Pergamon

0031-9422(95)00333-9

Phytochemistry, Vol. 40, No. 3, pp. 967–973, 1995

0031 9422/95 $9.50 + 0.00

CONSTITUENTS OF *ISOLONA MAITLANDII**†

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(*Received* 8 *February* 1995)

Key Word Index—*Isolona maitlandii*; Annonaceae; aporphine alkaloids; unonopsine; hexalobines; *ent*-3,6-hexalobine C.

Abstract—From extracts of the stem bark of *Isolona maitlandii*, 16 hexalobine-type compounds were isolated, besides aporphinoids, amides and sterols. The leaf extract contained only hexalobines. Structures were established by spectroscopic methods. Among the isolated constituents are *ent*-hexalobine C and five new hexalobines.

INTRODUCTION

Plants of the genus *Isolona* grow only in Africa. *Isolona maitlandii* is described as a forest tree of Cameroon [2], but recently has also been found in Ghana (Enti, A. A., personal communication). In contrast to some other *Isolona* species, which are used in folk medicine and have already been investigated phytochemically [3, 4], there are no reports on the constituents of *I. maitlandii*.

RESULTS AND DISCUSSION

Repeated chromatography of the petrol and dichloromethane extracts of the stem bark and the leaves resulted in the isolation of the 27 compounds summarized in Table 1.

The presented structures are mainly the result of spectroscopic investigations. In addition, most structures of the known compounds were corroborated by comparison with authentic substances. Besides three steroids (**1**–**3**), two amides (**4** and **5**) and six alkaloids (**6**–**11**) of the aporphine type, we isolated 16 indole alkaloids (**12**–**27**), which all belong to the recently described hexalobines [1, 14–16].

Regarding the hexalobines, the structures of the C_5 substituents and the substitution pattern of the indole ring system could easily be recognized from the ^1H and ^{13}C NMR spectra [1, 15]. For hexalobines carrying two structurally different C_5-substituents, the individual positions of substitution of the indole were revealed by heteronuclear long-range COSY experiments and/or by the ^{13}C NMR shifts of the indole carbon atoms and/or by observation of an allylic coupling between H-2 and H-1′ (e.g. in **22**). Compound **15** exhibited spectroscopic data identical with those measured for 3,6-hexalobine C [1, 15], but it showed an opposite $[\alpha]_D$ value and opposite circular dichroism (CD) maxima. Therefore, **15** represents *ent*-3,6-hexalobine C.

The configurations at the double bonds in **18** and **19** were deduced from NOE experiments. The absolute configurations of **18**, **19** and **23** were established via their hydrogenation products, which exhibited CDs identical with that of (*R*)-3-(2,3-epoxy-3-methylbutyl)-5-(3-methylbutyl)indole [1].

Compound **16** was converted into **20**, as well as to **21**, which revealed the identical absolute configurations of these substances. Furthermore, hydrogenation of **20** removed the double bond, as well as the arylketone group and produced the 2′,3′-diol with a saturated C_5 substituent at C-5. The same compound had been prepared earlier from 3,5-hexalobine **B** and had been subjected to the determination of its absolute configuration by CD measurements of the dimolybdenium tetraacetate complex [1, 17, 18].

We regard **15**, **18**, **19** and **23** as genuine natural products, since they were detectable in the extracts immediately after a careful and smooth extraction. Among these components, **22** could not be detected, which is probably due to its very low concentration. On the other hand, **21** and **24** were only present in methanol extracts; both compounds could not be found, when dichloromethane had been used for the extraction. They might, therefore, be artefacts.

Six of the hexalobines isolated from *I. maitlandii* (**18**, **19**, **21**–**24**) represent new natural products, and **15** is the enantiomer of (+)-3,6-hexalobine C, which is already known as a constituent of *Hexalobus crispiflorus* and *H. monopetalus* [1, 15].

*Dedicated to Prof. Dr. F. Eiden, München, on the occasion of his 70th birthday.

†Part 70 in the series 'Constituents of Tropical Medicinal Plants'. For Part 69 see ref. [1].

Table 1. Compounds isolated or detectable by TLC in the stem bark and leaves from *Isolona maitlandii*

