Ross, and S-O. Ögren, *Acta Pharm. Suec.*, **12**, 149 (1975).
(3) B. Carnmalm, M-L. Persson, S. B. Ross, S-O. Ögren, and N. E. Stjernström, *Acta Pharm. Suec.*, 12, 205 (1975).
(4) D. Seebach in "Houben-Weyl Methoden der Organischen Chemie", Vol. IV/4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1971.
(5) E. Buchta and K. Geibel, *Justus Liebigs Ann. Chem.*, **648**, 36 (1961).
(6) Reference 4, p 46.
(7) British Patent 805 664 (1958); *Chem. Abstr.*, **53**, 10075 (1959).
(8) J. W. Wilt, R. A. Dabek, and K. C. Welzel, *J. Org. Chem.*, **37**, 425 (1972).
(9) C. J. Michejda and R. W. Comnick, *J. Org. Chem.*, **40**, 1046 (1975).
(10) B. A. Callingham in "Antidepressant Drugs", S. Garattini and M. N. G. Dukes, Ed., Excerpta Medica, Amsterdam, 1966, p 35.
(11) S. B. Ross and A. L. Renyi in "Symposium on Pharmacology of Catecholaminergic and Serotonergic Mechanisms", J. Knoll and K. Magyar, Ed., Akademiai Kiadó, Budapest, 1976, p 1.
(12) S. B. Ross, S-O. Ögren, and A. L. Renyi, *Acta Pharmacol. Toxicol.*, **39**, 152 (1976).
(13) N. E. Andén, S. G. Butcher, H. Corrodi, K. Fuxe, and U. Ungerstedt, *Eur. J. Pharmacol.*, 11, 303 (1970).
(14) N. E. Andén and U. Strömbom, *Psychopharmacologia*, **38**, 91 (1974).
(15) K. Fuxe, L. Agnati, and B. Everitt, *Neurosci. Lett.*, 1, 283 (1975).
(16) A. Carlsson, *Handb. Exp. Pharmakol.*, **19**, 529 (1965).
(17) H. Corrodi and L. C. F. Hansson, *Psychopharmacologia*, **10**, 116 (1966).
(18) B. Carnmalm, E. Jacupovic, L. Johansson, T. de Paulis, S. Rämsby, N. E. Stjernström, A. L. Renyi, S. B. Ross, and S-O. Ögren, *J. Med. Chem.*, 17, 65 (1974).
(19) J. Scheel-Krüger, *Eur. J. Pharmacol.*, **14**, 47 (1971).
(20) J. V. Dingell, M. L. Owens, M. R. Norvich, and F. Sulser, *Life Sci.*, **6**, 1155 (1967).
(21) S. B. Ross, *Acta Pharmacol. Toxicol.*, **41**, 392 (1977).
(22) S. B. Ross, A. L. Renyi, and S-O. Ögren, *Eur. J. Pharmacol.*, 17, 107 (1972).
(23) D. J. Finney "Probit Analysis", 2nd ed, Charles Griffin, London, 1952.
(24) H. N. Cripps, J. K. Williams, and W. H. Sharkey, *J. Am. Chem. Soc.*, **81**, 2723 (1959).
(25) I. Lillien and L. Handloser, *J. Org. Chem.*, **34**, 3058 (1969).

# Thiazolinone Analogues of Indolmycin with Antiviral and Antibacterial Activity

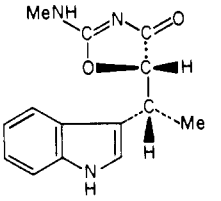
Michael R. Harnden,* Stuart Bailey, Malcolm R. Boyd, Denis R. Taylor, and Nicholas D. Wright

*Beecham Pharmaceuticals Research Division, Brockham Park, Betchworth, Surrey, England.* *Received June 27, 1977*

Total synthesis of a series of thiazolinone and thiazolidinone analogues of the antibacterial oxazolinone antibiotic indolmycin is described. The synthetic route involves nucleophilic displacement of mesyloxy and chloro groups from methyl 2-substituted-3-(indol-3-yl)propionates **3** and **4** and butyrate **19** with N-substituted thioureas. The formation of the rearranged chloro esters **29**, **43**, and **44** from β(*RS,RS*)-methyl indolmycenate (**27**), α(*RS,SR*)-methyl 2-hydroxy-3-(2-methylindol-3-yl)butyrate (**39**), and α-methyl 2-hydroxy-3-(indol-3-yl)valerate (**41**) supports a reaction mechanism involving neighboring group participation by the indole C-3 carbon during nucleophilic displacement on the β-carbon of a C-3 substituent. Structure–activity relationships are discussed. Although neither indolmycin nor its diastereoisomer isoindolmycin is antiviral, 2-monoalkylaminothiazolinone analogues have in vitro activity against both RNA viruses and bacteria. The most active compound is the sulfur isostere of indolmycin, and only the levorotatory enantiomer **46**, with the same absolute stereochemistry as natural indolmycin, has antimicrobial activity.

Since replication of viruses occurs only within host cells, and host cell metabolism and viral replication are closely integrated, the development of compounds which selectively interfere with virus-specific processes is one of the more intriguing remaining problems in antimicrobial chemotherapy.

One possible approach involves selective interference with the synthesis or functioning of specific enzymes, either introduced into or induced in the host cell by the virus.[1-5] The absence of detailed information concerning the amino acid sequence and conformation of these enzymes does, however, make it difficult to design rationally compounds that will bind to them selectively. The approach that we have taken involves total synthesis of analogues of a naturally occurring oxazolinone antibiotic, indolmycin. Although there was little a priori reason for believing that indolmycin analogues would bind selectively to a viral enzyme, it seemed that, by modification of a fairly complex structure possessing features consistent with noncovalent bonding to nucleic acids or proteins, and for which a precise stereochemical requirement for biological activity had been demonstrated,[6] the probability of obtaining a compound which bound preferentially to a single macromolecule would be substantially increased.




indolmycin

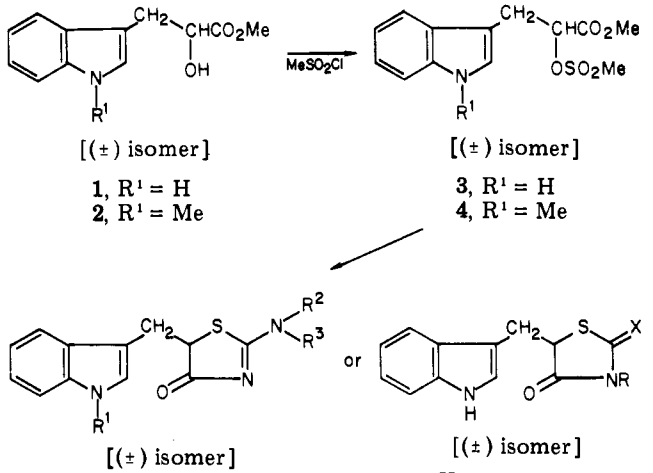
The present paper describes the synthesis of a series of thiazolinone and thiazolidinone analogues of indolmycin and structural requirements for antiviral and antibacterial activity.

