Total Synthesis of Thiazolinone Analogues of Indolmycin

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The synthesis of thiazolinone analogues of the naturally occurring oxazolinone antibiotic indolmycin is described. Relative reactivities of isomeric intermediates, rearrangements, and the stereochemistry of products, are explained by a mechanism involving an indole-3-spirocyclopropylium ion.

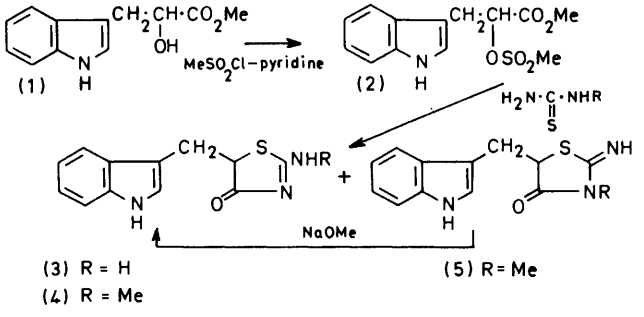
WITH the continuing accumulation of information concerning the biochemistry of viral replication, and in particular the demonstrated presence in infected cells of specific enzymes either introduced or induced by the virus, one can contemplate realistically the development of non-toxic antiviral agents acting by selective interference with the synthesis or functioning of these enzymes.

One approach to such compounds involves modification of a naturally occurring antibiotic possessing structural features necessary for non-covalent bonding to nucleic acids or proteins. By commencing with a complex structure for which precise stereochemistry is essential for biological activity, the probability of obtaining a compound which binds preferentially to a single macromolecule should be substantially increased.

In this report the total synthesis of thiazolinone analogues of indolmycin, for evaluation as antiviral and antibacterial agents, is described.

Indolmycin {(5*S*)-5-[(1*R*)-1-indol-3-ylethyl]-2-(methylamino)-Δ^2-oxazolin-4-one}, originally isolated from a *Streptomyces albus* strain,[1] is active against both Gram positive and Gram negative bacteria and *Mycobacterium tuberculosis* and is well tolerated in animals.[2]

Two total syntheses[3,4] have been reported. In that developed by Preobrazhenskaya *et al.*[4] the three stereoisomers of the naturally occurring antibiotic were also prepared; these do not possess significant antibacterial activity.



SCHEME 1

The reaction sequence which we have used commences with the indolmycenic acid methyl esters (6) and (12), prepared as described previously.[4]

Preliminary investigations were carried out in a *C*-demethyl model series (Scheme 1), since with these com-

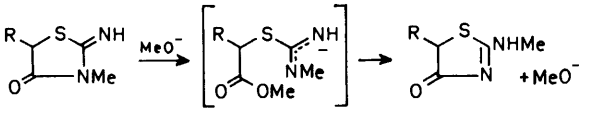
[1] W. S. Marsh, A. L. Garretson, and E. M. Wesel, *Antibiotics and Chemotherapy*, 1960, **10**, 316.

[2] E. Padeiskaya, G. N. Pershin, S. N. Kutchak, L. N. Gerchikov, E. F. Egorova, M. N. Preobrazhenskaya, and N. N. Suvorov, *Antibiotiki*, 1972, **17**, 927.

[3] M. Schach von Wittenau and H. Els, *J. Amer. Chem. Soc.*, 1963, **85**, 3425.

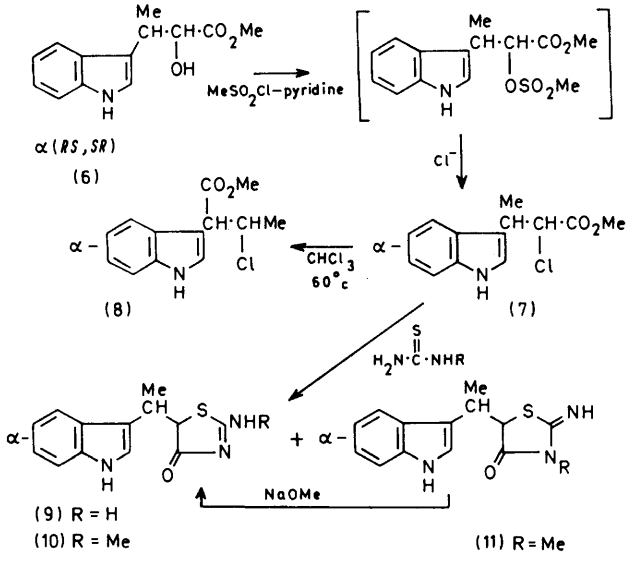
[4] M. N. Preobrazhenskaya, E. G. Balashova, K. F. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron*, 1968, **24**, 6131.

pounds possible complications due to formation of mixtures of diastereoisomers by epimerisation at one asymmetric centre are avoided. (±)-Methyl 3-(indol-3-yl)lactate (1), obtained by esterification of the corresponding acid, was treated with methanesulphonyl chloride in pyridine at 0 °C to give a stable crystalline *O*-mesylate (2) in high yield. Displacement of the mesyloxy-group and subsequent cyclisation occurred readily with thiourea in refluxing ethanol, and the 2-aminothiazolinone (3) was obtained in good yield. Upon treatment of the mesylate (2) with *N*-methylthiourea under similar conditions, a lower yield of the 2-methylaminothiazolinone (4) was obtained. In this reaction the formation of a compound with higher chromatographic mobility on silica gel was also noted. When the reaction was carried out in methanol at 20 °C, this faster moving component was the major product, and was isolated and identified as the 2-imino-3-methyl isomer (5). Methoxide-catalysed rearrangement of the 2-imino-compound (5) to the 2-methylaminothiazolinone (4) occurred readily in refluxing methanol. A mechanism proposed [5] for this rearrangement involves initial attack of methoxide ion at a thiazolinone C-4 carbonyl group (Scheme 2).