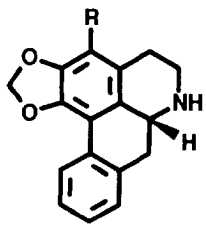
Class	Compound	Extract*	Content* [%] Stem bark	Leaves	Reference
Sterols	β-Sitosterol (**1**)	P-I	5		
		P-II	+		
	Stigmasterol (**2**)	P-I	7	—	
		P-II	+		
	6β-Hydroxy-4-stigmasten-3-one (**3**)	P-I	0.06		[5]
		P-II	—		
Amides	(*E*)-N-(4-Hydroxyphenethyl)-4-hydroxycinnamamide (**4**)	M-I	0.09		[6, 7]
		M-II	—		
	Pellitorine (**5**)	P-I	0.3		[8, 9]
		P-II	—		
Alkaloids	Anonaine (**6**)	M-I	1		[10]
		M-II	+		
	Norstephalagine (**7**)	M-I	0.6	—	[11, 12]
		M-II	+		
	3-Hydroxy-6a,7-dehydronuciferine (**8**)	M-I	0.05		[12]
		M-II	+		
	Liriodenine (**9**)	M-I	0.65		[10]
		M-II	+		
	Lysicamine (**10**)	M-I	0.03		[10]
		M-II	—	—	
	Unonopsine (**11**)	P-I	0.4		[13]
		P-II	+		
Hexalobines	3,6-Hexalobine A (**12**)	P-I	8.8	—	[1, 14, 15]
		P-II	+	—	
	3,6-Hexalobine B (**13**)	P-I	0.15	—	[1, 15]
		P-II	—	—	
	3,5-Hexalobine C (**14**)	P-I	0.6	0.5	[1, 15]
		P-II	+	+	
	ent-3,6-Hexalobine C (**15**)	P-I	0.75	3.7	
		P-II	+	—	
	3,5-Hexalobine D (**16**)	P-I	2.2	5	[1, 16]
		P-II	+	+	
		M-I	1.4		
		M-II	+		
	3,5-Hexalobine E (**17**)	P-I	—		[1, 16]
		P-II	5.5		
	3,6-(*E*)-Hexalobine E (**18**)	P-I	—	2	
		P-II	7	1.2	
	3,6-(*Z*)-Hexalobine E (**19**)	P-I	—		
		P-II	—	2	
	(*R*)-3-(2,3-Dihydroxy-3-methylbutyl)-5-(3-methyl-1-oxo-2-butenyl)indole (**20**)	M-I	4.8		[1, 15, 16]
		M-II	+	—	
	(*R*)-3-(2-Hydroxy-3-methyl-3-methoxybutyl)-5-(3-methyl-1-oxo-2-butenyl)indole (**21**)	M-I	3.1	—	
		M-II	—		
	3-(2-Hydroxy-3-methyl-3-butenyl)-5-(3-methyl-1-oxo-2-butenyl)indole (**22**)	M-I	0.07	—	
		M-II	—	—	
	(*R*)-5-(3-Methyl-1,3-butadienyl)-3-(2,3-epoxy-3-methylbutyl)indole (**23**)	P-I	—	—	
		P-II	3.3	—	
		M-I	—		
		M-II	0.6	—	
	3-(2-Formyl-2-methylpropyl)-5-(3-methyl-1-oxo-2-butenyl)indole (**24**)	M-I	0.6		
		M-II	—	—	
	Palmitic acid (*R*)-3-hydroxy-3-methyl-2-[6-(3-methyl-2-butenyl)indole-3-yl]butyl ester (**25**)	P-I	0.09		[1, 15, 16]
		P-II	—	—	

Continued overleaf

Table 1. *Continued*

Class	Compound	Extract*	Content* [%] Stem bark	Leaves	Reference
	Oleic acid (*R*)-3-hydroxy-3-methyl-2-[6-(3-methyl-2-butenyl)indole-3-yl]butyl ester (**26**)	P-I	0.09	—	[1, 15, 16]
		P-II	–	—	
	Linoleic acid (*R*)-3-hydroxy-3-methyl-2-[6-(3-methyl-2-butenyl)indole-3-yl] butyl ester (**27**)	P-I	0.15	—	[1, 15, 16]
		P-II	–	—	

*Estimated concentrations in % of petrol (P) or CH_2Cl_2 (M) extracts; I = first, II = second collection of plant material. +: detectable by TLC; –: not detectable by TLC.



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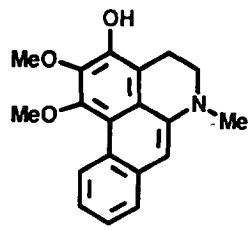
7 R = OMe



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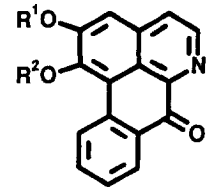
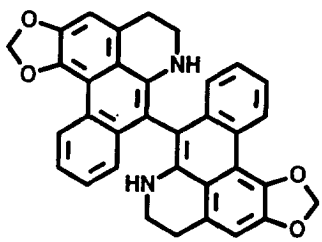


9 R^1,R^2 = $-CH_2-$
10 R^1 = R^2 = Me



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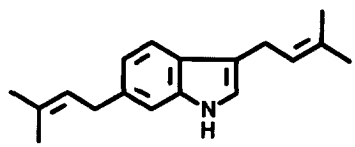

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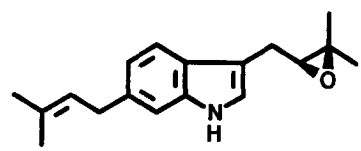

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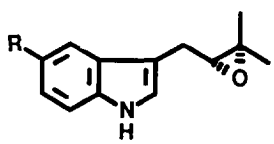
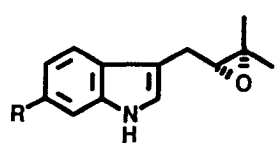
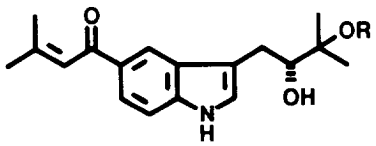


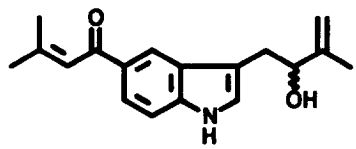


	R
14	(*S*)-2,3-Epoxy-3-methylbutyl
16	3-Methyl-1-oxo-2-butenyl
17	3-Hydroxy-3-methyl-1-butenyl
23	3-Methyl-1,3-butadienyl

	R
15	(*R*)-2,3-Epoxy-3-methylbutyl
18	(*E*)-3-Hydroxy-3-methyl-1-butenyl
19	(*Z*)-3-Hydroxy-3-methyl-1-butenyl



20 R = H
21 R = Me



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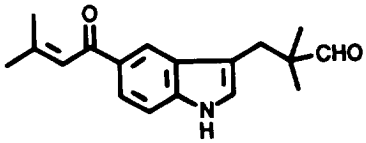

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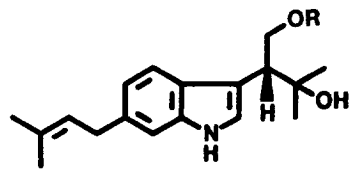

	R
25	palmitoyl
26	oleoyl
27	linoleoyl

Whereas earlier investigations on *Isolona* species report in all plants aporphinoid alkaloids and, sometimes, also bis-benzylisoquinoline alkaloids or the triterpene polycarpol [3, 4], hexalobine-type compounds prevail in *I. maitlandii* and represent the major constituents in the stem bark and the only compounds in the leaves (Table 1).

