Conversion of N-Hydroxytryptophans into α,β-Dehydrotryptophan. An Approach to the Neoechinulin Series

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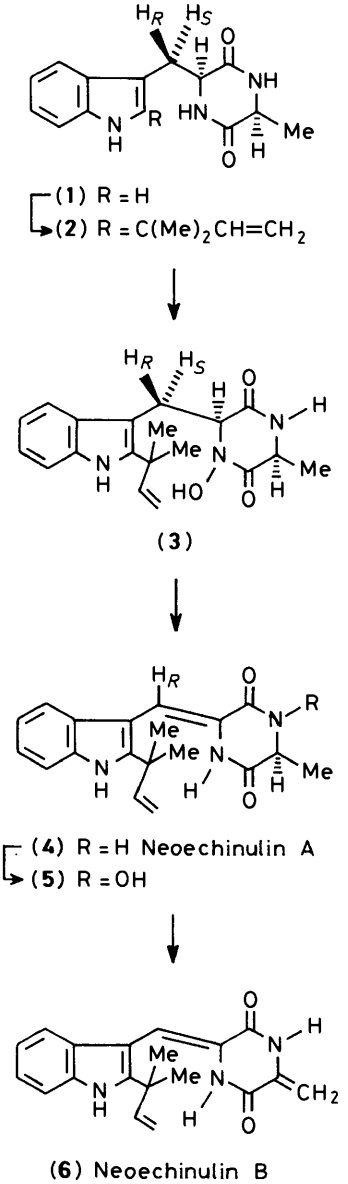
Reaction of the *N*-hydroxytryptophan derivative (**21b**) with pyruvoyl chloride gives access to the *N*-hydroxydioxopiperazine (**28b**). *O*-Tosylation of the latter compound, followed by base treatment, affords the dioxopiperazine (**30b**), an *N*(1)-allyl derivative of the fungal metabolite neoechinulin B (**6**). The biogenetic relevance of this reaction sequence is discussed.

The neoechinulins have been isolated from *Aspergillus amstelodami* and related fungi.[1] Two representatives of this rapidly growing class of fungal metabolites are neoechinulin A (**4**) and B (**6**)[1] (Scheme 1). They are characterised by the presence of non-protein amino acids as structural elements.



Scheme 1.

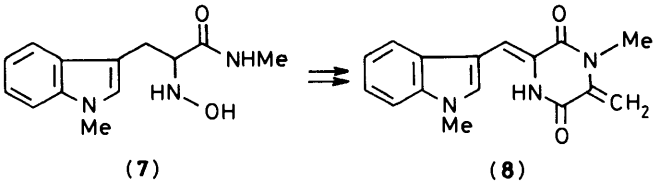
Neoechinulin A can be regarded as a condensation product of an alanine derivative and an α,β-dehydrotryptophan derivative having an isoprenyl group at C(2) of the indole nucleus. In neoechinulin B the presence of two α,β-dehydroamino acid moieties can be recognised.

The structural similarity of all neoechinulins has led to considerable speculation on their biosynthesis. Cyclo(-L-Ala-L-Trp-) (**1**) has been shown to be an efficient precursor,[2] and further labelling studies have demonstrated that during the formal α,β-desaturation of L-tryptophan the *pro*-(*S*)-hydrogen atom of compound (**2**) is removed stereospecifically.[3] More details concerning the nature of this desaturation remain obscure, however.

Recently, we suggested a mechanism for the formation of α,β-dehydroamino acids from amino acids by invoking the intermediacy of *N*-hydroxyamino acids. With this hypothesis in mind, the biosynthesis of the neoechinulins might be as depicted in Scheme 1. Tryptophan–alanine anhydride (**1**) is prenylated at C(2) of the indole nucleus to yield pre-echinulin (**2**), one of the naturally occurring co-metabolites.[4] Oxidation of compound (**2**) gives the *N*-hydroxy(dioxo)piperazine (**3**) which, after dehydration and isomerisation, yields neoechinulin A (**4**). Simultaneously with or subsequently to the oxidation of the tryptophan moiety, the second amino acid is oxidised to give compound (**5**), which is converted into neoechinulin B (**6**).

We reasoned that the proposed role of *N*-hydroxyamino acid derivatives (**3**) and (**5**) in the biosynthetic conversion of amino acid derivatives into α,β-dehydroamino acid derivatives might be more probable if the latter could be obtained chemosynthetically by starting from compound (**3**) or a derivative thereof.†

To study the viability of our approach we previously prepared the didehydrocyclodipeptide (**8**) from the hydroxylamine (**7**)[5] (Scheme 2). Despite the low yield and the

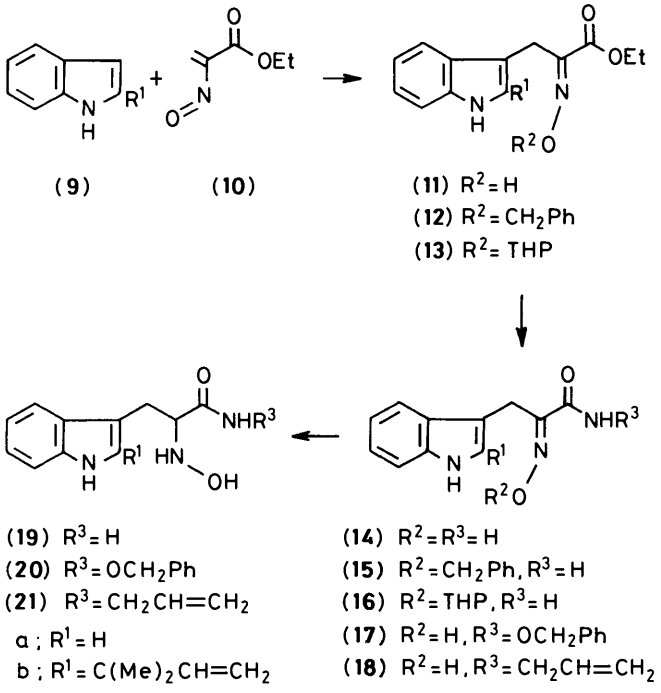


Scheme 2.

† Our postulate has been strengthened lately by the following findings. Recently, astechrome has been isolated, a natural product having *N*-hydroxytryptophan as a characteristic structural element: K. Arai, S. Sato, S. Shimizu, K. Nitta, and Y. Yamamoto, *Chem. Pharm. Bull.*, 1981, **29**, 1510. Moreover *N*-hydroxytryptophan plays a role as biosynthetic intermediate in the formation of glucosinolates: B. L. Møller, in 'Cyanide in Biology,' eds. B. Vennesland, E. E. Conn, C. J. Knowles, and J. Westley, Academic Press, London, 1981, p. 197; S. Mahadevan, *Ann. Plant Physiol.*, 1973, **24**, 69.

considerable difference between the structure (**8**) and that of the target molecule (**6**) this result gave impetus to the repetition of the sequence of reactions aimed at the total synthesis of neoechinulin B (**6**). The results of this study are reported here.[6]

N-*Hydroxytryptophan Amides* (**19b**) *and* (**21b**).—Reaction of an excess of the indole (**9b**)[7] with the nitroso olefin (**10**)—prepared *in situ*[5] from ethyl β-bromo-α-(hydroxyimino)-propanoate—gave the adduct (**11b**) in 80% yield[8] (Scheme 3).



Scheme 3.

In this reaction the indole (**9b**) was used in five-fold excess to suppress, as much as possible, the formation of the diadduct (**22**). This 2:1 adduct is formed invariably as a side-product[5] in the addition reaction. The oxime (**11b**) was obtained as a single isomer. It seemed reasonable to assume that the pathway to this oxime, starting with the cycloaddition of (**9b**) and (**10**), will afford the *E*-isomer. However, for reasons outlined below unambiguous proof of this structure was required. Therefore a single-crystal *X*-ray structure determination of oxime (**11b**) was performed,[9] the result of which is depicted in the Figure. It confirms that the compound formed is the *E*-isomer (**11b**).[10]

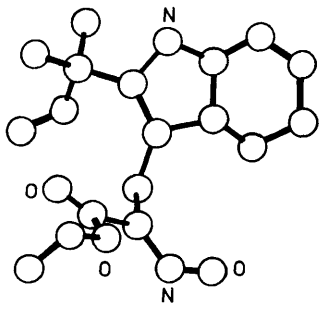
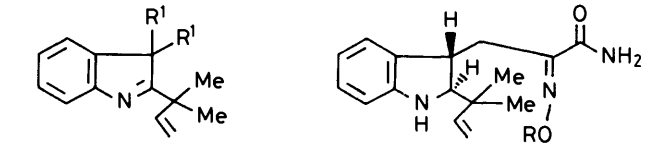


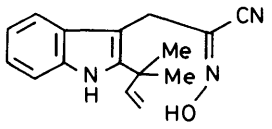
Figure. Pluto drawing of (**11b**)

Subsequently we studied the conversion of the oxime ester (**11b**) into an *N*-hydroxyamino amide, *e.g.* (**19b**). This was required as we had planned to apply the known pyruvoyl chloride reaction[11] for the construction of the dioxopiperazine ring of compound (**6**) (*vide infra*).