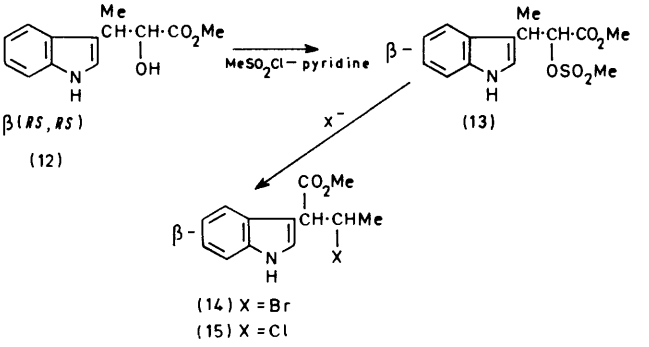
SCHEME 2

When the above reaction sequence was attempted with methyl α(*RS,SR*)- and β(*RS,RS*)-indolmycenates different results were obtained in each diastereoisomeric series.



SCHEME 3

By using conditions and isolation procedures identical with those used for the preparation of the C-demethyl *O*-mesylate (2), the sole product isolated from mesylation of (±)-methyl α-indolmycenate (6) (Scheme 3) was the 2-chloro-ester (7). The chloro-ester (7) reacted readily at 20 °C with thiourea in ethanol, yielding the 2-aminothiazolinone (9). With *N*-methylthiourea under similar conditions, a mixture containing both the 2-methylaminothiazolinone (10) and its 2-imino-3-methyl isomer

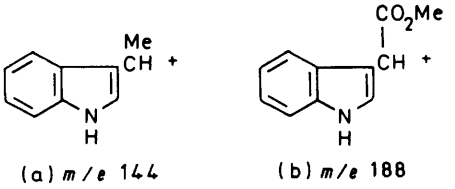


SCHEME 4

(11) was obtained. The yield of the 2-methylamino-isomer (10) was improved by refluxing the mixture of products obtained at 20 °C in methanol in the presence of methoxide. As with indolmycin,[4] in the ^{1}H n.m.r. spectrum of the 2-methylaminothiazolinone (10) two NMe bands are present. The major one (δ 3.02) shows coupling to NH and is assigned the 2-methylamino structure (10); the minor one (δ 2.94) is then its 2-methyliminothiazolidinone tautomer.

Upon mesylation of (±)-methyl β-indolmycenate (12), under the same conditions, the β-*O*-mesylate (13) was obtained as an oil (Scheme 4). Since no crystalline product was obtained, the mesylate (13) was treated with benzyltriethylammonium chloride in refluxing chloroform in an attempt to obtain the diastereoisomer of the 2-chloro-ester (7). From this reaction a crystalline rearranged chloro-ester (15) was the sole product isolated. Under similar conditions, reaction with benzyltriethylammonium bromide yielded the rearranged bromo-ester (14). The 2-chloro-ester (7) also rearranged slowly in chloroform at 60 °C, yielding the chloro-ester (8) diastereoisomeric with (15).

The structures of the chloro-esters (7), (8), and (15) were unequivocally assigned from mass spectral data. The most abundant fragment was in each case the ion resulting from cleavage β to the aromatic system. For the chloro-ester (7) this has *m/e* 144 (a) and for the rearranged chloro-esters (8) and (15) *m/e* 188 (b). Some

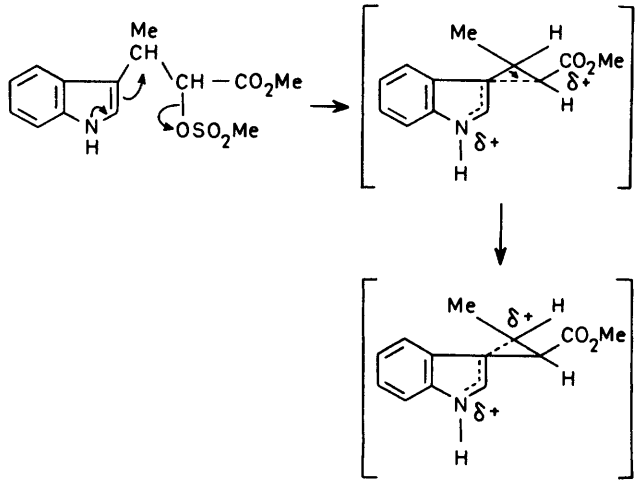


rearrangement in the spectrometer results in a low abundance of the *m/e* 188 fragment from the chloro-ester (7) also, but the *m/e* 144 fragment is completely

[5] H. Najer, R. Guidicelli, C. Morel, and J. Menim, *Bull. Soc. chim. France*, 1963, 1018.

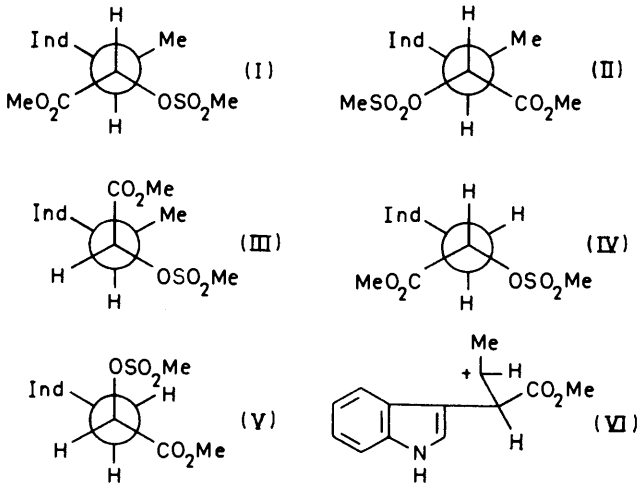
absent in the spectra of the rearranged chloro-esters (8) and (15).

In order to account for the greater reactivity of the mesylate and the chloro-ester (7) derived from methyl α-indolmycenate (6) in comparison with that of the mesylate (13) derived from methyl β-indolmycenate (12), and for the formation of rearranged halogeno-esters, neighbouring group participation involving the electron-rich C-3,[6,7] of the indole ring, is proposed (Scheme 5).