Hexalobine-type indole alkaloids obviously are characteristic constituents of the Annonaceae. They were isolated first from the West African species, *Uvaria elliotiana* [14], *H. crispiflorus* [1, 15] and *H. monopetalus* [1]; a recent report describes the 3,7-diprenylated indole, leiocarpadiol, from a Brazilian species of Rutaceae [19].

In biological tests, various hexalobines exhibit significant antifungal activity [1, 16] and therefore might be of some physiological importance as phytoalexins. The observed biological activity prompted us to perform synthetic studies on hexalobines [20].

EXPERIMENTAL

General. TLC was performed on precoated plates (Nano plates Sil-20 UV, Macherey-Nagel) using $CHCl_3$–MeOH and cyclohexane–EtOAc mixts. Detection: anisaldehyde [21] and ceric ammonium sulphate [22] reagent. If not stated otherwise, $[\alpha]_D$ and IR in $CHCl_3$, UV/VIS in MeOH. EIMS were obtained at 70 eV and DCIMS using isobutane. Unless stated otherwise, only ions with $m/z > 100$ and rel. int. > 10 are given. Unless otherwise stated, ^{1}H NMR were measured at 400, 360 or 90 MHz and ^{13}C NMR at 100, 90 or 22.5 MHz in $CDCl_3$ with TMS as int. standard.

Plant material. Stem bark and leaves of *I. maitlandii* Keay were collected during 1987 (I) and 1990 (II) in Ghana and identified by Mr. A. A. Enti (Forestry Enterprises). A voucher specimen is kept in our institute in Erlangen under No. 87-04.

Extraction and chromatography. (a) 800 g dried and powdered stem bark (I = first collection) were extracted successively with petrol and then MeOH at room temp., yielding 3.3 g and 71 g crude extracts. The MeOH extract was redissolved in 1 l of MeOH–H_2O (1:1) and extracted with CH_2Cl_2 to yield 7.2 g CH_2Cl_2 extract. (b) 40 g leaves (I) were extracted as described under (a) to yield 0.4 g petrol, 2.1 g MeOH and 1.3 g CH_2Cl_2 extract. (c) 500 g stem bark (II = second collection) were first extracted with petrol and then with CH_2Cl_2 to yield 1.9 g petrol extract and 5 g CH_2Cl_2 extract. (d) 180 g leaves (II) were extracted the same way as described under (c) to yield 2.2 g petrol extract and 3 g CH_2Cl_2 extract.

Petrol extracts were repeatedly chromatographed on silica gel using petrol–EtOAc and petrol–Me_2CO mixts and then on Fractogel PVA 500 using MeOH.

Compounds **1** and **2**, as well as **25**–**27** eluted from the columns as mixts; they were eventually sepd by HPLC on silica gel RP-18 with MeOH and MeOH–H_2O (9:1), respectively.

CH_2Cl_2 extracts were subjected to CC on silica gel or alumina with $CHCl_3$–MeOH and cyclohexane–EtOAc mixts. Further purification was achieved on Fractogel PVA 500 using MeOH.

β-Sitosterol (**1**). Crystals: 6 mg by HPLC sepn of a small part (18 mg) of its mixt. with **2**. Mp 135–137°. TLC: R_f 0.39 [petrol–Me_2CO (7:3)]; anisaldehyde reagent: violet. $[\alpha]_D^{21}$ −40° (*c* 0.50). IR, ^{1}H NMR, ^{13}C NMR, MS identical with authentic sample.

Stigmasterol (**2**). Crystals: 8 mg by HPLC sepn of a small part (18 mg) of its mixt. with **1**. Mp 162–163°. TLC: R_f 0.39 [petrol–Me_2CO (7:3)]; anisaldehyde

reagent: violet. $[\alpha]_D^{21}$ −44° (*c* 0.66). IR, ^{1}H NMR, ^{13}C NMR, MS identical with authentic sample.

6β-Hydroxy-4-stigmasten-3-one (**3**). Crystals: 2 mg. Mp 211° (ref. [5]: mp 212–214°). TLC: R_f 0.33 [cyclohexane–EtOAc (3:2)]; anisaldehyde reagent: yellow. $[\alpha]_D^{21}$ +25° (*c* 0.18) (ref. [5]: $[\alpha]_D$ +24°). IR, ^{1}H NMR, MS in agreement with published data [5].

(E)-*N*-(*4-Hydroxyphenethyl*)-*4-hydroxycinnamamide* (**4**). Crystals: 1.5 mg. Mp 242° (ref. [6]: mp 240–245°). TLC: R_f 0.22 [$CHCl_3$–MeOH (9:1)]. IR, UV, ^{1}H NMR, MS in agreement with published data [6, 7].

Pellitorine (**5**). Crystals: 7 mg. Mp 88–90° (ref. [8]: mp 89–90°). TLC: R_f 0.40 [petrol–Me_2CO (7:3)]; anisaldehyde reagent: blue. IR, UV, ^{1}H NMR, MS in agreement with published data [8, 9].

Anonaine (**6**). Crystals: 33 mg. Mp 121–122° (ref. [10]: mp 122°). TLC: R_f 0.17 [$CHCl_3$–MeOH (19:1)]; Ce^{IV} reagent: pink. $[\alpha]_D^{21}$ −52° (EtOH; *c* 0.28) (ref. [12]: $[\alpha]_D^{20}$ −64° (EtOH; *c* 0.77)). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [10, 12].

Norstephalagine (**7**). Oil: 23 mg. TLC: R_f 0.19 [$CHCl_3$–MeOH (19:1)]; Ce^{IV} reagent: green. $[\alpha]_D^{21}$ −34° (EtOH; *c* 0.32) (ref. [23]: $[\alpha]_D^{20}$ −35° (EtOH; *c* 0.98)). IR, UV, ^{1}H NMR, MS in agreement with published data [23].

