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LIGNANOLIDES FROM *BUPLEURUM SALICIFOLIUM*

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Key Word Index—*Bupleurum salicifolium*; Umbelliferae; roots; lignans; ^{1}H NMR; ^{13}C NMR.

Abstract—Three new lignans isolated from the roots of *Bupleurum salicifolium* were characterised as guamarol, isoguamarol and guamarolin on the basis of chemical and spectral evidence. The known lignans, kaerophyllin, isokaerophyllin and matairesinol, were also obtained.

INTRODUCTION

Bupleurum salicifolium, a member of the Umbelliferae and endemic to the Canary Islands, is rich in lignans. Seven new lignans from this plant, (one from the branches [1], four from the leaves [2, 3] and two from the seeds [4]), have already been described and now three more new lignans have been obtained from the roots. Two belong to the benzylidenebenzyl-γ-butyrolactone group, *viz* guamarol (**1**) [*E* 2(3′-hydroxy-4′-methoxybenzylidene)-3(3″,4″-methylenedioxybenzyl-3*R*-γ-butyrolactone] and *iso*-guamarol (**2**) [*Z* 2(3′-hydroxy-4′-methoxybenzylidene)-3(3″,4″-methylenedioxybenzyl)-3R-γ-butyrolactone]) while the third, guamarolin (**3**) [2*R*(3′-hydroxy-4′-methoxybenzyl)-3*R*-(3″,4″-methylenedioxybenzyl)-γ-butyrolactone] is a dibenzyl-γ-butyrolactone. The structures and stereochemistry of all these compounds were determined from their spectral data and chemical transformations.

The most distinctive structural feature of **1**–**3** is the presence of a 3-hydroxy-4-methoxyphenyl group, which is very unusual in naturally occurring lignans. To date it has only been found in prestegane A and prestegane B, dibenzyl-γ-butyrolactones from *Steganotaenia araliacea* [5], and provides yet another instance of the intriguing properties of *B. salicifolium*.