SCHEME 5

The preferred conformation * of the mesylate derived from the α-ester (6), in which steric interactions are minimized, is shown in (I). In this rotamer, the mesyloxy grouping is *trans* to the indole C-3, so that ready displacement can occur. At 20 °C or below, nucleophilic attack by chloride ion takes place while the charge in the cyclopropylium ion intermediate is still predominantly centred on the carbon atom from which the mesyloxy-group has been displaced. Since this is essentially a double S_N2 mechanism, the α-stereochemistry of the hydroxy-ester (6) is retained in the chloro-ester (7). The same mechanism is proposed for subsequent displacement of chloride ion by thioureas.



In the case of the β-mesyloxy-ester (13) the preferred conformation is (II) and a considerable potential energy barrier to the formation of conformer (III), in which the mesyloxy-grouping is *trans* to the indole C-3, exists. Under the conditions required for displacement of the mesyloxy-grouping from the β-mesyloxy-ester (13), redistribution of charge in the cyclopropylium ion intermediate to the carbon atom bearing the methyl group occurs more rapidly than attack by halide ion. Subsequent attack at this position, followed by cleavage of the bond to the indole C-3, results in rearranged halogeno-esters (14) and (15). The same mechanism could apply in the rearrangement of the α-chloro-ester (7) at elevated temperatures.

The proposed mechanism is also consistent with the reaction rates and products obtained in the *C*-demethyl model series. Steric interactions are similar in two preferred conformations, (IV) and (V), of the mesyloxy-ester (2). Since rotamer (IV) is the one required for displacement of the mesyloxy-grouping by the indole C-3, the reactivity of the mesyloxy-ester (2) is between those of the α- and β-mesyloxy-esters.

Moreover, since in the intermediate cyclopropylium ion there is no contribution from an electron-donating methyl substituent to stabilisation of the charge on the methylene carbon atom, no rearrangement products are obtained in the *C*-demethyl series.

The isolation of diastereoisomeric rearranged chloro-esters, (15) and (8), from the β-mesyloxy-ester (13) and from rearrangement of the α-2-chloro-ester (7) indicates that the reactions occurring during rearrangement are stereospecific. The intermediacy of a discrete carbocation (VI) seems unlikely, since this would lead to racemisation at the methyl-bearing carbon atom, and mixtures of diastereoisomers.

It is therefore probable that in each case attack of halide ion on the cyclopropylium ion intermediate occurs at the methyl-bearing carbon atom from the side remote from the bond to the indole C-3, leading to the stereochemistry shown (Scheme 6).

(±)-α-Indolmycenic acid has been resolved by fractional crystallisation of its (−)- and (+)-2-phenylethylamine salts. The two α-indolmycenic acid enantiomers (16) and (17) were esterified and converted into the (−)- and (+)-α-2-chloro-esters (20) and (21) and 2-methylaminothiazolinones (22) and (23) by the reaction sequence described for the racemates. As with the racemic compounds, there was no evidence for epimerisation at either asymmetric centre in any of the reactions.

The absolute stereochemistry of l-α-indolmycenic acid (16), the isomer obtained from hydrolysis of natural indolmycin,[3] has been established from synthetic [8] and

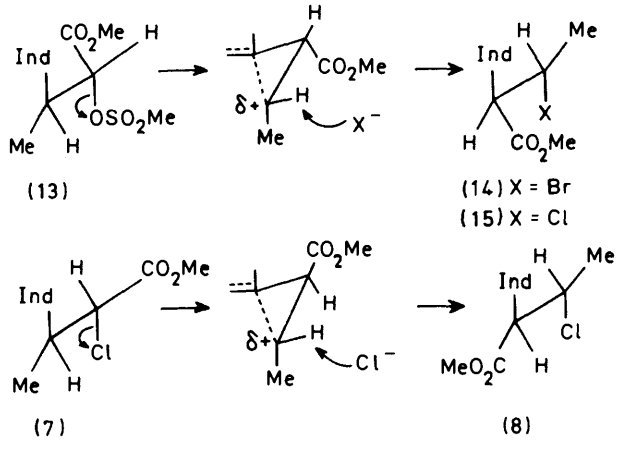
* To simplify the discussion, conformations of one enantiomer only are illustrated.

[6] K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, 1954, **22**, 1433.

[7] M. N. Preobrazhenskaya and N. N. Suvorov, *Zhur. Vsesoyuz Khim. obshch. im. D. T. Mendeleeva*, 1969, **14**, 477.

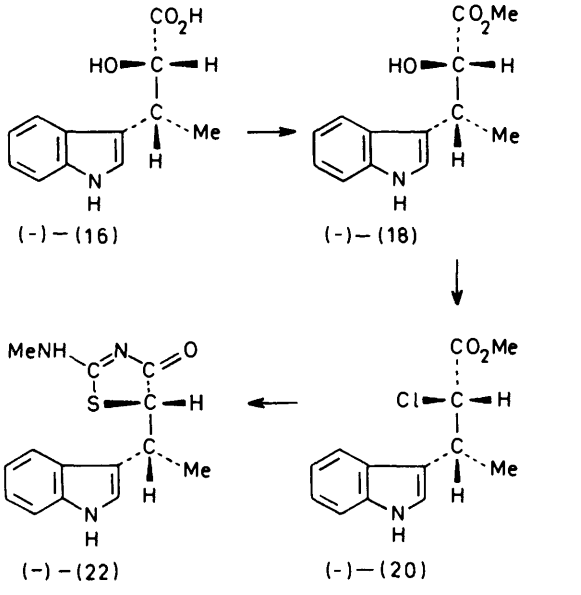
[8] T. H. Chan and R. K. Hill, *J. Org. Chem.*, 1970, **35**, 3519.

biosynthetic [9] studies. The mechanism which we have proposed would result in conservation of stereochemistry throughout the entire reaction sequence [10] (Scheme 7).



