Conversion of *N*-Hydroxytryptophan into α-Functionalised Tryptophans. An Approach to the Sporidesmin Series[1]

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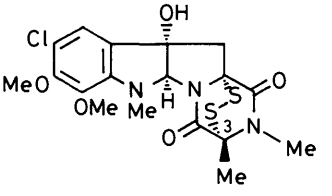
Reaction of the *N*-hydroxytryptophan derivative (**5a**) with pyruvoyl chloride gives access to the *N*-hydroxypiperazines (**6a**) and (**13**). *O*-Alkylation of the latter compounds, followed by base treatment in the presence or absence of methanol, affords the dioxopiperazines (**7a**) and (**20**), respectively. Subsequent oxidative ring closure using singlet oxygen yields the corresponding tetracyclic compounds (**8a**) and (**25**)—(**29**). The compounds (**25**) and (**8a**) having the skeleton and stereochemistry of the spirodesmins (**1a**—**c**) can be separated from their stereoisomers (**26**) and (**27**), respectively, by column chromatography. They are potential precursors of the fungal metabolites. Until now, attempts to replace the C-11a methoxy group of (**25**) and (**8a**) by a sulphur substituent have failed.

Finally, the properly substituted *N*-hydroxytryptophan derivative (**5b**) has been prepared by cycloaddition of (**2b**) with the nitroso olefin (**3**), followed by aminolysis of the addition product and subsequent selective reduction of the oxime function.

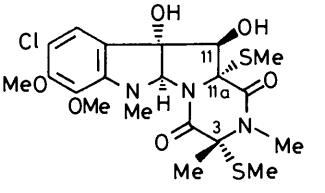
Secondary metabolites are distinct from primary metabolites in that they are frequently of relatively complex structure. Moreover, their distribution is more restricted than that of primary metabolites, and is characteristic of specific sources.

An illustrative example of secondary metabolites characterised by the presence of non-protein amino acids as structural elements is the class of the sporidesmins.[2] Three representative examples, sporidesmins B, D, and F (**1a**—**c**), can be regarded as condensation products of an α-mercaptotryptophan derivative and an α-mercapto- or an α,β-dehydro-alanine derivative. Recently, it has been suggested[1,3,4] that the biogenetic relationship between protein amino acids and α-substituted or α,β-dehydro amino acids might proceed *via* *N*-hydroxyamino acid derivatives.† Moreover, it was demonstrated that *N*-hydroxyamino acids deserve attention as synthons in the preparation of natural products having α-substituted or α,β-dehydro amino acids as structural elements.

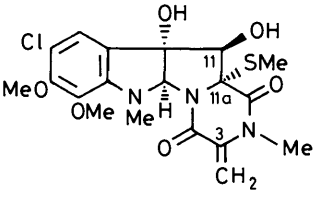
Here we show that the *N*-hydroxytryptophan derivative (**5a**) opens up a new approach to the spirodesmin series, both in terms of strategy and methodology.[5]‡ Our approach featuring transposition of the *N*-hydroxy functionality in (**5a**) into an α-functionality in compound (**7a**) is efficient in that the number of protecting groups is small.[6]



(1a) Sporidesmin B



(1b) Sporidesmin D



(1c) Sporidesmin F

Discussion

We felt that a synthetic procedure for the skeleton of type (**1**) has to create an intermediate that contains a preformed dioxopiperazine ring having additional functional groups at the α-positions, *e.g.* as in (**7**) (Scheme 1).

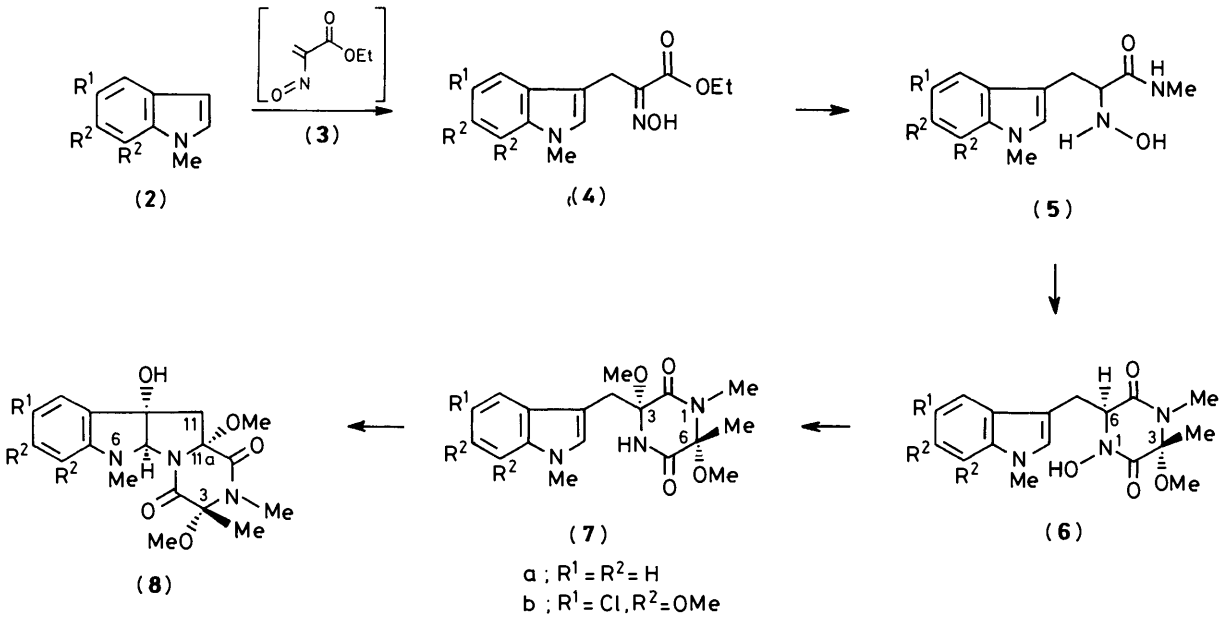
We thought that two particular reactions, run consecutively, might create such an intermediate. The condensation of compound (**5**) with pyryvoyl chloride and subsequent ring closure§ should introduce the α-functionalised alanine moiety present in structure (**6**). The transposition of the *N*-hydroxy group in structure (**6**) into an α-functionality might then be achieved by treatment of compounds (**6**), or better their *O*-benzyl derivatives, with a base and methanol to yield compounds (**7**).¶ Were these procedures to be successful, oxidative ring closure of (**7**) should then give the desired tetracyclic skeleton (**8**). We hoped that the conversion of compounds (**8**) into the corresponding, sulphur-bridged, bismethylthio or methylthio dioxopiperazine derivatives [*cf.* (**1a**), (**1b**), (**1c**), respectively] should be possible according to a reaction sequence worked out previously in a synthetic study on

† With astechrome – a metabolite from *Aspergillus terreus* – a natural product has been isolated which contains *N*-hydroxytryptophan as part of a dipeptide structure; K. Arai, S. Sato, S. Shimizu, K. Nitta, and Y. Yamamoto, *Chem. Pharm. Bull.*, 1981, **29**, 1510. Moreover, *N*-hydroxytryptophan has been proposed as an intermediate in the biosynthesis of glucosinolates (Glucobrassicins); B. L. Møller in 'Cyanide in Biology,' eds. B. Vennesland, E. Conn, G. J. Knowles, and J. Westley, Academic Press, London, 1981, p. 197 and references cited therein; S. Mahadevan, *Annu. Rev. Plant Physiol.*, 1973, **24**, 69.

‡ Total synthesis of other members of the spirodesmin group has not yet been reported.

§ We employed this reaction previously for the construction of α-methoxy and dioxopiperazines; see *e.g.*, refs. 3 and 4.

¶ We employed this reaction previously as a practical route to simple α-methoxyamino acid derivatives; see *e.g.* ref. 3.



Scheme 1.

gliotoxin analogues.[7] Total synthesis of sporidesmins (**1**) might then be feasible by using the properly substituted *N*-hydroxytryptophan derivative (**5b**), the synthesis of which will be described in this paper.

Results

Formation of the Dioxopiperazine (**6a**).—Acylation of compound (**5a**) with pyruvoyl chloride[8,9] and the subsequent, acid-catalysed ring closure to a dioxopiperazine was re-examined as we had observed previously[4] that in this one-pot reaction sequence the yield of the desired, ring-closed product is affected by the formation of the mixture of the *N*- and *O*-acylated products (**9**) and (**10**), respectively (Scheme 2) and by formation of a bridged dioxopiperazine (**12**) (Scheme 3). Only after several experiments did we find that treatment of compound (**5a**) with pyruvoyl chloride in CH_2Cl_2–dimethyl ether at room temperature gave **quantitatively** a 1:1 mixture of the two hydroxamic acids; the structures (**9**) (*cis*) and (**9**) (*trans*) could be assigned on the basis of ^1H n.m.r. studies.*

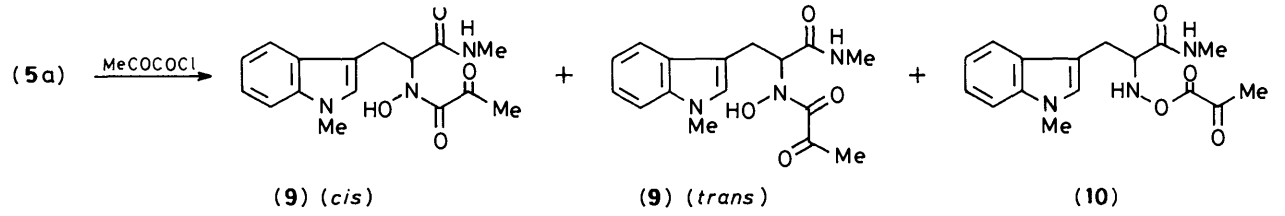
Obviously the solvent mixture used acts as a weak Lewis base under these reaction conditions. Employment of neat pyridine as solvent and carrying out the reaction at −78 °C caused formation of the *O*-pyruvoylated product (**10**) in 90% yield. Mixtures of products (**9**) and (**10**) in varying ratios were obtained when the acylation was carried out at 0—20 °C in the presence of a base (Et_3N).[4] Apparently, the *O*-acylated product (**10**) is formed mainly at low reaction temperatures. This can be rationalised by assuming that (**10**) is the kinetically favoured product, which is formed rapidly in the presence of a sufficiently strong base to deprotonate the hydroxy group of compound (**5a**). Attempts to rearrange (**10**) into the (assumedly) thermodynamically controlled product (**9**) were unsuccessful, however.