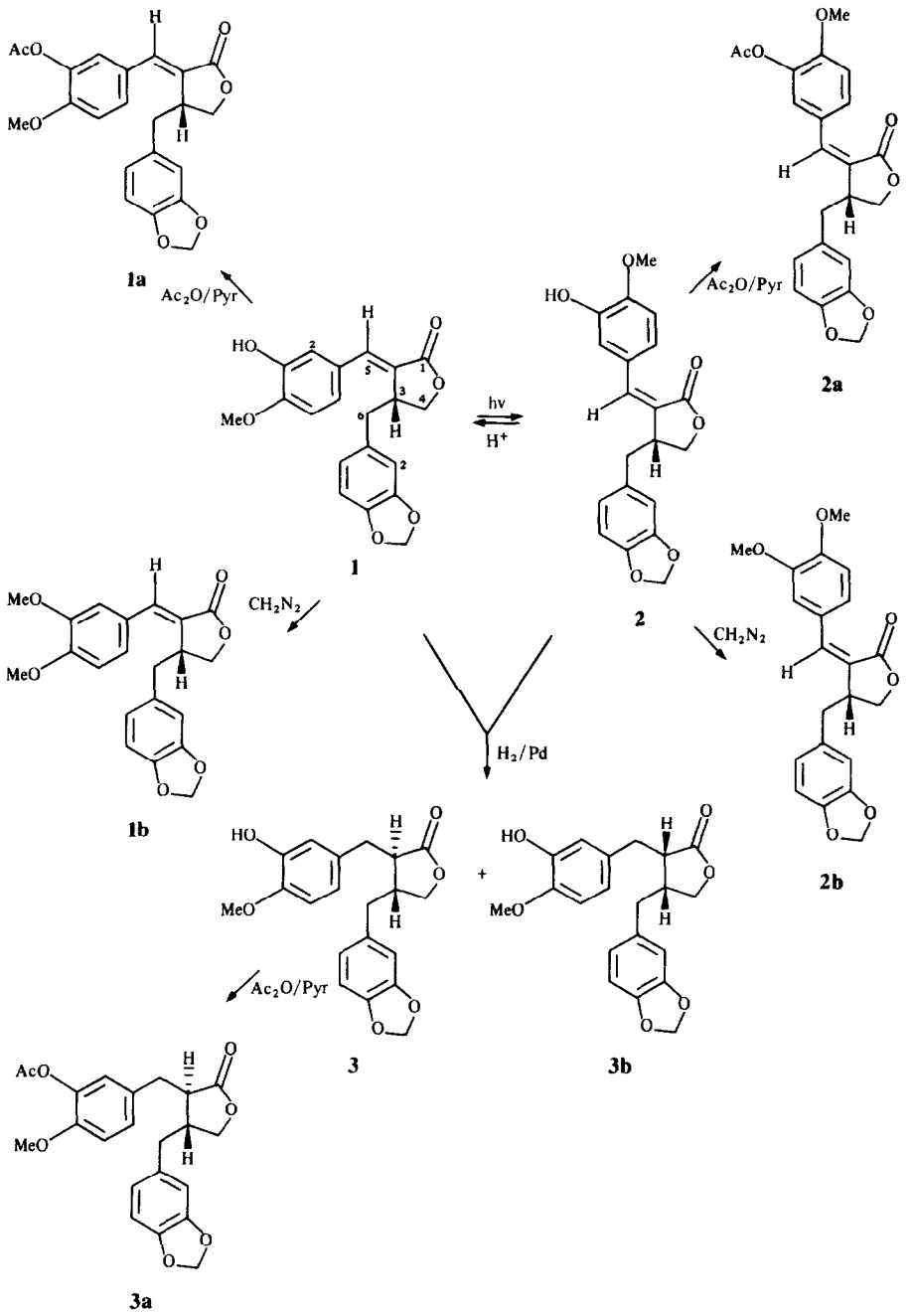
The known lignans, kaerophyllin (**1b**) [*E* 2(3′,4′-dimethoxybenzylidene)-3(3″,4″-methylenedioxyphenylmethyl)-3*R*-γ-butyrolactone], isokaerophyllin (**2b**) [*Z*-2(3′,4′-dimethoxybenzylidene)-3(3″,4″-methylenedioxyphenylmethyl)-3*R*-γ-butyrolactone] and matairesinol [2(3′-methoxy-4′-hydroxyphenylmethyl)-3(3″-methoxy-4″-hydroxyphenylmethyl)-2*R*,3*R*-γ-butyrolactone], were also obtained. *B. salicifolium* exhibits an interesting specificity for elaborating lignans, which are substances that have been shown to inhibit topo-isomerase II, an enzyme associated with the replication of the HIV-1 virus responsible for AIDS [6].

RESULTS AND DISCUSSION

Six lignans were separated from an ethanol extract of the roots of *B. salicifolium* and treated and chromatographed as described in the Experimental. Three of the lignans were new to the literature. One, guamarol (**1**), had a $[M]^+$ *m/z* 354, molecular formula $C_{20}H_{18}O_6$, ν_{max} 1740 cm^{-1} (C=O) and 3420 cm^{-1} (OH); its mass fragmentation pattern showed peaks for two aromatic groups, a piperonylmethyl group on C-3 (*m/z* 135, $[C_6H_3(OCH_2O)CH_2]^+$), (*m/z* 162, $[C_6H_3(OCH_2O)-CH_2C_2H_3]^+$) and an isoguayacyl group on the olefinic C-5 (*m/z* 123, 9%, $[C_6H_3(OH)(OMe)]^+$). The ^{1}H NMR spectrum of guamarol (Table 1) had the characteristic 2-benzylidene-3-benzyl-γ-butyrolactone-type *E* isomer signals [7], notably a multiplet centred at δ3.79 corresponding to H-3 and two doublets at δ4.25 (2H, H-4) and δ7.50 (1H) ascribed to the olefinic H-5. The ^{1}H NMR also had signals for six benzene protons, three of which were those of a piperonylmethyl group. The signals of the other three benzene protons must be those of a 3-hydroxy-4-methoxyphenyl group because they were not consonant with those of the 3-methoxy-4-hydroxyphenyl (guayacyl) group common to many lignans of the benzylidene benzyl-γ-butyrolactone type such as 3″-deoxy-γ-thujaplicatin-4-*O*-methyl ether [δ 7.04 *d* (H-2′); 6.99 *d* (H-5′); 7.21 *dd* (H-6′)] [8]. The equivalent values in guamarol (see Table 1) differed by 34 Hz for H-2′ and 20 Hz for H-6′, which, when taken in conjunction with the results of COSY experiments, sited the OH at C-3′ in the benzene ring. ROESY experiments [9] revealed the couplings shown in Fig. 1, which unequivocally confirmed the relative configuration proposed for compound **1**. The ^{13}C NMR spectrum of guamarol (Table 2) is very similar to that of kaerophyllin (**1b**) [10] but with a δ6 downfield shift for the C-2′ signals and a δ4.8 upfield shift for those of C-3′.

