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A BIOMIMETIC APPROACH TO SPORIDESMINS. SYNTHESIS OF AN α,β-EPOXYTRYPTOPHAN DERIVATIVE

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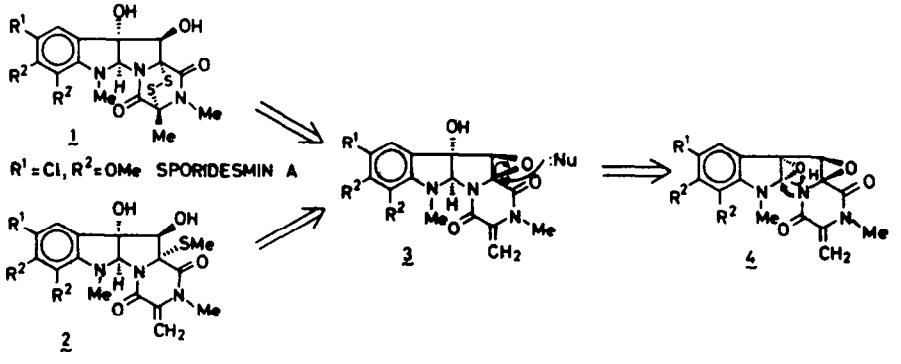
Abstract: The reaction of **19** - prepared efficiently from **16** - with DDQ affords **22**. This epoxide may serve as a model compound to investigate the biosynthesis of *sporidesmins*, *e.g.* **1** and **2**.

INTRODUCTION

The sporidesmins make up a group of naturally ocurring, fungal metabolites featuring α- or α,α'-substituted dioxopiperazines. They are the active principle causing facial exzema in sheep and were obtained from the fungus *Pithomyces chartarum* which occurs in certain pasture areas of New Zealand and Australia[1a,2]. Consideration of the structures of the sporidesmins[1b,c], *e.g.* sporidesmin A (**1**) and sporidesmin F (**2**), suggests a biosynthetic derivation from the amino acids tryptophan and alanine[3], although, an extensive series of peripheral changes must have taken place. Labeling studies have demonstrated that the N-methyl groups are derived from methionine and the sulfur atoms are delivered either by sodium sulfate, cysteine or methionine[3].

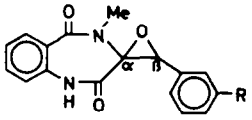
The metabolic steps leading from tryptophan to the sporidesmins have not been investigated in any detail. In particular, details concerning the introduction of the sulfur atoms and the two hydroxyl groups remain obscure. Kirby[4] studied the stereochemistry of hydrogen loss involved in the hydroxylation of the sporidesmin skeleton at the β-position. From labeling experiments involving C(β) ^{3}H-labeled derivatives he concluded that hydroxylation at C(β) in the biosythesis of **1** takes place with retention of configuration at this carbon atom. This leaves us with the intriguing question by what mechanism the hydroxyl group is introduced biosynthetically. The most likely pathway has been provided by Sammes[5], who invoked the intermediacy of the di-epoxide **4** (Scheme I). This system might react to yield the mono-epoxide **3**; subsequent attack by a sulfur nucleophile would create the α-mercapto-β-hydroxy tryptophan moieties of **1** or **2**[6]. This scheme is supported by the following considerations. Firstly, several mould metabolites, *e.g.* **5a,b**[7] and **6**[8] have an α,β-epoxy amino acid moiety as a

SCHEME I



structural feature. Secondly, the conversion 4→3 has a close resemblance to the well-documented mechanism proposed for the biosynthesis of gliotoxin[9]. Thirdly, in another synthetic approach to the sporidesmins, we employed successfully an oxidative ring closure based on the conversion of 4→3[10].

Here we wish to report the first synthesis of an α,β-epoxy tryptophan derivative, *cf.* 10 (Scheme II). This synthesis provides further support to the proposed intermediacy of 3 and 4 in the biosynthesis of the sporidesmins[5].