We had observed previously[4] that the acid-catalysed ring closure between the amide nitrogen and the pyruvoyl α-carbonyl group in compound (**9**) gives compound (**13**) but also leads invariably to a considerable amount of the side-product (**12**). Here we report that the formation of the tetracycle (**12**) could be suppressed completely by merely keeping the reaction mixture, that led to the two hydroxamic acids (**9**) (*cis*) and (**9**) (*trans*) at room temperature for 18 h. In this way compound (**13**) was obtained in 90% yield. Obviously, the combination of the solvent mixture used (CH_2Cl_2–dimethyl ether) and the amount of HCl formed is ideally suited to prevent formation of by-product (**12**).

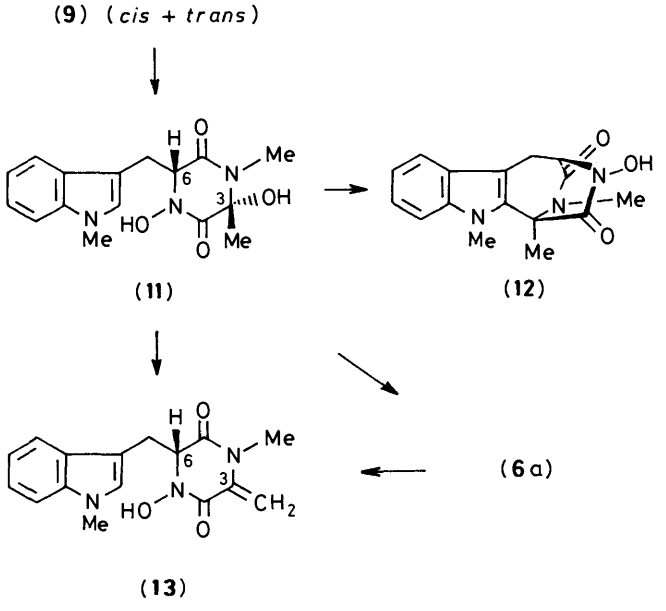
The formation of (**13**) can be rationalised by invoking the intermediacy of the alcohol (**11**);† protonation and subsequent dehydration yields compound (**13**). We were able to trap the intermediate carbonium ion; when methanol (10% v/v) was added to the reaction mixture after (**9**) (*cis*) and (**9**) (*trans*) had been formed completely—the reaction was monitored by ^1H n.m.r. spectroscopy—the α-functionalised dioxopiperazine (**6a**) could be isolated in 80% yield. This finding was even more gratifying since (**6a**) was formed completely diastereoselectively. Exposure of compound (**6a**) to CF_3CO_2H in CH_2Cl_2 yielded, quantitatively, compound (**13**).

* Temperature-dependent ^1H n.m.r. studies in [$^2H_8$]toluene indicated that the products (**9**) *cis* and (**9**) *trans* are isomers having a rotation barrier of $\Delta G^{\ddagger}$ 16.5 kcal mol^{-1}. The value was calculated using the Eyring equation; see H. Guenther, H. Meier, and B. Zeeh, 'Spektroskopische Methoden in der organischen Chemie,' G. Thieme, Stuttgart, 1979, p. 144; H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 219. This calculated $\Delta G^{\ddagger}$-value is slightly greater than that calculated by Kolasa for *N*-formyl hydroxamic acids ($\Delta G^{\ddagger}$ 16.0 kcal mol^{-1}); T. Kolasa, *Tetrahedron*, 1983, **39**, 1753.

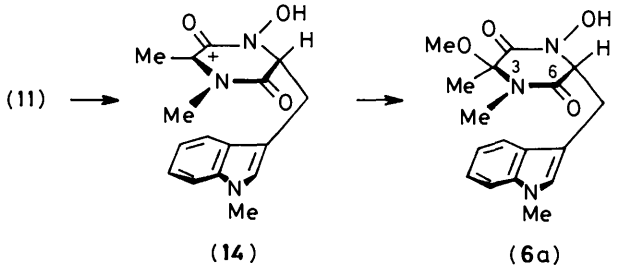
† In some cases the alcohol (**11**) was isolated as a minor product. This compound appeared to be a single stereoisomer by ^1H n.m.r. spectroscopy; structure (**11**)—having 6-H and the 3-Me in a *cis*-orientation—was assigned to this diastereoselectivity formed compound on account of the following considerations. On the basis of analogy it seems reasonable to assume that compound (**11**) has a folded conformation as discussed for derivative (**13**) (Scheme 4, *vide infra*). The δ-value observed for the 3-Me group of compound (**11**) (δ 1.48) indicates that the methyl group is not in the shielding zone of the indole nucleus (*vide infra*). Consequently, the 3-OH group is located in this zone and the 3-Me group is facing 6-H. The diastereoselectivity of this ring closure has been observed and rationalised before in related systems; see ref. 7.



Scheme 2.



Scheme 3.



Scheme 4.

The stereochemistry of compound (**6a**) was deduced from its ^{1}H n.m.r. spectrum. The C-3 methyl group experiences a strong shielding effect (δ 0.28). This indicates that in solution (**6a**) exists in a folded conformation,* the indole nucleus being positioned under the dioxopiperazine ring so as to shield the C-3 methyl group [see structure (**6a**) in Scheme 4]. Consequently, 6-H and the C-3 methoxy group are in a *cis* relationship. The diastereoselective formation of compound (**6a**) can be understood by the assumption that the intermediate carbonium ion (**14**) has one diastereotopic face shielded by the aromatic side-chain. Therefore, the incoming methoxy group is directed so as to face 6-H.†

Formation of C-6-*Functionalised Dioxopiperazines.*—Transposition of the *N*-hydroxy group in compounds (**6a**) or (**13**) into an α-functionality has to proceed by the intermediacy of an acylimine [*viz.* (**18**), Scheme 5]. Subsequent addition of a nucleophile leads to the desired α-functionalised dioxopiperazine.‡

We observed, however, that direct elimination of water in (**6a**) or (**13**) to yield the corresponding imine was not feasible. Therefore, compound (**13**) was converted into the tosyl derivative (**15**) by a standard procedure. However, treatment of the latter compound with a base (NaOMe) in the presence of methanol as an external nucleophile again did not yield the desired α-methoxydioxopiperazine (**20**) but gave back the hydroxamic acid (**13**). Obviously the nucleophile causes substitution of the tosylester; methyl toluene-*p*-sulphonate is formed in addition to compound (**13**). Treatment of compound (**15**) with a base in the absence of a nucleophile caused formation of the neoechinulin analogue (**19**).[4] Apparently, the intermediate acylimine is formed under these conditions but rearranges to the dioxopiperazine.

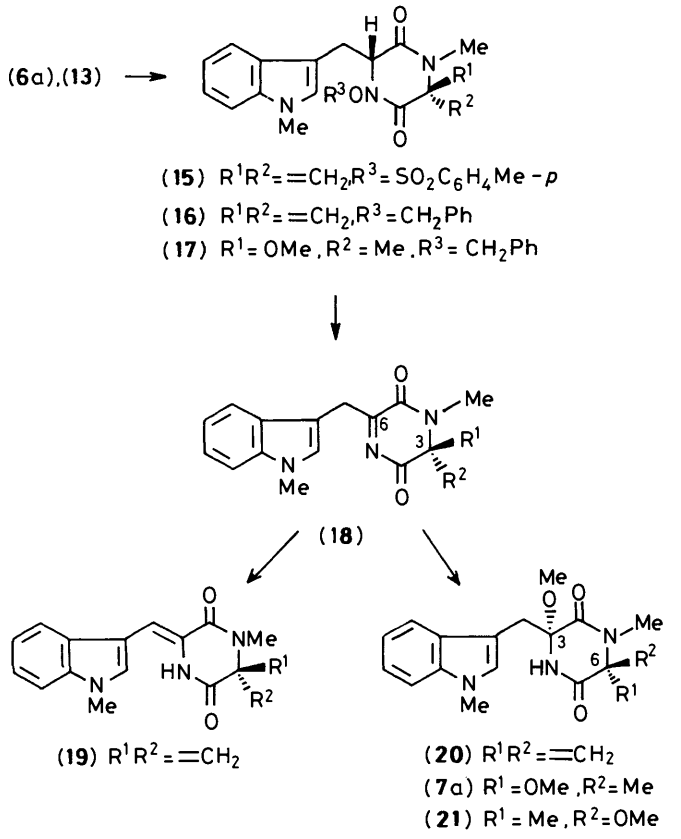
With these experiences we realised that it would be better if the *N*-hydroxy group of compound (**13**) were to be alkylated rather than acylated in order to get a useful intermediate for the transposition. Therefore, compound (**13**) was *O*-benzylated to give compound (**16**) in 81% yield. Treatment of the latter compound with Bu^{t}OK and trapping of the intermediate acylimine (**18**) with MeOH gave the desired 6-methoxydioxopiperazine (**20**) in 79% yield. In the same way component (**6a**) was converted (83%) into its *O*-benzylated derivative (**17**) and subsequently into a 5:3 mixture of the diastereoisomers (**7a**) and (**21**) (86% yield). Although the desired stereoisomer (**7a**) is the main product, it is formed only in 25% diastereoisomeric excess. This low stereoselectivity might be due to the unfolded conformation in which the intermediate (**18**) will exist because of the sp^2-hybridisation of C-6.

The stereochemical structure of product (**7a**) was confirmed by single-crystal *X*-ray analysis,[10] the result of which is depicted in the Figure. The centre of the C-6 methyl group of (**7a**) is positioned just above the centre of the indole moiety in the side-chain, the distance being 3.6 Å. This explains why in the ^{1}H n.m.r. spectra of compounds (**7a**) and (**21**) the 6-Me group (δ

* Derivatives of cyclic dipeptides, containing aromatic amino acid residues have been reported to exist preferentially in a folded form in which the aromatic ring faces the dioxopiperazine ring. Resonances of protons facing the aromatic side-chain were found to be shifted to higher field: P. G. Sammes in 'Fortschritte der Chemie organischer Naturstoffe,' eds. W. Herz, H. Grisebach, and G. W. Kirby, Springer, Wien, 1975, vol 32, p. 51 and references cited therein; I. J. Frigerio, I. D. Rae, and H. G. Wong, *Aust. J. Chem.*, 1982, **35**, 1609; T. Fukujama, S. Nakatsuka, and Y. Kishi, *Tetrahedron*, 1981, **37**, 2045.