The acetyl derivative, **1a**, was also formed from guamarol: ($[M]^+$ *m/z* 398, $C_{22}H_{22}O_7$, *m/z* 135 (base peak) and *m/z* 165, 4% $[C_6H_3(OMe)(OCOMe)]^+$). Its ^{1}H NMR spectrum (Table 1) featured signals for H-6′ 62 Hz downfield from those of H-6′ in guamarol confirming that the OH group was at C-3′. Had it been at C-4′, the shift of the H-6′ signals would be very slight and less than that of H-2′ and H-5′, as can be seen from a comparison of the literature data for this group with a *para* hydroxyl group [8].

The negative optical activity of guamarol indicated a β orientation of the H-3 hydrogen, which was confirmed by hydrogenation of the prochiral double bond of guamarol



with H_2 and Pd/C when more of the diasteroisomer **3b** (75%) than of the diasteroisomer **3** (25%) was formed due to the steric hindrance of the piperonylmethyl group. The transformation of guamarol to kaerophyllin (**1b**) when treated with diazomethane confirmed its structure as **1**.

The other benzylidene benzyl-γ-butyrolactone isolated from the roots of *B. salicifolium*, isoguamarol (**2**), showed a $[M]^+$ *m/z* 354, formula $C_{20}H_{18}O_6$, negative optical activity and spectroscopic data corresponding to the structure of the *Z*-isomer of guamarol. The mass spectrum of isoguamarol had the same fragments as that of guamarol, while its ^1H NMR spectrum displayed the signals of a *Z*-isomer, *viz.* a multiplet centred at δ 3.26 due to H-3, two double doublets centred at δ 4.09 (H-4a) and δ 4.32 (H-4b), and a singlet at δ 6.65 attributed to the olefinic H-5. In the ^{13}C NMR spectra, the signals of the C-2 are shifted δ5.1 upfield, those of C-5, δ 3.1 downfield and those of C-6, δ 3.3 downfield, compared to guamarol (Table 2). Isoguamarol also formed an acetate, **2a** ($[M]^+$ *m/z* 398, $C_{22}H_{22}O_7$), with signals in its ^1H NMR spectrum for a 42 Hz shift of H-6′ in relation to those of the H-6′ in isoguamarol.

Table 1. ^{1}H NMR data of compounds **1**, **1a**, **2**, **2a**, **3** and **3a** (200 MHz, $CDCl_3$)*

