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DIBENZYLBUTYROLACTONE LIGNANS FROM *PIPER CUBEBA**

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Key Word Index—*Piper cubeba*; Piperaceae; dibenzylbutyrolactone lignans; structural determination.

Abstract—Six more lignans have been isolated from the hot petrol extract of *Piper cubeba* fruits. Of these, three compounds which have been isolated from a natural source for the first time were characterized as (2*R*,3*R*)-2-(5″-methoxy-3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone [(−)-cubebinone], (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone [(−)-isoyatein] and (2*R*,3*R*)-2-(3″,4″,5″-trimethoxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone [(−)-di-*O*-methyl thujaplicatin methyl ether, i.e. (−)-thujaplicatin trimethyl ether]. The other three compounds were identified as (−)-yatein, (−)-cubebininolide and (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′-dimethoxybenzyl) butyrolactone.

INTRODUCTION

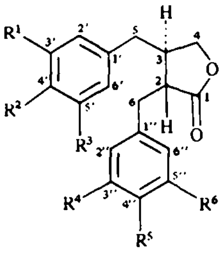
The isolation and characterization of six lignans, viz. (−)-cubebin, (−)-hinokinin, (−)-clusin, (−)-dihydrocubebin, (−)-dihydroclusin and (−)-cubebinin from the fruits of *Piper cubeba* have been reported earlier by us [1]. Koul *et al.* have also isolated a number of lignans from *P. clusii* [2, 3]. All these compounds belonged to either dibenzylbutanediol, butyrolactone or butyrolactol class.

In the present study we wish to report the structures of six dibenzylbutyrolactone lignans isolated in minor yields from the hot petrol extract of *P. cubeba* fruits. These were characterized as (−)-yatein (**1**) [4], (−)-cubebininolide (**2**) [1, 3] [(−)-cordigerine] [5], (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (**3**) [6], (2*R*,3*R*)-2-(5″-methoxy-3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone (**4**) [(−)-cubebinone], (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone (**5**) [(−)-isoyatein] and (2*R*,3*R*)-2-(3″,4″,5″-trimethoxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (**6**) [(−)-di-*O*-methyl thujaplicatin methyl ether]. To the best of our knowledge, compounds **4**, **5** and **6** are hitherto unreported from any natural source. However, compound **6** has been obtained by MacLean and Murakami [7] by the diazomethane treatment of thujaplicatin methyl ether (**7**).

RESULTS AND DISCUSSION

On concentration and cooling, the petrol extract deposited (−)-cubebin [8]. The rest of the lignans were obtained as minor components from the mother liquor by repeated CC and TLC. Of these, the known lignans, viz. (−)-yatein (**1**) [4], (−)-cubebininolide (**2**) [1] and (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone (**3**) [6] were identified by the comparison of their physical and spectroscopic properties with those reported. It is interesting to note here that all these six lignans gave negative Cotton effects in their CD curves, suggesting an identical (2*R*,3*R*) configuration [4, 9].

Compound **4**, viscous mass, $C_{23}H_{26}O_8$, ($[M]^+$ m/z 430), $[\alpha]_D^{25}$ −36.1° ($CHCl_3$), revealed the presence of a γ-lactonic carbonyl (1770 cm^{-1}) and methylenedioxy (930 cm^{-1}) groups in its IR spectrum. The ^1H NMR spectrum of the compound was typical of a *trans*-2,3-dibenzylbutyrolactone lignan [4]. The four proton envelope between δ2.52 and 2.62 was assigned to the C-5 benzylic and two methine protons at C-2 and C-3. The C-6 benzylic protons gave rise to another envelope between δ2.88 and 2.98. One of the C-4 methylene protons appeared as a multiplet centred at δ4.21, while the multiplet due to the other proton merged with the signals of four aromatic methoxyls in the region δ3.82–4.00. The two protons of the methylenedioxy group produced a



