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Chemical constituents of *Simarouba versicolor*

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ABSTRACT

From the roots, stems and fruits of *Simarouba versicolor* (Simaroubaceae) were isolated quassinoids (**3**, **5-7**), triterpenoids (**8-14**), a mixture of steroids (**15-17**), the flavonoid kaempferol (**18**) and the squalene derivative 11,14-diacetoxy-7,10; 15,18-diepoxy-6,19-dihydroxy-6,7,10,11,14,15,18,19-octahydrosqualene (**19**). Spectral data were used for structural characterization.

Key words: *Simarouba versicolor*, Simaroubaceae, quassinoids, triterpenoids, steroids, flavonoid, squalene derivative.

INTRODUCTION

Some species of the small family Simaroubaceae (28 genera containing 25 species of tropical and semitropical shrubs and trees) have furnished wood for construction and others have been used in folk medicine. In the last few years, the therapeutic purposes have increased because of its antimalarial, anti-inflammatory, antileukemic, antifeedant, and antiviral activities (Engler and Prantl 1872). In Brazil, the Simaroubaceae family is represented by the genera *Quassia* and *Picrolemma*, in the Amazonian Region, *Castela* and *Picrasma*, in the south of the country, and *Simaba*, *Simarouba* and *Picrolemma* which are present throughout Brazil (Hall et al. 1983).

Species of the genus *Simarouba* have been reported previously as bioproducts of anticancer, antiviral, antimalarial, anti-inflammatory (Polonsky 1973), insecticide and amoebicide agents (Polonsky 1985). This latter species has been used in the traditional medicine and is very known in China and Mexico.

Epilupeol (**1**), four quassinoids (**2-5**) and β -sitosterol (**15**) were previously isolated from the leaves and stems of a specimen of *Simarouba versicolor* collected in the State of Paraná, Brasil (Ghosh et al. 1977).

The present paper deals with the isolation of the known quassinoids (**3**, **5-7**), triterpenoids (**8-14**), a mixture of steroids (**15-17**), the flavonoid kaempferol (**18**) and a squalene derivative (**19**) from specimens of *Simarouba versicolor* collected in Cascavel (stems and fruits) and Pacatuba (roots) in the

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State of Ceará, in the northeastern of Brazil. This region has a very distinct climate, which is different from the place where the specimen was collected for the previous investigation. The structures of the compounds reported in this paper were established on the basis of spectral data, including 2D NMR experiments of **19**.

RESULTS AND DISCUSSION

The secondary metabolites isolated from *Simarouba versicolor*, known quassinoids (**3**, **5-7**), triterpenoids (**8-14**), a mixture of steroids (**15-17**), the flavonoid kaempferol (**18**) and squalene derivative (**19**), were identified by their IR, MS, ^1H and ^{13}C NMR data, including preparation of some acetyl derivatives (**11a**, **12a**, **13a**, **14a** and **18a**) and comparison with literature data (Merrien and Polonsky 1971, Connolly and McCrindle 1971, Polonsky et al. 1975, Kupchan and Lacadie 1975, Jolad et al. 1981, Suzuki et al. 1985, Hashimoto et al. 1988a,b). The characterization of the squalene derivative **19** involved additional results obtained by interpretation of homonuclear and heteronuclear 2D shift-correlated spectra facilitated by comparison with data reported in the literature (Itokawa et al. 1991, Morita et al. 1993). The compounds isolated from *S. versicolor* (Fig. 1) reported in this paper were previously obtained from plants classified in the same or other genera of Simaroubaceae or other families.

11-Acetylarolide (**3**) was isolated from a specimen of *S. versicolor* collected in Paraná, state located in the South of Brazil (Ghosh et al. 1977).

Glaucarubinone (**5**) (Alves-de-Lima et al. 1983, Alves-de-Lima et al. 1984, Polonsky et al. 1975) and glaucarubin (**6**) (Mesquita et al. 1997, Polonsky et al. 1975) were previously obtained from *Simarouba glauca* (Buckingham 1994a).