**Chemistry.** 2-Aminothiazolinones **5–11** and **20–25** and 2-iminothiazolidinones **12–15** and **26** were prepared by nucleophilic displacement of 2-mesyloxy or chloro groups from methyl 3-(indol-3-yl)propionates **3** and **4** and butyrate **19** with N-substituted thioureas.[7]

The 2-alkylaminothiazolinones **6** and **8** and the isomeric 2-imino-3-alkylthiazolidinones **12** and **14**, respectively, were both isolated from reactions in which *N*-monoalkylthioureas were used. Because of the possibilities for tautomerization[8] and both intra- and intermolecular hydrogen bonding,[9] it is not possible to assign thiazolinone

0022-2623/78/1821-0082$01.00/0 

Scheme I



[(±) isomer]

1, $R^1$ = H
2, $R^1$ = Me

[(±) isomer]

3, $R^1$ = H
4, $R^1$ = Me



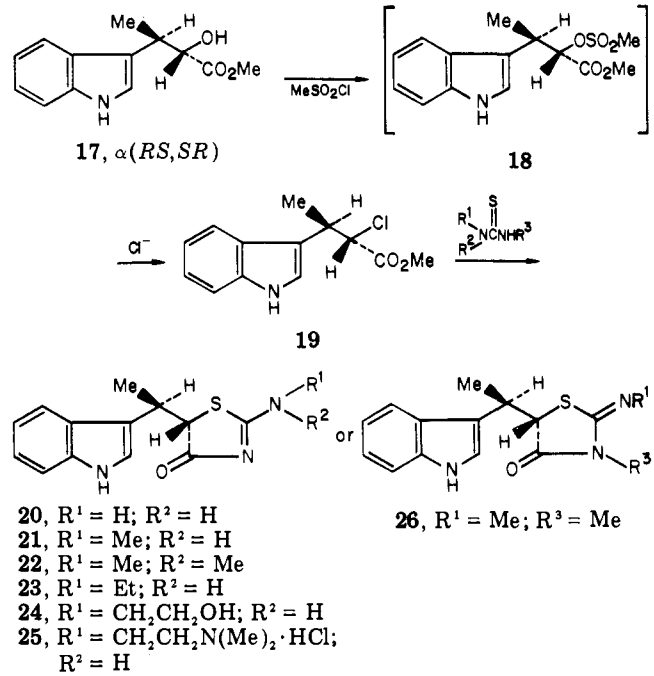
[(±) isomer]

5, $R^1$ = H; $R^2$ = H; $R^3$ = H
6, $R^1$ = H; $R^2$ = Me; $R^3$ = H
7, $R^1$ = H; $R^2$ = Me; $R^3$ = Me
8, $R^1$ = H; $R^2$ = Et; $R^3$ = H
9, $R^1$ = H; $R^2$ = $CH_2CH_2OH$; $R^3$ = H
10, $R^1$ = H; $R^2$ = $CH_2C_6H_5$; $R^3$ = H
11, $R^1$ = Me; $R^2$ = Me; $R^3$ = H

[(±) isomer]

12, X = NH; R = Me
13, X = NMe; R = Me
14, X = NH; R = Et
15, X = $NC_6H_5$; R = H
16, X = S; R = H

Scheme II[a]



17, α(*RS*,*SR*)

18

19

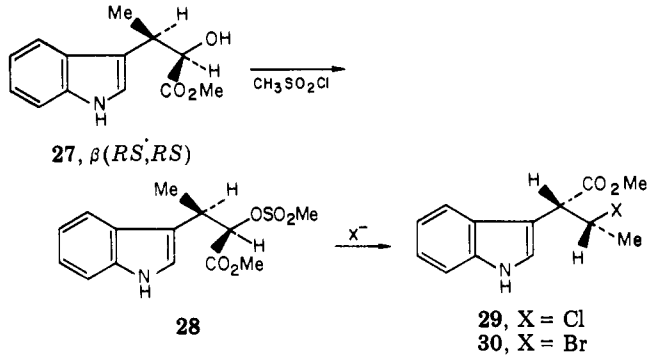
20, $R^1$ = H; $R^2$ = H
21, $R^1$ = Me; $R^2$ = H
22, $R^1$ = Me; $R^2$ = Me
23, $R^1$ = Et; $R^2$ = H
24, $R^1$ = $CH_2CH_2OH$; $R^2$ = H
25, $R^1$ = $CH_2CH_2N(Me)_2 \cdot HCl$; $R^2$ = H

26, $R^1$ = Me; $R^3$ = Me

[a] Although compounds **17–30**, **39**, **41**, **43**, and 44 are racemic mixtures, in order to simplify the presentation and to clarify the stereochemical course of each reaction, the reaction sequence is in each case shown for one enantiomer only.

or thiazolidinone structures unequivocally from NMR and IR spectral data. However, we have recently described[7] the facile methoxide-catalyzed rearrangement of the 2-imino compound **12** to the 2-methylaminothiazolinone **6** in refluxing methanol; this is consistent with conditions reported previously[10] for a thiazolidinone → thiazolinone rearrangement. Furthermore, there are five other compounds in the series for which structural assignment is unequivocal. The structure of the (−)-2-methylaminothiazolinone **46** has been determined by x-ray crystal analysis,[11] and of the two *N*,*N*-dimethyl isomeric pairs **7** and **13**, and **22** and **26**, **7** and **22** can only exist as thiazolinones and **13** and **26** can only exist as thiazolidinones. In all cases the thiazolidinones have lower melting points and higher solubility in organic solvents than do their thiazolinone isomers. Additionally, upon thin-layer chromatography on silica gel using ethyl acetate as the eluting solvent, the 2-alkyl- and dialkylaminothiazolinones **6–8**, **11**, **21–23**, **46**, and **47** have much lower mobility ($R_f$ 0.10–0.17) than do the 3-alkylthiazolidinones **12–14** and **26** ($R_f$ 0.42–0.60).

Scheme III[a]



27, β(*RS*,*RS*)

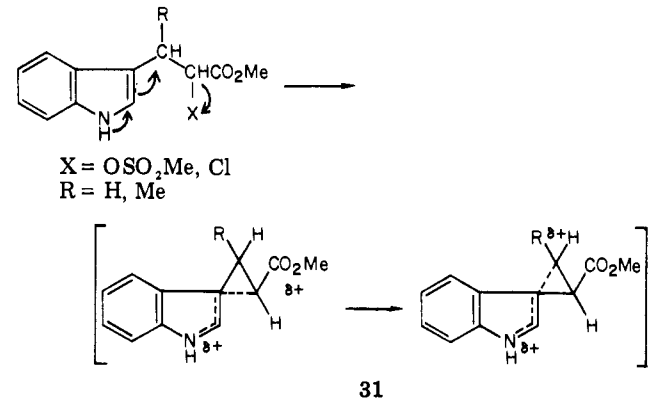
28

29, X = Cl
30, X = Br

[a] See corresponding footnote in Scheme II.

The above route was applicable to the synthesis of *C*-demethyl analogues (Scheme I) and to thiazolinone and thiazolidinone diastereoisomers (Scheme II) derived from (±)-α-methyl indolmycenate (**17**), which has (2*R*,3*S*)-(2*S*,3*R*) stereochemistry,[12] but under the conditions required for displacement of the mesyloxy grouping from (±)-β-methyl 2-mesyloxy-3-(indol-3-yl)butyrate (**28**), which has (2*R*,3*R*)(2*S*,3*S*) stereochemistry, only the rearranged halo esters **29** and **30** were obtained (Scheme III).[7]

The relative reactivities of the mesyloxy esters **3**, **18**, and **28** and the chloro ester **19**, rearrangements, and the stereochemistry of the products obtained have been explained[7] by a reaction mechanism involving neighboring group participation by the indole C-3 carbon, resulting in the intermediacy of spiro-substituted cyclopropylium ions (**31**).