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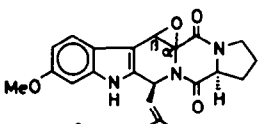
a: R = H CYCLOPENIN
b: R = OH CYCLOPENOL



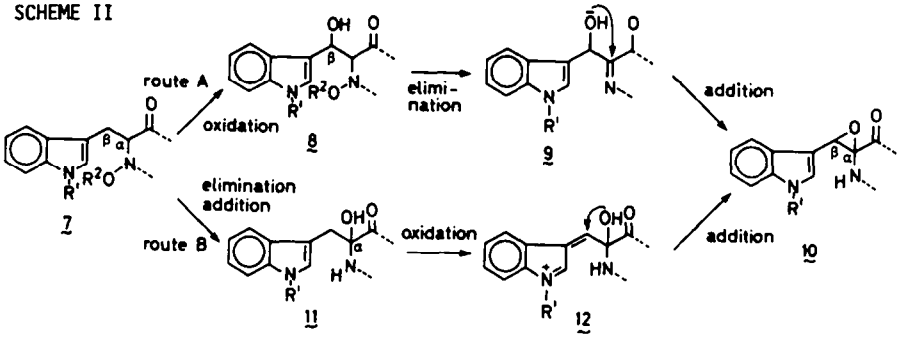
6

EPOXY-FUMITREMORGIN C

STRATEGY

Compound 10 was selected as a model for the putative sporidesmin precursors, *i.e.*: 3 and 4. This compound is not directly accessible *via* straightforward epoxidation of the corresponding α,β-dehydrotryptophan derivative[11], because of the presence of the indole nucleus. Therefore, two alternative approaches were explored (Scheme II). Initially we studied the β-oxidation of an

SCHEME II

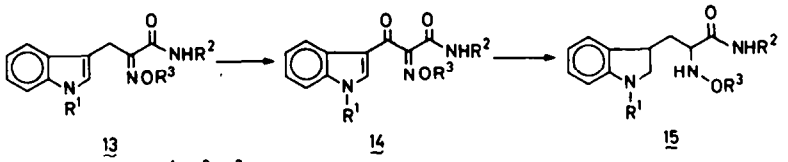


N-hydroxytryptophan derivative[12] (route A, 7→8). Subsequent elimination of R^2-OH might yield the acylimine 9, which should yield the α,β-epoxide 10. As this approach failed (*vide infra*), we first prepared the α-functionalized tryptophan derivative 11 (route B). Oxidation gave indeed 10; we rationalize this conversion by the intermediacy of 12.

Route A

β-Oxydation of an N-hydroxytryptophan derivative (*cf.* 7→8) was studied using

SCHEME III



13

a: $R^1 = R^2 = R^3 = H$
b: $R^1 = R^2 = Me$; $R^3 = H$
c: $R^1 = R^2 = H$; $R^3 = CH_2C_6H_5$
d: $R^1 = R^2 = Me$; $R^3 = CH_2C_6H_5$

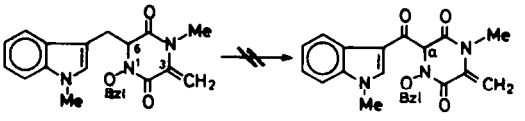
14

15

the oxime 13 (Scheme III) and the dioxopiperazine 16 (Scheme IV). Treatment of 13c - prepared from 13a by O-benzylation - with DDQ in aqueous tetrahydrofuran[13] as an oxidizing agent afforded the β-keto derivative 14c in 89% yield. The dimethyl derivative 14d was obtained analogously from 13d. Subsequently, the oxime C=N bond of 14c or 14d had to be reduced selectively. Unfortunately, all attempts failed. Treatment of 14d with the trimethylamine borohydride complex - a reagent introduced by us for related reductions[14] gave the 2,3-dihydrotryptophan derivative 15 in 53% yield. Having observed this we reasoned that reduction of the oxime had to preceed the β-oxidation. Accordingly,

the next compound we studied was 16[18] (Scheme IV). Treatment with DDQ gave, however, an untractable reaction mixture. We ascribe this failure to the high acid-

SCHEME IV



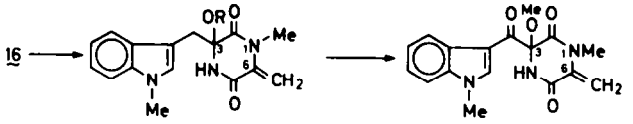
16 17

ity of the α-proton of 17 facilitating the elimination of benzyl alcohol.