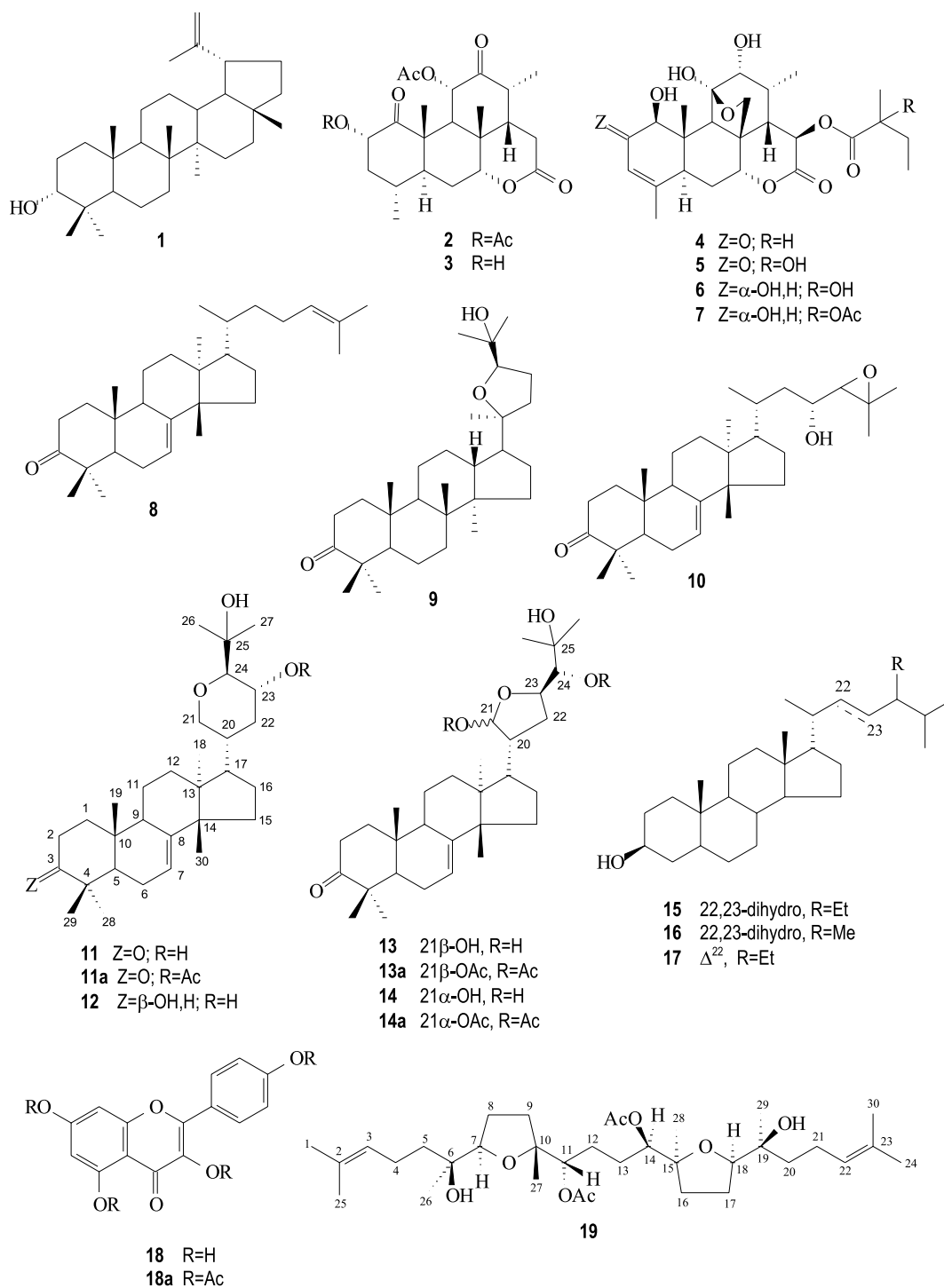
2'-Acetylglaucarubin (**7**) (Alves-de-Lima et al. 1984) and tirucalla-7,24-dien-3-one (**8**) (Alves-de-Lima et al. 1983, Siqueira et al. 1985) were reported as bioproducts from *S. amara* (Buckingham 1994b).