H	1	1a	2	2a	3	3a
2	—	—	—	—	2.30–2.60 *m*	2.40–2.60 *m*
3	3.79 *m*	3.72 *m*	3.26 *m*	3.32 *m*	2.30–2.60 *m*	2.40–2.60 *m*
4a			4.09 *dd* (3.8, 9.0)	4.09 *dd* (3.8, 9.1)	3.94 *dd* (2.9, 6.5)	3.83 *dd* (7.0, 10.2)
	4.25 *t* (2.6, 6.1)	4.26 *m*				
4b			4.32 *dd* (7.3, 9.0)	4.32 *dd* (6.9, 9.1)	4.10 *dd* (6.5, 9.2)	4.10 *dd* (7.0, 9.2)
5a					2.01 *dd* (5.2, 14.0)	
	7.50 *d* (1.9)	7.51 *d* (1.8)	6.65 *s*	6.60 *br s*		2.93 *d* (5.7)
5b					2.82 *dd* (6.9, 14.0)	
6a	2.61 *dd* (10.3, 14.2)	2.59 *dd* (10.1, 14.2)	2.72 *dd* (8.9, 13.7)	2.76 *dd* (8.9, 13.2)		
					2.30–2.60 *m*	2.40–2.60 *m*
6b	3.03 *dd* (4.2, 14.2)	2.99 *dd* (4.1, 14.2)	2.92 *dd* (6.9, 13.7)	2.92 *dd* (6.3, 13.2)		
2′	7.21 *d* (2.1)	7.28 *d* (2.2)	7.44 *d* (2.0)	7.78 *d* (2.0)	6.73 *d* (2.0)	6.79 *d* (2.0)
5′	6.91 *d* (8.4)	7.03 *d* (8.6)	6.81 *d* (8.4)	6.94 *d* (8.6)	6.70 *d* (8.2)	6.71 *d* (8.2)
6′	7.11 *dd* (2.1, 8.4)	7.42 *dd* (2.2, 8.6)	7.15 *dd* (2.1, 8.4)	7.70 *dd* (2.0, 8.6)	6.66 *dd* (2.0, 8.2)	6.99 *dd* (2.1, 8.2)
2″	6.71 *d* (1.5)	6.77 *d* (1.6)	6.59 *d* (1.7)	6.68 *br s*	6.46 *d* (1.7)	6.48 *br s*
5″	6.75 *d* (7.8)	6.73 *d* (7.8)	6.76 *d* (7.8)	6.76 *d* (7.9)	6.78 *d* (8.0)	6.88 *d* (8.3)
6″	6.66 *dd* (1.6, 7.8)	6.63 *dd* (1.7, 7.8)	6.62 *dd* (1.7, 7.8)	6.62 *dd* (1.8, 7.9)	6.46 *dd* (1.8, 8.0)	6.48 *dd* (2.0, 8.3)
OMe	3.95 *s*	3.89 *s*	3.92 *s*	3.86 *s*	3.88 *s*	3.81 *s*
OCH_2O	5.94 *s*	5.94 *s*	5.96 *s*	5.96 *s*	5.93 *s*	5.94 *s*
OH	5.78 *s*	—	5.98 *s*	—	6.60 *s*	—
OAc	—	2.36 *s*	—	2.32 *s*	—	2.31 *s*

*Values in δ; coupling constants (Hz) in parentheses.

The structure of the new lignan, isoguamarol, was confirmed by the following reactions. It could be transformed to isokaerophyllin (**2b**) by reaction with diazomethane; it was isomerised to guamarol (**1**) by UV irradiation reaching a photostationary equilibrium; it could be hydrogenated to form the γ-butyrolactones **3** and **3b**, and it was obtained by isomerisation of **1** in an acid medium.

The absolute configuration of the only chiral centre, C-3, in guamarol and isoguamarol was settled beyond question because treatment with CH_2N_2 converted these compounds into kaerophyllin and isokaerophyllin, respectively. The latter are lignans with a known absolute configuration [2, 11, 12].* The physical and spectral data of these methylation products proved to be totally compatible with those of natural kaerophyllin and isokaerophyllin.

The third new lignan, guamarolin (**3**), was an oil with a $[M]^+$ *m/z* 356, $C_{20}H_{20}O_6$, ν_{max} 1760 cm^{-1} (C=O), 3440 cm^{-1} (OH) and negative optical activity. Its mass spectrum suggested the presence of a hydroxymethoxybenzyl group bonded with C-2 (*m/z* 137, base peak) and a piperonylmethyl group (*m/z* 135, 67%) attached to C-3, which was confirmed by the presence of the fragment at

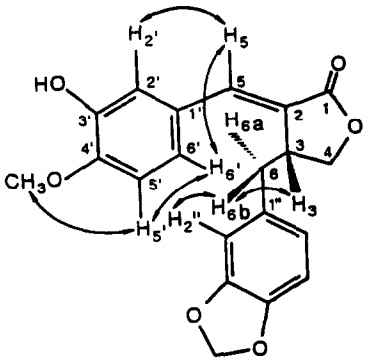


Fig. 1. NOEs observed in compound **1**.