However, aminolysis of (**11b**) using conventional reagents (*i.e.* aqueous ammonia, ammonia–methanol, ammonia–sodium methanolate–methanol, and sodium amide–diglyme) failed to give the desired amide (**14b**). As this failure surprised us, we first secured unequivocally the structure of compound (**11b**) by *X*-ray analysis (*vide supra*). Consequently, we reasoned that the failure to prepare the amide might be due to the presence of the oxime OH group. This was indeed found to be the case; treatment of the benzyl oxime (**12b**)—prepared from (**11b**) by reaction with benzyl bromide and a base—with ammonia–methanol gave the amide (**15b**) in 93% yield.

Unfortunately, selective reduction of the oxime double bond of (**15b**) could not be achieved. Treatment with trimethylamine (TMA)–borohydride in the presence of ethanolic hydrogen chloride[5] gave the 2,3-dihydroindole derivative (**24**). Apparently, the presence of the *O*-benzyl group hampers the reduction of the oxime double bond. So we decided to remove the protecting group of the oxime hydroxy function prior to reduction.





(25)

Accordingly, the sequence of reactions (**13b**) ⟶ (**16b**) ⟶ (**14b**) ⟶ (**19b**) was studied. Aminolysis of the THP ether ester (**13b**) with ammonia–MeOH gave the amide (**16b**), which was deprotected to give amide (**14b**) in 51% overall yield. Finally, reduction of the oxime double bond of compound (**14b**) with trimethylamine–borohydride gave the desired *N*-hydroxy-tryptophan derivative (**19b**) in 56% yield.*

Subsequently, we were able to show that protection of the oxime hydroxy group of (**11b**) is not a prerequisite for its conversion into (**14b**). Two methods were found that allow direct conversion of (**11b**) into (**14b**). One procedure uses rhodium trichloride as a catalyst[12] in the reaction of ester (**11b**) with ammonia–MeOH. It gave amide (**14b**) in 66% yield, but completion of the conversion required five weeks. The method of choice was found to be aminolysis of (**11b**) using $ClAlMeNH_3$[13,14] at 50 °C in benzene to yield amide (**14b**) in 74% yield.†

* The rather low yield of this reduction is due to the formation of the 2,3-dihydroindole derivative (**23**) as a side-product.

† Using this reagent the formation of (**14b**) was always accompanied with the formation of the nitrile (**25**) in up to 20% yield. This conversion of the amide (**14b**) into the nitrile (**25**) might be of general applicability.

For reasons outlined below we also prepared the derivatives (**20a**) and (**21b**) using this procedure. So, reaction of (**11a**) with benzylhydroxylamine hydrochloride and trimethylaluminium gave (**17a**) in 70% yield. Similarly, reaction of (**11b**) with allylamino(dimethyl)aluminium—prepared from trimethylaluminium and allylamine[14,*],—at room temperature gave the allyl amide (**18b**) in 90% yield. Reduction of compounds (**17a**) and (**18b**) with trimethylamine–borohydride gave the hydroxylamines (**20a**) (73%) and (**21b**) (84%), respectively.†

Formation of the Dioxopiperazine.—We thought that two particular reactions, run consecutively, might create the dioxopiperazine ring system. The condensation of amide (**19b**) with pyruvoyl chloride[15] and subsequent ring closure[5] [(**19b**) ⟶ (**26b**) ⟶ (**27b**), Scheme 4] should introduce the dehydroalanine moiety present in (**6**). The transposition of the *N*-hydroxy group in compound (**27b**) into an α,β-dehydrotryptophan moiety might then be achieved by treatment of compound (**27b**), or better an *O*-activated derivative, with a base to yield neoechtnulin B (**6**).

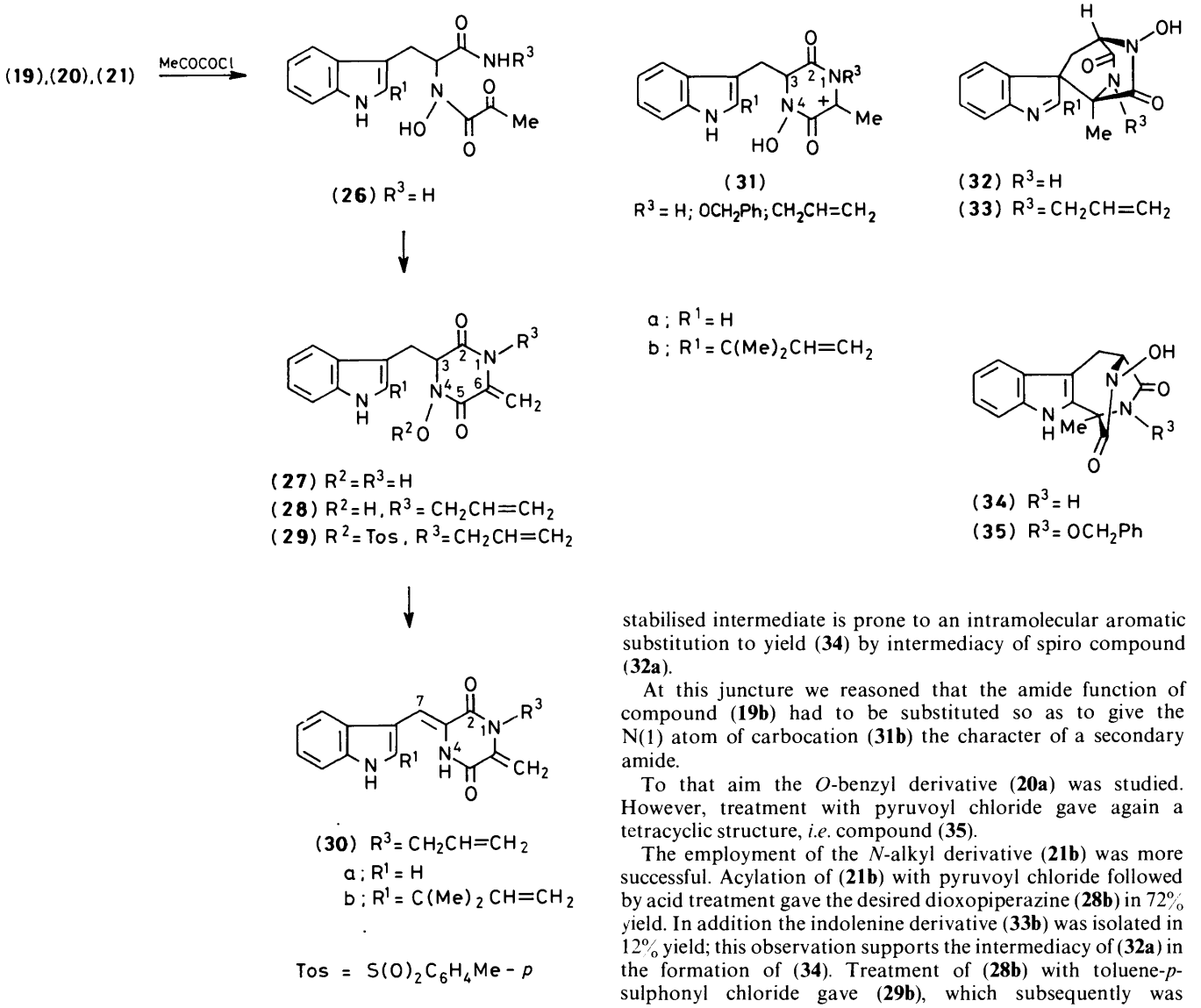
Puyruvoyl chloride[15] and amide (**19b**) did indeed react to give compound (**26b**). However, attempts to perform the subsequent, acid-catalysed ring closure to give (**27b**) failed. This was surprising, as we have employed a similar reaction, using *N*-methyl carboxamides, for the construction of other dioxopiperazines.[5] This failure cannot be attributed to the presence of the isoprenyl group at the indole C(2) carbon atom; reaction of amide (**19a**) with pyruvoyl chloride gave not the expected product (**27a**) but the tetracyclic indole derivative (**34**).