20,24-Epoxy-25-hydroxydammaran-3-one (ocotillone, **9**) (Alves-de-Lima et al. 1982, Siqueira et al. 1985) was reported in the literature as a con-

stituent of *Dipterus hispidus* and *Dryanobulanops* spp., The CH-24 epimer, cabraleone, has been isolated from *Cabralea polytricha* (Buckingham 1994c). The relative configurations of carbon atoms C-20 and CH-24 of **9** were deduced by comparison of the chemical shifts of CH-24 (δ_{C} 83.56) and CH₃-21 (δ_{C} 23.75). The significant differences among values reported in the literature for these carbons (Fig. 2) in ocotillone [**9**: δ_{C} 84.3 (CH-24) and δ_{C} 23.3 (CH₃-21)] and cabraleone [24-epiocotillone: δ_{C} 87.4 (CH-24) and δ_{C} 26.3 (CH₃-21)], two CH-24 epimeric compounds (Tanaka and Yahara 1978), were used to characterize the compound isolated from *S. versicolor* as identical to **9**. The lower chemical shifts of CH-24 (δ_{C} 83.56) and CH₃-21 (δ_{C} 23.75) observed in the ^{13}C NMR spectrum of **9** when compared with the corresponding values of cabraleone (Fig. 2) can be explained by the reciprocal γ -effects of these carbon atoms in **9**.

24,25-Epoxy-23-hydroxytirucall-7-en-3-one (nilocitin, **10**) (Alves-de-Lima et al. 1982, Siqueira et al. 1985) was previously isolated from *Simaba cedron*, Simaroubaceae (Vieira et al. 1998).

21,24-Epoxy-23,25-dihydroxytirucall-7-en-3-one (bourjutinolone A, **11**) (Siqueira et al. 1985) and 21,24-epoxy-3,23,25-trihydroxytirucall-7-ene (3-episapelin A, **12**) (Siqueira et al. 1985) were also isolated from *Simaba cedron*, Simaroubaceae (Vieira et al. 1998), *Trichilia hispida*, Meliaceae (Jolad et al. 1981), *Entandrophragma angolense* and *E. utile*, Meliaceae (Okorie and Taylor 1977). The relative configurations of the stereogenic carbon atoms CH-23 and CH-24 of **11** were established by comparative analysis of the ^{13}C chemical shifts 37.51 (CH-20), 70.06 (CH₂-21), 36.44 (CH₂-22), 64.57 (CH-23), 86.44 (CH-24) and 74.05 (C-25) and values described in the literature (Jolad et al. 1981, Vieira et al. 1998) for bourjutinolone A (**11**), in combination with the value of the coupling constant ($J = 9.0$ Hz) observed in the ^1H NMR spectra of **11** and its acetyl derivative **11a**, as summarized in Figure 3. Analogous analysis using data obtained by ^1H NMR spectra of **12** and its acetyl derivative **12a** (Fig. 4) was employed to identify episapelin A (**12**).

Fig. 1 – Structures for compounds isolated from *S. versicolor* and derivatives.