3-Hydroxy-6a,7-dehydronuciferine (**8**). Oil: 2 mg. TLC: R_f 0.35 [cyclohexane–EtOAc (4:1)]; Ce^{IV} reagent: yellow. IR, UV, ^{1}H NMR, MS in agreement with published data [23].

Liriodenine (**9**). Yellow crystals: 33 mg. Mp 281° (ref. [10]: mp 280–282°). TLC: R_f 0.33 [$CHCl_3$–MeOH (19:1)], Ce^{IV} reagent: orange. IR, UV, ^{1}H NMR, MS in agreement with published data [10].

Lysicamine (**10**). Yellow crystals: 1 mg. Mp 208–209° (ref. [10]: mp 210–211°). TLC: R_f 0.25 [$CHCl_3$–MeOH (19:1)]; Ce^{IV} reagent: yellow. IR, UV, ^{1}H NMR in agreement with published data [10].

Unonopsine (**11**). Amorphous: 11 mg. TLC: R_f 0.21 [cyclohexane–EtOAc (9:1)], Ce^{IV} reagent: red. IR, UV, ^{1}H NMR, MS in agreement with published data [13].

3,6-Hexalobine A (= 3,5-bis(*3-methyl-2-butenyl*) *indole*, **12**). Crystals: 271 mg. Mp 35–36° (ref. [15]: mp 36–37°). TLC: R_f 0.22 [petrol–Me_2CO (9:1)]; Ce^{IV} reagent: yellow. IR, UV, ^{1}H NMR, ^{13}C NMR in agreement with published data [1, 14, 15].

3,6-Hexalobine B (= (S)-3-(2,3-*epoxy*-3-*methylbutyl*)-6-(3-*methyl*-2-*butenyl*)*indole*, **13**). Crystals: 5 mg. Mp 72–73° (ref. [15]: mp 72–73°). TLC: R_f 0.22 [cyclohexane–Me_2CO (9:1)]; Ce^{IV} reagent: brown. $[\alpha]_D^{21}$ +6° (*c* 0.4) (ref. [15]: $[\alpha]_D^{20}$ +9°). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1, 15].

3,5-Hexalobine C (= (2′*R*,2″S)-3,5-bis(2,3-*epoxy*-3-*methylbutyl*)*indole*, **14**). Oil: 18 mg. TLC: R_f 0.33 [cyclohexane–EtOAc (3:2)]; anisaldehyde reagent: violet. $[\alpha]_D^{21}$ +4° (*c* 1.3) (ref. [15]: $[\alpha]_D^{20}$ +6°). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1, 15].

ent-*3,6-Hexalobine C* (= (2′R,2″R)-3,6-bis(2,3-*epoxy*-3-*methylbutyl*)*indole*, **15**). Oil: 43 mg. TLC: R_f 0.29 [cyclohexane–EtOAc (3:2)]; anisaldehyde reagent: violet. $[\alpha]_D^{21}$ −12° (*c* 1.6). CD (EtOH): λ_{max} nm ($\Delta\varepsilon$): 232 (+0.6). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1, 15].

3,5-Hexalobine D (= (2′R)-3-(2,3-*epoxy*-3-*methylbutyl*)-5-(3-*methyl*-1-*oxo*-2-*butenyl*)*indole*, **16**). Crystals: 169 mg. Mp 132–133°. TLC: R_f 0.28 [cyclohexane–EtOAc (3:2)]; Ce^{IV} reagent: brown–yellow. $[\alpha]_D^{21}$ +6° (*c* 0.9) (ref. [1]: $[\alpha]_D^{22}$ +6° (*c* 1.1)). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1].

Compound **20** *by hydrolysis of* **16**. Compound **16** (5 mg) was treated with oxalic acid (20 mg) in Me_2CO–H_2O for 24 hr at room temp. Extraction with $CHCl_3$ and subsequent CC on PVA 500 with MeOH yielded an oil (3 mg), whose physicochemical data were in agreement with those of **20**.

Compound **21** *by methanolysis of* **16**. Compound **16** (7 mg) was treated with oxalic acid (20 mg) in MeOH for 2 hr at room temp. After addition of H_2O (5 ml) and extraction with $CHCl_3$, CC on PVA 500 with MeOH yielded an oil (4 mg), whose physicochemical data were in agreement with those of **21**.

3,5-Hexalobine E (= (2′R)-3-(2,3-*epoxy*-3-*methylbutyl*)-5-(3-*hydroxy*-3-*methyl*-1-*butenyl*)*indole*, **17**). Oil: 111 mg. TLC: R_f 0.20 [cyclohexane–EtOAc (3:2)]; Ce^{IV} reagent: yellow. $[\alpha]_D^{21}$ −6° (*c* 0.25) (ref. [1]: $[\alpha]_D^{20}$ −3.3 (*c* 1.3)). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1].