1 $R^1 + R^2 = OCH_2O$; $R^3 = H$, $R^4 = R^5 = R^6 = OMe$
2 $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = OMe$
3 $R^1 = R^2 = OMe$; $R^3 = R^6 = H$, $R^4 + R^5 = OCH_2O$
4 $R^1 = R^2 = R^3 = R^6 = OMe$; $R^4 + R^5 = OCH_2O$
5 $R^1 = R^2 = R^3 = OMe$; $R^4 + R^5 = OCH_2O$, $R^6 = H$
6 $R^1 = R^2 = R^4 = R^5 = R^6 = OMe$; $R^3 = H$
7 $R^1 = R^4 = R^6 = OMe$; $R^2 = R^5 = OH$, $R^3 = H$
8 $R^1 = R^2 = R^3 = R^4 = OMe$; $R^5 = OH$, $R^6 = H$
9 $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$; $R^6 = H$

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*Part 2 in the series "Lignans from *Piper cubeba*". For Part 1 see ref. [1].

sharp singlet at δ5.97. Further, this compound exhibited three singlets at δ6.26, 6.34 and 6.36 integrating for two, one and one proton(s), respectively. Of these, the latter two signals were suggestive of the presence of a 3,4-methylenedioxy-5-methoxy substituted aromatic ring, while the former signal indicated 3,4,5-trimethoxy substitution in the other aromatic ring. It has been observed in the study of ^{1}H NMR spectra of (2*R*,3*R*)-2-(4″-hydroxy-3″-methoxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone (**8**) [10] and *trans*-2-(3″,4″-dimethoxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone (**9**) [11] that the two *meta*-oriented protons of the 3,4,5-trimethoxybenzyl group attached to C-3, appeared at δ6.20 and 6.18, respectively. These values are consistently upfield by more than 0.1 ppm from the values for the same protons when the 3,4,5-trimethoxybenzyl group is attached to C-2 of the γ-lactone. This observation was further corroborated by the appearance of two signals, *ca* 0.15 ppm apart, for two sets of *meta*-protons of cubebininolide (**2**) [1, 3, 5]. On this basis, the two-proton singlet at δ6.26, observed in the case of compound **4**, was assigned to H-2′ and H-6′ of the trimethoxybenzyl group at C-3. The mass spectral fragmentation of compound **4** confirmed the presence of trimethoxybenzyl (*m/z* 181, base peak) and methoxymethylenedioxybenzyl (*m/z* 165) groups. That the latter group was attached to C-2 and not C-3 was conclusively proved by the appearance of a prominent ion at *m/z* 222 rather than at *m/z* 238 (Fig. 1). Thus, taking into consideration the negative Cotton effects at 232 nm and 278 nm, the structure of compound 4 could be deduced as (2*R*,3*R*)-2-(5″-methoxy-3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone and has been named as (−)-cubebinone. This is the first report of a 2,3-dibenzylbutyrolactone lignan in which one of the aromatic rings has a methylenedioxy as well as a methoxy group.