An explanation of this undesired reaction can be found in the stability of the intermediate carbocation (**31a**). This resonance-stabilised intermediate is prone to an intramolecular aromatic substitution to yield (**34**) by intermediacy of spiro compound (**32a**).

At this juncture we reasoned that the amide function of compound (**19b**) had to be substituted so as to give the N(1) atom of carbocation (**31b**) the character of a secondary amide.

To that aim the *O*-benzyl derivative (**20a**) was studied. However, treatment with pyruvoyl chloride gave again a tetracyclic structure, *i.e.* compound (**35**).

The employment of the *N*-alkyl derivative (**21b**) was more successful. Acylation of (**21b**) with pyruvoyl chloride followed by acid treatment gave the desired dioxopiperazine (**28b**) in 72% yield. In addition the indolenine derivative (**33b**) was isolated in 12% yield; this observation supports the intermediacy of (**32a**) in the formation of (**34**). Treatment of (**28b**) with toluene-*p*-sulphonyl chloride gave (**29b**), which subsequently was converted into (**30b**) (72% yield) by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The stereochemistry of product (**30b**) was deduced from its ^{1}H n.m.r. spectrum. The C(7) proton experiences a deshielding effect (δ 7.35), due to the C(2) carbonyl group. Consequently, structure (**30b**) having a *Z*-geometry can be assigned to the product resulting from the



Scheme 4.

* See footnote † on p. 2474.

‡ No reduction of the indole C(2)=C(3) double bond [*cf.* (**14b**) ⟶ (**19b**) + (**23**)] was observed.

elimination reaction.* We have no rationale for the stereoselectivity of the conversion of (**29b**) into (**30b**).

We expected that the remaining reaction—*i.e.* removal of the N(1)-protection group of (**30b**)—would occur readily; the allyl group has been used in several examples *e.g.* in the synthesis of biotin.[16] Deprotection was then achieved by isomerisation into the corresponding allylamide by treatment with a rhodium catalyst, followed by hydrolysis. As yet we have not been able, however, to remove the *N*-protecting group from compound (**30b**). Treatment with rhodium trichloride or Wilkinson's catalyst in aqueous alcoholic solution caused decomposition of the starting material. We assume that this failure has to be ascribed to similar side-reactions as observed with the natural product.[17]

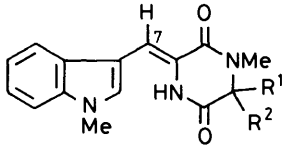
No attempts have been made to design an alternative route to neochinulin B (**6**) employing another protecting group for N(1). We feel, however, that the three-step synthesis of *N*-allylneoechinulin B (**30b**) from the *N*-hydroxytryptophan derivative (**21b**) demonstrates the utility of *N*-hydroxyamino acids in natural-product syntheses. The sequence of reactions (**21b**) ⟶ (**28b**) ⟶ (**30b**) might be of biogenetic relevance; it resembles the proposed biosynthesis of compound (**6**) (Scheme 1).

Experimental

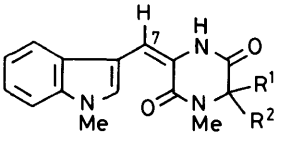
M.p.s were taken on a Koefler hot-stage (Leitz–Wetzlar) and are uncorrected. U.v. spectra were measured with a Perkin-Elmer spectrometer, Model 555. ^{1}H Nuclear magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ-values relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a double-focussing VG 7070E spectrometer. T.l.c. was carried out on Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualised with a u.v. hand lamp, iodine vapour, Cl_2–TDM,[18] or cinnamaldehyde–HCl (for indole detection †).

Ethyl (E)-β-[2-(α,α-*Dimethylallyl*)*indol*-3-*yl*-α-(*hydroxyimino*)]*propanoate* (**11b**) *and diadduct* (**22**).—A solution of ethyl β-bromo-α-(hydroxyimino)propanoate[2] (16.7 mmol, 3.50 g) in CH_2Cl_2 (75 ml) was added dropwise to a stirred suspension of the indole (**9b**) (35 mmol, 6.50 g) and Na_2CO_3 (70 mmol, 7.5 g) in CH_2Cl_2 (75 ml) at room temperature under argon. The mixture was stirred at room temperature for a further 16 h, then was filtered through a layer (~1 cm) of silica gel 60, and the filtrate was concentrated to dryness. The residue was subjected to column chromatography (silica gel 60 H; MeOH–CH_2Cl_2 1:99) to yield the title product (**11b**) (4.20 g, 80%), adduct (**22**) (0.68 g; 18.5%), and excess of starting indole (**9b**).

* Neoechinulin B analogues (**36a**) (*Z*) (ref. 8) and (**36b**) (*Z*) isomerise in polar solvents. The two isomers can be distinguished by ^{1}H n.m.r. spectroscopic analysis of the C(7) proton signals: (**36a**) (*Z*) δ 7.30, (**36a**) (*E*) δ 6.86, (**36b**) (*Z*) δ 7.28, (**36b**) (*E*) δ 6.65.



(**36**) (*Z*)



(**36**) (*E*)

a; R^1 R^2 = CH_2
b; R^1, R^2 = OMe, Me

† Anfaerbereagentien fuer die Papier- und Duennschicht-chromatographie Fa. Merck, Darmstadt, F.R.G., 1970.

Compound (**11b**) was recrystallised from CH_2Cl_2–*n*-hexane, m.p. 86—88 °C (Found: C, 66.5; H, 6.85; N, 8.5. $C_{18}H_{22}N_2O_3 \cdot \frac{1}{6}CH_2Cl_2$ requires C, 66.42; H, 6.85; N, 8.53%); R_F 0.30 (MeOH–CH_2Cl_2 4:96; $\lambda_{max.}$(MeOH) 288sh, 280, and 222 nm; $\lambda_{min.}$ 248 nm. CIMS *m/z* 315 ($[M + 1]^+$, 100%), 247 (14), and 198 ($[C_{14}H_{16}N]^+$, 32) (Found: $[M + H]^+$, 315.1712. $C_{18}H_{23}N_2O_3$ requires *m/z* 315.1709); δ_H (90 MHz; $CDCl_3$) 9.2 (br s, 1 H, NOH), 8.90 (s, 1 H, indole NH), 7.60—6.90 (m, 4 H, indole CH), 6.19 (dd, $^3J_{trans}$ 17.6, J_{cis} 10.5 Hz, 1 H, C*H*=CH_2), 5.19 and 5.16 (2 dd, $^3J_{trans}$ 17.6, $^3J_{cis}$ 10.5, $^2J_{gem}$ 1.2 Hz, 2 H, CH=CH_2), 4.21 (s, 2 H, indole 3-CH_2), 4.14 (q, 2 H, OCH_2Me), 1.58 (s, 6 H, CMe_2), and 1.12 (t, 3 H, OCH_2*Me*). The *E*-configuration of the oxime was confirmed by single-crystal *X*-ray crystallography.

Compound (**22**) was crystallised from EtOAc–n-hexane, m.p. 165—167 °C (Found: C, 56.9; H, 6.1; N, 8.3. $C_{23}H_{29}N_3O_6 \cdot \frac{2}{3}CH_2Cl_2$ requires C, 56.85; H, 6.11; N, 8.40%); R_F 0.25 (MeOH–CH_2Cl_2 4:96; $\lambda_{max.}$(MeOH) 210 nm; EIMS *m/z* 443 ($[M]^+$, 5%), 358 (6), and 314 (100). Found: M^+, 443.2053. $C_{23}H_{29}N_3O_6$ requires *M*, 443.2056); δ_H (90 MHz; $CDCl_3$) 9.0 (br s, 2 H, 2 NOH), 7.20—6.70 (m, 4 H, indolenine H), 6.44 (dd, $^3J_{trans}$ 17.6, $^3J_{cis}$ 10.5 Hz, 1 H, C*H*=CH_2), 5.18 and 5.08 (2 dd, $^3J_{trans}$ 17.6, $^3J_{cis}$ 10.5, $^2J_{gem}$ 1.2 Hz, 2 H, CH=CH_2), 4.1 (m, 4 H, OCH_2Me), 3.2 and 3.0 (dd, $^2J_{AB}$ 16 Hz, 4 H, indolenine 3-CH_2), 1.43 (s, 6 H, CMe_2), and 1.22 (t, 6 H, OCH_2*Me*).