3,6-(E)-Hexalobine E (= (2′R,E)-3-(2,3-*epoxy*-3-*methylbutyl*)-6-(3-*hydroxy*-3-*methyl*-1-*butenyl*)*indole*, **18**). Crystal 157 mg. Mp 129–131°. TLC: R_f 0.34 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: rose. $[\alpha]_D^{21}$ +1° (*c* 0.5). IR ν_{max} cm^{-1}: 3600, 3480. UV λ_{max} nm (log ε): 251 (4.46), 295 (4.14). ^{1}H NMR (400 MHz): δ 1.34, 1.43 (3H each, *s*, Me-4′, Me-5′), 1.45 (6H, *s*, Me-4″, Me-5″), 2.90–3.02 (2H, *m*, H_A-1′, H_B-1′), 3.07 (1H, *dd*, $J_1 = J_2 = 6$ Hz, H-2′), 6.37, 6.68 (1H each, AB-system, $J = 16$ Hz, H-1″, H-2″), 7.07 (1H, *d*, $J = 2.2$ Hz, H-2), 7.24 (1H, *dd*, $J_1 = 8$, $J_2 = 1.5$ Hz, H-5), 7.35 (1H, *m*, H-7), 7.57 (1H, *d*, $J = 8$ Hz, H-4), 8.02 (1H, *br s*, NH). ^{13}C NMR (22.5 MHz): δ 18.9 (C-5′), 24.8 (C-4′), 25.3 (C-1′), 30.0 (C-4″, C-5″), 58.6 (C-3′), 64.2 (C-2′), 71.1 (C-3″), 109.4 (C-7), 112.8 (C-3), 118.3, 118.9 (C-4, C-5), 122.3 (C-2), 127.3, 127.4 (C-1″, C-3a), 131.6 (C-6), 135.9 (C-2″), 136.8 (C-7a). EIMS *m/z* (rel. int.): 285.1730 (100, $[M]^+$, calcd for $C_{18}H_{23}NO_2$: 285.1729), 270 (26), 242.1548 (13, calcd for $C_{16}H_{20}NO$: 242.1545), 214.1229 (51, calcd for $C_{14}H_{16}NO$: 214.1231), 199 (12), 198 (92), 196 (12), 180 (20), 156 (16).

3,6-(Z)-Hexalobine E (= (2′R,Z)-3-(2,3-*epoxy*-3-*methylbutyl*)-6-(3-*hydroxy*-3-*methyl*-1-*butenyl*)*indole*, **19**). Oil: 42 mg. TLC: R_f 0.41 [cyclohexane–EtOAc (3:2)]: Ce^{IV} reagent: brown–violet. $[\alpha]_D^{21}$ −2° (*c* 1.1). IR ν_{max} cm^{-1}: 3595, 3479. UV λ_{max} nm (log ε): 231 (4.39), 242 (4.38), 292 (3.99). ^{1}H NMR (360 Hz): δ 1.35 (3H, *s*, Me-5′ or Me-4′), 1.39 (6H, *s*, Me-4″, Me-5″), 1.42 (3H, *s*, Me-4′ or Me-5′), 2.87–3.02 (2H, *m*, H_A-1′, H_B-1′), 3.07 (1H, *dd*, $J_1 = J_2 = 6$ Hz, H-2′), 5.75, 6.60 (1H each, AB-system, $J = 12.5$ Hz, H-1″, H-2″), 7.05 (1H, *br d*, $J = 2.1$ Hz, H-2), 7.10, (1H, *dd*, $J_1 = 8$, $J_2 = 1.5$ Hz, H-5), 7.45 (1H, *br s*, H-7), 7.57 (1H, *d*, $J = 8$ Hz, H-4), 8.12 (1H, *br s*, NH).

^{13}C NMR (90 MHz): δ18.8 (C-5'), 24.8 (C-4'), 25.2 (C-1'), 31.2, 31.3 (C-4'', C-5''), 58.7 (C-3'), 64.1 (C-2'), 72.1 (C-3''), 111.6 (C-7), 112.4 (C-3), 118.6, 120.9 (C-4, C-5), 122.4 (C-2), 126.6, 128.8 (C-3a, C-1''), 131.2 (C-6), 136.2 (C-2''), 138.3 (C-7a). EIMS *m/z* (rel. int.): 285.1727 (73, $[M]^+$, calcd for $C_{18}H_{23}NO_2$: 285.1729), 270 (26), 242 (16), 214.1229 (53, calcd for $C_{14}H_{16}NO$: 214.1231), 199 (18), 198.0919 (100, calcd for $C_{13}H_{12}NO$: 198.0918), 182 (10), 180 (18), 170 (17), 168 (11), 167 (11), 156 (29), 154 (17), 143 (15).

Dihydro-3,6-hexalobine E (= (2'R)-3-(2,3-*epoxy*-3-*methylbutyl*)-6-(3-*hydroxy*-3-*methylbutyl*)*indole*). Compound **18** (3 mg) (or **19**) were hydrogenated in EtOH in the presence of PtO_2 for 1 hr at room temp. CC on PVA 500 with MeOH yielded the identical product (2 mg). TLC: R_f 0.24 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: brown. CD (MeOH) λ_{max} nm (Δε): 233 (+0.7). IR ν_{max} cm^{-1}: 3608, 3480. UV λ_{max} nm (log ε): 224 (4.56), 282 (3.77), 292 (3.71). ^{1}H NMR (360 MHz): δ1.30 (6H, *s*, Me-4'', Me-5''), 1.34, 1.42 (3H each, *s*, Me-4', Me-5'), 1.77–1.88 (*AA'*BB'-system, H_A-2'', H_B-2''), 2.78–2.85 (2H, AA'*BB'*-system, H_A-1'', H_B-1''), 2.90–3.09 (3H, *m*, H_A-1', H_B-1', H-2'), 6.98–7.04 (2H, *m*, H-2, H-5), 7.20 (1H, *dd*, J_1 = 1.5, J_2 = 0.9 Hz, H-7), 7.55 (1H, *br d*, J = 8 Hz, H-4), 7.91 (1H, *br s*, NH). EIMS *m/z* (rel. int.): 287 (100, $[M]^+$), 272 (12), 244 (20), 216 (31), 214 (10), 200 (11), 198 (16), 156 (23), 143 (22), 142 (14).

(R)-3-(2,3-*Dihydroxy*-3-*methylbutyl*)-5-(3-*methyl*-1-*oxo*-2-*butenyl*)*indole* (**20**). Oil: 294 mg. TLC: R_f 0.23 [$CHCl_3$–MeOH (9:1)]; Ce^{IV} reagent: orange. $[\alpha]_D^{21}$ +64° (*c* 0.31) (ref. [1]: $[\alpha]_D^{20}$ +62° (*c* 0.3)). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1].