† The same reasoning with the same outcome holds for a rotamer of compound (**14**) in which the dioxopiperazine ring is placed underneath the aromatic system. On the basis of analogy with the conformation of compound (**7a**), determined by *X*-ray analysis (*vide infra*), we are inclined, however, to speculate that (**14**) is the relevant rotamer.

‡ We employed this reaction previously for the construction of α-methoxy and dioxopiperazines; see *e.g.*, refs. 3 and 4.



Scheme 5.

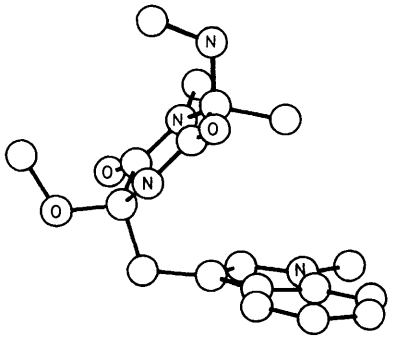


Figure. PLUTO Drawing of compound (7a)

0.51) and the 6-OMe group (δ 2.22) are strongly shielded. These observations support the assignment of structures (**11**) and (**6a**) discussed above. Attempts to prepare compound (**7a**) by exposure of compound (**20**) to an acid (CF_3CO_2H in CH_2Cl_2) in the presence of MeOH failed; only starting material (**20**) and compound (**19**) could be isolated.

Oxidative Ring Closure.—The oxidative ring closure (**7**) ⟶ (**8**) was studied using *N*-acetyltryptophan methylamide as a model compound. The following reagents were used: iodosobenzene diacetate,[5a] benzoyl peroxide,[5b] peracetic acid,[11] *N*-halogenosuccinimides,[12] and singlet oxygen.[13] In our hands a slight modification of Kametani's procedure[13] using singlet oxygen proved to be the method of choice. The modification involves the use of Methylene Blue[14] as a sensitiser, and a reaction temperature of −78 °C. Exposure of compound (**20**) to these reaction conditions and subsequent reduction of the hydroperoxide (**24**) ($R^1R^2 = CH_2$) with Me_2S at −78 °C gave the ring-closed isomers (**25**) (57%), (**26**) (19),* and the formylkynurenine derivative (**23**)[15] (7%) (Scheme 6). The relative stereochemistry of compounds (**25**) and (**26**) was assigned on the basis of the following considerations. A CPK model shows clearly that the C-11a methoxy group of compound (**26**) is shielded by the benzene ring. Consequently, structure (**26**) was assigned to the isomer showing a shielded C-11a methoxy group in its ^1H n.m.r. spectrum (δ 2.83); the δ-value of the other isomer [*i.e.* (**25**)] is considerably higher (δ 3.13). Salient features of the ^1H n.m.r. spectra are given in the Table.

Encouraged by this result we subjected compounds (**7a**) and (**21**) to the same reaction conditions. A mixture of two diastereoisomers, *viz.* (**8a**) (42%) and (**27**) (42%), was isolated from the *cis*-compound (**7a**); the *trans*-compound (**21**) yielded the isomers (**28**) (26%) and (**29**) (26%).* The stereochemical relationship between C-10b and C-11a was established using the same line of reasoning applied to compounds (**25**) and (**26**). Structures (**27**) and (**29**) were assigned to the isomers showing unusually low δ-values (δ 2.86 and 2.87, respectively) for the C-11a methoxy group in their ^1H n.m.r. spectra. The data from the Table invariably show small but significant differences in δ-values and some coupling constants of selected protons.†

In the series (**8a**) and (**27**)—(**29**), compound (**27**) seems to be the thermodynamically most stable one; compound (**8a**) was converted completely into (**27**) by treatment with H_2S in CH_2Cl_2 (*vide infra*). This conversion involves epimerisation of C-3 as well as C-11a.

Reactions of the Tetracyclic Indole Derivatives (**8a**) *and* (**25**)—(**29**).—For the conversion of compounds (**25**) and (**8a**) into the skeletons of the sporidesmins (**1a**—**c**) we attempted a reaction sequence previously developed for analogous transformations[3,7,16] (see Scheme 7). As yet we have not been able, however, to replace the C-11a methoxy group of (**25**) or (**8a**) by a sulphur nucleophile. The following attempts were made.

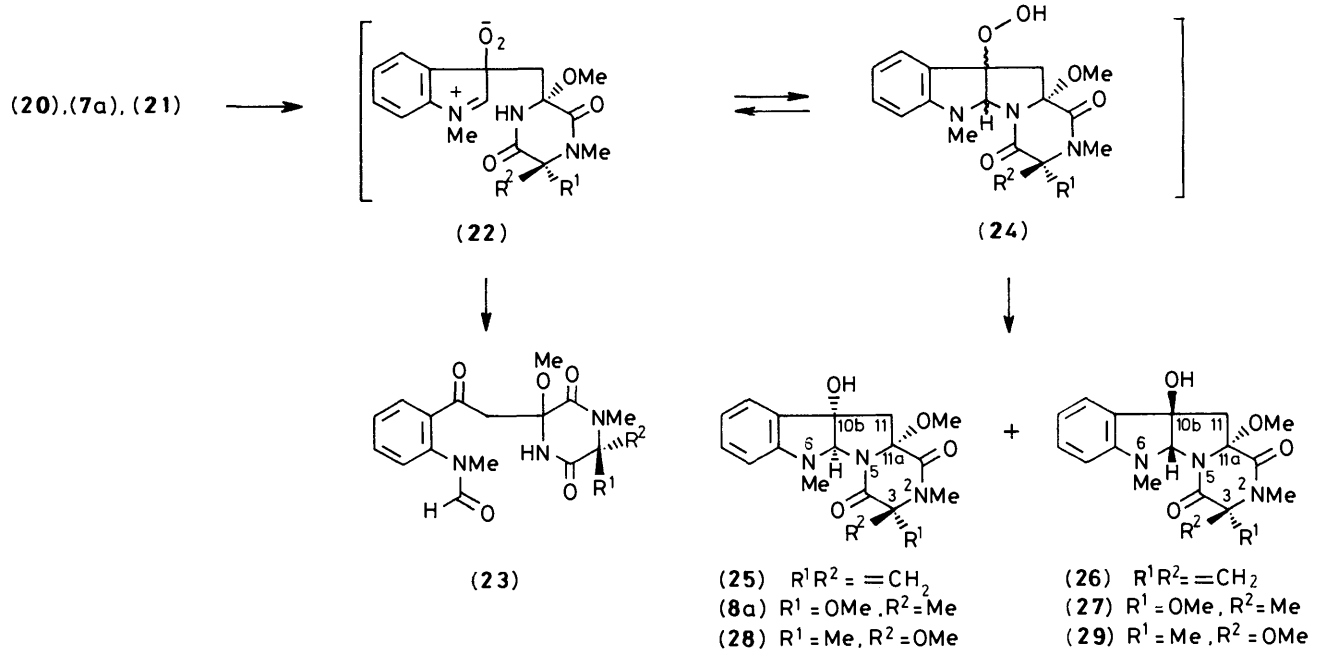
Treatment of compounds (**25**) or (**26**) with an excess of $ZnCl_2$ and H_2S gave quantitatively the aromatised derivative (**34**), the congener of a degradation product of the sporidesmins.[17] Under less acidic reaction conditions (H_2S in CH_2Cl_2) the dioxopiperazine (**35**) was isolated in 90% yield. Apparently, in order to avoid formation of a double bond between C-10b and C-5a employment of $ZnCl_2$ has to be avoided. The following experiment showed that formation of the C-11=C-11a double bond can be avoided when a proper nucleophile is used. Reaction of a mixture of (**25**) and (**26**) with H_2S in CH_2Cl_2–ethanol (90:10) gave compound (**36**) as the major product (80%). Obviously, the C-11a methoxy group is readily displaced by alcohols, but not by the softer nucleophile H_2S. We have no explanation for this observation as it turns out to be contrary to the successful conversion of the piperazinediones (**30**) and (**31**) into α-thio amino acid derivatives (Scheme 7). Compounds (**8a**) and (**27**) showed similiar behaviour. Treatment of compound

* These yields are based on converted starting material, of which considerable amounts (60—83%) were recovered in each experiment. Unfortunately, prolonged exposure of the starting compound to singlet oxygen under the reaction conditions used led invariably to lower yields of the desired product and an increased amount of by-product (**24**).

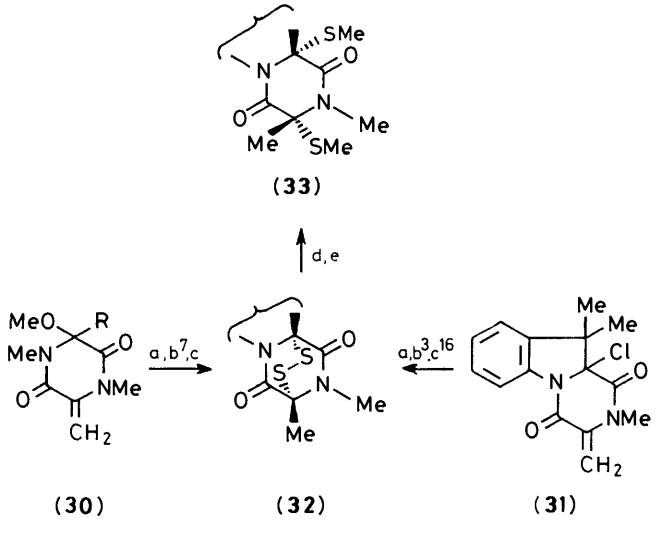
† Compounds having a *trans*-relationship between the 11a-OMe group and the 10b-OH group [i.e. (**26**), (**27**), (**29**)] show a larger δ-value and a smaller coupling constant for the 11-H_2 protons, a larger δ-value for the 5a-H protons, and a smaller value of $\Delta = |\delta(H_B) - \delta(H_A)|$ for the C-11 protons than for the corresponding isomers (**25**), (**8a**), and (**28**) respectively.