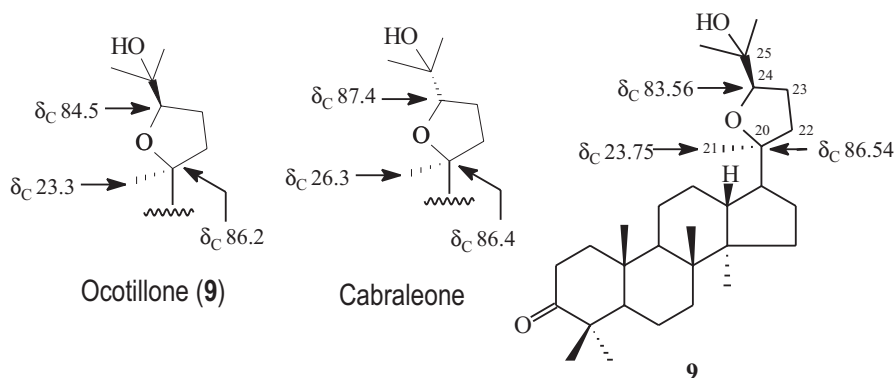


Fig. 2 – Comparison of the ^{13}C chemical shifts of the CH-24 methine carbon and CH₃-21 methyl of **9** with values described in the literature (Tanaka and Yahara 1978) for ocotillone (**9**) and cabraleone (24-epiocotillone).

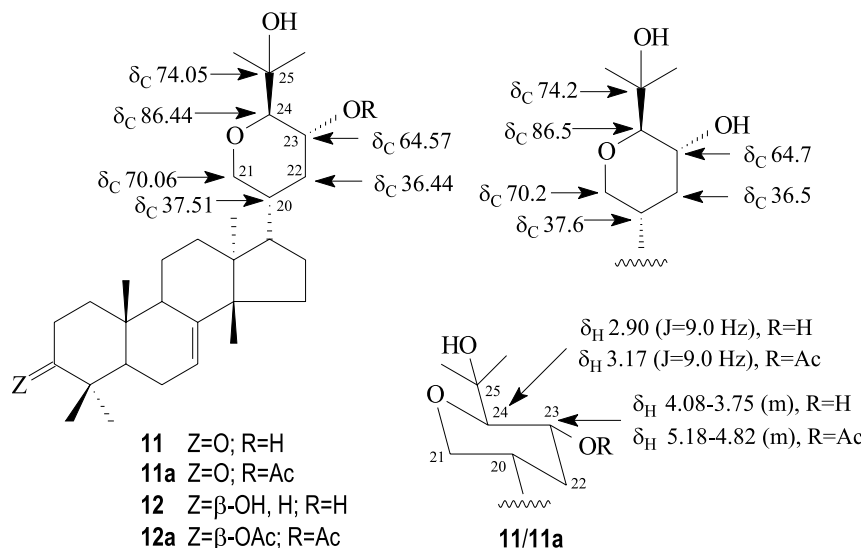


Fig. 3 – Comparison of the chemical shifts of C-20 to C-25 of **11** with the corresponding values of sapelin A ($Z=\alpha\text{-OH,H}$; $R=\text{H}$) reported in the literature (Jolad et al. 1981). The coupling constant ($J = 9.0$ Hz) observed for signals of **11** and **11a** reveal an axial-axial interaction between H-24 and H-23.

21,23-Epoxy-21 β ,24,25-trihydroxytirucall-7-en-3-one (**13**) and 21,23-epoxy-21 α ,24,25-trihydroxytirucall-7-en-3-one (**14**) were isolated as a mixture, clearly recognizable by the signals observed in the ^{13}C NMR spectrum at δ_{C} 102.00/96.97

(**13/14**) and 83.50/78.70 (**13/14**) attributed to the methine carbons CH-21 and CH-23, respectively (Fig. 5). The lower chemical shifts of CH-21 (δ_{C} 96.97) and CH-23 (δ_{C} 78.70) in the epimer **14** (major component) can be explained by a γ -effect on