*A typographical error in ref. [2] stated isokaerophyllin to be 3*S* and not 3*R*.

Table 2. ^{13}C NMR data of compounds **1**, **1a**, **2**, **2a**, **3** and **3a** (50 MHz, $CDCl_3$)*

C	1	1a	2	2a	3	3a
1	172.83	173.94	172.70	174.24	178.44	178.13
2	131.83	129.60	126.76	126.68	46.44	46.61
3	40.11	40.03	44.35	44.16	41.50	41.30
4	69.60	69.62	69.93	69.71	71.08	71.06
5	137.46	136.27	140.52	139.52	34.88	34.18
6	37.56	37.57	40.87	40.69	38.39	38.51
1′	131.83	131.58	131.70	130.84	130.96	130.40
2′	115.21	112.54	117.30	116.03	115.37	123.97
3′	146.70	147.23	146.91	146.63	145.75	151.70
4′	146.09	146.05	146.70	146.63	145.56	144.12
5′	110.90	109.07	112.84	112.56	110.83	112.97
6′	124.09	123.95	124.33	123.94	121.56	123.97
1″	124.09	131.58	124.13	132.52	131.75	131.73
2″	108.66	108.46	108.55	108.22	108.86	109.04
3″	148.30	149.61	148.13	148.05	147.87	148.09
4″	148.13	148.36	147.80	148.05	146.36	146.24
5″	110.90	112.54	110.22	111.65	108.38	108.46
6″	122.28	122.08	122.44	122.09	120.69	127.43
OMe	56.22	56.06	56.10	56.06	55.98	56.09
OCH_2O	101.19	101.05	101.19	101.04	100.98	101.02
OAc	—	171.10	—	170.50	—	171.22
		20.56		20.61		20.54

*Chemical shifts are given in δ.

m/z 162 $[C_6H_3(OCH_2O)CH_2+C_2H_3]^+$. The ^1H NMR spectrum of **3** had signals for a 2,3-*trans*-γ-butyrolactone (Table 1) and for two aromatic groups, one of which coincided in all respects with piperonylmethyl. The signals of the other group did not match those of the 4-hydroxy-3-methyoxybenzyl group present in pluviatolide [13], a γ-butyrolactone found in the seeds of *B. salicifolium* [4], which had signals at δ 6.66 (H-2′), 6.69 (H-5′), 6.62 (H-6′) and 3.85 (OMe). The signals of guamarolin were 14 Hz downfield for H-2′, 8 Hz for H-6′ and 6 Hz upfield for the OMe group and thus this group in **3** must be a *meta*-phenolic hydroxyl. This was confirmed by the ^{13}C NMR spectrum (Table 2) where peaks were observed which were similar to those shown by prestegane A and B, the only natural lignans with an isoguayacyl group [5].

Guamarolin formed an acetate, **3a**, as an oil with $[M]^+$ *m/z* 398, $C_{22}H_{22}O_7$, in the ^1H NMR spectrum of which (Table 1) the H-6′ signals appeared 67.4 Hz downfield as had been the case with **1** and **2** and their respective acetates. The stereochemistry of guamarolin was established as 2*R*,3*R* since guamarolin was formed in 25% yield when guamarol and isoguamarol were hydrogenated. The physical and spectral data of the hydrogenation product, guamarolin, were exactly the same as those of the natural product.

Kaerophyllin (**1b**) [10], isokaerophyllin (**2b**) [2] and matairesinol [14] were also isolated from the roots of *B. salicifolium*.

EXPERIMENTAL

Mps are uncorr. IR spectra were recorded as films, UV spectra in EtOH. ^1H and ^{13}C NMR spectra were run at 200 and 50 MHz, respectively, with TMS as int. standard. Schleicher–Schüll F-100/LS 254 and prep. TLC 1510/LS 254 foils were used for TLC while silica gel (0.2–0.63 mm) and Sephadex LH-20 were used for CC.