(R)-3-(2,3-*Dihydroxy*-3-*methylbutyl*)-5-(3-*methylbutyl*)*indole from* **20**. $AlCl_3$–$LiAlH_4$ (188 and 50 mg) dissolved in Et_2O was added to **20** (5 mg) dissolved in THF (at 0°) and the mixt. stirred for 1 hr at room temp. Addition of H_2O, extraction and evapn of the organic layer, followed by CC on PVA 500 with MeOH afforded (*R*)-3-(2,3-dihydroxy-3-methylbutyl)-5-(3-methylbutyl)indole (1 mg) as an oil. TLC: R_f 0.25 [$CHCl_3$–MeOH (19:1)]; Ce^{IV} reagent: brown–yellow. $[\alpha]_D^{21}$ +2° (*c* 0.1) (ref. [1]: $[\alpha]_D^{20}$ +2° (*c* 0.3)). CD (EtOH) λ_{max} nm (Δε): 230 (+). CD (in DMSO + $Mo_2(OAc)_4$ [18]) λ_{max} nm (Δε): 275 (+), 315 (−), 365 (−). IR, UV, ^{1}H NMR, ^{13}C NMR, MS in agreement with published data [1].

(R)-3-(2-*Hydroxy*-3-*methoxy*-3-*methylbutyl*)-5-(3-*methyl*-1-*oxo*-2-*butenyl*)*indole* (**21**). Oil: 59 mg. TLC: R_f 0.10 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: brown–yellow. $[\alpha]_D^{21}$ +76° (*c* 1.40). IR ν_{max} cm^{-1}: 3476, 1653. UV λ_{max} nm (log ε): 217 (4.22), 268 (4.44), 311 (4.06). ^{1}H NMR (400 MHz): δ1.27, 1.29 (3H each, *s*, Me-4', Me-5'), 2.03 (3H, *d*, J = 1.5 Hz, Me-4''), 2.20 (3H, *d*, J = 1 Hz, Me-5''), 2.43 (1H, *br s*, OH), 2.78 (1H, *ddd*, J_1 = 15, J_2 = 10.5, J_3 = 0.5 Hz, H_A-1'), 3.04 (1H, *ddd*, J_1 = 15, J_2 = 2, J_3 = 0.9 Hz, H_B-1'), 3.30 (3H, *s*, OMe), 3.85 (1H, *dd*, J_1 = 10.5, J_2 = 2 Hz, H-2'), 6.85 (1H, *m*, H-2''), 7.21 (1H, *d*, J = 2.1 Hz, H-2), 7.36 (1H, *br d*, J = 8.5 Hz, H-7), 7.84 (1H, *dd*, J_1 = 8.5, J_2 = 1.5 Hz, H-6), 8.27 (1H, *br s*, NH), 8.29 (1H, *m*, H-4). ^{13}C NMR (22.5 MHz): δ19.7, 20.7 (C-4', C-5'), 21.0 (C-5''), 27.3 (C-1'), 27.7 (C-4''), 49.2 (OMe), 76.8 (C-2'), 77.3 (C-3'), 110.9 (C-7), 115.3 (C-3), 120.7 (C-4), 122.2 (C-2''), 122.6 (C-6), 123.9 (C-2), 127.4 (C-3a), 131.3 (C-5), 138.8 (C-7a), 153.9 (C-3''), 192.2 (C-1''). EIMS *m/z* (rel. int.): 315.1843 (14, $[M]^+$, calcd for $C_{19}H_{25}NO_3$: 315.1843), 243.1263 (16, calcd for $C_{15}H_{17}NO_2$: 243.1259), 213 (10), 212.1076 (22, calcd for $C_{14}H_{14}NO$: 212.1075), 200 (23), 83 (27), 73 (100).

3-(2-*Hydroxy*-3-*methyl*-3-*butenyl*)-5-(3-*methyl*-1-*oxo*-2-*butenyl*)*indole* (**22**). Oil: 1.5 mg. TLC: R_f 0.23 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: brown–yellow. $[\alpha]_D^{21}$ −6° (*c* 0.13). IR ν_{max} cm^{-1}: 3607, 3475, 1652. UV λ_{max} nm (log ε): 216 (4.24), 267 (4.41), 311 (4.05). ^{1}H NMR (400 MHz): δ1.87 (3H, *s*, Me-5'), 2.04 (3H, *d*, J = 1.5 Hz, Me-4''), 2.21 (3H, *d*, J = 1.5 Hz, Me-5''), 2.97 (1H, *ddd*, J_1 = 15, J_2 = 8.5, J_3 = 0.9 Hz, H_A-1'), 3.14 (1H, *ddd*, J_1 = 15, J_2 = 4.3, J_3 = 0.9 Hz, H_B-1'), 4.42 (1H, *dd*, J_1 = 8.5, J_2 = 4.3 Hz, H-2'), 4.90, 5.03 (1H each, *m*, H_A-4', H_B-4'), 6.85 (1H, *m*, H-2''), 7.18 (1H, *br d*, J = 2.2 Hz, H-2), 7.39 (1H, *dd*, J_1 = 8.5, J_2 = 0.5 Hz, H-7), 7.86 (1H, *dd*, J_1 = 8.5, J_2 = 1.5 Hz, H-6), 8.25 (1H, *br s*, NH), 8.29 (1H, *m*, H-4). EIMS *m/z* (rel. int.): 283.1567 (8, $[M]^+$, calcd for $C_{18}H_{21}NO_2$: 283.1572), 213 (42), 212.1070 (100, calcd for $C_{14}H_{14}NO$: 212.1075), 130 (10), 129 (10).