X = $OSO_2Me$, Cl
R = H, Me

31

Although the indole-*N*-methyl analogue **11** of the *C*-demethyl 2-methylaminothiazolinone **6** was readily obtained by this route (Scheme I), attempts to prepare α-thiazolinone analogues with methyl groups on the indole C-2 carbon, or with an ethyl group instead of methyl on the C-3 substituent, were unsuccessful. The 2-hydroxy esters **39** and **41** were readily accessible (Scheme IV), but in each case the predominant product from mesylation was the rearranged chloro ester **43** or **44**, respectively (Scheme V).

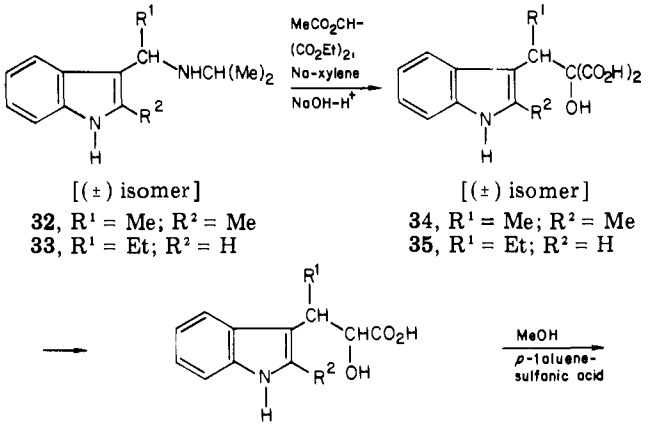
The structures of the rearranged chloro esters **29**,[7] **43**, and **44** were assigned unequivocally from NMR and mass

Table I. Biological Activity[a]

| Compd | Antibacterial,[b] MIC, μg/mL | | | | | | Antiviral and cytotoxicity | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Influenza A/NWS-BHK cells | | | Coxsackie B1-HeLa cells | | |
| | *B.s.* | *S.a.* Oxford | *S.a.* Russel | *S.a.* 1517 | *S.f.* I | *S.p.* CN10 | Inhibn zone, mm | $PDD_{50}$, μg/mL | MCC, μg/mL | Inhibn zone, mm | $PDD_{50}$, μg/mL | MCC, μg/mL |
| **5** | >200 | 200 | 200 | 200 | 200 | >200 | 0 | ND[c] | ND | 0 | ND | ND |
| **6** | >200 | 20 | 20 | 20 | 20 | 200 | 14 | 10 | 30 | 9 | 100 | >100 |
| **20** | 200 | ND | 20 | 20 | 20 | 200 | 0 | 50 | 100 | 0 | ND | ND |
| **21** | 20 | 2 | 2 | 2 | 2 | 200 | 36 | 3 | 10 | 29 | 5 | 30 |
| **22** | >200 | 20 | 20 | 20 | >200 | >200 | 0 | ND | ND | 0 | ND | ND |
| **23** | 200 | 20 | 20 | 20 | 20 | 200 | 34 | 5 | 10 | 16 | 10 | >100 |
| **24** | >200 | 200 | 200 | 200 | 200 | 200 | 8 | >30 | 100 | 20 | 16 | >100 |
| **46** | 20 | 2 | 2 | 2 | 2 | 200 | ND | 1.2 | 4 | ND | 3 | 12 |
| *dl*-Indolmycin | 20 | 2 | 2 | 2 | 2 | 200 | 0 | >100 | >100 | 0 | ND | ND |
| *dl*-Isoindolmycin | >200 | 200 | 200 | 200 | 200 | >200 | 0 | >100 | >100 | 0 | ND | ND |
| Ampicillin | 2 | 2 | 2 | 20 | 2 | 2 | ND | ND | ND | ND | ND | ND |
| Ribavirin[d] | ND | ND | ND | ND | ND | ND | 28 | 1 | >100 | 0 | >100 | >100 |
| HBB[e] | ND | ND | ND | ND | ND | ND | 0 | >100 | >100 | 24 | 20 | 100 |

[a] Compounds **7-16**, **25**, **26**, and **47** exhibited no antibacterial activity against any of the organisms at concentrations up to 200 μg/mL and no antiviral activity or cytotoxicity at concentrations up to 100 μg/mL. [b] *B.s.* = *Bacillus subtilis*; *S.a.* = *Staphylococcus aureus*; *S.f.* = *Streptococcus faecalis*; *S.p.* = *Streptococcus pyogenes*. [c] ND = not done. [d] Ribavirin = 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. [e] HBB = 2-(α-hydroxybenzyl)benzimidazole.

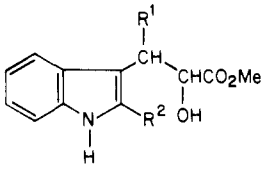
Scheme IV




[(±) isomer]
**32**, $R^1$ = Me; $R^2$ = Me
**33**, $R^1$ = Et; $R^2$ = H

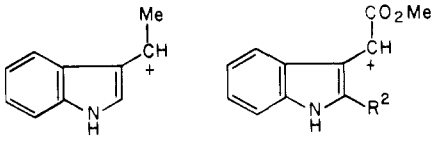
[(±) isomer]
**34**, $R^1$ = Me; $R^2$ = Me
**35**, $R^1$ = Et; $R^2$ = H

**36**, (±)-α and (±)-β; $R^1$ = Me; $R^2$ = Me
**37**, (±)-α(*RS,SR*); $R^1$ = Et; $R^2$ = H
**38**, (±)-β(*RS,RS*); $R^1$ = Et; $R^2$ = H




**39**, (±)-α(*RS,SR*); $R^1$ = Me; $R^2$ = Me
**40**, (±)-α(*RS,RS*); $R^1$ = Me; $R^2$ = Me
**41**, (±)-α(*RS,SR*); $R^1$ = Et; $R^2$ = H
**42**, (±)-β(*RS,RS*); $R^1$ = Et; $R^2$ = H

spectral data. The most abundant fragment was in each case the ion **45** resulting from cleavage β to the aromatic

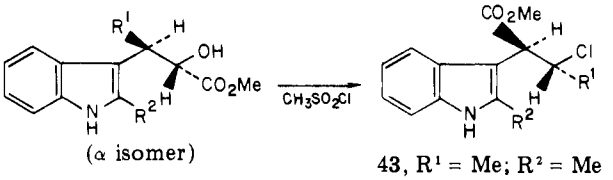



**45** (a) **45** (b)

system. For the chloro ester **19** this has *m/e* 144 (a) and for the rearranged chloro esters **29**, **43**, and **44**, *m/e* 188, 202, and 188 (b), respectively.

This increased propensity for rearrangement with alkyl-substituted α-diastereoisomers may be a consequence

Scheme V[a]



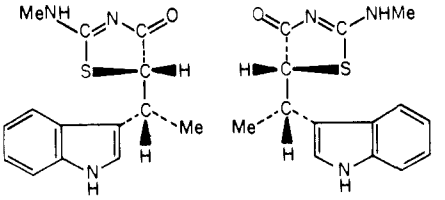

(α isomer)
**39**, $R^1$ = Me; $R^2$ = Me
**41**, $R^1$ = Et; $R^2$ = H

**43**, $R^1$ = Me; $R^2$ = Me
**44**, $R^1$ = Et; $R^2$ = H

[a] See corresponding footnote in Scheme II.

of increased stabilization of the cyclopropylium ion with the charge on the alkyl bearing carbon, as a result of introduction of more highly electron-donatory alkyl substituents. For stabilization by the indole C-2 methyl substituent, retention of at least partial bonding between the indole C-3 and the charge-bearing carbon would also seem to be required, supporting the proposed mechanism.

