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STYRYL-PYRONES FROM *GONIOTHALAMUS ARVENSIS*

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Key Word Index—*Goniothalamus arvensis*; Annonaceae; stem bark; styryl-pyrones; styryl-lactones; (+)-garvensintriol; (+)-etharvendiol.

Abstract—Two novel styrl-pyrones, (+)-garvensintriol and (+)-etharvendiol, together with a known cytotoxic furano-furone, (+)-goniofufurone, have been isolated from the stem bark of *Goniothalamus arvensis*. A different relative configuration, *cis-erythro-erythro* for garvensintriol and *cis-threo-erythro* for etharvendiol, is established, and their absolute stereochemistry is discussed. © 1998 Elsevier Science Ltd. All rights reserved

INTRODUCTION

Phytochemical studies on *Goniothalamus* species have led to the isolation and characterization of a large number of styryl-lactones, which were found to possess significant cytotoxic activities against several human tumour cell lines [1–12]. In a previous work on the methanolic extract of *G. arvensis* stem bark, we described the isolation of a new styryl-lactone, (+)-goniotharvensin, and two known compounds, (+)-altholactone and (+)-isoaltholactone [13]. Further investigation on the same plant material has revealed the presence of additional styryl-lactone derivatives, (+)-garvensintriol (**1**) and (+)-etharvendiol (**2**), two novel styryl-pyrone compounds, together with the known, (+)-goniofufurone (**3**), a cytotoxic furano-furone previously isolated from *G. giganteus* [14], for which a configuration [4*R*, 5*S*, 6*S*, 7*R*, 8*R*] has been established by synthesis [15] (Fig. 1). Structures were determined from IR, ^{1}H NMR, ^{13}C NMR, 2D-NMR (^{1}H-^{1}H COSY) and mass spectroscopic data.

RESULTS AND DISCUSSION

Purification of the crude methanolic extract of the stem bark from *G. arvensis* and chromatographic fractionation led to the isolation of three compounds identified as (+)-garvensintriol (**1**), (+)-etharvendiol (**2**) and (+)-goniofufurone (**3**), on the basis of spectral evidence.

Compound **1**, was isolated as a yellow oil and showed UV absorption maxima at 220 (2.22), 250 (2.07) and 256 (2.08) nm (log ε), and strong IR absorption bands at 768 and 700 cm^{-1}, indicative of an aromatic system. The proton resonances at δ 7.30–7.39 (*m*, H-10 to 14) and carbon signals at δ 140.21 (one C), δ 128.8 (two CH), δ 128.2 (one CH) and δ 126.1 (see Table 1) (two CH) in NMR experiments, corroborated the existence of a monosubstituted phenyl group in **1** (Table 1).

The molecular formula of **1** was deduced to be $C_{13}H_{16}O_5$ from the LSI mass spectrum (*m/z* 253 $[M+H]^+$), in agreement with the 13 carbon atoms observed in the ^{13}C NMR (two quaternary, nine methines and two methylenes). The presence of three hydroxyl groups was suggested by successive losses of water from the $[M+H]^+$ in the CI mass spectrum at *m/z* 235 $[M+H-H_2O]^+$, *m/z* 217 $[M+H-2H_2O]^+$ and *m/z* 199 $[M+H-3H_2O]^+$, and a broad IR absorption band at 3380 cm^{-1}. The M_r and the existence of three free hydroxyl groups were confirmed by the preparation of a triacetate derivative (**1a**), which gave peaks in the CI mass spectrum at *m/z* 379 $[M+H]^+$, corresponding with the molecular formula, $C_{19}H_{22}O_8$, and at *m/z* 320 $[M+H-OCOCH_3]^+$, *m/z* 259 $[M+H-2HOCOCH_3]^+$ and *m/z* 201 $[M-3OCOCH_3]^+$. Three singlet proton resonances at δ 2.17, δ 2.04 and δ 1.88 (3 *s*, 9H, $OCOCH_3$) in the ^{1}H NMR spectrum of **1a** were also observed.