Table. Part of the ^{1}H n.m.r. spectra of some hexahydropyrazino[1′,2′:1,5]pyrrolo[2,3-*b*]indoles

	Relative stereochemistry					δ-Values 11-H_2						
Compd.	at C-3—C-11a	at C-10b—C-11a	5a-H	6-Me	2-Me	δ_B	δ_B	$\Delta(\delta_B - \delta_A)$	$^2J_{AB}$ (Hz)	11a-OR	3-OMe	3-Me
(25)		*cisoid*	5.50	3.29	3.20	2.93	2.37	0.56	14.7	3.13		
(26)		*transoid*	5.61	3.23	3.14	3.05	2.67	0.38	13.8	2.83		
(8a)	*cis*	*cisoid*	5.55	3.40	3.27	3.05	2.29	0.76	14.8	3.15	2.92	1.67
(27)	*cis*	*transoid*	5.63	3.23	3.12	3.14	2.48	0.66	13.9	2.86	2.95	1.70
(28)	*trans*	*cisoid*	5.55	3.34	3.15	2.96	2.35	0.61	14.8	3.10	2.92	1.67
(29)	*trans*	*transoid*	5.63	3.15	3.15	3.15	2.58	0.57	14.1	2.87	2.93	1.66
(36)		*transoid*	5.62	3.23	3.14	3.06	2.62	0.44	13.5	3.06 (q) 0.62 (t)		
(38)	?	*transoid*	5.62	3.16	3.07	3.15	2.65	0.50	14.4	2.94		1.85



Scheme 6.



Scheme 7. *Reagents*, etc.: a, H_2S, $ZnCl_2$; b, I_2, pyridine; c, resolution; d, $NaBH_4$; e, MeI

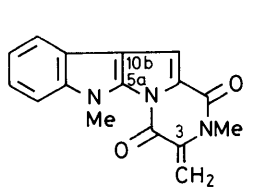
(**27**) with H_2S–EtSH gave (**37**) in 38% yield. Exposure of the same compound to H_2S and a trace of $ZnCl_2$ afforded (35%) the C-3,C-11a-functionalised dioxopiperazine (**38**).

Synthesis of Compound (**5b**).—Our approach to the key intermediate (**5b**) features a reaction of the properly substituted *N*-methylindole derivative (**2b**), prepared according to the literature method[18] with the transient nitroso olefin (**3**) used before in the synthesis of compound (**4a**)[4] (Scheme 1). Oxime (**4b**), prepared according to this procedure in 87% yield, was subjected to aminolysis and subsequently reduced using $Me_3N{\cdot}BH_3$ to give the required compound (**5b**) in 60% yield.

Conclusions

The synthesis of (**25**) and (**8a**) demonstrates the utility of *N*-hydroxytryptophan derivatives, *e.g.* (**5a**), in the synthesis of natural products featuring α-functionalised tryptophan derivatives. Through an oxidative ring closure—which might have biomimetic implications—we derived tetracyclic structures (**25**) and (**8a**), quite similar to the sporidesmins (**1a—c**).

Our approach provides these precursors in relatively few



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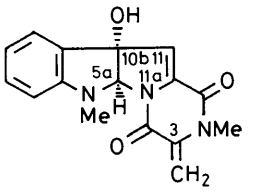

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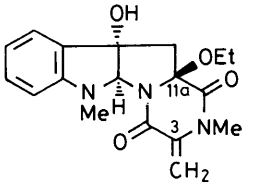

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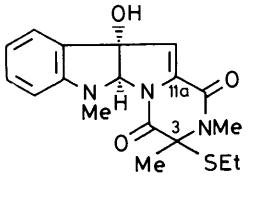

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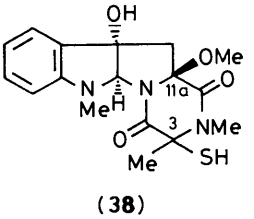

(38)

steps and in satisfactory overall yield. The methodology used seems sufficiently flexible to be adapted to the preparation of other α-functionalised amino acid derivatives. The transformation of compound (**8a**) into a sulphur-bridged dioxopiperazine—the structural feature of sporidesmin B (**1a**)—is currently under investigation. When this conversion can be accomplished, a total synthesis of compound (**1a**) will then be feasible by using the properly substituted *N*-hydroxytryptophan derivative (**5b**) prepared now from the indole (**2b**).

In addition, we are searching for an approach allowing functionalisation of the C-11 carbon of compound (**8**) [see *e.g.* structures (**1b**) and (**1c**)]. In this context we are reinvestigating the successful reaction (**7**) ⟶ (**8**) in order to achieve not only the oxidative ring closure but simultaneously the functionalisation of C-11.

Experimental

M.p.s were taken on a Koefler hot-stage (Leitz–Wetzlar) and are uncorrected. U.v. spectra were measured with a Perkin-Elmer spectrometer, Model 555. ^{1}H N.m.r. spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ-values relative to Me_4Si as internal standard unless stated otherwise. Mass spectra were obtained with a double-focussing Varian Associates SMI-B spectrometer. T.l.c. was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm) or reversed-phase (RP-8) F-254 S plates. Spots were visualised with a u.v. lamp, iodine vapour, cinnamaldehyde–HCl (for indole detection[19]), $AgNO_3$–Na_2CrO_7 (for the detection of sulphides[20]), or iron(III) chloride. Solvent systems used were as follows: sytem I: CH_2Cl_2–MeOH (9:1); system II: CH_2Cl_2–MeOH (93:7); system III: acetonitrile; system IV: CH_2Cl_2–MeOH (95:5). For flash column chromatography Merck silica gel H (type 60), and for preparative h.p.l.c. Merck silica gel (type 60), were used. Singlet oxygen oxygenations were carried out using a Philips G/92/2 400 W sodium lamp (strong emission between 550—700 nm). Methylene Blue was used as a sensitiser (strong absorption between 540—700 nm). The lamp and the 50 ml reaction tube were suspended in a silver-coated Dewar vessel which was filled with a filter solution (sodium dichromate; cut-off 520 nm) and kept at 25 °C by means of a thermostatted cooling system. A slow air flow was maintained to promote mixing of the filter solution. The reaction tube was kept at low temperatures using a Colora ultracryostat, model KT 90S. Hydrogen sulphide reactions were performed in a Fischer and Porter glass autoclave, suspended in a safety jacket.

Ethyl-β-(5-*Chloro*-6,7-*dimethoxy*-N-*methylindol*-3-*yl*)-α-(*hydroxyimino*)*propanoate* (**4b**).—A solution of ethyl β-bromo-α-(hydroxyimino)propanoate[4] (1.05 g, 5 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a stirred suspension of the indole (**2b**)[18] (3.38 g, 15 mmol) and Na_2CO_3 (15 mg, 10 mmol) in CH_2Cl_2 (20 ml) at room temperature under argon. The mixture was stirred for 16 h, then was filtered through a thin layer of silica gel 60 and concentrated to dryness. The residue was subjected to column chromatography (silica gel 60; eluant MeOH–CH_2Cl_2 2:98) to yield the *title compound* (**4b**) (1.5 g, 87%) as a foam which was homogeneous on t.l.c. R_F 0.40 (solvent system IV); $\lambda_{max.}$(MeOH) 226sh, 286, and 300 nm; $\lambda_{min.}$ 255 nm; EIMS (70 eV) *m/z* 354/356 ($[M]^+$, 100%), 339/341 ($[M - CH_3]^+$, 49), 337/339 ($[M - OH]^+$, 31), 264/268 ($C_{13}H_{13}ClN_2O_2]^+$, 15), 263/265 (24), and 238/240 ($[C_{12}H_{13}ClNO_2]^+$, 49) (Found: M^+, 354.0980. $C_{16}H_{19}ClN_2O_5$ requires *M*, 354.0982); δ_H (60 MHz; $CDCl_3$) 10.1 (br s, 1 H, NOH), 7.45 (s, 1 H, indole 4-H), 6.8 (s, 1 H, indole 2-H), 4.3 (q, 2 H, OCH_2Me), 4.0 (s, 3 H, NMe), 3.95 (s, 2 H, β-H_2), 3.9 (s, 6 H, 2 × OMe), and 1.3 (t, 3 H, OCH_2Me).

β-(5-*Chloro*-6,7-*dimethoxy*-N-*methylindol*-3-*yl*)-α-(*hydroxyamino*)-N-*methylpropanamide* (**5b**).—An aqueous solution of $MeNH_2$ (35 ml of a 35% solution) was added all at once to a stirred solution of ester (**4b**) (1.42 g, 4 mmol) in dioxane (10 ml) at room temperature under argon. The mixture was stirred at room temperature for 15 h. The solvents were then removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with 1M-HCl, dried over Na_2SO_4, and concentrated to dryness to yield the *methylamide oxime* (1.23 g, 91%) as a foam which was homogeneous on t.l.c. R_F 0.35, solvent system IV); $\lambda_{max.}$(MeOH) 228sh, 290, and 300sh nm; $\lambda_{min.}$ 270 nm; EIMS (70 eV) *m/z* 339/341 ($[M]^+$, 79%), 322/324 ($[M - OH]^+$, 100), 265/267 (79), 264/266 (51), and 238/240 ($[C_{12}H_{13}ClNO_2]^+$, 41) (Found: M^+, 339,0992. $C_{15}H_{18}ClN_3O_4$ requires *M*, 339,0986); δ_H (60 MHz; $CDCl_3$) 10 (br s, 1 H, NOH), 7.5 (s, 1 H, indole 4-H), 6.9 (s, 1 H, indole 2-H), 6.75 (br q), 1 H, N*H*Me), 4.05 (s, 2 H, β-H_2), and 3.95, 3.90, and 3.85 (3 × s, 9 H, 2 × OMe) and indole NMe), 2.8 (d, 3 H, NH*Me*).