SCHEME 6

X-Ray crystallographic structural determinations have been carried out on the (—)-2-hydroxy-ester (18), the



SCHEME 7

(—)-2-chloro-ester (20), and the (—)-2-methylamino-thiazolinone (22). The results [11] confirm the above stereochemical assignments, and unequivocally establish that the laevorotatory isomer (22) has the same absolute stereochemistry as natural indolmycin. (5*S*)-5-[(1*R*)-1-Indol-3-ylethyl]-2-methylamino-Δ^2-thiazolin-4-one (22) has activity against both RNA viruses and bacteria, and is being evaluated as a potential chemotherapeutic agent for treatment of respiratory infections.

[9] U. Hornemann, L. H. Hurley, M. K. Speedie, and H. G. Floss, *J. Amer. Chem. Soc.*, 1971, **93**, 3028.
[10] W. Lwowski, *Angew. Chem.*, 1958, **70**, 483.
[11] T. J. King, personal communication.

EXPERIMENTAL

M.p.s were determined with a Reichert hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 157 spectrometer. ^{1}H N.m.r. spectra were determined for solutions in deuteriated solvents at 60 MHz with a Varian EM 360 spectrometer (tetramethylsilane as internal standard). The calculations described by Pople, Schneider, and Bernstein [12] were used for interpretation of ABX systems. Mass spectra were obtained with an A.E.I. MS9 instrument operating at 70 eV. Optical rotations were measured (1 dm tubes) with a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by the microanalytical laboratory of Beecham Pharmaceuticals. For chromatographic separations, silica gel refers to Kieselgel H, type 60. Analytical t.l.c. was carried out on Eastman Chromagram sheets of silica gel with fluorescent indicator, and spots were located under u.v. light (254 nm). All evaporations were carried out under reduced pressure with a rotary evaporator.

(±)-*Methyl* 3-(*Indol-3-yl*)-2-*mesyloxypropionate* (2).—To a solution of (±)-methyl 3-(indol-3-yl)lactate (1) (11.0 g, 0.05 mol) in dry pyridine (250 ml) at 0 °C, methanesulphonyl chloride (8 ml, 0.1 mol) was added. The mixture was stored at 5 °C for 3 days, then poured into iced water (1 l), and extracted with ether (4 × 500 ml). The combined extracts were washed with 5N-hydrochloric acid (500 ml) and water (2 × 500 ml), dried (Na_2SO_4), and evaporated, yielding an oil (12.8 g). Trituration with benzene (150 ml) and storage at 5 °C for 2 h yielded white crystals of the *mesylate* (2) (9.9 g, 67%), m.p. 89—90°, $\nu_{max.}$ (Nujol) 3 430 (NH), 1 760 (C=O), and 1 368 and 1 165 cm^{-1} (SO_2), δ ($CDCl_3$) 2.75 (3 H, s, CH_3S), 3.38 (2 H, d, *J* 6 Hz, CH_2), 3.75 (3 H, s, CH_3O), 5.23 (1 H, t, *J* 6 Hz, CH), 6.93—7.77 (5 H, m, aromatic), and 8.17br (1 H, s, D_2O-exchangeable, NH) (Found: C, 52.7; H, 5.1; N, 4.8; S, 11.0. $C_{13}H_{15}NO_5S$ requires C, 52.5; H, 5.1; N, 4.7; S, 10.8%).

(±)-2-*Amino*-5-(*indol*-3-*ylmethyl*)-Δ^2-*thiazolin*-4-*one* (3).—A solution of the (±)-ester (2) (2.97 g, 0.01 mol) and thiourea (0.76 g, 0.01 mol) in ethanol (100 ml) was boiled under reflux for 6 h. The ethanol was then evaporated off and sodium acetate (1.64 g) in water (200 ml) added. The white solid obtained was recrystallised from ethanol, yielding the *thiazolinone* (3) (1.73 g, 71%), m.p. 220—223° (decomp.), $\nu_{max.}$ (Nujol) 3 430 and 3 150 (NH), 1 675 (C=O), and 1 630 cm^{-1} (C=N), δ [$(CD_3)_2SO$] 3.27 and 3.30 (2 H, 2q, AB or ABX, Δ ν_{AB} 28.5 Hz, J_{AB} 15 Hz, CH_2), 4.68 (1 H, q, X or ABX, J_{AX} 10.5, J_{BX} −5.5 Hz, CH·S), 6.85—7.95 (5 H, m, aromatic), 8.82 and 9.02 (2 H, 2s, D_2O-exchangeable, NH_2), and 11.00 (1 H, s, D_2O-exchangeable, indole NH), *m/e* 246 (M^+ + 1, 32%), 245 (M^+, 2%), 131 (25), 130 (100), and 117 (73) (Found: C, 58.7; H, 4.5; N, 16.9; S, 13.3. $C_{12}H_{11}N_3OS$ requires C, 58.7; H, 4.5; N, 17.1; S, 13.1%).

(±)-5-(*Indol*-3-*ylmethyl*)-2-*methylamino*-Δ^2-*thiazolin*-4-*one* (4).—A solution of the (±)-ester (2) (1.49 g, 0.005 mol) and *N*-methylthiourea (0.45 g, 0.005 mol) in ethanol (60 ml) was boiled under reflux for 3 h. Sodium ethoxide [from sodium (0.23 g, 0.01 mol)] in ethanol (20 ml) was then added and the solution boiled under reflux for a further 3 h, cooled, and added to acetic acid (0.6 g) in water (240 ml). A white precipitate was collected, dried (1.12 g), dissolved in ethyl acetate (2 ml), and chromatographed on silica gel (70 ml). Ethyl acetate eluted a yellow band, then methanol eluted a

[12] J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High-Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New York, Toronto, and London, 1959.