Route B

On the basis of the above findings we felt that β-oxidation had to be carried out subsequent to α-functionalization the reverse order of reaction steps would invariably lead to elimination reactions before the β-carbon would have reached the proper oxidation state. Accordingly, the α-methoxy derivative 18 was prepared by treatment of 16 with sodium methoxide in methanol (Scheme V). Oxidation of 18 using again DDQ in aqueous THF yielded a mixture of the desired compound 20 (30%) and the α-hydroxy derivative 19 (58%). Unfortunately, attempts to reduce the β-carbonyl group of 20 into a hydroxy group failed. Possibly the

SCHEME V



18 : R=Me
19 : R=H

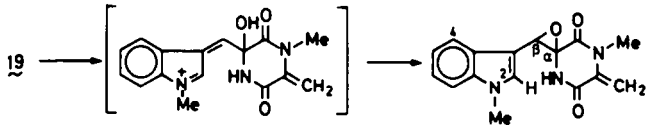
20

presence of an α-NH-proton precludes this conversion.

Having observed this failure, we realized that the oxidation has to be interrupted as soon as the β-carbon atom is in the oxidation state of a secondary alcohol. We reasoned that intramolecular trapping to yield an epoxide (*viz.* 12→10) might be possible starting from an α-hydroxy derivative, *viz.* 11. This approach was found to be viable indeed.

When the α-hydroxy derivative 19 - prepared from 18 (95% yield) or from 16 (83% yield) by treatment with aqueous sodium hydroxide, respectively - was treated with a molar equivalent of DDQ in tetrahydrofuran a product was formed to which we assigned structure 22 on basis of the following observations (Scheme

SCHEME VI



19 21 22

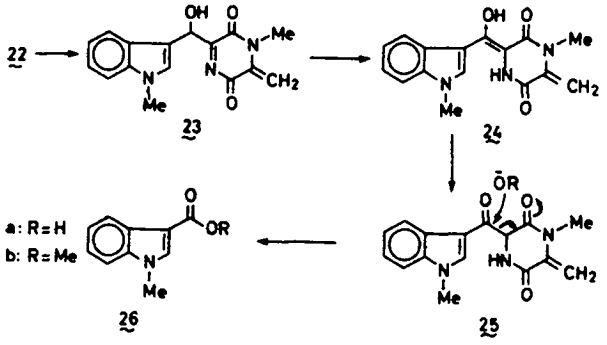
VI). Firstly, upon spraying with picric acid - a reagent indicative for epoxides[15] - a positive (red) colour reaction was observed, whereas all other compounds reported here were negative in this test. Secondly, the ^{1}H-NMR spectrum of 22 showed a downfield shift for the indole C(2)-proton (δ=8.56 ppm) as compared to the spectrum of 19 (δ=6.87 ppm)[16]. Thirdly, the electron impact mass spectrum showed an ion corresponding to the loss of oxygen from the molecular ion[17], this fragmentation is a typical feature of epoxides, *e.g.* of 5a and 5b[7].

The epoxide 22 is an unstable compound; whereas it is formed quantitatively it decomposes slowly under chromatographic conditions using silica gel. So far we have not been able to convert 22 into an α,β-difunctionalized amino acid derivative by nucleophilic ring opening of the epoxide. Treatment with sodium hydroxide or sodium methylmercaptide gave the acid 26a, and reaction with sodium methoxide gave the ester 26b (Scheme VII). The formation of these degradation products can be rationalized as depicted in Scheme VII. This type of fragmentation is precedented by the formation of benzoic acid from 5a upon treatment with sodium hydroxide[18].

DISCUSSION

The two step synthesis of 22 from 16 demonstrates the utility of N-hydroxytryptophan derivatives in the synthesis of natural products featuring

SCHEME VII



an α,β-epoxy tryptophan derivative. The methodology used seems sufficiently flexible to be adapted to the preparation of other α,β-epoxy amino acids having an aromatic side chain in the β-position, a moiety occurring in 5 and 6. We feel that the reaction sequence 16→19→22 may be of biosynthetic significance.

We are currently investigating the conversion of 22 into a pentacyclic epoxyhexahydropyrrolo[2,3-b]indole derivative (*cf.* 4→3). We anticipate that this derivative will be more stable than 22, the lability of which we ascribe to the presence of the indole C(2)-C(3) double bond and the NH-function in the dioxopiperazine moiety (*cf.* Scheme VII).