Ethyl (E)-α-(*Benzyloxyimino*)-β-[2-(α,α-*dimethylallyl*)*indol*-3-*yl*]*propanoate* (**12b**).—To a solution of the oxime (**11b**) (0.8 mmol, 0.25 g) and potassium t-butoxide (1 mmol, 0.11 g) in 1,2-dimethoxyethane (DME) (15 ml) was added a solution of benzyl bromide (1.1 mmol, 0.19 g) in DME (5 ml) under argon at room temperature. The mixture was stirred for a further 6 h at room temperature. Then the solvent was removed under reduced pressure. A solution of the residue in CH_2Cl_2 was washed successively with 1M HCl and brine, and subsequently dried over Na_2SO_4. The residue obtained by evaporation of the solvent was subjected to column chromatography (silica gel 60 H; CH_2Cl_2) to give the *O*-benzyl oxime (**12b**) (0.28 g, 87%) as an oil, which was homogeneous on t.l.c.: R_F 0.7 (CH_2Cl_2 1:99); $\lambda_{max.}$(MeOH) 288, 280, and 222 nm; $\lambda_{min.}$ 252 nm; EIMS (70 eV) *m/z* 404 ($[M]^+$, 2%), 223 (50), 198 ($[C_{14}H_{16}N]^+$, 80), and 91 (100); δ_H (60 MHz; $CDCl_3$) 7.8 (br s, 1 H, indole NH), 7.4—6.8 (m, 4 H, indole CH), 7.2 (s, 5 H, Ph), 6.0 (dd, 1 H, C*H*=CH_2), 5.25 (s, 2 H, CH_2Ph), 5.1 and 4.9 (2 dd, 2 H, CH=CH_2), 4.1 (s, 2 H, indole 3-CH_2), 4.0 (q, 2 H, OCH_2Me), 1.5 (s, 6 H, CMe_2), and 1.0 (t, 3 H, OCH_2Me).

(E)-β-[2-(α,α-*Dimethylallyl*)*indol*-3-*yl*]-α-(*hydroxyimino*)-*propanamide* (**14b**).—*Procedure A. Ethyl* (E)-β-[2-(α,α-*dimethylallyl*)*indol*-3-*yl*]-α-(*tetrahydropyran*-2-*yloxyimino*)*propanoate* (**13b**). A solution of compound (**11b**) (2 mmol, 630 mg) and dihydropyran DHP, (7 mmol, 590 mg) in dry dioxane (25 ml) was acidified with toluene-*p*-sulphonic acid (0.1 mmol, 20 mg). After being stirred at room temperature for 4 days the solution was neutralised with Et_3N. Subsequently, the solution was concentrated under reduced pressure and CH_2Cl_2 (50 ml) was added. The resulting solution was washed successively with 5% aqueous $NaHCO_3$ and brine. Drying (Na_2SO_4), followed by evaporation of the solvent, gave compound (**13b**) as an oil, which was used in the synthesis of the amide (**16b**) without further purification.

(E)-β-[2-(α,α-*Dimethylallyl*)*indol*-3-*yl*]-α-(*tetrahydropyran*-2-*yloxyimino*)*propanamide* (**16b**). To a stirred solution of crude ester (**13b**) (800 mg, 2 mmol) in MeOH (25 ml), saturated with NH_3, was added sodium in small portions (a total of 50 mg). After the mixture had been stirred for 18 h at room temperature under argon all starting material had been consumed. The solution was neutralised with EtOH–HCl (1M) and evaporated

to give the amide (**16b**) as an oil, which was used in the synthesis of the target compound (**14b**) without further purification.

To a solution of the crude product (**16b**) (700 mg, 1.9 mmol) in EtOH (5 ml) was added EtOH–HCl (7M) (3 ml). After the mixture had been stirred for 3 days the *O*-protecting group of compound (**16b**) had been removed completely. The solution was neutralised with $NaHCO_3$, and evaporated. A solution of the residue in CH_2Cl_2 was washed with brine and dried over Na_2SO_4. Evaporation of the solvent, and column chromatography of the residue, gave the *title compound* (**14b**) [295 mg, 52% calc. on (**11b**) as the starting material].

Compound (**14b**) was recrystallised from CH_2Cl_2–*n*-hexane, m.p. 84—87 °C; $\lambda_{max.}$(MeOH) 292sh, 280, and 222 nm; $\lambda_{min.}$ 248 nm; EIMS *m/z* 285 ($[M]^+$, 10%), 268 ($[M - OH]^+$, 11), 251 (4), 216 ($[M - C_5H_9]^+$, 14), 198 ($[C_{14}H_{16}N]^+$, 10), 182 (70), and 169 (100%) (Found: M^+, 285.1472. $C_{16}H_{19}N_3O_2$ requires *M*, 285.1477); δ_H (90 MHz; $CDCl_3$) 8.1 (br s, 1 H, NOH), 7.9 (br s, 1 H, indole NH), 7.55—6.90 (m, 4 H, indole CH), 6.4 and 5.2 (2 br 5, 2 H, $CONH_2$), 6.21 (dd, $^3J_{trans}$ 17.4, $^3J_{cis}$ 10.5 Hz, 1 H, CH=CH_2), 5.26 and 5.22 (2 dd, $^3J_{trans}$ 17.4, $^3J_{cis}$ 10.5 $^2J_{gem}$ 1.2 Hz, CH=CH_2), 4.20 (s, 2 H, indole 3-CH_2), and 1.67 (s, 6 H, CMe_2).

Procedure B. In a glove-box under nitrogen a 2.0M solution of trimethylaluminium in hexane (Aldrich Chemical Co.) (23 ml, 45 mmol) was slowly added to a suspension of NH_4Cl (45 mmol, 2.4 g) in dry benzene (25 ml) at room temperature. The mixture was stirred at room temperature for 45 min. Then a solution of ester (**11b**) (5 mmol, 1.57 g) in dry benzene (25 ml) was added slowly and the mixture was kept at 50 °C under nitrogen for 48 h. The reaction was carefully quenched with dil. HCl (10 ml) and the reaction mixture was extracted in turn with EtOAc (2 × 20 ml) and CH_2Cl_2 (2 × 20 ml). The combined layers were dried (Na_2SO_4), and concentrated to dryness, and the residue was subjected to flash column chromatography (Merck Silica gel 60; MeOH–CH_2Cl_2 2:98) to yield the amide (**14b**) (1.05 g, 74%), R_F 0.33 (MeOH–CH_2Cl_2 7:93) and the *propanonitrile* (**25**) (0.27 g, 20%), R_F 0.58 (MeOH–CH_2Cl_2 2:93).

Compound (**25**) was recrystallised from CH_2Cl_2–n-hexane, m.p. 126—128 °C (Found: C, 71.9; H, 6.4; N, 15.6. $C_{16}H_{17}N_3O$ requires C, 71.89; H, 6.41; N, 15.72%); $\nu_{max.}$($CHCl_3$) 2 220 cm^{-1} (C≡N); $\lambda_{max.}$(MeOH) 288sh, 280, and 222 nm; $\lambda_{min.}$ 246 nm; EIMS *m/z* 268 ($[M]^+$, 100%) and 198 ($[C_{14}H_{16}N]^+$, 16). (Found: $[M + H]^+$, 268.1457. $C_{16}H_{18}N_3O$ requires *m/z*, 268.1450); δ_H (90 MHz; $CDCl_3$) 10.1 (br s, 1 H, NOH), 9.1 (br s, 1 H, indole NH), 7.40—7.00 (m, 4 H, indole H), 6.15 (dd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 10.3 Hz, 1 H, CH=CH_2), 5.25 and 5.15 (2 dd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 10.3, $^2J_{gem}$ 1.2 Hz, 2 H, CH=CH_2), 4.06 (s, 2 H, indole 3-CH_2), and 1.54 (s, 6 H, CMe_2).