second yellow band. Removal of solvent from this second eluate gave an oil which was dissolved in ethyl acetate (5 ml) and cooled to 0 °C, yielding pale yellow crystals of the *thiazolinone* (4) (0.32 g, 24%), m.p. 181—183°, $\nu_{max.}$ (Nujol) 3 350 (NH), 1 680 (C=O), and 1 620 cm^{-1} (C=N), δ (CD_3CN) 3.15 (3 H, s, NCH_3), 3.37 and 3.42 (2 H, 2q, AB of ABX, $\Delta\nu_{AB}$ 26 Hz, J_{AB} 15 Hz, CH_2), 4.65 (1 H, q, X of ABX, J_{AX} 11, J_{BX} −5 Hz, CH·S), 6.97—7.80 (5 H, m, aromatic), and 9.30 (1 H, s, D_2O-exchangeable, NH), *m/e* 259 (M^+, 44%), 170 (13), 131 (43), 130 (100), and 129 (21) (Found: C, 59.9; H, 5.1; N, 15.9; S, 12.3. $C_{13}H_{13}N_3OS$ requires C, 60.2; H, 5.0; N, 16.2; S, 12.4%).

(±)-2-*Imino*-5-(*indol*-3-*ylmethyl*)-3-*methylthiazolidin*-4-*one* (5).—A solution of the (±)-ester (2) (1.49 g, 0.005 mol) and *N*-methylthiourea (0.45 g, 0.005 mol) in methanol (50 ml) was maintained at 20 °C for 2 weeks. The methanol was evaporated off and water (100 ml) added. A small quantity of white precipitate was filtered from the aqueous solution (pH 3) and the pH was adjusted to 7 with M-sodium carbonate. A white precipitate was collected and dried (0.64 g). T.l.c. on silica (elution with ethyl acetate) indicated that this contained a major component (R_F 0.45) and a minor one [R_F 0.10, corresponding with the thiazolinone (4)]. The precipitate was dissolved in ethyl acetate (2 ml) and chromatographed on silica gel (70 ml) (elution with ethyl acetate). Concentration of the fractions containing the faster moving component and cooling to 0 °C gave crystals of the 3-*methylthiazolidinone* (5) (0.50 g, 38.5%), m.p. 142—144°, $\nu_{max.}$ (Nujol) 3 375 and 3 250 (NH), 1 698 (C=O), and 1 615 cm^{-1} (C=N), δ ($CDCl_3$) 3.51 and 3.56 (2 H, 2q, AB of ABX, $\Delta\nu_{AB}$ 33.5 Hz, J_{AB} 14 Hz, CH_2), 3.23 (3 H, s, NCH_3), 4.60 (1 H, q, X of ABX, J_{AX} 10.5, J_{BX} −4.5 Hz, CH·S), 7.07—7.97 (5 H, m, aromatic), and 8.47 (1 H, s, D_2O-exchangeable, NH), *m/e* 259 (M^+, 23%), 131 (38), and 130 (100) (Found: C, 60.3; H, 4.9; N, 16.4; S, 12.5. $C_{13}H_{13}N_3OS$ requires C, 60.2; H, 5.0; N, 16.2; S, 12.4%).

Rearrangement of the (±)-2-*Imino*-3-*methylthiazolidinone* (5) *to the* (±)-2-*Methylaminothiazolinone* (4).—A solution of the (±)-iminothiazolidinone (5) (0.50 g) in methanol (25 ml) containing sodium methoxide (20 mg) was boiled under nitrogen for 2 h. After cooling, water (50 ml) was added and the solution neutralised with 0.1N-hydrochloric acid. Evaporation left a yellow oil which was dissolved in ethyl acetate (1 ml) and chromatographed on silica gel (35 ml); ethyl acetate eluted a yellow band containing the thiazolidinone (5), and methanol then eluted a second yellow band. Removal of solvent from this second eluate gave an oil (0.50 g), which was dissolved in ethyl acetate (2 ml) and cooled to 0 °C, yielding the thiazolinone (4) (0.36 g, 72%).

(±)-α-*Methyl* 2-*Chloro*-3-(*indol*-3-*yl*)*butyrate* (7).—To a solution of (±)-methyl α-indolmycenate (4.70 g, 0.02 mol) in dry pyridine (50 ml) at 0 °C, methanesulphonyl chloride (3.1 ml, 0.04 mol) was added. The mixture was stored at 5 °C for 3 days and then poured into iced water (230 ml), and extracted with ether (4 × 200 ml). The combined extracts were washed with 5N-hydrochloric acid (3 × 200 ml) and water (2 × 200 ml), dried (Na_2SO_4), and evaporated, yielding an oil (4.80 g) which crystallised. Recrystallisation from toluene yielded white plates of the 2-chloro-ester (7) (3.10 g, 60%), m.p. 98—100°, $\nu_{max.}$ (Nujol) 3 320 (NH) and 1 732 cm^{-1} (C=O), δ ($CDCl_3$) 1.55 (3 H, d, *J* 7 Hz, CH_3), 3.61 (3 H, s, CH_3O), 3.85 (1 H, m, C*H*·CH_3), 4.64 (1 H, d, *J* 7 Hz, CHCl), 7.00—7.90 (5 H, m, aromatic), and 8.20br (1 H, s, D_2O-exchangeable, NH), *m/e* 253 (M^+, 5%), 251 (M^+, 15%), 188 (23), 145 (16), and 144 (100) (Found: C, 61.7; H, 5.6; Cl, 14.4; N, 5.4. $C_{13}H_{14}ClNO_2$ requires C, 62.0; H, 5.6; Cl, 14.1; N, 5.6%).