Isolation. Root bark of wild specimens of *B. salicifolium* Soland (0.61 kg) gathered in the Barranco Rio Badajoz de Güimar, Tenerife were extd with EtOH. This ext. was treated successively with H_2O, Me_2CO and *n*-hexane to afford a dark residue (27.5 g) which was chromatographed on a Sephadex column (78.5 cm × 5 cm) eluting with *n*-hexane–$CHCl_3$–MeOH (2:2:1). There frs, A–C, were sepd and studied. They were all chromatographed on a silica gel column using mixts of *n*-hexane EtOAc of increasing polarity as eluants. Isokaerophyllin (**2b**) (20.8 mg) and kaerophyllin (**1b**) (16.1 mg) were sepd from fr. A (0.5 g). Fr. B (0.28 g) afforded guamarolin (**3**) (28.2 mg) and fr. C (0.24 g) yielded matairesinol (72.3 mg) ($[M]^+$ *m/z* 358, $C_{20}H_{22}O_6$, base peak *m/z* 137), guamarol (**1**) (24.2 mg), and isoguamarol (**2**) (14.8 mg).

Guamarol (**1**). Yellow oil. UV λ_{max} nm: 232, 291 and 331. IR ν_{max} cm^{-1}: 3420 (br), 1740, 1685, 1662, 1640, 1360, 1285, 1250, 1195. $[\alpha]_D$ 25°−44° ($CHCl_3$; *c* 0.04). ^1H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 354.1110 (13%, $[M]^+$, calc. for $C_{20}H_{18}O_6$, 354.1098), 219 (35, $C_{12}H_{11}O_4$). 177 (2, $C_{10}H_9O_3$), 135.0466 (100, calc. for $C_8H_7O_2$, 135.0444), 123 (2, $C_7H_7O_2$), 121 (2, $C_7H_5O_3$).

Guamarol acetate (**1a**). Guamarol (2 mg) was dissolved in 1 drop of pyridine, Ac_2O (0.2 ml) added and the soln left at room temp. for 24 hr, giving an acetyl derivative, **1a** (2.2 mg), as an oil. UV λ_{max} nm: 228, 294 and 312. IR ν_{max} cm^{-1}: 1748, 1642, 1609, 1442, 1185, 1097. ^1H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 396.1239 (10%, $[M]^+$, calc. for $C_{22}H_{20}O_7$, 396.1210), 354 (2, $C_{20}H_{18}O_6$). 165.0496 (4, calc. for $C_9H_9O_3$, 165.0479), 135 (36, $C_8H_7O_2$).

Methylation. Guamarol (2 mg) was dissolved in Et_2O, and CH_2N_2 in Et_2O (10 drops) was added to give kaerophyllin (**1b**)

which was identified by comparison with natural kaerophyllin by TLC, ^{1}H NMR, ^{13}C NMR, MS and optical activity.

Hydrogenation. Guamarol (10 mg) was dissolved in dry benzene (2.5 ml), Pd/C added and the mixt. stirred under an H_2 atm. at room temp. for 4 hr. The mixt. of products obtained was resolved by GCC using benzene–EtOAc (4:1). The hydrogenation product with the greatest R_f (25%) was identified as guamarolin (**3**) and that of least R_f (75%) as *cis*-2(3-hydroxy-4-methoxyphenyl)-3(2,3-dioxymethylenephenyl)-γ-butyrolactone (**3b**): $[M]^+$ *m/z* 356, base peak *m/z* 137, $C_{20}H_{20}O_6$; ^{1}H NMR ($CDCl_3$) δ: 2.27 (1H, *t*, *J* = 13.3, H-5a), 2.59 (1H, *m*, H-3), 2.89 (1H, *m*, H-5b), 3.06 (1H, *m*, H-2), 3.25 (1H, *m*, H-6b), 3.90 (3H, *s*, OMe), 4.02 (2H, *m*, H-4), 5.64 (1H, *br s*, OH), 5.92 (2H, *s*, OCH_2O), 6.48 (1H, *br s*, H-2″), 6.51 (1H, *m*, H-6″), 6.68 (1H, *d*, *J* = 8.1, H-5′), 6.75 (1H, *m*, H-6), 6.82 (1H, *d*, *J* = 8.3, H-5″), 6.85 (1H, *d*, *J* = 2.0, H-2′).