EXPERIMENTAL SECTION

Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin-Elmer spectrometer, Model 555. Proton 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 (parts per million) relative to Me_4Si as an internal standard. Mass spectra were obtained with a 7070E Analytical Mass double-focussing Varian Associates SMI-B spectrometer. Thin layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV lamp, iodine vapor, Cl_2-TDM[19] or cinnamaldehyde/HCl (for indole detection[20]).

1-[(E)-hydroxylimino]-2-(indol-3-yl)propanamide (13a)

Ethyl-1-[(E)-hydroxylimino]-2-(indol-3-yl)propanoate[21] (2 mmol, 493 mg) was added to a stirred solution of NH_3 in ethanol (5 ml of a saturated solution). Stirring at 80 °C in a pressure vessel was continued for 5 days. The solvent was then removed *in vacuo*. The residue was subjected to flash column chromatography ($MeOH/CH_2Cl_2$, 6/94, v/v) to give 370 mg of 13a (85%); m.p. 188-190 °C (CH_2Cl_2/n-hexane). UV (MeOH) λ_{max}=289, 280, 273 (sh), 219 nm; λ_{min}=286, 248 nm. CIMS (100 eV) m/e=218 ([M+1]$^+$, 80%), 200 ([M-OH]$^+$, 30%), 130 ([C_9H_8N]$^+$, 80%), exact mass calcd. for $C_{11}H_{12}N_3O_2$ 218.0930, found 218.0935. ^{1}H-NMR (90 MHz, CD_3OD), δ=7.70-6.85 (m, 5H, indole C(2), C(4)-C(7)H, 4.00 (s, 2H, indole C(3)CH_2). Anal. calcd. for $C_{11}H_{11}N_3O_2$ C 60.81, H 5.11, N 19.35; found C 60.11, H 5.01, N 19.20.

1-[(E)-Benzyloximino]-2-(indol-3-yl)propanamide (13c)

A solution of benzyl bromide (1.1 mmol, 190 mg) in dimethoxyethane (5 ml) was added dropwise to a stirred solution of 13a (1 mmol, 217 mg) and potassium *tert*-butoxide (1.1 mmol, 125 mg) in dimethoxyethane (10 ml) at room temperature and in an argon atmosphere. Stirring was continued for 3 hrs. Then the solvent was removed *in vacuo*. A solution of the residue in CH_2Cl_2 was washed with 1N HCl

and with brine, and subsequently dried (Na_2SO_4). The residue obtained by evaporation of the solvent was subjected to flash column chromatography (CH_2Cl_2) to give 280 mg of **13c** (91%); m.p. 120-122 °C (CH_2Cl_2/n-hexane), tlc R_f 0.2 (CH_2Cl_2). UV (MeOH) λ_{max}=286, 222 nm; $\lambda_{min.}$ 255 nm. EIMS (70 eV) m/e=307 ([M]$^+$, 5%), 216 ([M-$CH_2C_6H_5$]$^+$, 9%), 200 ([M-$OCH_2C_6H_5$]$^+$, 25%), 171 (15%), 155 (50%), 130 ([C_9H_8N]$^+$, 55%), exact mass calcd. for $C_{18}H_{17}N_3O_2$ 307.1321, found 307.1325. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=8.2 (s(br), 1H, indole NH), 7.6-6.9 (m, 5H, indole-C(2), C(4)-C(7)H), 7.3 (s, 5H, C_6H_5), 6.5 (s(br), 2H $CONH_2$), 5.15 (s, 2H, OCH_2), 4.0 (s, 2H, indole C(3)-CH_2).

1-[(E)-Benzyloximino]-2-(N-methylindol-3-yl)N-methylpropanamide (13d)