Since (±)-α-2-methylamino-5-[1-(indol-3-yl)ethyl]-$\Delta^2$-thiazolin-4-one (**21**), the sulfur isostere of *dl*-indolmycin, was the most biologically active racemic compound prepared, α-indolmycenic acid was resolved[7] and the enantiomers each converted to the 2-methylaminothiazolinone enantiomers **46** and **47**,[7] using the reaction sequence de-




**46**, (−) isomer **47**, (+) isomer

scribed for the racemate **21**.

**Structure–Activity Relationships.** In this series of thiazolinones and thiazolidinones there are highly specific structural requirements for both antiviral and antibacterial activity in vitro (Table I). The only racemic compounds with significant antiviral activity are the 2-monoalkylaminothiazolinones **6**, **21**, **23**, and **24**. These compounds inhibit the replication of influenza and coxsackie, both RNA viruses, but do not inhibit replication of Herpes simplex, a DNA virus. 2-Dimethylaminothiazolinones **7**

and **22**, 2-iminothiazolidinones **12–15** and **26**, and the 2-thione **16** are not antiviral. Alkylation of the indole nitrogen, as in **11**, also reduces activity.

Each of the four antiviral thiazolinones **6**, **21**, **23**, and **24** has antibacterial activity, and their relative levels of antibacterial activity parallel the antiviral activity. However, although the spectrum of antibacterial activity is in each case similar to that of *dl*-indolmycin, neither *dl*-indolmycin nor its diastereoisomer, *dl*-isoindolmycin, possesses antiviral activity.

The enantiomers **46** and **47** of the 2-methylaminothiazolinone **21** were evaluated separately and only the levorotatory isomer **46** has antiviral and antibacterial activity. The absolute stereochemistry of this thiazolinone is identical with that of natural *l*-indolmycin.[7,11]

Thus the structural and stereochemical requirements for antiviral activity are similar to those for antibacterial activity, except that the thiazolinone ring and a 2-monoalkylamino substituent are essential additional requirements. If indolmycin exerts its antibacterial activity through binding to a bacterial receptor such as an enzyme,[13] it is possible that the thiazolinone **46** can also bind to the same receptor and additionally to an enzyme or enzyme substrate involved in the intracellular replication of RNA viruses.

The spectrum of antimicrobial activity exhibited by (5*S*)-5-[(1*R*)-1-(indol-3-yl)ethyl]-2-methylamino-$\Delta^2$-thiazolin-4-one (**46**) is of considerable interest for the treatment of respiratory infections, and this compound is currently undergoing further evaluation in animal models.

## Experimental Section

Melting points were determined using a Reichert hot-stage apparatus. IR spectra were recorded with a Perkin-Elmer 157 spectrometer. $^1$H NMR spectra were determined for solutions in deuterated solvents at 60 MHz with a Varian EM360 spectrometer (tetramethylsilane as internal standard). The calculations described by Pople et al.[14] were used for interpretation of ABX systems. Mass spectra were obtained with an A.E.I. Model MS9 instrument operating at 70 eV. Elemental analyses were performed by the microanalytical laboratory of Beecham Pharmaceuticals. For chromatographic separations, silica gel refers to Kieselgel H, type 60 (E. Merck, Darmstadt). Analytical TLC was carried out on Eastman Chromagram sheets of silica gel with fluorescent indicator; the sheets were eluted with ethyl acetate and spots were visualized under UV light (254 nm). All evaporations were carried out under reduced pressure with a rotary evaporator.

**(±)-Methyl 2-Hydroxy-3-(1-methylindol-3-yl)propionate (2).** A solution of (±)-methyl 2-hydroxy-3-(indol-3-yl)propionate (**1**)[7] (2.19 g, 0.01 mol) in anhydrous ether (50 mL) was added dropwise to a stirred solution of sodium (0.25 g, 0.11 mol) in liquid ammonia (50 mL) containing a few crystals of ferric nitrate nonahydrate. After 10 min a solution of methyl iodide (2.84 g, 0.02 mol) in anhydrous ether (20 mL) was added. The ammonia was allowed to evaporate, water (30 mL) added, and the product extracted into ether (3 × 60 mL). The combined extracts were dried ($MgSO_4$) and evaporated, yielding an oil. The *N*-methyl propionate **2** was purified by distillation (0.80 g, 34%): bp 146–148 °C (0.5 mm); $\nu_{max}$ (film) 3430 (OH) and 1735 cm$^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) $\delta$ 2.95 (d, 1, $J$ = 6 Hz, $D_2O$ exchangeable OH), 3.15–3.40 (m, 2, $CH_2$), 3.75 (s, 6, $OCH_3$ and $NCH_3$), 4.56 (m, 1, C*H*OH), 7.0–8.0 (m, 5, aromatic). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

**(±)-Methyl 2-Mesyloxy-3-(1-methylindol-3-yl)propionate (4).** To a solution of the 2-hydroxypropionate **2** (0.63 g, 0.003 mol) in dry pyridine (20 mL) at 0 °C, methanesulfonyl chloride (0.63 g, 0.006 mol) was slowly added. The mixture was maintained at 5 °C for 2 days and then poured into iced 2 N hydrochloric acid (200 mL). The aqueous mixture was extracted with chloroform (3 × 60 mL); the chloroform solutions were dried ($MgSO_4$) and evaporated. The oil obtained was dissolved in ether and after cooling to 0 °C, white crystals of the mesyl ester **4** were obtained (0.84 g, 31%): mp 71 °C; $\nu_{max}$ (Nujol) 1755 cm$^{-1}$ (C=O); $^1$H NMR ($CDCl_3$) $\delta$ 2.76 (s, 3, $OSO_2CH_3$), 3.33 (d, 2, $J$ = 6 Hz, $CH_2$), 3.67 (s, 6, $NCH_3$ and $COOCH_3$), 5.27 (t, 1, $J$ = 6 Hz, CHO), 7.0–7.8 (m, 5 aromatic); $m/e$ 311 (M$^+$, 36%), 252 (22), 215 (38), 185 (15), 144 (100), 141 (42), 102 (60). Anal. ($C_{14}H_{17}NO_5S$) C, H, N.

**(±)-Thiazolinones and (±)-Thiazolidinones. General Reaction Conditions.** Unless otherwise stated, a solution of either the mesyloxy ester **3**,[7] **4**, or the $\alpha$-2-chloro ester **19**[7] (0.005 mol) and the appropriate N-substituted thiourea (0.005 mol) in ethanol (50 mL) was maintained at 20 °C for 4 days. The ethanol was then evaporated, water (50 mL) added, and the solution adjusted to pH 7.0 with 1 M sodium carbonate. The oil or solid which precipitated was collected and dissolved in ethyl acetate, and the solution was dried ($MgSO_4$).

**Isolation Procedures. (±)-2-Dimethylamino-5-[(indol-3-yl)methyl]-$\Delta^2$-thiazolin-4-one (7).** Evaporation of the solvent gave a solid which was recrystallized from methanol to yield 53% (0.72 g) of the crystalline thiazolinone **7**: mp 209–211 °C; TLC $R_f$ 0.14; $\nu_{max}$ (Nujol) 3250 (NH), 1681 (C=O), 1580 cm$^{-1}$ (C=N); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.10 (s, 3) and 3.25 (s, 3) [$N(CH_3)_2$], 3.48 and 3.55 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 20.5 Hz, $J_{AB}$ = 15 Hz, $CH_2$), 4.81 (q, 1, X proton of ABX system, $J_{AX}$ = 12 Hz, $J_{BX}$ = –6 Hz, CHS), 7.0–7.8 (m, 5, aromatic), 11.13 (s, br, 1, indole NH). Anal. ($C_{14}H_{15}N_3OS$) C, H, N, S.

