.43 (4 H, m), 3.77 (3 H, s), 4.03 (3 H, s), 7.17—7.80 (4 H, m), and 8.10 (1 H, m); *m/e* 386 (M^+), 355, 327, 299, 202, 201, 198, 188, 158, 157, 156, 144, 143, and 142.

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