A solution of benzyl bromide (2.2 mmol, 380 mg) in dimethoxyethane (10 ml) was added dropwise to a stirred solution of **13b**[22] (2 mmol, 490 mg) and potassium *tert.*-butoxide (2.2 mmol, 250 mg) in dimethoxyethane (20 ml) at room temperature and in an argon atmosphere. Stirring was continued for 3 hrs. Then the solvent was removed *in vacuo*. A solution of the residue in CH_2Cl_2 was washed with 1N HCl and with brine, and subsequently dried (Na_2SO_4). Evaporation of the solvent and flash column chromatography (CH_2Cl_2) of the residue gave 640 mg of **13d** (96%); m.p. 64-65.5 °C (CH_2Cl_2/n-hexane), tlc R_f 0.2 (CH_2Cl_2). UV (MeOH) λ_{max}=286, 220 nm; $\lambda_{min.}$ 256 nm. EIMS (70 eV) m/e=335 ([M]$^+$, 27%), 228 ([$C_{13}H_{14}N_3O$]$^+$, 100%), 171 ([$C_{11}H_{11}N_2$]$^+$, 94%), 170 ([$C_{11}H_{10}N_2$]$^+$, 33%), 169 ([$C_{11}H_9N_2$]$^+$, 47%), 144 ([$C_{10}H_{10}N$]$^+$, 80%); exact mass calcd. for $C_{20}H_{21}N_3O_2$ 335.1634, found 335.1628. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=7.71-6.88 (m, 5H, indole C(2), C(4)-C(7)H), 7.34 (s, 5H, C_6H_5), 6.7 (m, 1H, CH_3NH), 5.21 (s, 2H, OCH_2), 4.02 (s, 2H, indole C(3)-CH_2), 3.64 (s, 3H, indole NCH_3), 2.76 (d, ^{3}J=5 Hz, 3H, CH_3NH).

1-[(E)-Benzyloximino]-2-(indol-3-yl)-2-oxo-propanamide (14c)

To a solution of **13c** (0.2 mmol, 63 mg) in THF/H_2O (9/1, v/v, 5 ml) was added DDQ (0.4 mmol, 91 mg). After stirring for 2 hrs the solvents were evaporated and CH_2Cl_2 was added to the residue. The suspension was filtered and the filtrate was washed, dried (Na_2SO_4) and the solvent evaporated. Flash column chromatography (MeOH/CH_2Cl_2, 4/96, v/v) gave 57 mg of **14c** (89%) as an oil which was homogeneous on tlc R_f 0.16 (MeOH/CH_2Cl_2, 6/94, v/v). UV (MeOH) λ_{max}=305, 260 (sh), 236 (sh), 204 nm; $\lambda_{min.}$ 277 nm. EIMS (70 eV) m/e=321 ([M]$^+$, 28%), 144 ([C_9H_6NO]$^+$, 100%), 91 ([C_7H_7]$^+$, 100%); exact mass calcd. for $C_{18}H_{15}N_3O_2$ 321.1113, found 321.1110. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=9.7 (s(br), 1H, indole NH), 8.2-7.9 and 7.3-6.9 (m, 5H, indole C(2)H, C(4)-C(7)H), 7.10 (s, 5H, C_6H_5), 6.4 and 6.0 (s(br), 2H, NH_2), 4.93 (s, 2H, OCH_2).

1-(Benzyloximino)-2-(N-methylindol-3-yl)-2-oxo-N-methylpropanamide (14d)

To a solution of **13d** (1.7 mmol, 575 mg) in THF/H_2O (9/1, v/v, 10 ml) was added DDQ (3.5 mmol, 779 mg). After stirring for 3 hrs the solvents were evaporated and CH_2Cl_2 was added to the residue. The suspension was filtered and the filtrate was washed, dried (Na_2SO_4) and the solvent evaporated. Flash column chromatography gave 451 mg of **14d** (76%) as an oil which was homogeneous on tlc R_f 0.48 (MeOH/CH_2Cl_2, 6/94, v/v). UV (MeOH) λ_{max}=312, 266 (sh), 246, 208 nm; $\lambda_{min.}$ 280, 234 nm. EIMS (70 eV) m/e=349 ([M]$^+$, 22%), 158 ([$C_{10}H_8NO$]$^+$, 100%), 91 ([C_7H_7]$^+$, 45%); exact mass calcd. for $C_{20}H_{19}N_3O_2$ 349.1426, found 349.1419. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=8.3-8.1 and 7.4-7.1 (m, 5H, indole C(2)H, C(4)-C(7)H), 7.3 (s, 5H, C_6H_5), 6.7 (m, 1H, NH-CH_3), 5.16 (s, 2H, OCH_2), 3.69 (s, 3H, indole N-CH_3), 2.84 (d, ^{3}J=5 Hz, 3H, $NHCH_3$).