**(±)-2-Ethylamino-5-[(indol-3-yl)methyl]-$\Delta^2$-thiazolin-4-one (8) and (±)-3-Ethyl-2-imino-5-[(indol-3-yl)methyl]thiazolidin-4-one (14).** On partial evaporation of the solvent and cooling to 0 °C, the crystalline thiazolinone **8** was obtained in 39% (0.53 g) yield: mp 173–175 °C; TLC $R_f$ 0.13; $\nu_{max}$ (Nujol) 3380 (NH), 1692 (C=O), 1610 cm$^{-1}$ (C=N); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 1.12 (t, 3, $J$ = 6.8 Hz, $CH_3$), 3.38 and 3.46 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 21.5 Hz, $J_{AB}$ = 12 Hz, $CH_2CH$), 3.44 (q, 2, $CH_2CH_3$), 4.69 (q, 1, X proton of ABX system, $J_{AX}$ = 11.5 Hz, $J_{BX}$ = –4.5 Hz, CHS), 7.0–7.8 (m, 5, aromatic), 9.23 (s, br, 1, $NHC_2H_5$), 11.08 (s, 1, indole NH). Anal. ($C_{14}H_{15}N_3OS$) C, H, N, S.

On concentration of the filtrate and chromatography on silica gel eluted with ethyl acetate, the thiazolidinone **14** was obtained in 9% (0.12 g) yield: mp 156–158 °C; TLC $R_f$ 0.60; $\nu_{max}$ (Nujol) 3400, 3360 (NH), 1698 (C=O), 1610 cm$^{-1}$ (C=N); $^1$H NMR ($CD_3OD$) $\delta$ 0.98 (t, 3, $J$ = 7.1 Hz, $CH_3$), 3.45 and 3.49 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 20 Hz, $J_{AB}$ = 12 Hz, $CH_2CH$), 3.71 (q, 2, $CH_2CH_3$), 4.68 (q, 1, X proton of ABX system, $J_{AX}$ = 8 Hz, $J_{BX}$ = –5 Hz, CHS), 7.0–7.9 (m, 5, aromatic). Anal. ($C_{14}H_{15}N_3OS$) C, H, N, S.

**(±)-2-(2-Hydroxyethylamino)-5-[(indol-3-yl)methyl]-$\Delta^2$-thiazolin-4-one (9).** For the preparation of the 2-hydroxyethylaminothiazolinone **9**, *N*-(2-trimethylsilyloxyethyl)thiourea, prepared by reaction of *N*-(2-hydroxyethyl)thiourea with excess hexamethyldisilazane in pyridine at 20 °C, was used. After reaction, evaporation of the solvent gave an oil which crystallized from 10% acetonitrile in ethyl acetate to yield 20% (0.29 g) of the thiazolinone **9**: mp 185–186 °C; TLC $R_f$ 0.00; $\nu_{max}$ (Nujol) 1670 (C=O), 1590 cm$^{-1}$ (C=N); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 2.9–3.8 (m, 2, AB protons of ABX system, $CH_2CH$), 3.48 (s, 4, $CH_2CH_2OH$), 4.6 (q, 1, X proton of ABX system, CHS), 4.8 (s, br, 1, $D_2O$ exchangeable, OH), 6.8–7.94 (m, 5, aromatic), 9.25 (s, br, 1, $D_2O$ exchangeable, $NHCH_2$), 11.0 (s, 1, $D_2O$ exchangeable, indole NH); $m/e$ 289 (M$^+$, 12%), 130 (100). Anal. ($C_{14}H_{15}N_3O_2S$) C, H, N, S.

**(±)-2-Benzylamino-5-[(indol-3-yl)methyl]-$\Delta^2$-thiazolin-4-one (10).** Evaporation of the solvent gave an oil which, after chromatography on silica gel eluted with 10% methanol in ethyl acetate, yielded a solid which was recrystallized from methanol to yield 7% (0.15 g) of the crystalline thiazolinone **10**: mp 189–190 °C; TLC $R_f$ 0.27; $\nu_{max}$ (Nujol) 3300 (NH), 1677 (C=O), 1610 cm$^{-1}$ (C=N); $^1$H NMR ($Me_2SO$-$d_6$) $\delta$ 3.20 and 3.28 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 27.5 Hz, $J_{AB}$ = 12 Hz, $CH_2CH$), 4.54 (s, 2, $NCH_2$), 4.58 (q, 1, X proton of ABX system, $J_{AX}$ = 11.5 Hz, $J_{BX}$ = –5.5 Hz, CHS), 6.9–7.7 (m, 10, aromatic), 9.55 (s, br, 1, $D_2O$ exchangeable, $NHCH_2$), 11.04 (s, br, 1, indole NH); $m/e$ 335 (M$^+$, 18%), 206 (53), 130 (100), 117 (53), 107 (43), 106 (53). Anal. ($C_{19}H_{17}N_3OS$) C, H, N.

**(±)-2-Methylamino-5-[(1-methylindol-3-yl)methyl]-$\Delta^2$-thiazolin-4-one (11).** Evaporation of the solvent gave an oil, which was dissolved in methanol (200 mL) containing 2 N sodium hydroxide (0.5 mL), and the solution was boiled under reflux for

3 h. The oil obtained after evaporation of the solvent was dissolved in ethyl acetate (40 mL), and the solution was filtered and cooled to 0 °C, yielding 28% (0.38 g) of the crystalline thiazolinone 11: mp 183–184 °C; TLC $R_f$ 0.10; $\nu_{max}$ (Nujol) 1680 (C=O), 1620 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.76 and 2.87 (2 s, 3, $NHCH_3$), 2.6–3.8 (m, 2, AB protons of ABX system, $CH_2CH$), 3.67 (s, 3, $NCH_3$), 4.53 (q, 1, X proton of ABX system, CHS), 7.0–7.8 (m, 5, aromatic), 9.16 (s, br, 1, NH); $m/e$ 273 ($M^+$, 12%), 144 (100). Anal. ($C_{14}H_{15}N_3OS$) C, H, N.

**(±)-2-Methylimino-3-methyl-5-[(indol-3-yl)methyl]thiazolidin-4-one (13).** Evaporation of the solvent gave a solid which was recrystallized from toluene to yield 76% (1.04 g) of the crystalline thiazolidinone 13: mp 139–140 °C; TLC $R_f$ 0.50; $\nu_{max}$ (Nujol) 3195 (NH), 1718 (C=O), 1635 $cm^{-1}$ (C=N); $^1H$ NMR ($CDCl_3$) $\delta$ 3.13 (s, 3, $=NCH_3$), 3.20 (s, 3, $NCH_3$), 3.17 and 3.86 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 38.5 Hz, $J_{AB}$ = 15 Hz, $CH_2CH$), 4.52 (q, 1, X proton of ABX system, $J_{AX}$ = 10.5 Hz, $J_{BX}$ = –4.5 Hz, CHS), 7.10–7.90 (m, 5, aromatic), 8.48 (s, br, 1, indole NH). Anal. ($C_{14}H_{15}N_3OS$) C, H, N, S.