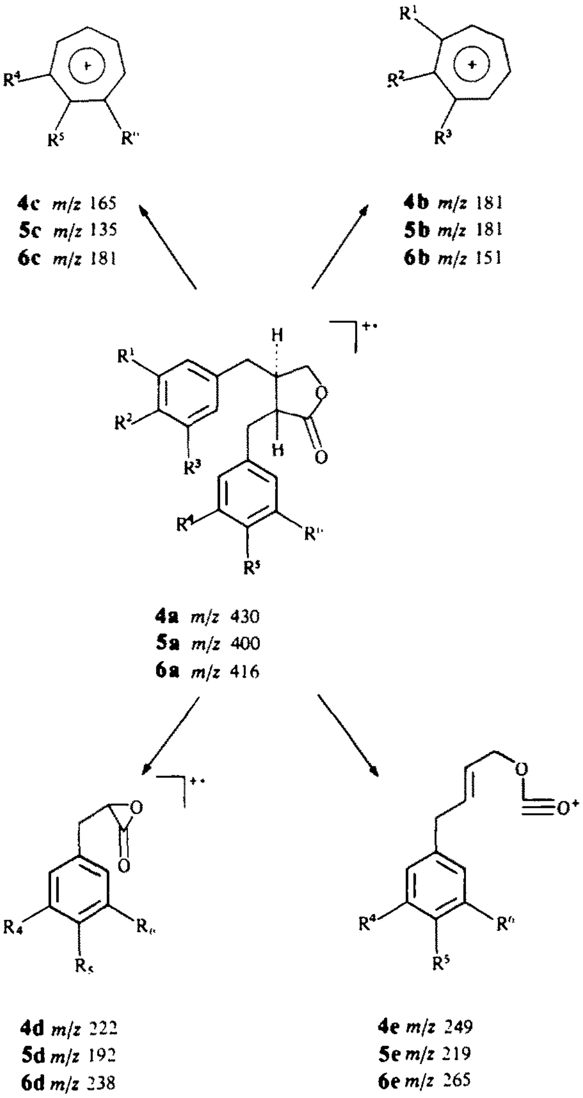

Fig. 1. Mass spectral fragmentation of dibenzylbutyrolactone lignans from *Piper cubeba*.

Compound **5**, viscous mass, $C_{22}H_{24}O_7$, ($[M]^+$ *m/z* 400), $[\alpha]_D^{25}$ $-49.6°$ ($CHCl_3$), showed prominent absorptions at 1770 and 939 cm^{-1} in its IR spectrum indicating the presence of γ-lactonic carbonyl and methylenedioxy groups, respectively. A study of its ^{1}H NMR spectrum revealed that this compound also belonged to the same class of lignans as **4**. As expected, C-5 methylene protons along with C-2 and C-3 methine protons appeared as a four-proton envelope between δ2.50 and 2.62. The other envelope centred at δ2.93 was attributed to the C-6 benzylic protons. The two C-4 protons gave rise to two multiplets at δ3.88–4.00 and δ4.06–4.32. A sharp singlet at δ3.86 integrating for nine protons indicated the presence of three aromatic methoxyl groups. The two-proton singlet at δ5.97 was attributed to a methylenedioxy group. A singlet integrating for two protons appeared at δ6.24. As discussed earlier, this signal could be attributed to the *meta*-oriented protons of a 3,4,5-trimethoxybenzyl group attached to C-3. The doublets centred at δ6.62 ($J = 8$ Hz) and δ6.76 ($J = 8$ Hz) suggested the presence of *ortho*-coupled protons in the other aromatic ring. These signals were assigned to H-5″ and H-6″. The signal due to H-2″ overlapped with one of the peaks of the doublets and appeared as an enhanced signal at δ6.66. The presence of trimethoxybenzyl and methylenedioxybenzyl groups was confirmed by the appearance of the ions at *m/z* 181 (base peak) and *m/z* 135, respectively. The diagnostic peak at *m/z* 192 placed the methylenedioxybenzyl group at C-2 of the butyrolactone ring (Fig. 1). The negative Cotton effects at 234 nm and 276 nm in its CD spectrum indicated a (2*R*,3*R*) configuration. Thus, compound **5** was characterized as (2*R*,3*R*)-2-(3″,4″-methylenedioxybenzyl)-3-(3′,4′,5′-trimethoxybenzyl)butyrolactone. It differs from yatein (**1**) in the respective positions of the similarly substituted benzyl groups. Therefore, we propose the name (−)-isoyatein for this compound.