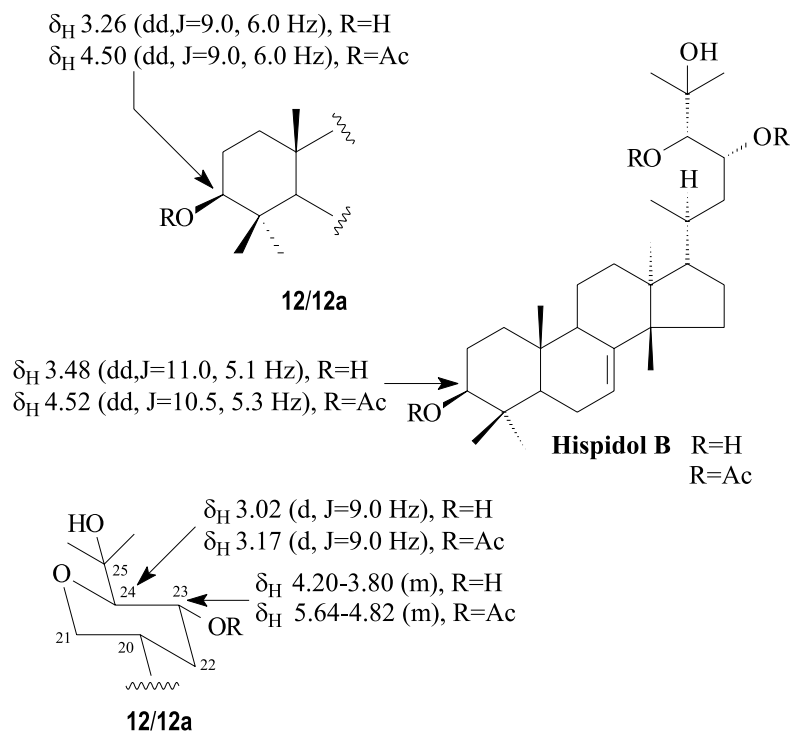


Fig. 4 – Comparison of the ^1H chemical shifts of H-3 of **12** and **12a** with the corresponding values for hispidol B and its acetyl derivative reported in the literature (Jolad et al. 1981). The coupling constant ($J = 9.0$ Hz) observed for signals of **12** and **12a** reveal an axial-axial interaction between H-24 and H-23.

CH-23 by the hydroxyl group located at CH-21 and on CH-21 by the methine carbon CH-24 (Siqueira et al. 1985). Compound **14** was previously obtained from *Samadera madagascariensis*, Simaroubaceae (Merrien and Polonsky 1971), when it was mainly characterized through ^1H NMR spectral data. On the basis of the relative intensities of the signals corresponding to H-21 in the ^1H NMR spectrum the epimer **13** (minor component) was now estimated as $< 10\%$ in the mixture isolated from *Simarouba versicolor*.

The presence of steroids **15-17** in a mixture was mainly deduced by ^{13}C NMR spectral data, which involved comparison with values reported in the literature (Blunt and Stother 1977, Chaurasia and Wichtl 1987). The peaks at m/z 414 ($[\text{M}]^+$ of **15**),

412 ($[\text{M}]^+$ of **17**) and 400 ($[\text{M}]^+$ of **16**) observed in the mass spectrum was also used for the identification of these compounds.

The flavonol kaempferol (**18**) obtained as its acetyl derivative (**18a**) (Arriaga et al. 1994) is frequently isolated of plants.

The number of linked hydrogens for each carbon signal of **19** (mp 149.8-153.2°C) was deduced by comparative analysis of HBBDD (30 singlet signals corresponding to 34 carbon atoms) and DEPT- ^{13}C NMR [signals corresponding to 8 quaternary carbons (including two carbonyl of acetyl groups at δ_{C} 170.92 and 170.78, which were also suggested by IR spectrum), 5 representing 6 methine carbons (two sp^2 and four oxygenated), 10 methylene carbons and 9 representing 10 methyl carbons (two of acetyl