**(±)-2-Phenylimino-5-[(indol-3-yl)methyl]thiazolidin-4-one (15).** The preparation of thiazolidinone 15 was carried out using dimethylformamide as solvent. After reaction, evaporation of the ethyl acetate gave an oil which, after chromatography on silica gel eluted with ether–cyclohexane (1:1), gave a solid which was recrystallized from ethyl acetate to yield 36% (0.58 g) of the crystalline thiazolidinone 15: mp 210–212 °C; TLC $R_f$ 0.27; $\nu_{max}$ (Nujol) 3385, 3230, and 3180 (NH), 1685 (C=O), 1635 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.38 and 3.43 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 21 Hz, $J_{AB}$ = 16 Hz, $CH_2CH$), 4.84 (q, 1, X proton of ABX system, $J_{AX}$ = 11.5 Hz, $J_{BX}$ = –6.5 Hz, CHS), 6.9–8.1 (m, 10, aromatic), 11.5 (s, 1, indole NH), 11.66 (s, br, 1, CONH); $m/e$ 321 ($M^+$, 15%), 192 (5), 130 (100). Anal. ($C_{18}H_{15}N_3OS$) C, H, N.

**5-[(Indol-3-yl)methyl]-2-thiothiazolidin-4-one (16).** For the preparation of the 2-thiothiazolidinone 16, ammonium dithiocarbamate was allowed to react with the mesylate 3. After reaction, evaporation of the solvent gave a gummy residue, which was chromatographed on silica gel eluted with cyclohexane–ethyl acetate (2:1), yielding a solid. Recrystallization from chloroform afforded 27% (0.35 g) of the thiazolidinone 16: mp 134–136 °C; TLC $R_f$ 0.51; $\nu_{max}$ (KBr) 3400 (NH), 1720 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 3.56 and 3.60 (2 q, 2, AB protons of ABX system, $\Delta\nu_{AB}$ = 18.8 Hz, $J_{AB}$ = 14 Hz, $CH_2$), 4.75 (q, 1, X proton of ABX system, $J_{AX}$ = 11.8 Hz, $J_{BX}$ = –6.8 Hz, CH), 6.9–7.9 (m, 5, aromatic), 8.22 (s, br, 2, $D_2O$ exchangeable, both NH); $m/e$ 262 ($M^+$, 16%), 130 (100). Anal. ($C_{12}H_{10}N_2OS_2$) C, H, N.

**(±)-α-2-Dimethylamino-5-[1-(indol-3-yl)ethyl]-Δ²-thiazolin-4-one (22).** Evaporation of the solvent gave an oil which was crystallized from ethanol to yield 57% (0.83 g) of the crystalline thiazolinone 22: mp 238–240 °C; TLC $R_f$ 0.15; $\nu_{max}$ (Nujol) 3230 (br, NH), 1680 (C=O), 1565 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.26 (d, 3, $J$ = 7 Hz, $CHCH_3$), 3.14 (s, 3) and 3.26 (s, 3) [$N(CH_3)_2$], 3.97 (m, 1, $CHCH_3$), 4.95 (d, 1, $J$ = 3.9 Hz, CHS), 7.0–7.9 (m, 5, aromatic), 10.90 (s, br, 1, indole NH); $m/e$ 287 ($M^+$, 53%), 144 (100). Anal. ($C_{15}H_{17}N_3OS$) C, H, N.

**(±)-α-2-Ethylamino-5-[1-(indol-3-yl)ethyl]-Δ²-thiazolin-4-one (23).** Evaporation of the solvent gave an oil which, after chromatography on silica gel eluted with ethyl acetate, yielded a solid which was recrystallized from ethyl acetate to yield 14% (0.20 g) of the crystalline thiazolinone 23: mp 195–197 °C; TLC $R_f$ 0.17; $\nu_{max}$ (Nujol) 3260 (br, NH), 1678 (C=O), 1585 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.11 (t, 3, $J$ = 8.5 Hz, $CH_2CH_3$), 1.20 (d, 3, $J$ = 7.0 Hz, $CHCH_3$), 3.0–4.0 (m, 3, $CHCH_3$ and $CH_2$), 4.83 (d, 1, $J$ = 3.2 Hz, CHS), 7.0–7.8 (m, 5, aromatic), 9.33 (s, 1, $D_2O$ exchangeable, $NHC_2H_5$), 11.12 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{15}H_{17}N_3OS$) C, H, N.

**(±)-α-2-(2-Hydroxyethylamino)-5-[1-(indol-3-yl)ethyl]-Δ²-thiazolin-4-one (24).** Evaporation of the solvent gave an oil which, after chromatography on silica gel eluted with 10% methanol in ethyl acetate and trituration with hot chloroform, yielded 13% of the crystalline thiazolinone 24: mp 195–197 °C; TLC $R_f$ 0.03; $\nu_{max}$ (KBr) 1670 (C=O), 1580 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.20 (d, 3, $J$ = 7 Hz, $CHCH_3$), 3.1–3.7 (m, 4, $CH_2CH_2$), 3.85 (m, 1, $CHCH_3$), 4.75 (d, 1, $J$ = 3 Hz, CHS), 4.80 (s, 1, $D_2O$ exchangeable, OH), 6.8–7.7 (m, 5, aromatic), 9.27 (s, br, 1, $D_2O$ exchangeable, $NHCH_2$), 10.86 (s, 1, $D_2O$ exchangeable, indole NH); $m/e$ 303 ($M^+$, 15%), 144 (100). Anal. ($C_{15}H_{17}N_3O_2S$) C, H, N.

**(±)-α-2-(2-*N*,*N*-Dimethylaminoethylamino)-5-[1-(indol-3-yl)ethyl]-Δ²-thiazolin-4-one Hydrochloride (25).** The white solid which separated from the original reaction mixture was collected and recrystallized from ethanol to yield 22% (0.40 g) of crystalline thiazolinone hydrochloride 25: mp 208–209 °C; TLC $R_f$ 0.11; $\nu_{max}$ (KBr) 3400, (br, NH), 1700 (C=O), 1620 $cm^{-1}$ (C=N); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 1.27 (d, 3, $J$ = 7.0 Hz, $CHCH_3$), 2.75 [s, 6, $N(CH_3)_2$], 3.23 (m, 2, $NHCH_2$), 3.97 (m, 3, $CH_2N^+$ and $CHCH_3$), 4.92 (d, 1, $J$ = 4.0 Hz, CH-S), 6.8–7.7 (m, 5, aromatic), 9.5 (s, br, 1, $D_2O$ exchangeable, $NHCH_2$), 11.05 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{17}H_{23}ClN_4OS$) C, H, Cl, N, S.

**(±)-α-2-Methylimino-3-methyl-5-[1-(indol-3-yl)ethyl]-thiazolidin-4-one (26).** Evaporation of the solvent gave an oil which was recrystallized from ether–cyclohexane (3:1) to yield 48% (0.67 g) of the crystalline thiazolidinone 26: mp 123–125 °C; TLC $R_f$ 0.53; $\nu_{max}$ (Nujol) 3210 (br, NH), 1722 (C=O), 1638 $cm^{-1}$ (C=N); $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (d, 3, $J$ = 7.0 Hz, $CHCH_3$), 3.17 (s, 3, $=NCH_3$), 3.25 (s, 3, $NCH_3$), 4.23 (m, 1, $CHCH_3$), 4.77 (d, 1, $J$ = 3.6 Hz, CHS), 7.0–8.0 (m, 5, aromatic), 8.51 (s, br, 1, indole NH); $m/e$ 287 ($M^+$, 11%), 144 (100). Anal. ($C_{15}H_{17}N_3OS$) C, H, N.