Reduction of the oxime double bond was achieved as follows. A solution of HCl in ethanol (5 ml of a 7M solution) was added to a stirred solution of the methylamide oxime (340 mg, 1 mmol) and NMe_3·BH_3 (90 mg, 1.2 mmol) in ethanol (5 ml) at room temperature. The mixture was stirred for 16 h at room temperature, then was concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 and the solution was washed successively with water and brine, dried over Na_2SO_4, and filtered. Evaporation of the filtrate and subsequent flash column chromatography of the residue gave the *title amide* (**5b**) (2.25 mg, 66%) as a crystalline compound, m.p. 77—79 °C (from CH_2Cl_2–n-hexane) (Found: C, 52.6; H, 5.9; N, 12.2. $C_{15}H_{20}ClN_3O_4$ requires C, 52.71; H, 5.90; N, 12.29%) (R_F 0.30, solvent system IV); $\lambda_{max.}$(MeOH) 230, 285, and 300sh nm; $\lambda_{min.}$ 252 nm; CIMS (70 eV) *m/z* 341/343 ($[M]^+$, 7%), 323/325 ($[M - H_2O]^+$, 20), and 238/240 ($[C_{12}H_{13}ClNO_2]^+$, 100) (Found: M^+, 341.1139. $C_{15}H_{20}ClN_2O_4$ requires *M*, 341.1142); δ_H (90 MHz; $CDCl_3$) 7.34 (s, 1 H, indole

4-H), 6.82 (s, 1 H, indole 2-H), 6.65 (br q, 1 H, NHMe), 4.20 (br s, 2 H, NHOH), 3.99, 3.91, and 3.89 (3 s, 9 H, 2 × OMe and indole NMe), 3.70 (X part of ABX spectrum, $^3J_{AX}$ 5, $^3J_{BX}$ 10 Hz, 1 H, α-H), 3.10 and 2.85 (AB part of ABX spectrum, $^3J_{AX}$ 5, $^3J_{BX}$ 10, $^2J_{AB}$ 15 Hz, 2 H, β-H_2), and 2.83 (d, 3 H, NH*Me*).

trans-1-*Hydroxy*-3-*methoxy*-3,4-*dimethyl*-6-[(N-*methylindol*-3-*yl*)*methyl*]*piperazine*-2,5-*dione* (**6a**).—Pyruvoyl chloride[9] (700 mg, 6.6 mmol) was added dropwise to a vigorously stirred solution of compound (**5a**) (1.25 g, 5.1 mmol) in a mixture of diethyl ether (dry, 100 ml) and dichloromethane (dry, 150 ml) at room temperature. After the reaction mixture had been stirred for 30 min, methanol (dry, 15 ml) was added and the mixture was stirred for 25 h. Then dichloromethane (500 ml) was added and the mixture was washed three times with water and once with brine, and dried over Na_2SO_4. Evaporation of the solution under reduced pressure gave the *title piperazinedione* (**6a**) (1.35 g, 80%) (R_F 0.5, solvent system I); $\lambda_{max.}$(MeOH) 221, 273sh, 284, and 296sh nm; $\lambda_{min.}$ 250 nm; EIMS (70 eV) *m/z* 331 ($[M]^+$, 1%), 299 ($[C_{16}H_{17}N_3O_3]^+$, 2), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 331.1530. $C_{17}H_{21}N_3O_4$ requires *M*, 331.1532); δ_H (90 MHz; $CDCl_3$) 7.65—6.95 (m, 4 H, indole 4- to 7-H), 6.90 (s, 1 H, indole 2-H), 4.72 (X part of ABX spectrum, 1 H, $^3J_{AX} \simeq {}^3J_{BX} \simeq$ 3.3 Hz, 6-H), 3.69 (s, 3 H, indole NMe), 3.59 (AB part of ABX spectrum, 2 H, CH_2CH), 2.93 (s, 3 H, OMe), 2.54 (s, 3 H, piperazine NMe), and 0.28 (s, 3 H, 3-Me).

α-(N-*Hydroxy*-N-*pyruvoylamino*)-N-*methyl*-(N-*methylindol*-3-*yl*)*propanamide* (**9**).—Pyruvoyl chloride[9] (130 mg, 1.2 mmol) was added dropwise to a vigorously stirred solution of the hydroxylamine (**5a**) (250 mg, 1.0 mmol) in a mixture of diethyl ether (dry, 20 ml) and dichloromethane (dry, 30 ml) at room temperature. The mixture was stirred for 30 min. Then dichloromethane (100 ml) was added and the mixture was washed three times with water, then once with brine, and dried (Na_2SO_4). Evaporation of the solution under reduced pressure gave quantitatively the *pyruvic acid derivative* (**9**) (315 mg) which was crystallised from CH_2Cl_2–n-hexane, m.p. 121—122 °C; R_F 0.6 (solvent system I); $\lambda_{max.}$(MeOH) 222, 273sh, 285, and 296sh nm; $\lambda_{min.}$ 252 nm; CIMS (100 eV) *m/z* 318 ($[M]^+$, 43%), 300 ($[C_{16}H_{18}N_3O_3]^+$, 34), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 317.1373. $C_{16}H_{19}N_3O_4$ requires *M*, 317.1376); δ_H (90 MHz; $CDCl_3$; 27 °C) 7.7—7.0 (m, 4 H, indole 4- to 7-H), 6.97 (s, 0.33 H, indole 2-H), 6.88 (s, 0.67 H, indole 2-H), 6.32 (m, 0.67 H, NHMe), 5.74 (m, 0.33 H, NHMe), 5.23—5.05 (X part of ABX spectrum, 1 H, α-H), 3.76 (s, 3 H, indole NMe), 3.48—3.33 (AB part of ABX spectrum, 2 H, β-H_2), 2.92 (d, 2 H, $^3J_{AX}$ 5.0 Hz, NH*Me*), 2.65 (d, 1 H, $^3J_{AX}$ 4.7 Hz, NH*Me*), and 2.26 and 1.33 [2 s, ratio 1:2, 3 H, COMe of (**9**) (*cis*) and (**9**) (*trans*)]; δ_H {90 MHz; [$^2H_8$]toluene; internal standard toluene δ(Ph*Me*) 2.3; measurement at 75 °C, the coalescence temperature of the COMe signals} 7.7—7.0 (m, 4 H, indole 4- to 7-H), 6.75 (s, 1 H, indole 2-H), 5.77 (br m, 1 H, NHMe), 5.31 (X part of ABX spectrum, 1 H, α-H), 3.68—3.48 (AB part of ABX spectrum, 2 H, β-H_2), 3.35 (s, 3 H, indole NMe), 2.58 (d, 3 H, $^3J_{AX}$ 5 Hz, NH*Me*), and 1.89 (s, 3 H, COMe).

N-*Methyl*-β-(N-*methylindol*-3-*yl*)-α-(*pyruvoyloxyamino*)-*propanamide* (**10**).—To a cooled (−78 °C) and vigorously stirred solution of compound (**5a**) (250 mg, 1.0 mmol) and pyridine (80 mg, 1.0 mmol) in dichloromethane (dry, 20 ml) was added pyruvoyl chloride[9] dropwise (110 mg, 1.05 mmol). The mixture was stirred for 24 h at −78 °C, then was washed with 0.1M-HCl and dried (Na_2SO_4). Evaporation of the solvent afforded *compound* (**10**) (285 mg, 90%) as an oil which was homogeneous on t.l.c.: R_F 0.4 (solvent system I); $\lambda_{max.}$(MeOH) 223, 273sh, 285, and 296sh nm; $\lambda_{min.}$ 248 nm; EIMS (70 eV) *m/z* 317 ($[M]^+$, 1%), 299 ($[C_{16}H_{17}N_3O_3]^+$, 1), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 317.1372. $C_{16}H_{19}N_3O_4$ requires *M*, 317.1376); δ_H (90 MHz; $CDCl_3$; 27 °C) 7.65—7.0 (m, 4 H, indole 4- to 7-H), 6.97 (s, 1 H, indole 2-H), 6.68 (m, 1 H, NHMe), 4.07—3.90 (X part of ABX spectrum, 1 H, α-H), 3.74 (s, 3 H, indole NMe), 3.53—3.01 (AB part of ABX spectrum, 2 H, β-H_2), 2.80 (d, 3 H, $^3J_{AX}$ 5 Hz, NH*Me*), and 2.37 (s, 3 H, COMe).

1-*Hydroxy*-4-*methyl*-3-*methylene*-6-[(N-*methylindol*-3-*yl*)-*methyl*]*piperazine*-2,5-*dione* (**13**).—Pyruvoyl chloride[9] (131 mg, 1.2 mmol) was added dropwise to a vigorously stirred solution of compound (**5a**) (0.25 g, 1.0 mmol) in a mixture of diethyl ether (dry, 20 ml) and dichloromethane (dry, 30 ml). The mixture was stirred for 17 h, then dichloromethane (100 ml) was added. The mixture was washed three times with water and once with brine, and dried over Na_2SO_4. Evaporation of the mixture gave the title compound (**13**) (270 mg, 90%). Spectroscopic data were identical with those described before.[4]

cis-1,3-*Dihydroxy*-3,4-*dimethyl*-6-[(N-*methylindol*-3-*yl*)-*methyl*]*piperazine*-2,5-*dione* (**11**).—This *compound* was occasionally isolated as a minor product (~10%) during the synthesis of compound (**13**); R_F 0.45 (solvent system I); m.p. 180—181 °C (from CH_2Cl_2); $\lambda_{max.}$(MeOH) 221sh, 272sh, 285, and 297sh nm; $\lambda_{min.}$ 252 nm; CIMS (100 eV) *m/z* 318 ($[M + 1]^+$ 37%), 300 ($[C_{16}H_{18}N_3O_3]^+$, 20), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 317.1373. $C_{16}H_{19}N_3O_4$ requires *M*, 317.1376); δ_H (90 MHz; $CDCl_3$) 7.6—7.1 (m, 4 H, indole 4- to 7-H), 7.01 (s, 1 H, indole 2-H), 4.72 (X part of ABX spectrum, 1 H, $^3J_{AX} \simeq {}^3J_{BX} \simeq$ 3.4 Hz, 6-H), 3.73 (s, 3 H, indole NMe), 3.62—3.55 (AB part of ABX spectrum, 2 H, CH_2CH), 2.67 (s, 3 H, piperazine NMe), 1.48 (s, 3 H, 3-Me).