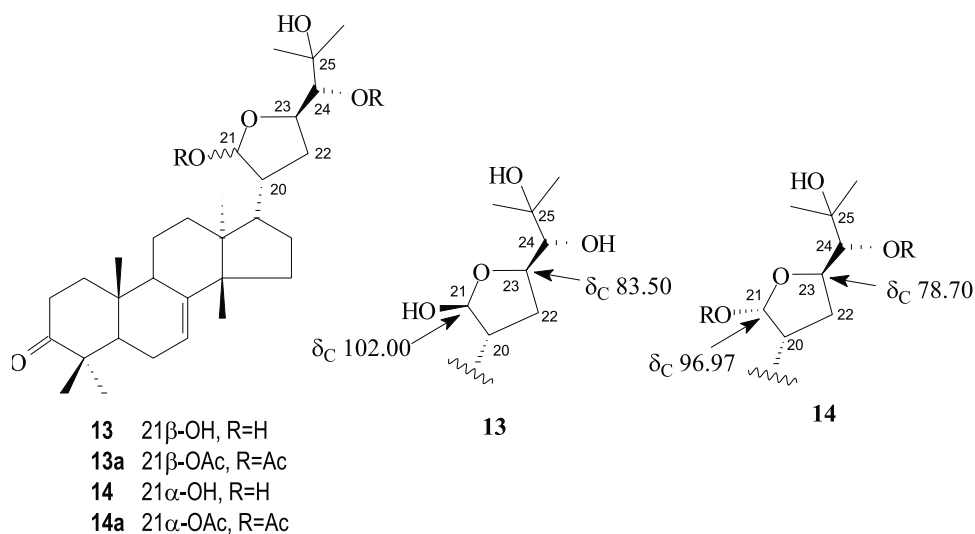


Fig. 5 – Comparison of the ^{13}C chemical shifts of atoms CH-21 and CH-23 of **13** and **14** and deduction of the relative configurations.

groups at δ_{C} 21.13 and 21.07, in accordance with the singlet signals observed in the ^1H NMR at δ_{H} 2.03 and 2.04] spectra (Table I). These data in combination with results obtained by ^1H NMR (1D and 2D ^1H - ^1H -COSY) and by heteronuclear 2D ^1H - ^{13}C -COSY- $^n\text{J}_{\text{CH}}$ ($n=1$, direct correlation via one bond – HETCOR – ^{13}C detected, conventional method; $n=2$ and 3, long-range spin-spin interaction – COLOC – ^{13}C detected, conventional method) spectra and comparison with values reported in literature for eurylene (**19**) (Itokawa et al. 1991, Morita et al. 1993) were used to complete ^1H and ^{13}C chemical shift assignments unambiguously. The differences observed in the comparison of the ^{13}C chemical shifts (Table I) may be attributed to mistakes previously reported using CDCl_3 as solvent (Itokawa et al. 1991), which was also used in our experiments, or to a solvent effect when the comparative analysis involves data obtained in CDCl_3 and pyridine- d_5 (Morita et al. 1993), as summarized in Table I. The ^{13}C NMR spectral data obtained in pyridine- d_5 (Morita et al. 1993) were used to eliminate the mistakes observed in the previous attribution when was used CDCl_3 (Itokawa et al. 1991). However, the mistakes corre-

sponding to CH_3 -25/ CH_3 -30 (δ_{C} 17.58 and not 25.7 or 25.8), shielded as consequence of the γ -effect attributed to CH_2 -4/ CH_2 -21, and CH_3 -1/ CH_3 -24 (δ_{C} 25.24 and not 17.6 or 17.7), free of this γ -effect, were maintained (Table I). On the basis of this γ -effect, the ambiguous assignments may now be eliminated, as shown in Table I. The results obtained by ^1H - ^1H -NOE difference spectra (Table I) were also used to confirm these data and to obtain stereochemical information on some stereogenic carbon atoms of **19**. The absolute configuration of eurylene (**19**), mp 146-148 $^\circ\text{C}$, $[\alpha]_{\text{D}} +4.32^\circ$, was established by X-ray analysis and Mosher's method (Itokawa et al. 1991, Morita et al. 1993).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURE

Melting points (mp) were measured on a Mettler (FP-52) micro-melting point apparatus and are uncorrected; IR spectra were recorded on a Perkin-Elmer 720 spectrophotometer; ^1H and ^{13}C NMR spectra (1D and 2D) were run on Bruker AC-200 (^1H : 200 MHz; ^{13}C : 50 MHz) and Varian XL 100