(±)-α-*Methyl* 3-*Chloro*-2-(*indol*-3-*yl*)*butyrate* (8).—A solution of (±)-ester (7) (0.10 g, 0.4 mmol) in deuteriochloroform (1 ml) was maintained at 60 °C for 3 days, after which conversion into the 3-chloro-ester (8) was shown, by n.m.r. spectroscopy, to be 95% complete. The chloroform was evaporated off and the residual oil dissolved in ether–cyclohexane (1 : 1) and cooled to 5 °C. The clear cubic crystals deposited were collected, washed with cyclohexane, and dried, yielding the 3-*chloro-ester* (8) (0.07 g, 70%), m.p. 89—90°, $\nu_{max.}$ (Nujol) 3 340 (NH) and 1 718 cm^{-1} (C=O), δ ($CDCl_3$) 1.33 (3 H, d, *J* 7 Hz, CH·C*H*$_3$), 3.67 (3 H, s, CO_2CH_3), 4.04 (1 H, d, *J* 11 Hz, C*H*·CO_2CH_3), 4.40—4.90 (1 H, m, CHCl), 7.1—7.9 (5 H, m, aromatic), and 8.37br (1 H, s, NH), *m/e* 253 (M^+, 5%), 251 (M^+, 14%), 192 (14), 189 (13), and 188 (100) (Found: C, 61.9; H, 5.5; Cl, 14.1; N, 5.5. $C_{13}H_{14}ClNO_2$ requires C, 62.0; H, 5.6; Cl, 14.1; N, 5.6%).

(±)-α-2-*Amino*-5-(1-*indol*-3-*ylethyl*)-Δ^2-*thiazolin*-4-*one* (9).—A solution of the 2-chloro-ester (7) (0.50 g, 0.002 mol) and thiourea (0.15 g, 0.002 mol) in ethanol (50 ml) was maintained at 20 °C for 3 days. The ethanol was then evaporated off and M-sodium carbonate (8 ml) and water (50 ml) added to the residual oil. The precipitate obtained was collected, dried, and recrystallised from methanol (8 ml), yielding white crystals of the 2-*aminothiazolinone* (9) (0.28 g, 53%), m.p. 228—230°, $\nu_{max.}$ (Nujol) 3 380 and 3 220 (NH), 1 675 (C=O), and 1 610 cm^{-1} (C=N), δ [$(CD_3)_2SO$] 1.29 (3 H, d, *J* 7 Hz, CH_3), 3.98 (1 H, m, C*H*·CH_3), 4.91 (1 H, d, *J* 3.6 Hz, CH·S), 7.0—7.9 (5 H, m, aromatic), and 9.06br (2 H, d, D_2O-exchangeable, NH_2) (Found: C, 59.9; H, 5.2; N, 15.9. $C_{13}H_{13}N_3OS$ requires C, 60.2; H, 5.0; N, 16.2%).

(±)-α-2-*Methylamino*-5-(1-*indol*-3-*ylethyl*)-Δ^2-*thiazolin*-4-*one* (10).—A solution of the 2-chloro-ester (7) (0.50 g, 0.002 mol) and *N*-methylthiourea (0.18 g, 0.002 mol) in ethanol (50 ml) was maintained at 20 °C for 8 days. The ethanol was then evaporated off and M-sodium carbonate (8 ml) and water (50 ml) were added to the residual oil. The precipitate obtained was collected and dried (yield 0.50 g). T.l.c. on silica (elution with ethyl acetate) indicated that this material contained two components, R_F 0.42 and 0.10. The solid was dissolved in methanol (30 ml), N-sodium hydroxide (0.1 ml) was added, and the solution was boiled under reflux for 8 h. After cooling, water (20 ml) was added and the solution brought to pH 8 with 0.1N-hydrochloric acid. Evaporation yielded a yellow oil, which was dissolved in a minimal amount of methanol–ethyl acetate (1 : 1) and chromatographed on silica gel (70 ml); ethyl acetate eluted traces of one yellow material, and methanol then eluted a second yellow band. This second eluate was evaporated and the oil thus obtained was dissolved in hot ethyl acetate. Cooling to 0 °C yielded white crystals of the 2-*methylaminothiazolinone* (10) (0.25 g, 46%), m.p. 208—210°, $\nu_{max.}$ (Nujol) 3 200br (NH), 1 680 (C=O), and 1 590 cm^{-1} (C=N), δ [$(CD_3)_2SO$] 1.27 (3 H, d, *J* 7 Hz, C·CH_3), 2.94 (0.7 H, s) and 3.02 (2.3 H, d, *J* 4 Hz, collapses to singlet on D_2O-exchange) (NH·C*H*$_3$), 3.99 (1 H, m, C*H*·CH_3), 4.90 (1 H, d, *J* 3 Hz, CH·S), 7.0—7.9 (5 H, m, aromatic), 9.30br and 9.67br (1 H, both s, D_2O-exchangeable, N*H*·CH_3), and 11.11 (1 H, s, D_2O-exchangeable, indole NH), *m/e* 273 (M^+, 3%) and 144 (100) (Found: C, 61.7; H, 5.6; N, 15.1; S, 11.7. $C_{14}H_{15}N_3OS$ requires C, 61.5; H, 5.5; N, 15.4; S, 11.7%).

(±)-β-*Methyl* 3-(*Indol*-3-*yl*)-2-*mesyloxybutyrate* (13).—To

a solution of (±)-methyl β-indolmycenate (4.7 g, 0.02 mol) in dry pyridine (50 ml) at 0 °C, methanesulphonyl chloride (3.1 ml, 0.04 mol) was added. The mixture was stored at 5 °C for 3 days, then poured into iced water (300 ml) and concentrated hydrochloric acid (50 ml) and stirred at 5 °C for 1.5 h. The aqueous solution was decanted from the residual gum, which was dissolved in ether (250 ml), washed with water (2 × 60 ml), and dried ($MgSO_4$). The ether was evaporated off to leave the β-*mesylate* (13) as a pale brown oil (6.0 g, 97%), $\nu_{max.}$ (film) 3 370 (NH) and 1 740br cm^{-1} (C=O), δ ($CDCl_3$) 1.43 (3 H, d, *J* 7 Hz, CH·C*H*$_3$), 2.75 (3 H, s, SO_2CH_3), 3.46 (3 H, s, CO_2CH_3), 3.72 (1 H, m, C*H*·CH_3), 5.20 (1 H, d, *J* 6 Hz, CH·O), 6.9—7.8 (5 H, m, aromatic), and 8.48br (1 H, s, NH) (Found: C, 54.0; H, 5.8; N, 4.6; S, 10.6. $C_{14}H_{17}NO_5S$ requires C, 54.0; H, 5.5; N, 4.5; S, 10.3%).