1-*Benzoyl*-4-*methyl*-3-*methylene*-6-[(N-*methylindol*-3-*yl*)-*methyl*]*piperazine*-2,5-*dione* (**16**).—Benzyl bromide (330 mg, 2.0 mmol) and subsequently potassium t-butoxide (190 mg, 1.74 mmol) were added to a stirred solution of compound (**13**) (520 mg, 1.74 mmol) in 1,2-dimethoxyethane (DME) (dry, 20 ml) at room temperature. After being stirred for 1 h at room temperature the reaction mixture was neutralised by addition of ammonium chloride (100 mg). The mixture was stirred for 17 h, after which the solvent was evaporated off. After addition of dichloromethane and filtration removal of the suspended salts, the filtrate was dried (Na_2SO_4), and concentrated under reduced pressure to give an oil, which consisted of compound (**16**) and unchanged benzyl bromide. Flash column chromatography (CH_2Cl_2–MeOH 99.5:0.5) gave compound (**16**) (550 mg, 81%) as an *oil*, which was homogeneous on t.l.c.: R_F 0.75 (solvent system II); $\lambda_{max.}$(MeOH) 220, 283, and 296sh nm; $\lambda_{min.}$ 278 nm; EIMS (70 eV) *m/z* 389 ($[M]^+$, 7%), 144 ($[C_{10}H_{10}N]^+$, 56), and 91 ($[C_7H_7]^+$, 100) (Found: M^+, 389.1742. $C_{23}H_{23}N_3O_3$ requires *M*, 389.1739); δ_H (90 MHz; $CDCl_3$) 7.5—6.9 (m, 4 H, indole 4- to 7-H), 7.45—7.36 (m, 5 H, Ph), 6.78 (s, 1 H, indole 2-H), 5.13 (B part of AB spectrum, 1 H, $^2J_{AB}$ 10.8 Hz, OCHHPh), 5.09 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.2 Hz, C=C$H_B$$H_A$), 4.93 (A part of AB spectrum, 1 H, $^2J_{AB}$ 10.8 Hz, OCHHPh), 4.32 (X part of ABX spectrum, 1 H, $^3J_{AX} \simeq {}^3J_{BX} \simeq$ 3.6 Hz, 6-H), 3.86 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.2 Hz, C=C$H_A$$H_B$), 3.77 (s, 3 H, indole NMe), 3.42—3.33 (AB part of ABX spectrum, 2 H, CH_2CH), and 2.46 (s, 3 H, piperazine NMe).

1-*Benzyloxy*-3-*methoxy*-3,4-*dimethyl*-6-[(N-*methylindol*-3-*yl*)*methyl*]*piperazine*-2,5-*dione* (**17**).—Benzyl bromide (70 mg, 0.41 mmol) and subsequently potassium t-butoxide (40 mg, 0.36 mmol) were added to a stirred solution of compound (**6a**) (120 mg, 0.36 mmol) in DME (dry, 10 ml) at room temperature. After being stirred for 45 min at room temperature the reaction

mixture was neutralised by addition of ammonium chloride (20 mg). The mixture was stirred for 17 h and then treated as described for the preparation of compound (**16**), to yield the *title product* (**17**) (125 mg, 83%), R_F 0.75 (solvent system II); $\lambda_{max.}$(MeOH) 219, 273sh, 285, and 296sh nm; $\lambda_{min.}$ 249 nm; EIMS (70 eV) *m/z* 421 ($[M]^+$, 36%), 389 ($[C_{23}H_{23}N_3O_3]^+$, 1), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 421.2010. $C_{24}H_{27}N_3O_4$ requires *M*, 421.2002); δ_H (90 MHz; $CDCl_3$) 7.5—7.0 (m, 4 H, indole 4- to 7-H and m, 5 H, Ph), 6.91 (s, 1 H, indole 2-H), 5.18 (B part of AB spectrum, 1 H, $^2J_{AB}$ 10.4 Hz, OC*H*HPh), 5.02 (A part of AB spectrum, 1 H, $^2J_{AB}$ 10.4 Hz, OCH*H*Ph), 4.38 (X part of ABX spectrum, 1 H, 6-H), 3.71 (s, 3 H, indole NMe), 3.52—3.42 (AB part of ABX spectrum, 2 H, CH_2CH), 2.85 (s, 3 H, OMe), 2.46 (s, 3 H, piperazine NMe), and 0.20 (s, 3 H, 3-Me).

3-*Methoxy*-1-*methyl*-6-*methylene*-3-[(N-*methylindol*-3-*yl*)-*methyl*]*piperazine*-2,5-*dione* (**20**).—To a stirred solution of compound (**16**) (1.14 g, 2.9 mmol) in methanol (dry, 150 ml) was added potassium t-butoxide (320 mg, 2.9 mmol) at room temperature. After being stirred for 4 days at room temperature the mixture was neutralised by addition of ammonium chloride (0.160 g). The mixture was then stirred for 17 h, after which the solvent was evaporated off under reduced pressure. Dichloromethane was added to the residue and the suspended salts were filtered off. The filtrate was concentrated to dryness to yield an oil, which consisted of compound (**20**) and benzyl alcohol. Column chromatography (CH_2Cl_2–MeOH, 98:2) gave *compound* (**20**) (735 mg, 81%), which was crystallised from CH_2Cl_2–n-hexane, m.p. 172—173 °C; R_F 0.35 (solvent system II); $\lambda_{max.}$(MeOH) 218, 225sh, 284, and 296sh nm; $\lambda_{min.}$ 281 nm; EIMS (70 eV) *m/z* 313 ($[M]^+$, 1%), 281 ($[C_{16}H_{15}N_3O_2]^+$, 10), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 313.1423. $C_{17}H_{19}N_3O_3$ requires *M*, 313.1426); δ_H (90 MHz; $CDCl_3$), 7.65—7.0 (m, 4 H, indole 4- to 7-H), 6.91 (s, 1 H, indole 2-H), 6.26 (m, 1 H, NH), 5.57 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C=CH_BH_A), 4.59 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C=CH_AH_B), 3.74 (s, 3 H, indole NMe), (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.5 Hz, indole 3-CH_AH_B), 3.35 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.5 Hz, indole 3-CH_AH_B), 3.27 (s, 3 H, OMe), and 2.98 (s, 3 H, piperazine NMe).

cis-3,6-*Dimethoxy*-1,6-*dimethyl*-3-[(N-*methylindol*-3-*yl*)-*methyl*]*piperazine*-2,5-*dione* (**7a**) *and* trans-3,6-*Dimethoxy*-1,6-*dimethyl*-3-[(N-*methylindol*-3-*yl*)*methyl*]*piperazine*-2,5-*dione* (**21**).—To a stirred solution of compound (**17**) (110 mg, 0.26 mmol) in methanol (dry, 15 ml) was added potassium t-butoxide (30 mg, 0.27 mmol) at room temperature. After being stirred for 6 days at room temperature the mixture was neutralised by addition of ammonium chloride (15 mg). The mixture was then stirred for 17 h at room temperature, after which it was treated as described for the preparation of compound (**20**). Column chromatography (CH_2Cl_2–MeOH 98:2) and recrystallisation from CH_2Cl_2–n-hexane gave compound (**7a**) (48 mg, 54%) and compound (**21**) (29 mg, 32%).

Compound (**7a**): R_F 0.25 (solvent system II), m.p. 179—180 °C (from CH_2Cl_2–n-hexane) (Found: C, 62.3; H, 6.75; N, 12.1. $C_{18}H_{23}N_3O_4$ requires C, 62.59; H, 6.71; N, 12.17%); $\lambda_{max.}$(MeOH) 200, 273sh, 284, and 296sh nm; $\lambda_{min.}$ 247 nm; CIMS (100 eV) *m/z* 345 ($[M]^+$, 4%), 314 ($[C_{17}H_{20}N_3O_3]^+$, 38), 282 ($[C_{16}H_{16}N_3O_2]^+$, 6), and 144 ($[C_{10}H_{10}N]^+$, 25) (Found: M^+, 345.1692. $C_{18}H_{23}N_3O_4$ requires *M*, 345.1689); δ_H (90 MHz; $CDCl_3$) 7.6—7.0 (m, 4 H, indole 4- to 7-H), 6.92 (s, 1 H, indole 2-H), 6.45 (s, 1 H, NH), 3.74 (s, 3 H, indole NMe), 3.65 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.0 Hz, CH_AH_B), 3.33 and 3.09 (2 s, 2 × 3 H, 3-OMe + 6-OMe), 3.09 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.0 Hz, CH_AH_B), 2.69 (s, 3 H, piperazine NMe), and 0.51 (s, 3 H, 6-Me).

Compound (**21**): R_F 0.3 (solvent system II), m.p. 174—176 °C (from CH_2Cl_2–n-hexane) (Found: C, 62.4; H, 6.6; N, 12.0); $\lambda_{max.}$(MeOH) 199, 273sh, 285, and 297sh nm; $\lambda_{min.}$ 247 nm; CIMS (100 eV) *m/z* 345 ($[M]^+$, 20%), 314 ($[C_{17}H_{20}N_3O_3]^+$, 100), 282 ($[C_{16}H_{16}N_3O_2]^+$, 29), and 144 ($[C_{10}H_{10}N]^+$, 100) (Found: M^+, 345.1695); δ_H (90 MHz; $CDCl_3$) 7.6—7.0 (m, 4 H, indole 4- to 7-H), 6.91 (s, 1 H, indole 2-H), 6.28 (s, 1 H, NH), 3.69 (s, 3 H, indole NMe), 3.54 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.4 Hz, CH_AH_B), 3.28 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.4 Hz, CH_AH_B), 3.24 (s, 3 H, 3-OMe), 2.82 (s, 3 H, piperazine NMe), 2.22 (s, 3 H, 6-OMe), 1.50 (s, 3 H, 6-Me).

cis-5a-cisoid-10b,11a-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-11a-*methoxy*-2,6-*dimethyl*-3-*methylenepyrazino*-[1′,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**25**), cis-5a-transoid-10b,11a-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-11a-*methoxy*-2,6-*dimethyl*-3-*methylenepyrazino*[1′,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4-(5aH)-*dione* (**26**), *and Kynurenine Derivative* (**23**).—A cooled (−70 °C) solution of compound (**20**) (500 mg, 1.60 mmol) and Methylene Blue (10 mg) in methanol (dry, 50 ml) was irradiated for 7 h under a slow stream of oxygen. Subsequently, the reaction mixture was quenched with dimethyl sulphide (5 ml) and stored at −20 °C for 17 h. The starch–potassium iodide test showed that all hydroperoxide had been reduced. After evaporation of the solvent the residue was subjected to preparative h.p.l.c. (MeOH–CH_2Cl_2 0.5:99.5 to give starting material (**20**) (60%) and products (**25**) (125 mg, 24%), (**26**) (42 mg, 8%), and (**23**) (38 mg, 7%) (based on converted starting material these yields are 57, 19, and 17%, respectively).