(E)-α-(*Benzyloxyimino*)-β-[2-(α,α-*dimethylallyl*)*indol*-3-*yl*]-*propanamide* (**15b**).—To a solution of ester (**12b**) (8 mmol, 3.22 g) in methanol (30 ml)—saturated at 0 °C with NH_3—was added sodium (100 mg) in small portions. After the mixture had been stirred for 24 h the methanol was evaporated off. A solution of the residue in CH_2Cl_2 (50 ml) was washed with HCl (1M), dried over Na_2SO_4, and concentrated to dryness. Column chromatography of the residue (silica gel 60 H; CH_2Cl_2) *compound* (**15b**) gave (2.98 g, 93%) as a foam, which was homogeneous on t.l.c. (Found: C, 73.4; H, 6.85; N, 11.2. $C_{23}H_{25}N_3O_2$ requires C, 73.57; H, 6.71; N, 11.19%); R_F 0.2 (CH_2Cl_2); $\lambda_{max.}$(MeOH) 288sh, 280, 220 nm; $\lambda_{min.}$ 253 nm; EIMS (70 eV) *m/z* 375 ($[M]^+$, 58%), 306 ($[M - C_5H_9]^+$, 17), 268 ($[M - C_7H_7O]^+$, 100), 223 (52), 198 ($[C_{14}H_{16}N]^+$, 29), 182 (39), and 169 (33) (Found: M^+, 375.1937. $C_{23}H_{25}N_3O_2$ requires 375.1947); δ_H (90 MHz; $CDCl_3$) 7.9 (br s, 1 H, indole NH), 7.45—6.82 (m, 9 H, indole H and Ph), 6.5 and 5.2 (2 br s, 2 H, $CONH_2$), 6.14 (dd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 10.3 Hz, 1 H, CH=CH_2), 5.29 (s, 2 H, CH_2Ph), 5.15 and 5.08 (2 dd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 10.3, $^2J_{gem}$ 1 Hz, 2 H, CH=CH_2), 4.16 (s, 2 H, indole 3-CH_2), and 1.53 (s, 6 H, CMe_2).

N-*Benzyloxy*-α-(*hydroxyimino*)-β-(*indol*-3-*yl*)*propanamide* (**17a**).—*Procedure A.* Aqueous NaOH (5 ml) was added to a solution of ester (**11a**) (10 mmol, 2.46 g) in MeOH–tetrahydrofuran: (40 ml; 1:1). After the mixture had been stirred for 16 h at room temperature the organic solvents were evaporated off, water was added, and the solution was neutralised by addition of 4M-HCl (5 ml). Extraction with ethyl acetate and crystallisation from aq. MeOH gave the corresponding *acid* (2.1 g, 96%), m.p. 163—165 °C (decomp.); $\lambda_{max.}$(MeOH) 289sh, 280, 273sh, and 223 nm; $\lambda_{min.}$ 245 nm; EIMS (70 eV) *m/z* 218 ($[M]^+$, 17%), 201 ($[M - OH]^+$, 6), 156 ($[C_{10}H_8N_2]^+$, 73), 155 (100), and 130 ($[C_9H_8N]^+$, 81). (Found: M^+, 218.0686. $C_{11}H_{10}N_2O_3$ requires *M*, 218.0691); δ_H (60 MHz; $CDCl_3$–CD_3OD) 7.9—7.0 (m, 5 H, indole CH), and 4.1 (s, 1 H, indole 3-CH_2).

To a stirred solution of the hydroxyimino acid (5 mmol, 1.1 g) and *O*-benzylhydroxylamine (5 mmol, 620 mg) in acetonitrile (dry; 50 ml) were added *N*,*N*′-dicyclohexylcarbodi-imide (5 mmol, 1.03 g,) and *N*-hydroxybenzotriazole (0.5 mmol, 75 mg). After the mixture had been stirred for 16 h at room temperature under argon, the acetonitrile was removed under reduced pressure and CH_2Cl_2 was added. The organic layer was washed successively with 5% aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated to dryness. Flash column chromatography of the residue (silica gel 60; MeOH–CH_2Cl_2 2:98) and recrystallisation (aq. MeOH) gave the *title compound* (**17a**) (1.23 g, 76%), m.p. 194—197 °C (decomp.) (Found: C, 66.6; H, 5.3; N, 12.9. $C_{18}H_{17}N_3O_3$ requires C, 66.86; H, 5.30; N, 13.00%); $\lambda_{max.}$(MeOH) 289sh, 280, and 219 nm; $\lambda_{min.}$ 248 nm; EIMS (70 eV) *m/z* 323 ($[M]^+$, 13%), 306 ($[M - OH]^+$, 29), 156 ($[C_{10}H_8N_2]^+$, 26), 155 (39), 130 ($[C_9H_8N]^+$, 53), and 91 ($[C_7H_7]^+$, 100) (Found: M^+, 323.1266. $C_{18}H_{17}N_3O_3$ requires *M*, 323.1270); δ_H (60 MHz; CD_3OD) 7.9—7.0 (m, 5 H, indole CH), 7.25 (s, 5 H, Ph), 4.7 (s, 2 H, CH_2Ph), and 4.0 (s, 2 H, indole 3-CH_2).

Procedure B. The reagent prepared from benzylhydroxylamine·HCl (10 mmol, 1.60 g) and a 2.0M solution of $AlMe_3$ in n-hexane (5 ml, 10 mmol) was added to a stirred solution of compound (**11a**) (5 mmol, 1.23 g) in acetonitrile (dry, 25 ml). The mixture was stirred for 2 days at 50 °C under argon. Then was cooled, quenched with 4M-HCl (3 ml), and filtered, and the filtrate was extracted with ethyl acetate. The combined extracts were washed successively with 1M-HCl and brine, dried (Na_2SO_4), and filtered, and the solvent was evaporated off. Recrystallisation from MeOH–n-hexane gave the amide (**17a**) (1.13 g, 70%).

(E)-N-*Allyl*-β-[2-(α,α-*Dimethylallyl*)*indol*-3-*yl*]-α-(*hydroxyimino*)*propanamide* (**18b**).—In a glove-box under nitrogen a 2.0M-solution of trimethylaluminium in n-hexane (5 ml, 10 mmol) was added carefully to a stirred solution of allylamine (10 mmol, 0.57 g) in CH_2Cl_2 (10 ml). The mixture was stirred for 30 min, after which a solution of ester (**11b**) (5.5 mmol, 1.73 g) was added carefully and the mixture was continued for a further 3 h at 35 °C. Subsequently the reaction mixture was carefully quenched with aqueous 1M-HCl (2 ml) and extracted with CH_2Cl_2 (3 ×). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated off. The residue was crystallised from CH_2Cl_2–n-hexane to give the *title amide* (**18b**) (1.61 g, 90%), R_F 0.40 (MeOH–CH_2Cl_2 4:96); m.p. 142—143 °C (Found: C, 69.2; H, 7.1; N, 12.7. $C_{19}H_{23}N_3O_2$ requires C, 70.13; H, 7.12; N, 12.91%); $\lambda_{max.}$(MeOH) 290sh, 280, and 222 nm; $\lambda_{min.}$ 248 nm; EIMS (70 eV) *m/z* 325 ($[M]^+$, 75%), 308 ($[M - OH]^+$, 100), 256 ($[M - C_5H_9]^+$, 52), 223 (35), 198 ($[C_{14}H_{16}N]^+$, 50),

and 130 ($[C_9H_8N]^+$, 24). (Found: M^+, 325.1799. $C_{19}H_{23}N_3O_2$ requires M, 325.1790); δ_H (90 MHz; $CDCl_3$) 9.0 (br s, 1 H, NOH), 7.9 (br s, 1 H, indole NH), 7.6—6.9 (m, 4 H, indole CH), 6.6 (br t, 1 H, CONH), 6.20 (dd, $^3J_{trans}$ 18.0, $^3J_{cis}$ 10.5 Hz, 1 H (Me_2CH=CH_2), 5.70 (m, 1 H, CH_2CH=CH_2), 5.30—4.80 (m, 4 H, 2 × CH=CH_2), 4.23 (s, 2 H, indole 3-CH_2), 3.80 (t, 2 H, CH_2CH=CH_2), and 1.58 (s, 6 H, CMe_2).