The presence of a saturated δ-lactone ring in **1** was suggested by an IR carbonyl absorption band at 1755 cm^{-1} and a small downfield carbon signal at δ 176.95 (C-2) in the ^{13}C NMR spectrum. Indeed, resonances at δ 2.59 (H-3b), δ 2.49 (H-3a), δ 2.25 (H-4b) and δ 2.05 (H-4a) in the ^{1}H NMR spectrum, and at δ 24.0 (C-4) and δ 28.2 (C-3) in the ^{13}C NMR (Table 1), were consistent with the existence of two methylene

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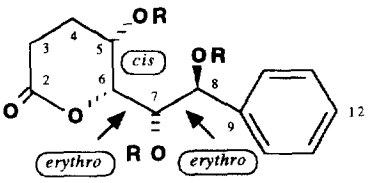
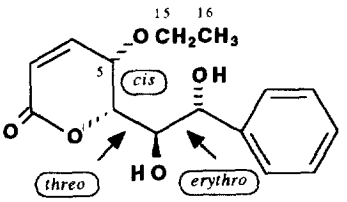
Styryl-pyrone skeleton

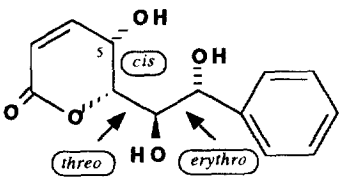


1: R= H: (+)-garvensintriol [5*S*, 6*R*, 7*S*, 8*S*]

1a: R= Ac

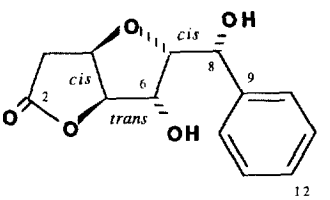


2: (+)-etharvendiol [5*S*, 6*R*, 7*R*, 8*R*]



4: (+)-goniotriol [5*S*, 6*R*, 7*R*, 8*R*]

Furano-furone skeleton



3: (+)-goniofufurone [4*R*, 5*S*, 6*S*, 7*R*, 8*R*]

Fig. 1. Styryl-pyrone and furano-furone configurations.

carbons. The remaining methine signals at δ 4.96, δ 4.62, δ 3.84 and δ 3.77 in the ^{1}H NMR and at δ 72.1, δ 73.8, δ 75.8 and δ 81.8 in the ^{13}C NMR, are in agreement with the presence in **1** of four oxygen-bearing carbons.

At this point, the presence of a saturated δ-lactone, a monosubstituted phenyl moiety and three hydroxyl groups in **1** is justified. NMR chemical shifts, selective homonuclear ^{1}H-^{1}H correlations and ^{1}H-coupling constants, suggested a styryl–pyrone skeleton in **1**, similar to that described for (+)-goniotriol (**4**) [16, 17].

^{1}H-^{1}H COSY correlations between methylenic protons and consecutive methine oxygenated ones, were consistent with the placement of hydroxyl groups at C-5, C-7 and C-8 (Fig. 2).

Comparison between the ^{1}H and ^{13}C NMR spectral data of **1** with those of the known styryl-pyrone (+)-goniotriol (**4**) (whose ^{13}C NMR was only reported in CD_3OD) [16, 17], and careful examination of the ^{1}H-^{1}H COSY spectrum of **1**, suggested that (+)-garvensintriol (**1**) might be a 3,4-dihydro-7,8-dihydroxy-styryl-5-hydroxy-2-pyrone compound (Tables 1 and 2). The coupling constants between H-5/H-6, H-6/H-7 and H-7/H-8 in (+)-goniotriol (**4**) were reported to be 4.0 Hz, 4.0 Hz and 8.0 Hz, respectively [16], whereas in (+)-garvensintriol (**1**), the corresponding coupling constants were 4.6 Hz, 1.8 Hz and 5.8 Hz. These values alone were sufficient to define uniquely the structural inter-relationships between protons H-5 to H-8 and suggested, for **1**, a H-6/H-7 relationships opposite to that of **4** (6,7-*threo*). Consequently, a 5,6-*cis*, 6,7-*erythro* and 7,8-*erythro* relative configuration was established for **1** (Fig. 1). In order to observe this original