Compound (**25**) had R_F 0.6 (solvent system I); oil; $\lambda_{max.}$(MeOH) 243, 298sh, and 328 nm; $\lambda_{min.}$ 218, 288, and 324 nm; CIMS (100 eV) *m/z* 330 ($[M + 1]^+$, 17%), 312 ($[C_{17}H_{18}N_3O_3]^+$, 3), 298 ($[C_{16}H_{16}N_3O_3]^+$, 12), and 148 ($[C_9H_{10}NO]^+$, 15) (Found: M^+, 329.1377. $C_{17}H_{19}N_3O_4$ requires *M*, 329.1376); δ_H (90 MHz; $CDCl_3$) 7.3—6.5 (m, 4 H, 7- to 10-H), 5.92 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C=CH_B), 5.50 (s, 1 H, 5a-H), 5.06 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C=CH_A), 3.29 (s, 3 H, 6-Me), 3.20 (s, 3 H, 2-Me), 3.13 (s, 3 H, OMe), 2.93 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.7 Hz, 11-H_AH_B), and 2.37 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.7 Hz, 11-H_AH_B).

Compound (**26**) had R_F 0.4 (solvent system I); m.p. 150 °C (from CH_2Cl_2–n-hexane) (Found: C, 61.7; H, 5.8; N, 12.7. $C_{17}H_{19}N_3O_4$ requires C, 62.0; H, 5.81; N, 12.76%); $\lambda_{max.}$(MeOH) 246 and 305 nm; $\lambda_{min.}$ 226 and 283 nm; CIMS (100 eV) *m/z* 330 ($[M + 1]$, 43%), 312 ($[C_{17}H_{18}N_3O_3]^+$, 16), 298 ($[C_{16}H_{16}N_3O_3]^+$, and 146 ($[C_9H_8NO]^+$, 40) (Found: M^+, 329,1377); δ_H (90 MHz; $CDCl_3$), 7.3—6.4 (m, 4 H, 7- to 10-H), 5.73 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C–CH_AH_B), 5.61 (s, 1 H, 5a-H), 5.01 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.5 Hz, C=CH_AH_B), 3.23 (s, 3 H, 6-Me), 3.14 (s, 3 H, 2-Me), 3.05 (B part of AB spectrum, 1 H, $^2J_{AB}$ 13.8 Hz, 11-H_AH_B), 2.83 (s, 3 H, OMe), and 2.67 (A part of AB spectrum, 1 H, $^2J_{AB}$ 13.8 Hz, 11-H_AH_B).

Compound (**23**) had R_F 0.3 (solvent system I); oil; EIMS (70 eV) *m/z* 345 ($[M]^+$, 1%), 313 ($[C_{17}H_{15}N_3O_4]^+$, 16), 285 ($[C_{15}H_{15}N_3O_3]^+$, 100), and 162 ($[C_9H_8NO_2]^+$, 82); δ_H (90 MHz; $CDCl_3$) 8.03 (s, 1 H, MeNC*H*O), 7.7—7.1 (m, 4 H, C_6H_4), 5.87 (B part of AB spectrum, 1 H, C=CH_BH_A), 5.02 (A part of AB spectrum, 1 H, C=CH_AH_B), 3.91 (B part of AB spectrum, 1 H, $^2J_{AB}$ 18.0 Hz, COCH_AH_B), 3.55 (A part of AB spectrum, 1 H, $^2J_{AB}$ 18.0 Hz, COCH_AH_B), 3.53 (s, 0.55 H) and 3.36 (s, 4.55 H) (together *Me*NCHO), 3.30 (s, 3 H, NMe), and 3.20 (s, 3 H, OMe).

(3RS,5aRS,10bSR,11aRS)-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-3,11a-*dimethoxy*-2,3,6-*trimethylpyrazino*[1′,2′:1,5]-

pyrrolo[2,3-b]*indole*-1,4-(5aH)-*dione* (**8a**) *and* (3RS,5aSR,-10bRS,11aRS)-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-3,11a-*dimethoxy*-2,3,6-*trimethylpyrazino*[1′,2′:1,5]-*pyrrolo*-[2,3-b]*indole*-1,4(5aH)-*dione* (**27**).—A cooled (−70 °C) solution of compound (**7a**) (210 mg, 0.6 mmol) and Methylene Blue (5 mg) in methanol (dry, 50 ml) was irradiated for 6.5 h under a slow stream of oxygen. Subsequently, the reaction mixture was quenched with dimethyl sulphide (2 ml) and stored at −20 °C for 17 h, after which a starch–potassium iodide test showed that all hydroperoxide had been reduced. After evaporation of the solvent the residual oil was subjected to preparative h.p.l.c. (MeOH–CH_2Cl_2 1.5:98.5) to give starting material (**7a**) (83%) and products (**8a**) (15 mg, 7%) and (**27**) (15 mg, 7%) (based on converted starting material these yields are 42% each).

Compound (**8a**) was an oil, R_F 0.7 (solvent system I); $\lambda_{max.}$(MeOH) 243 and 297 nm; $\lambda_{min.}$ 221 and 271 nm; EIMS (70 eV) *m/z* 361 ($[M]^+$, 81%) and 147 ($[C_9H_9NO]^+$, 100) (Found: M^+, 361.1644. $C_{18}H_{23}N_3O_5$ requires *M*, 361.1638); δ_H (90 MHz; $CDCl_3$) 7.3—6.5 (m, 4 H, 7- to 10-H), 5.55 (s, 1 H, 5a-H), 3.40 (s, 3 H, 6-Me), 3.27 (s, 3 H, 2-Me), 3.15 (s, 3 H, 11a-OMe), 2.92 (s, 3 H, 3-OMe), 3.05 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.8 Hz, 11-H_BH_A), 2.29 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.8 Hz, 11-H_BH_A), and 1.67 (s, 3 H, 3-Me).

Compound (**23**) was an oil, R_F 0.6 (solvent system I); $\lambda_{max.}$ 249 and 308 nm; $\lambda_{min.}$ 225 and 272 nm; EIMS (70 eV) *m/z* 361 ($[M]^+$, 90%) and 147 ($[C_9H_9NO]^+$, 100) (Found: M^+, 361.1644); δ_H (90 MHz; $CDCl_3$) 7.3—6.4 (m, 4 H, 7- to 10-H), 5.63 (s, 1 H, 5a-H), 3.23 (s, 3 H, 6-Me), 3.12 (s, 3 H, 2-Me), 3.14 (B part of AB spectrum, 1 H, $^2J_{AB}$ 13.9 Hz, 11-H_AH_B), 2.95 (s, 3 H, 3-OMe), 2.86 (s, 3 H, 11a-OMe), 2.48 (A part of AB spectrum, 1 H, $^2J_{AB}$ 13.9 Hz, 11-H_AH_B) and 1.70 (s, 3 H, 3-Me).

(3RS,5aSR,10bRS,11aSR)-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-3,11a-*dimethoxy*-2,3,6-*trimethylpyrazino*[1′,2′:1,5]-*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**28**) *and* (3RS,5aRS,-10bSR,11aSR)-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-3,11a-*dimethoxy*-2,3,6-*trimethylpyrazino*[1′,2′:1,5]*pyrrolo*-[2,3-b]*indole*-1,4(5aH)-*dione* (**29**).—A cooled (−70 °C) solution of compound (**21**) (250 mg, 0.594 mmol) and Methylene Blue (5 mg) in methanol (dry, 50 ml) was irradiated for 17 h under a slow stream of oxygen. Subsequently, the reaction mixture was quenched with dimethyl sulphide (2 ml) and stored at −20 °C for 24 h, after which a starch-potassium iodide test showed that all hydroperoxide had been reduced. Evaporation of the solvent and subsequent preparative h.p.l.c. (MeOH–CH_2Cl_2 0.75:99.25) gave starting material (**21**) (60%) and products (**28**) (23 mg, 11%) and (**29**) (24 mg, 11%) (based on converted starting material these yields are 26% each).

Compound (**28**) was an oil, R_F 0.6 (solvent system I); $\lambda_{max.}$(MeOH) 243 and 297 nm; $\lambda_{min.}$ 223 and 269 nm; EIMS (70 eV) *m/z* 361 ($[M]^+$, 80%) and 147 ($[C_9H_9NO]^+$, 100) (Found: M^+, 361.1646); (90 MHz; $CDCl_3$) 7.3—6.5 (m, 4 H, 7- to 10-H), 5.55 (s, 1 H, 5a-H), 3.34 (s, 3 H, 6-Me), 3.15 (s, 3 H, 2-Me), 3.10 (s, 3 H, 11a-OMe) 2.97 (s, 1 H, OH), 2.96 (B part of AB spectrum, 1H, $^2J_{AB}$ 14.8 Hz, 11-CH_AH_B), 2.92 (s, 3 H, 3-OMe), 2.35 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.8 Hz, 11-H_AH_B), and 1.67 (s, 3 H, 3-Me).