Isomerisation. Guamarol (3 mg) dissolved in Me_2CO (10 ml) was irradiated with UV light (254 nm) for 68 hr and was partially (26%) transformed to isoguamarol (**2**).

Isoguamarol (**2**). Yellow oil. UV λ_{max} nm: 236, 288, 334. IR ν_{max} cm^{-1}: 3542, 1732, 1648, 1614, 1284, 1249, 1038. ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 354.1108 ($[M]^+$, calc. for $C_{20}H_{18}O_6$, 354.1098), 219 (8, $C_{12}H_{11}O_4$), 177 (8, $C_{10}H_9O_3$), 135.0451 (100, calc. for $C_8H_7O_2$, 135.0444), 123 (4, $C_7H_7O_2$), 121 (5, $C_7H_5O_2$).

Isoguamarol acetate (**2a**). Isoguamarol (2.4 mg), when treated with excess Ac_2O in pyridine at room temp. for 24 hr, formed an acetyl derivative, **2a**, (2.6 mg) as an oil. UV λ_{max} nm: 223, 289, 311. IR ν_{max} cm^{-1}: 1743, 1651, 1609, 1491, 1443, 1369, 1277, 1194, 1128, 1092, 1041. $[\alpha]_D$ 25° −10° ($CHCl_3$; *c* 0.02). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 396.1221 (22%, $[M]^+$, calc. for $C_{22}H_{20}O_7$, 396.1210), 354 (5, $C_{20}H_{18}O_6$), 165.0599 (4, calc. for $C_9H_9O_3$, 165.0479), 261 (22, $C_{14}H_{13}O_5$), 135.0450 (100, calc. for $C_8H_7O_2$, 135.0444).

Methylation. Isoguamarol (2.8 mg), when treated with excess CH_2N_2 in Et_2O at room temp. formed isokaerophyllin (**2b**), identified by TLC, UV, IR, ^{1}H NMR, ^{13}C NMR, MS and optical activity comparison with an authentic sample.

Isomerisation. Isoguamarol (1.9 mg) was dissolved in $CHCl_3$ (2 ml) and 2 drops of HCl added. The soln was left at room temp. for 72 hr when **2** was transformed partially into **1** (84%).

Hydrogenation. Isoguamarol was hydrogenated under the same conditions as described for **1** to give a mixt. of **3** and **3b** in similar proportions to those obtained when guamarol was hydrogenated.

Guamarolin (**3**). Yellow oil. UV λ_{max} nm: 237, 290. IR ν_{max} cm^{-1}: 3440, 1760, 1590, 1510, 1440, 1350, 1230, 1225. $[\alpha]_D$ 25° −27.4° ($CHCl_3$; *c* 0.06). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 356.1278 (20%, $[M]^+$, calc. for $C_{20}H_{20}O_6$, 356.1254), 162.0687 (13, calc. for $C_{10}H_{10}O_2$, 162.0678), 137.0598 (100, calc. for $C_8H_9O_2$, 137.0600), 135 (52, $C_8H_7O_2$).

Guamarolin acetate (**3a**). Guamarolin (2.2 mg), when treated with pyridine (1 drop) and excess Ac_2O (10 drops) at room temp. for 24 hr, formed an acetate, **3b**, (2 mg). UV λ_{max} nm: 228, 280. IR ν_{max} cm^{-1}: 1766, 1603, 1444, 1369, 1269, 1201, 1125, 1040. $[\alpha]_D$ 25° −96° ($CHCl_3$; *c* = 0.05). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. MS *m/z* 398.1360 (33%, $[M]^+$, calc. for $C_{22}H_{22}O_7$, 398.1359), 356 (100, $C_{20}H_{20}O_6$), 179.0702 (6, calc. for $C_{10}H_{11}O_3$, 179.0715), 162.0687 (12, calc. for $C_{10}H_{10}O_2$, 162.0678), 135.0494 (52, calc. for $C_8H_7O_2$, 135.0444).

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