(R)-3-(2,3-*Epoxy*-3-*methylbutyl*)-5-(3-*methyl*-1,3-*butadienyl*)*indole* (**23**). Oil: 10 mg. TLC: R_f 0.52 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: yellow–green. $[\alpha]_D^{21}$ −4° (Me_2CO; *c* 0.66). IR ν_{max} cm^{-1}: 3479. UV λ_{max} nm (log ε): 266 (4.49), 273 (sh, 4.45), 305 (4.28). ^{1}H NMR [360 MHz, $(CD_3)_2CO$]: δ1.28, 1.40 (3H each, *s*, Me-4', Me-5'), 1.98 (3H, *m*, Me-5''), 2.89–3.03 (3H, *m*, H_A-1', H_B-1', H-2'), 4.98, 5.07 (1H each, *m*, H_A-4'', H_B-4''), 6.74, 6.93 (1H each, AB-system, J = 16 Hz, H-1'', H-2''), 7.20 (1H, *m*, H-2), 7.36 (2H, not resolved, H-6, H-7), 7.74 (1H, *br s*, H-4), 10.10 (1H, *br s*, NH). DCIMS *m/z* (rel. int.): 268 (67, $[M + H]^+$), 267 (59, $[M]^+$), 266 (11), 252 (22), 250 (15), 238 (16), 198 (30), 197 (23), 196 (100), 195 (22), 194 (24), 184 (10), 182 (15), 181 (13), 180 (16), 144 (10), HREIMS: 267.1623 (25, $[M]^+$, calcd for $C_{18}H_{21}N$: 267.1623), 196.1126 (20, calcd for $C_{14}H_{14}N$: 196.1126), 180.0814 (100, calcd for $C_{13}H_{10}N$: 180.0813).

(R)-3-(2,3-*Epoxy*-3-*methylbutyl*)-5-(3-*methylbutyl*)*indole*. Compound **23** (8 mg) was dissolved in EtOH and hydrogenated on PtO_2/C. CC on PVA 500 with MeOH yielded an oil (2.5 mg). TLC: R_f 0.26 [cyclohexane–EtOAc (4:1)]; anisaldehyde reagent: violet. $[\alpha]_D^{21}$ −5° (*c* 0.2). CD (MeOH) λ_{max} nm (Δε): 228 (+0.97). IR ν_{max} cm^{-1}: 3482. UV λ_{max} nm (log ε): 224 (4.68), 278 (3.92), 294 (3.77). ^{1}H NMR (360 MHz): δ0.95 (6H, *d*, J = 6.1 Hz, Me-4'', Me-5''), 1.35, 1.43 (3H each, *s*, Me-4', Me-5'), 1.53–1.67 (3H, H_A-2'', H_B-2'', H-3''), 2.72 (2H, *m*, H_A-1'', H_B-1''), 2.91 (1H, *ddd*, J_1 = 17.5, J_2 = 8.5, J_3 = 1 Hz, H_A-1'), 3.03–3.11 (2H, *m*, H_B-1', H-2'), 7.03 (1H, *m*, H-2), 7.05 (1H, *dd*, J_1 = 8.5, J_2 = 1.6 Hz, H-6), 7.28 (1H, *dd*, J_1 = 8.5, J_2 = 0.5 Hz, H-7), 7.42 (1H, *m*, H-4), 7.92 (1H, *br s*, NH). EIMS *m/z* (rel. int.): 271 (93, $[M]^+$), 257 (23), 256 (83), 229 (29), 228 (100), 215 (12), 214 (47), 201 (27), 200 (99), 157 (15), 156 (44), 154 (13), 144 (23), 143 (80), 142 (21), 130 (12), 128 (15), 115 (13). All

physicochemical data in agreement with those for the hydrogenation product of 3,5-hexalobine B [1].

3-(2-*Formyl*-2-*methylpropyl*)-5-(3-*methyl*-1-*oxo*-2-*butenyl*)*indole* (**24**). Oil: 16 mg. TLC: R_f 0.33 [cyclohexane–EtOAc (1:1)]; Ce^{IV} reagent: brown–yellow. IR ν_{max} cm^{-1}: 3475, 1723, 1654. UV λ_{max} nm (log ε): 215 (4.33), 267 (4.54), 310 (4.17). ^1H NMR (400 MHz): δ1.14 (6H, *s*, Me-4′, Me-5′), 2.04, 2.20 (3H each, *d*, J = 1.5 Hz, Me-4″, Me-5″), 2.98 (2H, *d*, J = 0.5 Hz, H_A-1′, H_B-1′), 6.82 (1H, *m*, H-2″), 7.02 (1H, *br d*, J = 2.3 Hz, H-2), 7.36 (1H, *dd*, J_1 = 8.5, J_2 = 0.5 Hz, H-7), 7.84 (1H, *dd*, J_1 = 8.5, J_2 = 1.5 Hz, H-6), 8.22 (1H, *m*, H-4), 8.31 (1H, *br s*, NH), 9.63 (1H, *s*, CHO). ^{13}C NMR (22.5 MHz): δ21.1 (C-5″), 21.9 (C-4′, C-5′), 27.8 (C-4″), 32.1 (C-1′), 47.2 (C-2′), 110.9 (C-7), 113.2 (C-3), 120.9 (C-4), 122.0 (C-2″), 122.6 (C-6), 124.6 (C-2), 128.1 (C-3a), 131.7 (C-5), 138.3 (C-7a), 154.2 (C-3″), 192.1 (C-1″), 206.3 (CHO). EIMS *m/z* (rel. int.): 283.1570 (25, $[M]^+$, calcd for $C_{18}H_{21}NO_2$: 283.1572), 213 (16), 212.1076 (100, calcd for $C_{14}H_{14}NO$: 212.1075), 210 (10), 129.0580 (10, calcd for C_9H_7N: 129.0578).