α-(*Hydroxyamino*)-β-(*indol*-3-*yl*)*propanamide* (**19a**).—A solution of HCl in ethanol (5 ml of a 7M solution) was added dropwise to a stirred solution of amide (**14a**) (1 mmol, 0.22 g) and TMA·BH_3 (1.2 mmol, 90 mg) in ethanol (5 ml) at room temperature. The mixture was stirred at room temperature for a further 18 h, neutralised with $NaHCO_3$, and concentrated to dryness under reduced pressure. Flash column chromatography of the residue (silica gel 60; MeOH–CH_2Cl_2 5:95) and subsequent crystallisation from CH_2Cl_2–n-hexane gave the *title product* (**19a**) (0.15 g, 68%), m.p. 160—162 °C (Found: C, 59.8; H, 6.0; N, 19.2. $C_{11}H_{13}N_3O_2$ requires C, 60.25; H, 5.99; N, 19.17%); $\lambda_{max.}$(MeOH) 289, 280, 273, and 219 nm; $\lambda_{min.}$ 286, 274, and 242 nm; EIMS (70 eV) m/z 219 ($[M]^+$, 9%), 201 ($[M - H_2O]^+$, 8), 186 ($[M - NHOH]^+$, 14), and 130 ($[C_9H_8N]^+$, 100) (Found: M^+, 219.1016. $C_{11}H_{13}N_3O_2$ requires M, 219.1008); δ_H (90 MHz; CD_3OD) 7.65—6.88 (m, 4 H, indole 4-to 7-H), 7.10 (s, 1 H, indole 2-H), 3.70 (X part of ABX spectrum, 1 H, $^3J_{AX}$ 5.4, $^3J_{BX}$ 8.4 Hz, α-H), 3.16 and 2.90 (AB part of ABX spectrum, 1 H, $^2J_{AB}$ 14.1, $^3J_{AX}$ 5.4, $^2J_{BX}$ 8.4 Hz, β-H_2).

β-[2-(α,α-*Dimethylallyl*)*indol*-3-*yl*]-α-(*hydroxyamino*)-*propanamide* (**19b**) *and* (E)-2,3(trans-β-[2-(α,α-*Dimethylallyl*)-*indolin*-3-*yl*]-α-(*hydroxyimino*)*propanamide* (**23**).—A solution of HCl in ethanol (15 ml of a 7M solution) was added dropwise to a stirred solution of amide (**14b**) (3.75 mmol, 1.07 g) and TMA·BH_3 (9.6 mmol, 0.70 g) in ethanol (15 ml) at room temperature. The mixture was stirred at room temperature for 24 h neutralised with $NaHCO_3$, and then concentrated to dryness under reduced pressure. Column chromatography of the residue (Merck silica gel 60 H; MeOH–CH_2Cl_2 4:96) gave compound (**19b**) (0.61 g, 56%), R_F 0.43 (MeOH–CH_2Cl_2 6:94) and compound (**23**) (0.35 g, 32%), R_F 0.53 (MeOH–CH_2Cl_2 6:94).

Compound (**19b**) was recrystallised from CH_2Cl_2–n-hexane, m.p. 171—175 °C (decomp.) (Found: C, 64.7; H, 7.1; N, 14.0. $C_{16}H_{21}N_3O_2 \cdot \frac{1}{6}CH_2Cl_2$ requires C, 64.44; H, 7.08; N, 13.94%); $\lambda_{max.}$(MeOH) 290sh, 282, and 222 nm; $\lambda_{min.}$ 252 nm; CIMS (100 eV) m/z 288 ($[M + 1]^+$, 30%), 272 (100), and 198 ($[C_{14}N_{16}N]^+$, 73) (Found: $[M + H]^+$, 288.1712. $C_{16}H_{22}N_3O_2$ requires m/z, 288.1712); δ_H (90 MHz; $CDCl_3$) 8.0 (br s, 1 H, indole NH), 7.70—7.00 (m, 4 H, indole CH), 6.41 and 5.45 (2 br s, 2 H, $CONH_2$), 6.15 (dd, $^3J_{trans}$ 17.7, $^3J_{cis}$ 10.2 Hz, 1 H, CH=CH_2), 5.19 and 5.18 (2 dd, $^3J_{trans}$ 17.7, $^3J_{cis}$ 10.2, $^2J_{gem}$ 1.0 Hz, 2 H, CH=CH_2), 4.65 (br s, 2 H, NHOH), 3.90 (X part of ABX spectrum, $^3J_{AX}$ 5.0, $^3J_{BX}$ 10.2 Hz, 1 H, α-H), 3.37 and 3.06 (AB part of ABX spectrum, $^3J_{AX}$ 5.0, $^3J_{BX}$ 10.2, $^2J_{AB}$ 15.0 Hz, 2 H, indole β-H_2), and 1.58 (s, 6 H, CMe_2).

Compound (**23**) was recrystallised from CH_2Cl_2–n-hexane, m.p. 157—160 °C; CIMS (100 eV) m/z 288 ($[M + 1]^+$, 100%), 218 ($[M - C_5H_9]^+$, 64), 186 (25), 157 (11), and 130 (23) (Found: $[M + H]^+$, 288.1714. $C_{16}H_{22}N_3O_2$ requires m/z 288.1712); δ_H (90 MHz; $CDCl_3$) 8.5 (br s, 1 H, NOH), 7.11—6.51 (m, 4-H, indoline 4- to 7-H), 5.71 (dd, $^3J_{trans}$ 18.0, $^3J_{cis}$ 9.5 Hz, 1 H, CH=CH_2), 5.3 (br s, 1 H, indoline NH), 5.01 and 4.97 (2 dd $^3J_{trans}$ 18.0, $^3J_{cis}$ 9.5, $^2J_{gem}$ 1.8 Hz, 2 H, CH=CH_2), 3.54 (X part of ABX spectrum, $^3J_{AX} = {}^3J_{BX}$ = 7.5, $^3J_{XM}$ 2.8 Hz, 1 H, indoline 3-H), 3.31 (d, $^3J_{XM}$ 2.8 Hz, 1 H, indoline 2-H), 2.98 and 2.88 (2 dd, AB part of ABXM spectrum, 2-H, indoline β-H_2), 1.7 (br s, 2 H, $CONH_2$), and 0.90 and 0.84 (2 s, 6 H, CMe_2).

N-*Benzyloxy*-α-(*hydroxyamino*)-β-(*indol*-3-*yl*)*propanamide*-(**20a**).—A saturated solution of HCl in dioxane (10 ml) was added to a stirred solution of the amide (**17a**) (2.3 mmol, 0.75 g) and TMA·BH_3 (2.5 mmol, 0.185 g) in dioxane (10 ml) at room temperature. After the mixture had been stirred for 5 h, NH_4Cl was added until the reaction mixture was neutral. The salts were filtered off and the residue was subjected to flash column chromatography (silica gel 60; MeOH–CH_2Cl_2 5:95) to give the title compound (**20a**) (0.55 g, 73%) as a foam which was homogeneous on t.l.c.: R_F 0.42 (MeOH–CH_2Cl_2 7:93); $\lambda_{max.}$(MeOH) 289sh, 281, 273sh, and 224 nm; $\lambda_{min.}$ 247 nm; EIMS (70 eV) m/z 325 ($[M]^+$, 15%), 155 (9), 130 (50), and 91 (100); δ_H (60 MHz; $CDCl_3$) 8.5 (br s, 1 H, indole NH), 7.6—6.8 (m, 5 H, indole CH), 7.1 (br s, 5 H, Ph), 6.0—5.0 (br s), 2 H, NHOH), 4.06 (s, 2 H, CH_2Ph), 3.8—3.5 (X part of ABX spectrum, 1 H, α-H), and 3.1—2.7 (AB part of ABX spectrum, 2 H, β-H_2).