Compound **6**, viscous mass, $C_{23}H_{28}O_7$, ($[M]^+$ *m/z* 416), $[\alpha]_D^{25}$ $-47.2°$ ($CHCl_3$), suggested the presence of a butyrolactone system ($>$C=O, 1770 cm^{-1}) in its IR spectrum. The aliphatic region in the ^{1}H NMR spectrum of this compound was similar to that of compounds **4** and **5**, thus suggesting the presence of the same *trans*-2,3-dibenzylbutyrolactone system. This was evident from the appearance of two envelopes at δ2.56–2.66 (C-5 benzylic and C-2, C-3 methine protons) and δ2.90–3.00 (C-6 benzylic protons). The multiplet centred at δ4.18 was attributed to one of the C-4 methylene protons while the corresponding multiplet for the other proton overlapped with the signals for five aromatic methoxyls in the region between δ3.80 and 4.00. Moreover, a singlet at δ6.40, integrating for two protons, could be assigned to two aromatic *meta*-coupled protons of a 3,4,5-trimethoxybenzyl group. As discussed earlier, the comparative downfield value for these protons, suggested that this group was present at C-2 position. The protons of the other aromatic ring displayed two doublets at $\delta 6.57$ ($J = 9$ Hz) and 6.79 ($J = 9$ Hz) indicating the presence of two *ortho*-coupled protons (H-5′ and H-6′). However, this entire region integrated for three protons. The signal for H-2′ was seen at $\delta 6.53$ as an enhanced peak of one of the doublets. Therefore, it was inferred that this compound contained 3,4-dimethoxy- and 3,4,5-trimethoxy- benzyl groups at C-3 and C-2, respectively. This was further corroborated by its mass spectral fragmentation. In addition to the $[M]^+$ peak at m/z 416, other prominent ions were seen at m/z 181 (base peak), m/z 151 and m/z 238 (Fig. 1). The absolute configuration of this compound was assigned as (2*R*,3*R*) since it showed negative Cotton effects at 236 nm and 276 nm in its CD spectrum. Consequently, the structure of compound **6** has been established as (2*R*,3*R*)-2-(3″,4″,5″-trimethoxybenzyl)-3-(3′,4′-dimethoxybenzyl)butyrolactone. It seems from spectral data that this compound is identical with di-*O*-methylthujaplicatin methyl ether, prepared by diazomethane treatment of its phenolic counterpart [7]. However, in all probability, it has not been reported so far from any natural source.

EXPERIMENTAL

^{1}H NMR (100 MHz): $CDCl_3$. MS (70 eV) direct insertion. $[\alpha]_D^{25}$: $CHCl_3$. UV: MeOH. CD: MeOH. IR: $CHCl_3$. Chromatographic sepns were carried out on silica gel. TLC was performed on silica gel G using C_6H_6–EtOAc. Spots were detected in UV (254 nm), exposing the plates in I_2 vapour and heating to 100° in an oven after spraying with 10% H_2SO_4.

Extraction and isolation of compounds. Isolation of (−)-cubebin and five other lignans has been described earlier [1]. Two of the fractions eluted prior to cubebin were chromatographed separately by silica gel CC, using increasing polarity of solvents from petrol to EtOAc. Further purification of the individual compounds was achieved by prep. TLC on silica gel. Thus, six lignans were obtained in pure form.

(−)-*Cubebinone* [(2R,3R)-2-(*5″-methoxy-3″,4″-methylenedioxybenzyl*)-3-(*3′,4′,5′-trimethoxybenzyl*)*butyrolactone*] (**4**). Viscous mass, $[\alpha]_D^{25}$ −36.1° ($CHCl_3$; *c* 0.083). UV λ_{max}^{MeOH} nm ($\log \varepsilon$): 275 (3.73). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2985, 1770, 1600, 1575, 1471, 1250, 1136 and 930. CD: $\Delta\varepsilon_{232}$ −2.26 and $\Delta\varepsilon_{278}$ −0.16 (MeOH; *c* 0.098). ^{1}H NMR (100 MHz): $\delta 2.52$–2.62 (4H, *m*, C-5 benzylic protons, $-CH_2-C\underline{H}-C\underline{H}-CH_2-$), 2.88–2.98 (2H, *m*, C-6 benzylic protons), 3.86, 3.90 (12H, *s* each, Ar–OMe), 3.82–4.00 (1H, *m*, C-4 methylene proton), 4.21 (1H, *m*, C-4 methylene proton), 5.97 (2H, *s*, $-OCH_2O-$), 6.26 (2H, *s*, H-2′ and H-6′), 6.34 (1H, *s*, H-2″ or H-6″) and 6.36 (1H, s, H-2″ or H-6″). MS m/z (rel. int): 430 $[M]^+$ (24), 249 (2), 248 (3), 235 (2), 222 (2), 207 (12), 203 (3), 194 (3), 182 (49), 181 (100), 166 (51) and 165 (70). (Found C, 63.97; H, 6.14. $C_{23}H_{26}O_8$ requires: C, 64.18; H, 6.05%.)