TABLE I

1D and 2D ^1H and ^{13}C NMR spectral data for compound 19, in CDCl_3 and TMS as internal standard, compared with values (in parenthesis, in CDCl_3 and pyridine- d_5 respectively) described in the literature (Itokawa et al. 1991, Morita et al. 1993) for eurylene (19). Chemical shifts in δ (δ_{H} and δ_{C} , ppm) and coupling constants (J , in parenthesis) in Hz.*

	δ_{C}	δ_{H}	$^2J_{\text{CH}}$	$^3J_{\text{CH}}$	
C		–			
2/23	131.54 (131.6, 130.9)	–	3H-1, 3H-24/ 3H-25, 3H-30		
6	71.92 (83.6, 72.0)	–	3H-26		
10	83.55 (72.0, 84.1)	–	H-11, 3H-27		
15	83.75 (72.7, 84.1)	–	H-14, 3H-28		
19	72.64 (83.8, 72.5)	–	3H-29		
AcO	170.92 (n. d., 170.9)	–			
AcO	170.78 (n. d., 170.7)	–			
CH					^1H - ^1H -NOE
3/22	124.43 (124.5, 125.8a/125.9a)	5.07 (t, 6.6)		3H-1, 3H-24/ 3H-25, 3H-30	
7	86.52 (86.6, 87.1)	3.68 (dd, 5.5, 9.2)		3H-26	
11	78.05 (78.2, 78.4)	4.83 (t, 7.0)		3H-27	
14	77.51 (77.6, 78.1)	4.85 (t, 7.0)		3H-28	
18	84.30 (84.60, 85.3)	3.74 (dd, 8.1, 6.8)		3H-29	
CH ₂					
4,21	22.03 (22.1, 22.7)	2.15-1.85 (m)			
5	37.21 (37.3, 39.8)	1.45-1.25 (m)		3H-26	
8	25.64 (25.8, 26.3)	2.05-1.95 (m), 1.80-1.70 (m)			
9	34.77 (34.9, 35.1)	1.66-1.50 (m)			
12	26.94 (27.1, 27.3b)	1.54 (m), 1.25 (m)			
13	26.76 (26.9, 27.5b)	1.54 (m), 1.25 (m)			
16	34.07 (34.2, 35.0)	1.96-1.82 (m), 1.58-1.46 (m)			
17	25.47 (25.6, 26.3)	2.05-1.95 (m), 1.80-1.70 (m)			
20	37.43 (37.6, 40.1)	1.45-1.25 (m)		3H-29	
CH ₃					
1/24	25.64 (17.6, 17.6c/17.7c)	1.65 (br s)		3H-25/3H30	H-3/H-22 (3%)
25/30	17.58 (25.7, 25.8)	1.58 (br s)		3H-1/3H-24	
26	24.10 (24.2, 23.2)	1.14 (s)			H-7 (2%)
27	22.71 (22.8, 22.9)	1.12 (s)			H-11 (< 1%)
28	22.50 (22.5, 22.1)	1.14 (s)			H-14 (< 1%)
29	23.97 (24.0, 23.1)	1.15 (s)			H-18 (2%)
AcO	21.13 (n. d., 21.1)	2.03 (s)			
Aco	21.07 (n. d., 21.0)	2.04 (s)			

*Chemical shifts (δ) and coupling constants (J in Hz, in parenthesis) obtained from the one-dimensional ^1H NMR spectrum. Multiplicity of signals of carbon atoms deduced by comparative analysis of HBBBD and DEPT- ^{13}C NMR spectra. 2D ^1H - ^1H -COSY NMR spectrum was also used for these assignments. Values with the same letter can be interchanged (Morita et al. 1993). n.d.= non described.

(^1H : 100 MHz; ^{13}C : 25 MHz) spectrometers, using CDCl_3 and pyridin- d_5 as solvents; EIMS were recorded on Micro Mass instrument at 70 eV.