N-*Allyl*-β-[2-(α,α-*dimethylallyl*)*indol*-3-*yl*]-α-(*hydroxy-amino*)*propanamide* (**21b**).—A solution of HCl in ethanol (15 ml of a 7M solution) was added dropwise to a stirred solution of compound (**18b**) (3 mmol, 0.98 g) and TMA·BH_3 (4 mmol, 0.29 g) in ethanol (15 ml) at room temperature. The mixture was stirred for a further 18 h at room temperature, neutralised with $NaHCO_3$, and then concentrated to dryness under reduced pressure. Flash column chromatography of the residue (silica gel 60 H; MeOH–CH_2Cl_2 2:98 gave the *title compound* (**21b**) (0.82 g, 84%), m.p. 146—148 °C (CH_2Cl_2–n-hexane) (Found: C, 69.2; H, 7.7; N, 12.6. $C_{19}H_{25}N_3O_2$ requires C, 69.70; H, 7.70; N, 12.83%); R_F 0.33 (MeOH–CH_2Cl_2 4:96); $\lambda_{max.}$(MeOH) 290sh, 282, and 222 nm; $\lambda_{min.}$ 248 nm; EIMS (70 eV) m/z 327 ($[M]^+$, 5%), 309 ($[M - H_2O]^+$, 5), 294 ($[M - NH_2OH]^+$, 8), 198 ($[C_{14}H_{16}N]^+$, 100), and 130 ($[C_9H_8N]^+$, 8) (Found: M^+, 327.1936. $C_{19}H_{25}N_3O_2$ requires M, 327.1947); δ_H (90 MHz; $CDCl_3$) 8.0 (br s, 1 H, indole NH), 7.7—7.0 (m, 4 H, indole CH), 6.5 (br t), 1 H, CONHCH$_2$), 6.15 (dd, $^3J_{trans}$ 17.7, $^3J_{cis}$ 9.9 Hz, 1 H, CMe_2CH=CH_2), 5.80 (m, 1 H, CH_2CH=CH_2), 5.35—5.00 (m, 4 H, 2 × CH=CH_2), 4.65 (br s, 2 H, NHOH), 4.00—3.80 (m, 3 H, indole α-H and NCH_2CH=CH_2), 3.05 (AB part of ABX spectrum, $^3J_{AX}$ 5.3, $^3J_{BX}$ 10.1, $^2J_{AB}$ 14.7 Hz, 2 H, β-H_2), and 1.58 (s, 6 H, CMe_2).

(E)-2,3-trans-α-(*Benzyloxyimino*)-β-[2-(α,α-*dimethylallyl*)-*indolin*-3-*yl*]*propanamide* (**24**).— A solution of compound (**15b**) (0.5 mmol, 0.19 g) in EtOH (5 ml) was treated with TMA·BH_3 (0.8 mmol, 0.06 g) and ethanolic HCl (7M; 5 ml) as described for the preparation of compound (**21b**). Column chromatography (silica gel 60 H; MeOH–CH_2Cl_2 1:99 gave the *indoline* (**24**) (0.137 g, 71%) as an oil which was homogeneous on t.l.c.: R_F 0.37 (MeOH–CH_2Cl_2 2:98); EIMS (70 eV) m/z 377 ($[M]^+$, 0.5%), 308 ($[M - C_5H_9]^+$, 10), 220 (8), 157 (10), and 130 (100) (Found: M^+, 277.2100. $C_{23}H_{27}N_3O_2$ requires M, 277.2103); δ_H (90 MHz; $CDCl_3$) 7.33 (s, 5 H, Ph), 7.34—6.40 (m, 4 H, indoline 4- to 7-H), 5.60 (dd, $^3J_{trans}$ 16.4, $^3J_{cis}$ 11.7 Hz, 1 H, CH=CH_2), 5.54 (br s, 1 H, indoline NH), 4.68 (s, 2 H, CH_2Ph), 4.99 and 4.84 (2 dd, $^3J_{trans}$ 16.4, $^3J_{cis}$ 11.7, $^2J_{gem}$ 1.8 Hz, 2 H, CH=CH_2), 3.45 (X part of ABXM spectrum, $^3J_{AX} = {}^3J_{BX}$ = 6.3, J_{XM} 2.9 Hz, 1 H, indoline 3-H, 3.23 (M part of ABXM spectrum, $^3J_{XM}$ 2.9 Hz, 1 H, indoline 2-H), 3.25 and 3.21 (AB part of ABX spectrum, 2 H, β-H_2), and 0.80 and 0.77 (2 s, 6 H, CMe_2).

1-*Allyl*-3-[2-(α,α-*dimethylallyl*)*indol*-3-*ylmethyl*]-4-*hydroxy*-3-*methylenepiperazine*-2,5-*dione* (**28b**) *and* 2-*Allyl*-2′-(α,α-*dimethylallyl*)-5-*hydroxy*-1-*methylspiro*[2,5-*diazabicyclo*-[2.2.2]-*octane*-7,3′-[3′H]*indole*]-3,6-*dione* (**33b**) Pyruvoyl chloride[15] (1, 1 mmol, 0.12 g) was added to a stirred solution of compound (**21b**) (1 mmol, 0.33 g) in dry CH_2Cl_2 (10 ml). After 15 min the starting material (**21b**) was completely converted into the

pyruvohydroxamic acid (**26b**) (red spot upon spraying a t.l.c. plate with $FeCl_3$). Subsequently, CF_3CO_2H (100 mg) was added. After the mixture had been stirred for 3 days at room temperature the solvent was evaporated off and the residue was submitted to flash column chromatography (silica gel 60; MeOH–CH_2Cl_2 2:98) to yield compound (**28b**) (0.27 g, 72%) as a form which was homogeneous on t.l.c. R_F 0.33 (MeOH–CH_2Cl_2 4:96), and a by-product (**33b**) (45 mg, 12%).

Compound (**28b**) had $\lambda_{max.}$(MeOH) 290sh, 284, and 225 nm; $\lambda_{min.}$ 255 nm; EIMS (70 eV) *m/z* 379 ($[M]^+$, 6%) and 198 ($[C_{14}H_{16}N]^+$, 100) (Found: M^+, 379.1897. $C_{22}H_{25}N_3O_3$ requires *M*, 379.1896); (60 MHz; $CDCl_3$) 7.9 (br s, 1 H, indole NH), 7.5—7.0 (m, 4 H, indole CH), 6.1 (dd, $^3J_{trans}$ 17, $^3J_{cis}$ 10 Hz, 1 H, $CMe_3CH{=}CH_2$), 5.7 (d, $^2J_{gem}$ 1.5 Hz, 1 H, piperazine C=CH_α), 5.5 (m, 1 H, $CH_2CH{=}CH_2$), 5.3—5.0 (m, 4 H, 2 × CH=CH_2), 4.9 (X part of ABX spectrum, 1 H, piperazine 3-H) 4.8 (d, $^2J_{gem}$ 1.5 Hz, 1 H, piperazine C=CH_β), 4.3 and 4.0 (A′B′ part of A′B′X′ spectrum, 2 H, $CH_2CH{=}CH_2$), 3.8—3.5 (AB part of ABX spectrum, 2 H, indole 3-CH_2), and 1.5 (s, 6 H, CMe_2).

Compound (**33b**) had m.p. 226—230 °C (from CH_2Cl_2–n-hexane); EIMS (70 eV) *m/z* 379 ($[M]^+$, 100%) and 362 ($[M - OH]^+$, 25) (Found: M^+, 379.1904. $C_{22}H_{25}N_3O_3$ requires *M*, 379.1896); δ_H (90 MHz; $CDCl_3$) 8.39 (br s, 1 H, NOH), 7.40—7.00 (m, 4 H, indoline CH), 6.02 (dd, $^3J_{trans}$ 17.0, $^3J_{cis}$ 10.8 Hz, 1 H, $CMe_2CH{=}CH_2$), 5.70 (m, 1 H, $CH_2CH{=}CH_2$), 5.30—4.95 (m, 4 H, 2 × CH=CH_2), 4.70 (X part of ABX spectrum, $^3J_{AX}$ = $^3J_{BX}$ = 3.8 Hz, 1 H, 4-H), 4.05 and 3.25 (AB part of ABX spectrum, $^3J_{AX}$ 5.9, $^3J_{BX}$ 4.8, $^2J_{AB}$ 10.5 Hz, $CH_2CH{=}CH_2$), 3.80 and 3.65 (AB part of ABX spectrum, $^3J_{AX}$ = $^3J_{BX}$ = 3.8, $^2J_{AB}$ 15.3 Hz, 2 H, 8-H_2), 1.98 (s, 3 H, 1-Me), and 1.52 s, 6 H, CMe_2).