Palmitic acid (R)-3-*hydroxy*-3-*methyl*-2-[6-(3-*methyl*-2-*butenyl*)*indole*-3-*yl*]*butyl ester* (**25**). Oil: 2 mg. TLC: R_f 0.20 [cyclohexane–EtOAc (4:1)]; anisaldehyde reagent: brown–violet. $[\alpha]_D^{21}$ − 17° (*c* 0.16) (ref. [1]: $[\alpha]_D^{20}$ − 19° (*c* 1.3)). DCIMS *m/z* (rel. int.): 526 (16, $[M + H]^+$), 525 (23, $[M]^+$), 510 (30), 509 (88), 508 (100, $[M + H - H_2O]^+$), 506 (11), 470 (10), 326 (14), 283 (22), 272 (13), 271 (79), 269 (100), 258 (22), 257 (96), 255 (10), 254 (12), 253 (15), 252 (70), 240 (15), 212 (29), 211 (89), 199 (12), 198 (72). IR, UV, ^1H NMR, ^{13}C NMR in agreement with published data [1].

Oleic acid (R)-3-*hydroxy*-3-*methyl*-2-[6-(3-*methyl*-2-*butenyl*)-*indole*-3-*yl*]*butyl ester* (**26**). Oil: 2 mg. TLC: R_f 0.20 [cyclohexane–EtOAc (4:1)]; anisaldehyde reagent: brown–violet. $[\alpha]_D^{21}$ − 21° (*c* 0.25) (ref. [1]: $[\alpha]_D^{20}$ − 20° (*c* 1.9)). DCIMS *m/z* (rel. int.): 552 (9, $[M + H]^+$), 551 (10, $[M]^+$), 536 (18), 535 (63), 534 (100, $[M + H - H_2O]^+$), 284 (13), 283 (56), 271 (47), 270 (100), 257 (16), 252 (42), 211 (75), 198 (35). IR, UV, ^1H NMR, ^{13}C NMR in agreement with published data [1].

(9Z,12Z)-*Linoleic acid* (R)-3-*hydroxy*-3-*methyl*-2-[6-(3-*methyl*-2-*butenyl*)*indole*-3-*yl*]*butyl ester* (**27**). Oil: 3 mg. TLC: R_f 0.20 [cyclohexane–EtOAc (4:1)]; anisaldehyde reagent: brown–violet. $[\alpha]_D^{21}$ − 18° (*c* 0.25) (ref. [1]: $[\alpha]_D^{20}$ − 20° (*c* 1.7)). DCIMS *m/z* (rel. int.): 550 (15, $[M + H]^+$), 549 (13, $[M]^+$), 534 (18), 533 (60), 532 (100, $[M + H - H_2O]^+$), 281 (24), 271 (46), 270 (100), 269 (24), 263 (11), 253 (10), 252 (46), 240 (10), 212 (13), 211 (69), 198 (45). IR, UV, ^1H NMR, ^{13}C NMR in agreement with published data [1].

Acknowledgements—Thanks are due to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

REFERENCES

1. Achenbach, H., Renner, C. and Waibel, R. (1995) *Liebigs Ann. Chem.* 1327.
2. Keay, R. W. J. (1952) *Kew Bulletin* (Royal Botanic Gardens, ed.), p. 149. HMSO, London.
3. Hocquemiller, R., Cabalion, P., Fournet, A. and Cavé, A. (1984) *Planta Med.* **50**, 23.
4. Hocquemiller, R., Cabalion, P., Bruneton, J. and Cavé, A. (1978) *Plant. Med. Phytother.* **12**, 230.
5. Nair, M. G. and Chang, F. C. (1973) *Phytochemistry* **12**, 903.
6. Yoshihara, T., Takamatsu, S. and Sakamura, S. (1978) *Agric. Biol. Chem.* **42**, 623.
7. Yoshihara, T., Yamaguchi, K., Takamatsu, S. and Sakamura, S. (1981) *Agric. Biol. Chem.* **45**, 2593.
8. Loder, J. W., Moorhouse, A. and Russell, G. B. (1969) *Aust. J. Chem.* **22**, 1531.
9. Gellért, M., Esedö, K., Reisch, J., Novák, I., Szendrei, K., Minker, E. and Koltai, M. (1974) *Acta Pharm. Hung.* **44**, 26.
10. Guinaudeau, H., Leboeuf, M. and Cavé, A. (1975) *Lloydia* **38**, 275.
11. Hocquemiller, H., Cavé, A. and Raharisololalao, A. (1981) *J. Nat. Prod.* **44**, 551.
12. Achenbach, H., Renner, C. and Addae-Mensah, I. (1982) *Liebigs Ann. Chem.* 1623.
13. Laprévote, O., Roblot, F., Hocquemiller, R. and Cavé, A. (1987) *J. Nat. Prod.* **50**, 984.
14. Achenbach, H. and Raffelsberger, B. (1979) *Tetrahedron Letters* 2571.
15. Achenbach, H., Renner, C. and Addae-Mensah, I. (1984) *Heterocycles* **22**, 2501.
16. Achenbach, H. (1986) *Pure Appl. Chem.* **58**, 653.
17. Achenbach, H., Renner, C. and Franke, D. (1986) *Sci. Pharm.* **54**, 137.
18. Frelek, J. and Snatzke, G. (1983) *Fresenius' Z. Anal. Chem.* **316**, 261.
19. Delle Monache, F., Delle Monache, G., De Moraes e Souza, M. A., Da Salete Lavaleanti, M. and Chiapetta, A. (1989) *Gazz. Chim. Ital.* **119**, 435.
20. Achenbach, H., Franke, D. and Renner, L. (1985) *Arch. Pharm. (Weinheim)* **318**, 1147.
21. Stahl, E. (1967) *Dünnschichtchromatographie*, 2nd Edn, p. 817 (reag. No. 15). Springer, Berlin.
22. Stahl, E. (1967) *Dünnschichtchromatographie*, 2nd Edn, p. 820 (reag. No. 39). Springer, Berlin.
23. Achenbach, H., Renner, C., Wörth, J. and Addae-Mensah, I. (1982) *Liebigs Ann. Chem.* 1132.