PLANT MATERIAL

The roots, stems and fruits of *S. versicolor* were collected in Pacatuba in 1981 and Cascavel in 1997, respectively, Ceará State, Brazil and were identified by Professors Afranio Fernandes and E. Nunes, Departamento de Biologia, Universidade Federal do Ceará (UFC), Fortaleza, Ceará, Brasil. A voucher specimen (number 20.795) has been deposited at Prisco Bezerra Herbarium, Departamento de Biologia, UFC.

EXTRACTION AND ISOLATION

Dry and powdered roots (480g) were extracted, at room temperature, with hexane and following with acetone. The residue obtained from the acetone extract, after evaporation of the solvent under vacuum, was chromatographed on a silica gel column to give the compounds **5** to **13**, **19** and a mixture of the steroids **15**, **16** and **17** (Alves-de-Lima et al. 1982, Alves-de-Lima et al. 1983, Alves-de-Lima et al. 1984, Siqueira et al. 1985).

The air-dried and powdered stems of *S. versicolor* (4.0 kg) were extracted with hot EtOH in a Soxhlet system. The organic layer was concentrated to give residue SVE (96.0g) which was filtered through 200g of silica gel 60 (Merck, 230-400 mesh) by elution with hexane, chloroform, ethyl acetate and methanol, furnishing after evaporation of the solvent SVH (13.4g), SVC (14.0g), SVAE (12.7g) and SVM (49.5g). SVH (7.5g) which were chromatographed over silica gel 60 (Merck, 230-400 mesh) column and eluted with hexane, chloroform and ethyl acetate. The fractions eluted with $\text{CH}_3\text{Cl}/\text{EtOAc}$ mixture of increasing polarity, afforded **19** (50.0 mg, mp. 149.8-153.2°C). SVC (5.6g) which was chromatographed over silica gel 60 (Merck, 230-400 mesh) column and eluted with hexane, chloroform and ethyl acetate mixtures of increasing polarity. The $\text{CH}_3\text{Cl}/\text{EtOAc}$ (20%) fraction furnished **3** (50.0 mg, mp. 158.1-159.3°C) after

recrystallization from methanol. SVAE (7.0 g) was chromatographed over silica gel 60 (Merck, 230-400 mesh) using pure hexane, mixture of hexane and chloroform, chloroform, ethyl acetate and methanol as solvents. The fractions eluted with EtOAc afforded colorless crystals (30.0 mg) of **6** (mp. 240.6-241.6°C).

The fruits (500.0g) were crushed and extracted with hot ethanol in a Soxhlet system. The organic layer was concentrated to give SVFE (11.8g). This residue was chromatographed on 100.0g silica gel 60 (Merck, 230-400 mesh) and eluted with hexane, chloroform, ethyl acetate and methanol to furnish SVFAE (9.0g) and SVFM (2.7g). SVFAE (3.2g) was acetylated with Ac_2O (32 mL) in the presence of pyridine (16 mL), at room temperature and stirred overnight. After the usual procedures, the product was extracted with Me_2O and chromatographed on a silica gel 60 (Merck, 230-400 mesh) column and eluted with hexane, chloroform, ethyl acetate and methanol. After recrystallization from MeOH, the $\text{CH}_3\text{Cl}/\text{EtOAc}$ (10%) fraction furnished the acetyl derivative **17a** (50.0 mg, mp. 182.6-185.0°C).

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RESUMO

Das raízes, galhos e frutos de *Simarouba versicolor* foram isolados quassinóides (**3**, **5-7**), triterpenóides (**8-14**), uma mistura de esteróides (**15-17**), o flavonóide canferol (**18**) e o derivado esqualênico 11,14-diacetoxi-7,10;15,18-diepóxi-6,19-diidroxi-6, 7, 10,11, 14, 15, 18, 19-octaidroesqualeno (**19**). Dados espectrais foram usados para caracterização estrutural.

Palavras-chave: *Simarouba versicolor*, Simaroubaceae,

quassinóides, triterpenóides, esteróides, flavonóide, derivado esqualênico.

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