1-*Allyl*-3-[2-(α,α-*dimethylallyl*)*indol*-3-*ylmethyl*]-6-*methylene*-4-*tosyloxypiperazine*-2,5-*dione* (**29b**).—To a cooled (0 °C) and stirred solution of the hydroxy compound (**28b**) (0.5 mmol, 0.19 g) in CH_2Cl_2 (10 ml) were added toluene-*p*-sulphonyl chloride (0.55 mmol, 0.105 g) and dried triethylamine (0.5 mmol, 50 mg) under argon. The mixture was stirred for 2 h, the solvent was evaporated off, and the residue was subjected to flash column chromatography (silica gel 60; MeOH–CH_2Cl_2 0.5:99.5 to give the title compound (**29b**) (0.24 g, 90%), R_F 0.43 (MeOH–CH_2Cl_2 1:99), which was recrystallised from CH_2Cl_2–n-hexane, m.p. 130—132 °C (decomp.); $\lambda_{max.}$(MeOH) 290sh, 282sh, 274sh, and 224 nm; δ_H (90 MHz; $CDCl_3$) 7.90 (br s, 1 H, indole NH), 7.8—6.9 (m, 8 H, indole CH and C_6H_4), 6.15 (dd, $^3J_{trans}$ 17.4, $^3J_{cis}$ 10.2 Hz, 1 H, $CMe_2CH{=}CH_2$), 5.66 (d, $^2J_{gem}$ 1.7 Hz, 1 H, piperazine C=CH_α), 5.50 (X′ part of A′B′X′ spectrum, 1 H, $CH_2CH_X{=}CH_2$), 5.8—5.0 (m, 4 H, 2 × CH=CH_2), 4.90 (X part of ABX spectrum, $^3J_{AX}$ 5.4, $^3J_{BX}$ 7.8 Hz, 1 H, indole 3-H), 4.85 (d, $^2J_{gem}$ 1.7 Hz, 1 H, piperazine C=CH_β), 4.30 and 3.95 (A′B′ part of A′B′X′ spectrum, $^3J_{AX}$ = $^3J_{BX}$ = 5.1, $^2J_{A'B'}$ 15.9 Hz, 2 H, $CH_{A'}H_{B'}CH_XCH_2$), 3.65 and 3.30 (AB part of ABX spectrum, $^3J_{AX}$ 5.4, $^3J_{BX}$ 7.8, $^2J_{AB}$ 14.7 Hz, 2 H, indole 3-CH_2), 2.43 (s, 3 H, $SO_2C_6H_4Me$), and 1.49 (s, 6 H, CMe_2).

(Z)-1-*Allyl*-3-[2-(α,α-*dimethylallyl*)*indol*-3-*ylmethylene*]-6-*methylenepiperazine*-2,5-*dione* (**30b**).—To a stirred solution of the tosyl derivative (**29b**) (0.38 mmol, 0.200 g) in dry CH_2Cl_2 (15 ml) was added DBU (0.40 mmol, 60 mg). The mixture was stirred for 30 h at room temperature under argon, then was washed (0.1M-HCl), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was subjected to flash column chromatography (silica gel 60; MeOH–CH_2Cl_2 1:99) to give the *title compound* (**30b**) (98 mg, 72%) as a yellow, crystalline material, m.p. 178—180 °C (from CH_2Cl_2–n-hexane) (Found: C, 72.9; H, 6.4; N, 11.4. $C_{22}H_{23}N_3O_2$ requires C, 73.11; H, 6.41; N, 11.63%); $\lambda_{max.}$(MeOH) 372, 272, and 225 nm; $\lambda_{min.}$ 320 and 246 nm; EIMS (70 eV) *m/z* 361 ($[M]^+$, 100%), 320 ($[M - C_3H_5]^+$, 13), 292 ($[M - C_5H_9]^+$, 52), 251 (27), and 182 (44) (Found: M^+, 361.1800. $C_{22}H_{23}N_3O_2$ requires *M*, 361.1790); δ_H (90 MHz; $CDCl_3$) 8.42 (br s, 1 H, CONH), 7.56 (br s, 1 H, indole NH), 7.40—7.00 (m, 4 H, indole CH), 7.35 (s, 1 H, indole 3-CH=C), 6.19 (dd, $^3J_{trans}$ 16.5, $^3J_{cis}$ 11.1 Hz, 1 H, $CMe_2CH{=}CH_2$), 5.80 (m, 1 H, $CH_2CH{=}CH_2$), 5.84 (d, ^2J 1.5 Hz, 1 H, piperazine C=CH_α), 5.37 (d, ^2J 1.5 Hz, 1 H, piperazine C=CH_β), 5.30—4.95 (m, 4 H, 2 × CH=CH_2), 4.59—4.53 (m, 2 H, $CH_2CH{=}CH_2$), and 1.53 (s, 6 H, CMe_2).

1,4,5,10-*Tetrahydro*-11-*hydroxy*-1-*methyl*-4,1-(*iminomethane*)*azepino*[3,4-b]*indole*-3,12-*dione* (**34**) Pyruvoyl chloride[15] (0.55 mmol, 60 mg) was added dropwise to a stirred solution of compound (**19a**) (0.5 mmol, 0.11 g) in Et_2O–CH_2Cl_2 (1:1; 5 ml) at room temperature. After 15 min, compound (**19a**) had been completely converted into the pyruvohydroxamic acid (**26a**) (red spot upon spraying a t.l.c. plate with $FeCl_3$). After the mixture had been stirred for 3 days at room temperature the intermediate (**26a**) had been converted completely into the required product (**34a**). Evaporation of the solvents, and flash column chromatography of the residue (silica gel 60 H; MeOH–CH_2Cl_2 10:90), gave *compound* (**34a**) (0.10 g, 74%), m.p. 261—263 °C; $\lambda_{max.}$(MeOH) 290, 283, 276sh, and 217 nm; $\lambda_{min.}$ 288 and 253 nm; EIMS *m/z* 271 ($[M]^+$, 18%) and 254 ($[M - OH]^+$, 25) (Found: M^+, 271.0957. $C_{14}H_{13}N_3O_3$ requires *M*, 271.0957); δ_H (90 MHz; CD_3COCD_3) 10.14 (br s, 1 H, CONH), 8.99 (br s, 1 H, NOH), 7.88 (br s, 1 H, indole NH), 7.36—6.76 (m, 4 H, indole CH), 4.46 (X part of ABX spectrum, 1 H, $^3J_{AX}$ 4.2, $^3J_{BX}$ 2.5 Hz, 4-H), 3.35 and 2.96 (AB part of ABX spectrum, 2 H, $^2J_{AB}$ 17.5, $^3J_{AX}$ 4.2, $^3J_{BX}$ 2.5 Hz, 5-H_2), 1.76 (s, 3 H, Me).

2-*Benzyloxy*-1,4,5,10-*tetrahydro*-11-*hydroxy*-1-*methyl*-4,1-(*iminomethano*)*azepino*[3,4-b]*indole*-3,12-*dione* (**35**).—Pyruvoyl chloride[15] (1.1 mmol, 120 mg) was added dropwise to a stirred solution of compound (**20a**) (1 mmol, 225 mg) in Et_2O–CH_2Cl_2 (1:1; 10 ml) at room temperature. Monitoring of the reaction by t.l.c. showed that the pyruvoylation was completed after 2 min (R_F 0.30; MeOH–CH_2Cl_2 7:93). After 2 h, the conversion into compound (**35**) was complete; R_F 0.60 (MeOH–CH_2Cl_2 7:93). Evaporation of the solvents and crystallisation from CH_2Cl_2–n-hexane gave the *title compound* (**35**) (0.27 g, 71%), m.p. 245—250 °C (decomp.) (Found: C, 66.8; H, 5.1; N, 10.9. $C_{21}H_{19}N_3O_4$ requires C, 66.83; H, 5.07; N, 11.13%); $\lambda_{max.}$(MeOH) 293, 285, 277sh, and 215 nm; $\lambda_{min.}$ 290 and 254 nm; CIMS *m/z* 378 ($[M + 1]^+$, 13%), 362 (4), 272 [($M - OCH_2C_6H_5$, 15%), 254 (9), 220 (32), 211 (5), 183 (4), 158* (5), 130 (10), 107 (23), 91 (33), and 41 (100) (Found: $[M + H]^+$, 378.145. $C_{21}H_{20}N_3O_4$ requires *m/z*, 378.145); δ_H (90 MHz; $CDCl_3$), 9.05 (br s, 1 H, NOH), 7.85 (br s, 1 H, indole NH), 7.40—6.80 (m, 9 H, indole CH and Ph), 4.86 (s, 2 H, OCH_2Ph), 4.73 (X part of ABX spectrum, $^3J_{AX}$ 3.0, $^3J_{BX}$ 3.6 Hz, 1 H, indole 4-H), 4.38 and 4.51 (AB part of ABX spectrum, $^3J_{AX}$ 3.0, $^3J_{BX}$ 3.6, $^2J_{AB}$ 17.4 Hz, 2 H, indole 5-H_2), and 1.90 (s, 3 H, Me).

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