1-(Benzyloxamino)-2-(N-methylindolin-3-yl)-N-methylpropanamide (15)

To a solution of **14d** (0.5 mmol, 175 mg) and $Me_3N{\bullet}BH_3$[14] (1 mmol, 80 mg) in ethanol (5 ml) a solution of HCl in ethanol (5 ml of a 7N solution) was added dropwise at room temperature in an argon atmosphere. After stirring the reaction mixture for 24 hrs another 4 equivalent of $Me_3N{\bullet}BH_3$ (2 mmol, 160 mg) were added. After 4 days the solvent was evaporated. Then the residue was dissolved in CH_2Cl_2 and the resulting solution was washed with 0.1N NaOH, dried (Na_2SO_4) and

filtered. Evaporation of the solvent gave a residue which was subjected to flash column chromatography (CH_2Cl_2) to give 90 mg of **15** (53%) as an oil which was homogeneous on tlc R_f 0.25 (MeOH/CH_2Cl_2, 4/96, v/v). UV (MeOH) λ_{max}=288, 248, 224 (sh), 204 nm; $\lambda_{min.}$ 276, 237 nm. EIMS (70 eV) m/e=339 ([M]$^+$, 17%), 215 ([$C_{13}H_{18}N_2O$]$^+$, 25%), 144 ([$C_{10}H_{10}N$]$^+$, 62%), 132 ([$C_9H_{10}N$]$^+$), 133 (26%), 131 (41%), 91 ([C_7H_7]$^+$, 46%); exact mass calcd. for $C_{20}H_{25}N_3O_2$ 339.1945, found 339.1947. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=7.2 (s, 5H, C_6H_5), 7.2-6.2 (m, 4H, indoline C(4)-C(7)H), 6.1 (m, 1H, $NHCH_3$), 4.6 (s, 2H, OCH_2), 3.7-3.5 (m, 1H, C(α)H), 3.4-2.5 (m, 5H, indoline $C(2)H_2$, C(3)H, and C(β)H), 2.7 (d, 3H, $NHCH_3$), 2.6 (s, 3H, indoline N-CH_3).

1-Methyl-3-methoxy-3-[(N-methylindol-3-yl)methyl]-6-methylenepiperazine-2,5-dione (18)

To a stirred solution of **16**[13] (1.14 g, 2.9 mmol) in methanol (dry, 150 ml) was added potassium *tert*-butoxyde (320 mg, 2.9 mmol) at room temperature. After stirring for 4 days at room temperature the mixture was neutralized by adding ammonium chloride (0.160 g). Stirring was continued for 17 hrs, where after the solvent was evaporated *in vacuo*. 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 **20** and benzyl alcohol. Column chromatography (CH_2Cl_2/MeOH, 98/2, v/v) gave 735 mg of **20** (81%), which was crystallized from CH_2Cl_2/n-hexane: m.p. 172-173 °C; tlc R_f 0.35 (solvent system II). UV (methanol) λ_{max}=218, 255 (sh), 284, 296 (sh) nm; λ_{min}=281 nm. EIMS (70 eV) m/e=313 ([M]$^+$, 1%), 281 ([$C_{16}H_{15}N_3O_2$]$^+$, 10%), 144 ([$C_{10}H_{10}N$]$^+$, 100%). exact mass calcd. for $C_{17}H_{19}N_3O_3$ m/e 313.1426, found 313.1423. ^{1}H-NMR (90 MHz, $CDCl_3$), δ7.65-7.0 (m, 4H, indole C(4)-C(7)H), 6.91 (s, 1H, indole C(2)H), 6.26 (m, 1H, NH), 5.57 (B part of AB spectrum, 1H, $^2J_{AB}$=1.5 Hz, C=CH_BH_A), 4.59 (A part of AB spectrum, 1H, $^2J_{AB}$=1.5 Hz, C=CH_AH_B), 3.74 (s, 3H, indole N-CH_3), (B part of AB spectrum, 1H, $^2J_{AB}$=14.5 Hz, indole C(3)-CH_AH_B), 3.35 (A part of AB spectrum, 1H, $^2J_{AB}$=14.5 Hz, indole C(3)-CH_AH_B), 3.27 (s, 3H, C(3)OCH_3), 2.98 (s, 3H, piperazine N-CH_3).