The preparation of the 2-aminothiazolinones 5 and 20, the 2-methylaminothiazolinones 6, 21, 46, and 47, and the 3-methylthiazolidinone 12 has been described previously.[7]

**(±)-2-Carboxy-2-hydroxy-3-(2-methylindol-3-yl)butyric Acid (34) and (±)-2-Carboxy-2-hydroxy-3-(indol-3-yl)valeric Acid (35).** The appropriate Mannich base 32[15] or 33[16] (0.28 mol), diethyl acetoxymalonate (76.0 g, 0.35 mol), and sodium (0.51 g) in dry xylene (350 mL) under nitrogen were boiled under reflux until no further isopropylamine was evolved (ca. 20 h). The reaction mixture was cooled to room temperature, ethanol (6 mL) was added, and the solvents were evaporated. The oil obtained was stirred with a solution of sodium hydroxide (72 g) in water (80 mL) and ethanol (320 mL), and a solid was obtained. The mixture was stored at 5 °C for 18 h, the solid was then separated, washed with ether (3 × 80 mL), and dissolved in water (600 mL), and the solution was acidified to pH 1 with concentrated hydrochloric acid (ca. 60 mL). The solution was then extracted with ethyl acetate (3 × 300 mL), and the extracts were dried ($Na_2SO_4$) and evaporated, yielding an oil. Trituration of this oil with dichloromethane gave the crude diacid 34 or 35 as a white solid, which was then recrystallized.

The 2-methylindole diacid 34 was obtained in 45% yield (34.9 g): mp 132–134 °C (from dichloroethane–ethyl acetate). Anal. ($C_{14}H_{15}NO_5$) C, H, N. The 2-carboxy-2-hydroxyvaleric acid 35 was obtained in 67.6% yield (52.0 g): mp 112–114 °C (from ethyl acetate–petroleum ether). Anal. ($C_{14}H_{15}NO_5$) C, H, N.

Infrared and $^1H$ NMR data for both compounds were consistent with the proposed structures.

**2-Hydroxy-3-(2-methylindol-3-yl)butyric Acid (36) and 2-Hydroxy-3-(indol-3-yl)valeric Acids (37, 38).** The hydroxy diacid 34 or 35 (45 g) was dissolved in β-picoline (1.2 L) and the solution boiled under reflux for 1 h. The β-picoline was evaporated and the residue dissolved in saturated sodium bicarbonate (500 mL). The solution was then washed with chloroform (3 × 300 mL), acidified to pH 1 with 5 N hydrochloric acid, and extracted with chloroform (3 × 400 mL). The extracts were dried ($MgSO_4$) and evaporated, yielding the crude hydroxy acids (36, 36 g, 95%, 37 and 38, 31 g, 82%) as mixtures of two racemic diastereoisomers.

The 2-hydroxyvaleric acid was recrystallized from chloroform to yield (±)-α-2-hydroxy-3-(indol-3-yl)valeric acid (37) (13.3 g, 43%): mp 144–146 °C; $\nu_{max}$ (Nujol) 3380 (NH, OH), 1725 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 0.74 (t, 3, $J$ = 7 Hz, $CH_3$), 1.75 (m, 2, $CH_2$), 3.13 (m, 1, $CH_2CH$), 4.11 (d, 1, $J$ = 6 Hz, CHOH), 6.8–7.6 (m, 5, aromatic), 10.75 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

The filtrate was evaporated and the residue was recrystallized from ethyl acetate–petroleum ether to yield (±)-β-2-hydroxy-3-(indol-3-yl)valeric acid (38) (6.0 g, 20%): mp 149–151 °C; $\nu_{max}$ (Nujol) 3450 (OH), 3380 (NH), 1710 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 0.82 (t, 3, $J$ = 7 Hz, $CH_3$), 1.77 (m, 2, $CH_2$), 3.20 (m, 1, $CH_2CH$), 4.28 (d, 1, $J$ = 4 Hz, CHOH), 6.8–7.7 (m, 5, aromatic), 10.70 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{13}H_{15}NO_3$) C, H, N.

**(±)-α-Methyl 2-Hydroxy-3-(2-methylindol-3-yl)butyrate (39) and (±)-β-Methyl 2-Hydroxy-3-(2-methylindol-3-yl)-butyrate (40).** A solution of the mixture of 2-methylindole hydroxy acids **36** (34 g, 0.15 mol) and *p*-toluenesulfonic acid (27.5 g, 0.16 mol) in methanol (700 mL) was boiled under reflux for 18 h. The methanol was evaporated, and the residue dissolved in ethyl acetate (800 mL). The solution was washed with 5% sodium carbonate (3 × 200 mL) and water (2 × 400 mL), dried ($Na_2SO_4$), and evaporated, yielding an oil. The oil was crystallized from chloroform (250 mL), yielding 12.4 g (35%) of (±)-α-methyl 2-hydroxy-3-(2-methylindol-3-yl)butyrate (**39**): mp 132–134 °C; $\nu_{max}$ (Nujol) 3450 (OH), 3260 (NH), 1720 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.48 (d, 3, $J$ = 7.0 Hz, $CH_3CH$), 2.37 (s, 3, $CH_3$), 2.73 (d, 1, $J$ = 6.0 Hz, $D_2O$ exchangeable, OH), 3.46 (m, 1, $CH_3CH$), 3.61 (s, 3, $CO_2CH_3$), 4.40 (pair of d, 1, $J_{CH}$ = 5.0 Hz, $J_{OH}$ = 6.0 Hz, $CHOH$), 6.95–7.70 (m, 4, aromatic), 7.77 (s, br, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

The filtrate was evaporated and the residue crystallized from benzene–cyclohexane (100:100 mL), yielding 10.3 g (29%) of (±)-β-methyl 2-hydroxy-3-(2-methylindol-3-yl)butyrate (**40**): mp 79–82 °C; $\nu_{max}$ (Nujol) 3450 (OH), 3250 (NH), 1720 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.58 (d, 3, $J$ = 8.0 Hz, $CH_3CH$), 2.31 (s, 3, $CH_3$), 2.59 (d, 1, $J$ = 7.0 Hz, $D_2O$ exchangeable, OH), 3.49 (m, 1, $CH_3CH$), 3.61 (s, 3, $CO_2CH_3$), 4.44 (pair of d, 1, $J_{CH}$ = 5.0 Hz, $J_{OH}$ = 7.0 Hz, $CHOH$), 6.95–7.75 (m, 4, aromatic), 7.81 (s, br, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