Compound (**29**) was an oil, R_F 0.4 (solvent system I); $\lambda_{max.}$(MeOH) 248 and 304 nm; $\lambda_{min.}$ 228 and 272 nm; EIMS (70 eV) *m/z* 361 ($[M]^+$, 99%) and 147 ($[C_9H_9NO]^+$, 100) (Found: M^+, 361.1644); δ_H (90 MHz; $CDCl_3$) 7.3—6.4 (m, 4 H, 7- to 10-H), 5.63 (s, 1 H, 5a-H), 3.15 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.1 Hz, 11-H_AH_B), 3.15 (s, 3 H, 6-Me), 3.15 (s, 3 H, 2-Me), 2.93 (s, 3 H, 3-OMe), 2.87 (s, 3 H, 11a-OMe), 2.58 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.1 Hz, 11-H_AH_B), 2.38 (s, 1 H, OH), and 1.65 (s, 3 H, 3-Me).

2,3-*Dihydro*-2,6-*dimethyl*-3-*methylenepyrazino*[1′,2′:1,5]-*pyrrolo*[2,3-b]*indole*-1,4(6H)-*dione* (**34**).—An autoclave containing a mixture of compounds (**25**) and (**26**) (3:1; 0.10 g, 0.30 mmol) and zinc chloride (0.10 g, 0.7 mmol) in dichloromethane (dry, 20 ml) was cooled to −78 °C. Hydrogen sulphide (2 ml) was condensed by bubbling the gas through the cooled solution. Subsequently, the autoclave was closed and the reaction mixture was stirred for 16 h at room temperature. The autoclave was opened and the dichloromethane solution was filtered to give, quantitatively, crystalline *product* (**34**) (82 mg), which was recrystallised from chloroform, m.p. 261—263 °C; R_F 0.9 (solvent system I); $\lambda_{max.}$(MeOH) 248, 256sh, 286sh, 292, and 397 nm; $\lambda_{min.}$ 231, 264, and 336 nm; CIMS (100 eV) *m/z* 280 ($[M + 1]^+$, 3%) (Found: M^+, 279.1013. $C_{16}H_{13}N_3O_2$ requires *M*, 279.1008); δ_H (90 MHz; $CDCl_3$) 7.8—7.1 (m, 4 H, 7- to 10-H), 7.56 (s, 1 H, 11-H), 6.06 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.6 Hz, C=CH_BH_A), 5.18 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.6 Hz, C=CH_AH_B), 4.26 (s, 3 H, 6-Me), and 3.35 (s, 3 H, 2-Me).

cis-2,3,6,10b-*Tetrahydro*-10b-*hydroxy*-2,6-*dimethyl*-3-*methylpyrazino*[1′,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**35**).—An autoclave containing a mixture of compounds (**25**) and (**26**) (3:1; 50 mg, 0.15 mmol) in dichloromethane (dry, 20 ml) was cooled to −78 °C. Hydrogen sulphide (2 ml) was condensed by bubbling the gas through the cooled solution. Subsequently, the autoclave was closed and the reaction mixture was stirred for 2 days at room temperature. The autoclave was opened and the solvent was evaporated off under reduced pressure. The residual oil was subjected to preparative h.p.l.c. (MeOH–CH_2Cl_2 1:99) to give *compound* (**35**) (40 mg, 90%), which was crystallised from CH_2Cl_2–n-hexane, m.p. 190—195 °C; R_F 0.4 (solvent system II); $\lambda_{max.}$(MeOH) 244, 276, 286sh, and 340sh nm; $\lambda_{min.}$ 224 and 257 nm; CIMS (100 eV) *m/z* 298 ($[M + 1]^+$, 100%) and 280 ($[C_{16}H_{14}N_3O_2]^+$, 34) (Found: M^+, 279.1115. $C_{16}H_{15}N_3O_3$ requires *M*, 297.1113); δ_H (90 MHz; $CDCl_3$) 7.35—6.50 (m, 4 H, 7- to 10-H), 6.34 (s, 1 H, 11-H), 5.90 (s, 1 H, 5a-H), 5.88 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.6 Hz, C=CH_BH_A), 5.01 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.6 Hz, C=CH_AH_B), and 3.20 and 3.23 (2 s, 2 × 3 H, 2 × NMe).

cis-5a-transoid-10b,11a-11a-*Ethoxy*-2,3,6,10b,11,11a-*hexahydro*-11b-*hydroxy*-2,6-*dimethyl*-3-*methylenepyrazino*-[1′,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**36**).—An autoclave containing a mixture of compounds (**25**) and (**26**) (3:1; 100 mg, 0.30 mmol) in a mixture of dichloromethane and ethanol (dry, 20 ml: 9:1) was cooled to −78 °C. Hydrogen sulphide (4 ml) was condensed by bubbling the gas through the cooled solution. Subsequently, the autoclave was closed and the reaction mixture was stirred for 6 days at room temperature. The autclave was opened and the solvents were evaporated off under reduced pressure, to give *compound* (**36**) (82 mg, 80%) as an oil, R_F 0.55 (solvent system II); $\lambda_{max.}$(MeOH) 205, 244, 292sh, and 304 nm; $\lambda_{min.}$ 224 and 280 nm; EIMS (70 eV) *m/z* 343 ($[M]^+$, 27%) and 147 ($[C_9H_9NO]^+$, 100) (Found: M^+, 343.1528. $C_{18}H_{21}N_3O_4$ requires *M*, 343.1532); δ_H (90 MHz; $CDCl_3$) 7.3—6.3 (m, 4 H, 7- to 10-H), 5.85 (B part of AB spectrum, 1 H, $^2J_{AB}$ 1.2 Hz, C=CH_BH_A), 5.62 (s, 1 H, 5a-H), 5.01 (A part of AB spectrum, 1 H, $^2J_{AB}$ 1.2 Hz, C=CH_AH_B), 3.23 (s, 3 H, 6-Me), 3.14 (s, 3 H, 2-Me), 3.06 (q, 2 H, ^3J 7 Hz, OCH_2), 3.06 (B part of AB spectrum, 1 H, $^2J_{AB}$ 13.5 Hz, 11-H_BH_A), 2.84 (s, 1 H, OH), 2.62 (A part of AB spectrum, 1 H, $^2J_{AB}$ 13.5 Hz, 11-H_BH_A), and 0.62 (t, 3 H, ^3J 7 Hz, OCH_2Me).

cis-3-*Ethylthio*-2,3,6,10b-*tetrahydro*-10b-*hydroxy*-2,3,6-*trimethylpyrazino*[1′,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**37**).—An autoclave containing a solution of compound (**27**) (30 mg, 0.1 mmol) in a mixture of dichloromethane and ethanethiol (20 ml; 9:1) was cooled to −78 °C. Hydrogen sulphide (2 ml) was condensed by bubbling the gas through the cooled solution. Subsequently, the autoclave was closed and the

reaction mixture was stirred for 8 days at room temperature. The autoclave was opened and the solvents were evaporated off under reduced pressure. The residual oil was subjected to preparative h.p.l.c. ($MeOH–CH_2Cl_2$ 1:99) to yield *compound* (**37**) (10 mg, 30%) as an oil which was homogeneous on t.l.c., R_F 0.6 (solvent system I); $\lambda_{max.}$(MeOH) 240, 254sh, 317, and 328sh nm; $\lambda_{min.}$ 220 and 295 nm; EIMS (70 eV) *m/z* 359 ($[M]^+$, 14%), 298 ($[C_{16}H_{16}N_3O_3]^+$, 38), and 147 ($[C_9H_9NO]^+$, 42) (Found: M^+, 359.1303. $C_{18}H_{21}N_3O_3S$ requires *M*, 359.1304); δ_H (90 MHz; $CDCl_3$) 7.30—6.40 (m, 4 H, 7- to 10-H), 6.27 (s, 1 H, 11-H), 5.85 (s, 1 H, 5a-H), 3.20 and 3.14 (2 s, 2 × 3 H, 2 × NMe), 2.51 (q, 2 H, ^3J 7.5 Hz, SCH_2Me), 1.90 (s, 3 H, 3-Me), and 1.21 (t, ^3J 7.5 Hz, 3 H, SCH_2Me).

cis-5a-transoid-10b,11a-2,3,6,10b,11,11a-*Hexahydro*-10b-*hydroxy*-3-*mercapto*-11a-*methoxy*-2,3,6-*trimethylpyrazino*-[1,2′:1,5]*pyrrolo*[2,3-b]*indole*-1,4(5aH)-*dione* (**38**).—An autoclave containing a mixture of compound of (**27**) (30 mg, 0.1 mmol) and zinc chloride (1 mg) in dichloromethane (dry, 20 ml) was cooled to −78 °C. Hydrogen sulphide (2 ml) was condensed by bubbling the gas through the cooled solution. Subsequently, the autoclave was closed and the reaction mixture was stirred for 24 h at room temperature. The autoclave was opened and the solution was filtered. Then the solvent was evaporated off under reduced pressure. The residual oil was subjected to preparative h.p.l.c. ($MeOH–CH_2Cl_2$ 0.5:99.5) to yield compound (**38**) (10 mg, 35%) and a small amount of compound (**34**). *Compound* (**38**) was an oil, R_F 0.55 (solvent system I); $\lambda_{max.}$(MeOH) 223sh, 247, 270sh, and 312 nm; $\lambda_{min.}$ 253 and 292 nm; EIMS (70 eV) *m/z* 363 ($[M]^+$, 15%), 331 ($[C_{16}H_{17}N_3O_3S]^+$, 7), 298 ($[C_{16}H_{16}N_3O_3]^+$, 3), and 146 ($[C_9H_8NO]^+$, 40) (Found: M^+ 363.1260. $C_{17}H_{21}N_3O_4S$ requires *M*, 363.1253); δ_H (90 MHz; $CDCl_3$) 7.30—6.40 (m, 4 H, 7- to 10-H), 5.62 (s, 1 H, 5a-H), 3.63 (d, 1 H, ^4J 0.9 Hz, SH), 3.16 (s, 3 H, 6-Me), 3.07 (s, 3 H, 2-Me), 3.15 (B part of AB spectrum, 1 H, $^2J_{AB}$ 14.4 Hz, 11-H_BH_A), 2.94 (s, 3 H, OMe), 2.65 (A part of AB spectrum, 1 H, $^2J_{AB}$ 14.4 Hz, 11-H_BH_A), and 1.85 (d, 3 H, ^4J 0.9 Hz, 3-Me).

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