(±)-β-*Methyl* 3-*Bromo*-2-(*indol*-3-*yl*)*butyrate* (14).—A solution of the (±)-ester (13) (0.69 g, 0.002 mol) and benzyltriethyl ammonium bromide (0.60 g, 0.002 2 mol) in dichloromethane (16 ml) was refluxed for 1.5 h. Evaporation yielded a yellow oil (0.6 g) which, after being washed with water (2 × 20 ml), was dissolved in chloroform (50 ml) and dried ($MgSO_4$). After filtering, the chloroform solution was concentrated and the residue chromatographed on silica gel (50 ml); ethyl acetate eluted a yellow band. Removal of solvent from the eluate afforded an oil which, on crystallisation from toluene–light petroleum (b.p. 60—80 °C) (1 : 1), gave pale yellow crystals of the 3-*bromobutyrate* (14) (0.58 g, 88%), m.p. 76—78°, $\nu_{max.}$ (Nujol) 3 375 (NH) and 1 720 cm^{-1} (C=O), δ ($CDCl_3$), 1.85 (3 H, d, *J* 7 Hz, CH·C*H*$_3$), 3.78 (3 H, s, CO_2CH_3), 4.36 (1 H, d, *J* 8 Hz, C*H*·CO_2CH_3), 4.85 (1 H, m, CH·CH_3), 7.1—8.0 (5 H, m, aromatic), and 8.37br (1 H, s, NH) (Found: C, 52.9; H, 4.9; Br, 26.7; N, 4.8. $C_{13}H_{14}BrNO_3$ requires C, 52.7; H, 4.8; Br, 27.0; N, 4.7%).

(±)-β-*Methyl* 3-*Chloro*-2-(*indol*-3-*yl*)*butyrate* (15).—Reaction of the (±)-ester (13) (0.82 g, 0.002 6 mol) with benzyltriethylammonium chloride (0.62 g, 0.002 6 mol) as for the preparation of the bromo-ester (14) afforded, without prior chromatographic purification, white crystals of the 3-*chlorobutyrate* (0.32 g, 48%), m.p. 88—90° [from toluene–light petroleum (b.p. 40—60°) (1 : 1)], $\nu_{max.}$ (Nujol) 3 330 (NH) and 1 718 cm^{-1} (C=O), δ ($CDCl_3$) 1.63 (3 H, d, *J* 6.5 Hz, CH·C*H*$_3$), 3.77 (3 H, s, CO_2CH_3), 4.28 (1 H, d, *J* 8 Hz, C*H*·CO_2CH_3), 4.79 (1 H, m, C*H*·CH_3), 7.1—7.9 (5 H, m, aromatic), and 8.33br (1 H, s, NH), *m/e* 253 (M^+, 9%), 251 (M^+, 26%), 192 (19), 188 (100), 160 (13), 157 (13), and 156 (14) (Found: C, 62.0; H, 5.7; Cl, 13.9; N, 5.5. $C_{13}H_{14}ClNO_2$ requires C, 62.0; H, 5.6; Cl, 14.1; N, 5.6%).

Resolution of (±)-α-*Indolmycenic Acid*.—To a solution of (±)-α-indolmycenic acid (33.8 g, 0.154 mol) in acetone (300 ml)–methylene chloride (300 ml), a solution of (−)-phenethylamine (18.7 g, 0.154 mol) in methylene chloride (75 ml) was added. The solvent was evaporated off, and the mixture of diastereoisomeric salts (47.7 g, 91%) washed with ethyl acetate (250 ml) and dissolved in hot acetone (1 l). On cooling, white crystals (18.96 g) separated. These were collected and after recrystallisation from acetone afforded pure (−)-α-*indolmycenic acid* (−)-*phenethylamine salt* (16.92 g, 64%), m.p. 173—175°, $[\alpha]_D^{20}$ −21.5° (*c* 10 in MeOH) (Found: C, 70.3; H, 7.0; N, 8.2. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%).

The filtrate from the first acetone crystallisation was concentrated to a gum, which was dissolved in ethyl acetate (1 l). The solution was washed with 0.1N-hydrochloric acid (100 ml) and then water (100 ml), dried ($MgSO_4$), and evaporated, yielding a gummy solid, which was dissolved in hot 1,2-dichloroethane (1.2 l). On cooling, crude (+)-α-indolmycenic acid separated as white crystals (14.06 g, 0.064 mol). These were dissolved in acetone (100 ml)–methylene chloride (100 ml) and a solution of (+)-phenethylamine (7.78 g, 0.064 mol) in methylene chloride (20 ml) was added. The solvent was evaporated off, and the residue (20.1 g) washed with ethyl acetate (150 ml) and dissolved in hot acetone (500 ml). On cooling, white crystals (15.11 g) separated. These were collected and on recrystallisation from acetone afforded pure (+)-α-*indolmycenic acid* (+)-*phenethylamine salt* (13.74 g, 52%), m.p. 174—176°, $[\alpha]_D^{20}$ +21.5° (*c* 10 in MeOH) (Found: C, 70.5; H, 7.0; N, 8.4. $C_{20}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%).