1-Methyl-3-hydroxy-3-[(N-methylindol-3-yl)methyl]-6-methylenepiperazine-2,5-dione (19)

From **16**:

To a stirred solution of **16**[13] (3.2 mmol, 1.24 g) in dimethoxyethane (60 ml) 0.5N NaOH (40 ml) was added at room temperature in an argon atmosphere. After 4 days the reaction mixture was treated with NH_4Cl. Then the solvent was evaporated, the residue was partitioned between water and CH_2Cl_2. The organic layer was dried and the solvent evaporated. Recrystallization (CH_2Cl_2/n-hexane) gave 0.79 g of **19** (83%), m.p. 163-165 °C. R_f 0.24 (MeOH/CH_2Cl_2, 7/93, v/v). UV (MeOH) λ_{max}=296 (sh), 284, 252 (sh), 221 nm; $\lambda_{min.}$ 280 nm. EIMS (70 eV) m/e=299 ([M]$^+$, 3%), 281 ([$C_{16}H_{15}N_3O_2$]$^+$, 6%), 144 ([$C_{10}H_{10}N$]$^+$, 100%); exact mass calcd. for $C_{16}H_{17}N_3O_3$ 299.1270, found 299.1263. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=7.50-6.90 (m, 4H, indole C(4)-C(7)H), 6.87 (s, 1H, indole C(2)H), 6.80 (s(br), 1H, piperazine NH), 5.37 (B part of AB spectrum, $^2J_{AB}$=2 Hz, 1H, =CH_AH_B), 4.44 (A part of AB spectrum, $^2J_{AB}$=2 Hz, 1H, =CH_AH_B), 4.30 (s(br), 1H, OH), 3.71 (s, 3H, indol N-CH_3), 3.50 (B part of AB spectrum, $^2J_{AB}$=14 Hz, 1H, CH_AH_B), 3.30 (A part of AB spectrum, $^2J_{AB}$=14 Hz, 1H, CH_AH_B, 2.78 (s, 3H, piperazine N-CH_3). From **18**:

To a solution of **18** (0.5 mmol, 150 mg) in THF/H_2O (9/1, v/v, 10 ml) was added 1N NaOH (1 ml) at room temperature in an argon atmosphere. After stirring the reaction mixture for 24 hrs the room temperatrue it was neutralized (NH_4Cl) and the solvent was evaporated. Usual work-up gave 135 mg (95%) of **19**, which was identical with the compound described above.

1-Methyl-3-methoxy-3-[(N-methylindol-3-yl)carbonyl]-6-methylenepiperazine-2,5-dione (20)

To a stirred solution of **18** (0.25 mmol, 78 mg) in THF/H_2O (9/1, v/v, 10 ml) was added DDQ (0.5 mmol, 114 mg). After stirring for 24 hours at room temperature in an argon atmosphere the solvents were evaporated and CH_2Cl_2 was added to the residue. The suspension was filtered and the filtrate was washed, dried (Na_2SO_4) and the solvent evaporated. Flash column chromatography (MeOH/CH_2Cl_2, 2/98, v/v) gave 25 mg of **20** (30%) and 44 mg of **19** (58%).

Compound **20**: oil, homogeneous on tlc, R_f 0.39 (MeOH/CH_2Cl_2, 6/94, v/v). UV (MeOH) λ_{max}=316, 268 (sh), 207 nm; $\lambda_{min.}$ 282, 237 nm. EIMS (70 eV) m/e=327 ([M]$^+$, 4%), 159 (29%), 158 ([$C_{10}H_8NO$]$^+$, 100%); exact mass calcd. for $C_{17}H_{17}N_3O_4$ 327.1219, found 327.1226. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=8.47 (s, 1H, indole C(2)H), 8.30-8.20 and 7.40-7.20 (m, 4H, indole C(4)-C(7)H), 5.93 (B part of AB spectrum, 1H, $^2J_{AB}$=5 Hz, C=CH_AH_B), 5.00 (A part of AB spectrum, 1H, $^2J_{AB}$=5 Hz, C=CH_AH_B, 3.89 (s, 3H, indole N-CH_3), 3.55 (s, 3H, OCH_3), 3.21 (s, 3H, piperazine N-CH_3).