**(±)-α-Methyl 2-Hydroxy-3-(indol-3-yl)valerate (41) and (±)-β-Methyl 2-Hydroxy-3-(indol-3-yl)valerate (42).** A solution of the (±)-2-hydroxyvaleric acid diastereoisomer **37** or **38** (4.0 g, 0.017 mol) and *p*-toluenesulfonic acid (3.6 g, 0.021 mol) in methanol (100 mL) was boiled under reflux for 18 h. The methanol was evaporated and the residue dissolved in ethyl acetate (100 mL). The solution was washed with 5% sodium carbonate (3 × 40 mL) and water (2 × 40 mL), dried ($Na_2SO_4$), and evaporated, yielding an oil which was crystallized from benzene–cyclohexane (1:1). The (±)-α-ester **41** was obtained in 70% yield (3.0 g): mp 96–97 °C; $\nu_{max}$ (Nujol) 3520 (OH), 3330 (NH), 1730 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) δ 0.80 (t, 3, $J$ = 7.2 Hz, $CH_2CH_3$), 1.89 (m, 2, $CH_2$), 3.30 (m, 1, $CH_2CH$), 3.52 (s, 3, $CO_2CH_3$), 4.30 (pair of d, 1, $J_{CH}$ = 6.0 Hz, $J_{OH}$ = 6.0 Hz, $CHOH$), 5.70 (d, 1, $J$ = 6.0 Hz, $D_2O$ exchangeable, OH), 6.9–8.1 (m, 5, aromatic), 11.04 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{14}H_{17}NO_3$) C, H, N. The (±)-β-ester **42** was obtained in 57% yield (2.2 g): mp 93–95 °C; $\nu_{max}$ (Nujol) 3580 (OH), 3350 (NH), 1745 $cm^{-1}$ (C=O); $^1H$ NMR ($Me_2SO$-$d_6$) δ 0.84 (t, 3, $J$ = 7.2 Hz, $CH_2CH_3$), 1.80 (m, 2, $CH_2$), 3.28 (m, 1, $CH_2CH$), 3.28 (m, 1, $CH_2CH$), 3.50 (s, 3, $CO_2CH_3$), 4.45 (pair of d, 1, $J_{CH}$ = 5.0 Hz, $J_{OH}$ = 6.0 Hz $CHOH$), 5.24 (d, 1, $J$ = 6.0 Hz, $D_2O$ exchangeable, OH), 6.9–7.8 (m, 5, aromatic), 11.0 (s, 1, $D_2O$ exchangeable, indole NH). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

**(±)-α-Methyl 3-Chloro-2-(2-methylindol-3-yl)butyrate (43) and (±)-α-Methyl 3-Chloro-2-(indol-3-yl)valerate (44).** To a solution of either the 2-hydroxy(2-methylindol-3-yl)butyrate **39** (2.50 g, 0.01 mol) or the 2-hydroxy(indol-3-yl)valerate **41** (2.50 g, 0.01 mol) in dry pyridine (25 mL) at 0 °C, methanesulfonyl chloride (1.60 mL, 0.02 mol) was added. The mixture was stored at 5 °C for 3 days, then poured into iced water (150 mL), and extracted with chloroform (4 × 100 mL). The combined extracts were washed with 5 N hydrochloric acid (3 × 100 mL) and water (2 × 100 mL), dried ($Na_2SO_4$), and evaporated, yielding an oil. After chromatography on silica gel, the 3-chloro esters **43** and **44** were obtained as clear pale brown oils, homogeneous on TLC. The (2-methylindol-3-yl)butyrate **43** was obtained in 56% yield (1.50 g): $\nu_{max}$ (film) 3350 (NH), 1730 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.30 (d, 3, $J$ = 6.5 Hz, $CHCH_3$), 2.42 (s, 3, $CH_3$), 3.64 (s, 3, $CO_2CH_3$), 4.0 (d, 1, $J$ = 11 Hz, $CHCO_2$), 4.99 (m, 1, $CHCl$), 7.0–7.85 (m, 4, aromatic), 8.01 (s, br, 1, $D_2O$ exchangeable, indole NH); $m/e$ 265 ($M^+$, 30%), 202 (100), 170 (30), 144 (20). Anal. ($C_{14}H_{16}ClNO_2$) C, H, N.

The 3-chlorovalerate **44** was obtained in 61% yield (1.62 g): $\nu_{max}$ (film) 3400 (NH), 1730 $cm^{-1}$ (C=O); $^1H$ NMR ($CDCl_3$) δ 1.00 (t, 3, $J$ = 7.0 Hz, $CH_2CH_3$), 1.65 (m, 2, $CH_2CH_3$), 3.78 (s, 3, $CO_2CH_3$), 4.25 (d, 1, $J$ = 11 Hz, $CHCO_2$), 4.65 (m, 1, CHCl), 7.1–8.1 (m, 5, aromatic), 8.70 (s, br, 1, $D_2O$ exchangeable , indole NH); $m/e$ 265 ($M^+$, 80%), 206 (51), 189 (78), 188 (100), 170 (33), 160 (54), 156 (49), 144 (34), 130 (56).

**Biological Evaluation (Table I). Antiviral.** Compounds were initially evaluated in simple diffusion assays. For this type of test, 100 mg/mL solutions of the compounds in dimethyl sulfoxide were diluted to a concentration of 1 mg/mL with Eagle's minimum essential medium and 0.02 mL introduced into wells 6 mm in diameter cut into an agar layer above virus-infected cell monolayers. Influenza A/NWS ($H_0N_1$) virus was grown in BHK 21 cells and Coxsackie B virus in HeLa cells, and in each case an infection level giving an even distribution of subconfluent plaques was used. The diameters of zones around the wells free from virus-induced plaques (inhibition zones) are reported.

More accurate quantitation of antiviral activity was achieved by incorporation of varying concentrations of the test compound into the agar overlay above the virus-infected cell monolayers. The lowest concentration of each compound causing a ≥50% reduction in the number of plaques in comparison with untreated controls ($PDD_{50}$) is given.

All of the thiazolinones and thiazolidinones reported in this paper were also screened for activity against Herpes simplex type 1 virus in chick embryo fibroblast cell monolayers, using a plaque reduction assay, but none was active.

The reported mininum cytotoxic concentration (MCC) is the lowest concentration of compound causing morphological abnormalities in cell monolayers stained either with carbol fuchsin or neutral red.

**Antibacterial.** Compounds were tested at 2, 20, and 200 μg/mL in diagnostic sensitivity test agar (Oxoid CM 261) + 5% horse blood, against the organisms shown. Bacterial inocula of approximately $10^4$–$10^6$ colony forming units/mL were used.

**Acknowledgment.** The authors wish to thank Mrs. P. A. Hunter for supplying the antibacterial data and Miss S. R. B. Harris for evaluation of compounds against Herpes simplex type 1 virus.

## References and Notes

(1) J. G. Tilles, *Annu. Rev. Pharmacol.*, **14**, 469 (1974).
(2) P. P. K. Ho and C. P. Walters, *Antimicrob. Agents Chemother.*, 68 (1968).
(3) D. C. Delong, J. N. Nelson, J. C. Cline, N. Neuss, and P. P. K. Ho, *Prog. Antimicrob. Anticancer Chemother.*, **2**, 53 (1970).
(4) S. S. Yang, F. Herrera, R. Smith, M. Reitz, G. Lancini, R. Ting, and R. Gallo, *J. Natl. Cancer Inst.*, **49**, 7 (1972).
(5) J. C. H. Mao, E. E. Robinshaw, and L. R. Overby, *J. Virol.*, **15**, 1281 (1975).
(6) M. N. Preobrazhenskaya, E. G. Balashova, K. R. Turchin, E. N. Padeiskaya, N. V. Uvarova, G. N. Pershin, and N. N. Suvorov, *Tetrahedron*, **24**, 6131 (1968).
(7) M. R. Harnden and N. D. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1012 (1977).
(8) H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.*, 1022 (1963).
(9) G. Rapi, M. Ginenneschi, E. Belgodere, and M. Chelli, *J. Heterocycl. Chem.*, **9**, 285 (1972).
(10) H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.*, 1018 (1963).
(11) T. J. King, personal communication.
(12) T. H. Chan and R. K. Hill, *J. Org. Chem.*, **35**, 3519 (1970).
(13) R. G. Werner, L. F. Thorpe, W. Reuter, and K. H. Nierhaus, *Eur. J. Biochem.*, **68** (1), 1 (1976).
(14) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, Toronto, London, 1959.
(15) R. P. Rao and A. H. Chalmers, *Ind. J. Chem.*, **6**, 336 (1968).
(16) British Patent 1 079 091 (to Chas. Pfizer and Co.) (Aug 9, 1967).