(−)- and (+)-α-indolmycenic acids were liberated from their phenethylamine salts in the following manner. The salt [(−),(−) 16.77 g; (+),(+) 13.52 g] was suspended in ethyl acetate (200 ml) and shaken with 0.5N-hydrochloric acid (100 ml). When all the solid had dissolved, the aqueous layer was separated and the ethyl acetate solution washed with water (100 ml), dried ($MgSO_4$), and evaporated. The solid thus obtained was triturated with 1,2-dichloroethane (50 ml), separated, and dried, yielding white crystals of (−)-α-*indolmycenic acid* (16) (10.08 g, 93%), m.p. 176—177°, $[\alpha]_D^{20}$ −9.3° (*c* 10 in MeOH) (Found: C, 65.7; H, 6.0; N, 6.4%), or (+)-α-*indolmycenic acid* (17) (7.98 g, 92%), m.p. 176—177°, $[\alpha]_D^{20}$ +9.3° (*c* 10 in MeOH) (Found: C, 65.9; H, 6.1; N, 6.5. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.2; N, 6.4%). The i.r. and ^1H n.m.r. spectra of the α-indolmycenic acid enantiomers (16) and (17) were identical with those described previously [4] for (±)-α-indolmycenic acid.

(−)- *and* (+)-*Methyl* α-*Indolmycenates* (18) *and* (19).—A solution of the α-indolmycenic acid enantiomer (16) or (17) (4.6 g, 0.024 mol) and toluene-*p*-sulphonic acid (4.1 g, 0.024 mol) in methanol (100 ml) was boiled under reflux for 18 h. The methanol was evaporated off and the residue dissolved in ethyl acetate (100 ml). The solution was washed with aqueous 5% sodium carbonate (40 ml) and water (2 × 40 ml), dried ($MgSO_4$), and evaporated. The oil obtained was dissolved in benzene (30 ml) and, after 3 h at 5 °C, yielded white crystals of the methyl ester enantiomer. (−)-Methyl α-indolmycenate (18) (4.6 g, 94%) had m.p. 80—81°, $[\alpha]_D^{20}$ −3.6° (*c* 10 in MeOH); (+)-methyl α-indolmycenate (19) (4.5 g, 92%) had m.p. 80—81°, $[\alpha]_D^{20}$ +3.6° (*c* 10 in MeOH). The i.r. and ^1H n.m.r. spectra of both enantiomers were identical with those of (±)-methyl α-indolmycenate (6).[4]

(−)- *and* (+)-α-*Methyl* 2-*Chloro*-3-(*indol*-3-*yl*)*butyrate* (20) *and* (21).—To a solution of the methyl α-indolmycenate enantiomer (18) or (19) (2.3 g, 0.001 mol) in dry pyridine (20 ml) at 0 °C was added a solution of benzyltriethylammonium chloride (0.24 g, 0.001 mol) in chloroform (2 ml), followed dropwise by methanesulphonyl chloride (1.6 ml, 0.02 mol). The mixture was stored at 5 °C for 3 days and then poured into iced water (150 ml). The mixture was extracted with chloroform (3 × 50 ml), and the extract stirred with 5N-hydrochloric acid (50 ml) for 15 min, washed with water (2 × 50 ml), dried ($MgSO_4$), and evaporated. The resulting oil was dissolved in dry ether (200 ml) and the solution filtered, concentrated to 30 ml, and stored at 5 °C for 3 h, yielding the 2-chloro-ester enantiomer as white plates. Recrystallisation from ether afforded (−)-α-methyl 2-chloro-3-(indol-3-yl)butyrate (20) (1.27 g, 51%), m.p. 123—125°, $[\alpha]_D^{20}$ −2.6° (*c* 10 in dioxan) or (+)-α-methyl 2-chloro-3-(indol-3-yl)butyrate (21) (1.69 g, 68%), m.p.

124—126°, $[\alpha]_D^{20}$ +2.6° (*c* 10 in dioxan). The i.r. and ^1H n.m.r. spectra of both enantiomers were identical with those of (±)-α-methyl 2-chloro-3-(indol-3-yl)butyrate (7).

(−)- *and* (+)-α-5-(1-*Indol*-3-*ylethyl*)-2-*methylamino*-Δ^2-*thiazolin*-4-*one* (22) *and* (23).—A solution of the α-methyl 2-chloro-3-(indol-3-yl)butyrate enantiomer (20) or (21) (0.68 g, 0.002 7 mol) and *N*-methylthiourea (0.25 g, 0.002 7 mol) in methanol (50 ml) was maintained at 20 °C for 3 days. The methanol was then evaporated off affording a yellow oil, to which water (50 ml) and 2N-sodium carbonate (3 ml) were added. The white precipitate obtained was collected, washed with water, and dried. The powder was dissolved in methanol (50 ml); N-sodium hydroxide (0.1 ml) was added, and the solution was boiled under reflux for 3 h, and cooled to 20 °C. Water (20 ml) was added and the solution was brought to pH 8 with N-hydrochloric acid. Evaporation afforded a yellow oil which was dissolved in a minimal amount of hot methanol. The solution was filtered and cooled to 5 °C. In the case of the product from the (−)-2-chloro-ester (20), white crystals were obtained. These were collected and after recrystallisation from methanol yielded (−)-α-5-(1-indol-3-ylethyl)-2-methylamino-Δ^2-thiazolin-4-one (22) (0.22 g, 30%), m.p. 225—227°, $[\alpha]_D^{20}$ −100.7° (*c* 0.3 in MeOH).

The methanolic filtrates were concentrated and chromatographed on silica gel (70 ml); ethyl acetate eluted one component, and methanol eluted a second. The second eluate was concentrated to an oil, which was dissolved in hot ethyl acetate, and the solution was cooled to 0 °C. A further crop of the (−)-thiazolinone (22) (0.14 g, 19%), identical with the first, was thus obtained.

With the product obtained from the (+)-2-chloro-ester (21), no crystallisation occurred prior to chromatography. However, after chromatography under the foregoing conditions the methanol-eluted component was obtained as a yellow oil which, after two crystallisations from methanol, yielded white crystals of (+)-α-5-(1-indol-3-ylethyl)-2-methylamino-Δ^2-thiazolin-4-one (23) (0.18 g, 25%), m.p. 226—228°, $[\alpha]_D^{20}$ +101.4° (*c* 0.3 in MeOH).

The i.r. and ^1H n.m.r. spectra of both enantiomers were identical with those of the (±)-thiazolinone (10).

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