1-Methyl-2,5-dioxo-6-methylen-piperazine-3-spiro-3'-(N-methylindol-3-yl)-2'-oxirane (22)

To a stirred solution of **19** (0.6 mmol, 185 mg) in dry THF (10 ml) was added DDQ (0.5 mmol, 110 mg). After stirring for 72 hrs at room temperature in an argon atmosphere Na_2CO_3 was added. The reaction mixture was filtered and the residue was washed with brine. The filtrate was concentrated to dryness to give **22** which was contaminated with $DDQH_2$. Flash column chromatography (MeOH/CH_2Cl_2, 2/98, v/v) gave a small amount of pure **22** as an amorphous solid which was homogeneous on tlc; R_f 0.20 (MeOH/CH_2Cl_2, 7/93, v/v). UV (MeOH) λ_{max}=314, 266 (sh), 248, 208 (sh), 203 nm; $\lambda_{min.}$ 281, 236 nm. EIMS (70 eV) m/e=297 ([M]$^+$, 4%), 281 ([M-O]$^+$, 4%), 158 ([$C_{10}H_8NO$]$^+$, 100%); exact mass calcd. for $C_{16}H_{15}N_3O_3$ 297.1113, found 297.1115; $C_{16}H_{15}N_3O_2$ 281.1164, found 281.1163. ^{1}H-NMR (90 MHz, d^6-DMSO), δ=9.30 (s(br), 1H, piperazine NH), 8.56 (s, 1H, indole C(2)H), 8.30-8.00 and 7.70-7.10 (m, 4H, indole C(4)-C(7)H), 5.64 (B part of AB spectrum, 1H, C=CH_AH_B), 5.11 (A part of AB spectrum), 1H, C=CH_AH_B, 3.91 (s, 3H, indole N-CH_3), 3.14 (s, 3H, piperazine N-CH_3), proton C(3')H probably superimposed by solvent pieks (H_2O δ=3.5-3.3, d^6-DMSO 2.5-2.7).

N-Methyl-indole-3-carboxylic acid (26a)

A solution of crude **22** (0.08 mmol, 23 mg) in THF (5 ml) prepared as described above was treated with 1N aqueous NaOH solution (2 ml) at room temperature. After 24 hrs the reaction mixture was treated with NH_4Cl. Subsequently, the solvents were evaporated and the residue dissolved in ethyl acetate. The organic layer was washed with water, brine, and dried (Na_2SO_4). Evaporation of the solvent gave 13 mg of **26a** (93%), which was crystallized from MeOH, m.p. 199-203 °C (lit.[23] 205-206°C); R_f 0.28 (MeOH/CH_2Cl_2, 6/94, v/v). UV (MeOH) λ_{max}298 (sh), 286, 243 (sh), 215 nm; λ_{min}=257 nm. EIMS (70 eV) m/e=175 ([M]$^+$, 100%), 158 ([$C_{10}H_8NO$]$^+$, 79%), exact mass calcd. for $C_{10}H_9NO_2$ 175.0633, found 175.0635. ^{1}H-NMR (60 MHz, $CDCl_3$), δ=8.3-8.1 and 7.5-7.2 (m, 4H, indole C(4)-C(7)H), 7.84 (s, 1H, indole C(2)H), 3.86 (s, 3H, indole N-CH_3).

Methyl (N-methylindole)-3-carboxylate (26b)

A solution of crude **22** (0.11 mmol, 33 mg) in THF (5 ml) prepared as described above was treated with a 1N solution of NaOMe in MeOH (1 ml) at room temperature. After 24 hrs the reaction mixture was treated with NH_4Cl. Subsequently, the solvents were evaporated and the residue was subjected to flash column chromatography (CH_2Cl_2) gave 20 mg of
26b (91%) as a foam which was homogeneous on tlc; R_f 0.71 (MeOH/CH_2Cl_2, 6/94, v/v). UV (MeOH) λ_{max}287 (sh), 226 (sh), 214 nm; λ_{min}=258 nm. EIMS (70 eV) m/e=189 ([M]$^+$, 90%), 158 ([$C_{10}H_8NO$]$^+$, 100%), exact mass calcd. for $C_{11}H_{11}O_2N$ 189.0790, found 189.0790. ^{1}H-NMR (90 MHz, $CDCl_3$), δ=8.10-7.90 and 7.40-7.00 (m, 4H, indole C(4)-C(7)H), 7.69 (s, 1H, indole C(2)H), 3.78 and 3.76 (2s, 6H, indol N-CH_3 and $COOCH_3$).

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