(−)-*Isoyatein* [(2R,3R)-2-(*3″,4″-methylenedioxybenzyl*)-3-(*3′,4′,5′-trimethoxybenzyl*)*butyrolactone*] (**5**). Viscous mass, $[\alpha]_D^{25}$ −49.6° ($CHCl_3$; *c* 0.035). UV λ_{max}^{MeOH} nm ($\log \varepsilon$): 232 sh (3.90) and 2.86 (3.32). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2941, 1770, 1600, 1504, 1460, 1258, 1136, 1047, 1026 and 939. CD: $\Delta\varepsilon_{234}$ −3.09 and $\Delta\varepsilon_{276}$ −0.12 (MeOH; *c* 0.06). ^{1}H NMR (100 MHz): $\delta 2.50$–2.62 (4H, *m*, C-5 benzylic protons, $-CH_2-C\underline{H}-C\underline{H}-CH_2-$), 2.93 (2H, C-6 benzylic protons), 3.86 (9H, *s*, Ar–OMe), 3.88–4.00, 4.06–4.32 (2H, *m* each, C-4 methylene protons), 5.97 (2H, *s*, $-OCH_2O-$), 6.24 (2H, *s*, H-2′ and H-6′), 6.62 (1H, *d*, $J = 8$ Hz, H-5″ or H-6″), 6.76 (1H, *d*, $J = 8$ Hz, H-5″ or H-6″) and 6.66 (1H, *s*, H-2″). MS m/z (rel. int): 400 $[M]^+$ (71), 219 (2), 207 (4), 206 (4), 194 (1), 192 (1), 181 (100), 136 (17) and 135 (94). (Found: C, 66.18; H, 6.09. $C_{22}H_{24}O_7$ requires: C, 66.0; H, 6.0%.)

(−)-*Di-O-methyl thujaplicatin methyl ether* [(2R,3R)-2-(*3″,4″,5″-trimethoxybenzyl*)-3-(*3′,4′-dimethoxybenzyl*)*butyrolactone*] (**6**). Viscous mass, $[\alpha]_D^{25}$ −47.2° ($CHCl_3$; *c* 0.165). UV λ_{max}^{MeOH} nm ($\log \varepsilon$): 228 (4.15) and 277 (3.51). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2967, 1770, 1600, 1515, 1471, 1250, 1136 and 1036. CD: $\Delta\varepsilon_{236}$ −3.9 and $\Delta\varepsilon_{276}$ −0.27 (MeOH; *c* 0.06). ^{1}H NMR (100 MHz): $\delta 2.56$–2.66 (4H, *m*, C-5 benzylic protons, $-CH_2-C\underline{H}-C\underline{H}-CH_2-$), 2.90–3.00 (2H, *m*, C-6 benzylic protons), 3.86, 3.88 (15H, *s* each, Ar–OMe), 3.80–4.00 (1H, *m*, C-4 methylene proton), 4.18 (1H, *m*, C-4 methylene proton), 6.40 (2H, *s*, H-2″ and H-6″), 6.57 (1H, *d*, $J = 9$ Hz, H-5′ or H-6′), 6.79 (1H, *d*, $J = 9$ Hz, H-5′ or H-6′) and 6.53 (1H, *s*, H-2′). MS m/z (rel. int): 416 $[M]^+$ (88), 265 (3), 264 (2), 251 (5), 238 (3), 219 (2), 182 (38), 181 (100), 177 (11), 167 (8), 165 (3), 152 (16) and 151 (41). (Found: C, 66.30; H, 6.69. $C_{23}H_{28}O_7$ requires: C, 66.35; H, 6.73%.)

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