Table 1. 1D and 2D NMR experiments (in $CDCl_3$) on compounds **1** and **2**

Position	δ_H (*J* Hz)	^1H-^1H COSY 45 correlation	δ_C (DEPT)
		(+)-Garvensintriol (**1**)*	
2	—	—	177.0 (C)
3a	2.49 *dtd* (17.9; 1.8; 1.4)	H-3b (2.59), H-4b (2.25), H-4a (2.05)	28.2 (CH_2)
3b	2.59 *ddd* (17.9; 5.3; 5.1)	H-3a (2.49), H-4b (2.25), H-4a (2.05)	
4a	2.05 *m* (17.8; 7.9; 5.3; 1.4)	H-4b (2.25), H-3b (2.59), H-3a (2.49), H-5 (4.62)	24.0 (CH_2)
4b	2.25 *m* (17.8; 7.4; 5.1; 1.8)	H-4a (2.05), H-3b (2.59), H-3a (2.49), H-5 (4.62)	
5	4.62 *td* (7.9; 7.4; 4.6)	H-4b (2.25), H-4a (2.05), H-6 (3.77)	75.8 (CH)
6	3.77 *dd* (4.6; 1.8)	H-5 (4.62), H-7 (3.84)	81.8 (CH)
7	3.84 *dd* (5.8; 1.8)	H-6 (3.77), H-8 (4.96)	72.1 (CH)
8	4.96 *d* (5.8)	H-7 (3.84)	73.8 (CH)
9	—	—	140.2 (C)
10–14	7.30–7.39 *m*	—	128.8 (2 CH)
			128.2 (CH)
			126.1 (2 CH)
		(+)-Etharvendiol (**2**)**	
2	—	—	167.1 (C)
3	6.00 *dd* (11.7)	H-4 (6.46)	120.8 (CH)
4	6.46 *dd* (11.7; 6.2)	H-3 (6.00), H-5 (5.65)	148.3 (CH)
5	5.65 *td* (6.2; 2.2)	H-4 (6.46), H-6 (4.59)	78.7 (CH)
6	4.59 *brtd* (5.2; 2.2)	H-5 (5.65), H-7 (4.14)	84.0 (CH)
7	4.14 *brd* (5.4; 5.2)	H-6 (4.59), H-8 (5.00)	73.6 (CH)
8	5.00 *d* (5.4)	H-7 (4.14)	79.0 (CH)
9	—	—	141.0 (C)
10–14	7.28–7.38 *m*	—	128.5 (2 CH)
			127.8 (CH)
			125.6 (2 CH)
15	4.20 *q* (7.0)	16-CH_3 (1.31)	60.9 (CH_2)
16	1.31 *t* (7.0)	15-CH_2 (4.20)	14.2 (CH_3)

* ^1H and ^{13}C NMR recorded at 400 MHz and 62.5 MHz, respectively.
** ^1H and ^{13}C NMR recorded at 300 MHz and 75 MHz, respectively.

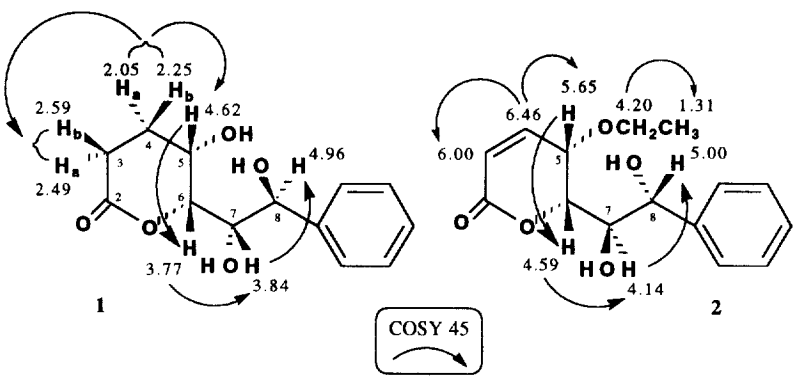


Fig. 2. Selective ^1H-^1H correlations (COSY 45) observed in compounds **1** and **2**.

stereochemistry, a 3D representation of the fully energy-minimized structure was calculated using a molecular modelling programme with the MM2-derived force field (Fig. 3). Thus, the novel styryl-pyrone (+)-garvensintriol (**1**) was identified as (+)-3,4-dihydro-7,8-diepi-goniotriol, with a [5*S*, 6*R*, 7*S*, 8*S*] absolute configuration different from that of (+)-goniotriol (**4**), whose absolute configuration [5*S*, 6*R*, 7*R*, 8*R*] was previously determined by X-ray crystallography [17].

Compound **2**, was also isolated as a yellowish oil and its M_r was indicated by a peak in the CI mass spectrum at m/z 279 $[M+H]^+$, corresponding with the molecular formula, $C_{15}H_{18}O_5$, consistent with the 15 carbon atoms of **2** (two quaternary, 11 methines, a methylene and a methyl). Like **1**, compound **2** exhi-

Table 2. ^{13}C NMR data (δ_C, CD_3OD) for compounds **1**, **2** and **4**

Carbon	(+)-Garvensintriol (**1**)*	(+)-Etharvendiol (**2**)*	(+)-Goniotriol (**4**)**
2	177.0	168.0	166.1
3	30.2	122.0	123.0
4	25.9	148.8	146.5
5	75.7	79.9	75.7
6	85.0	84.0	80.3
7	74.6	75.2	63.5
8	75.2	80.8	74.0
9	140.0	143.8	143.4
10–14	129.7	129.4	129.1
	129.4	128.7	128.8
	129.0	127.1	128.8
15		61.4	
16		14.5	

* Recorded at 100 MHz.

** ^{13}C NMR of **4** has only reported in CD_3OD at 50 MHz [17].

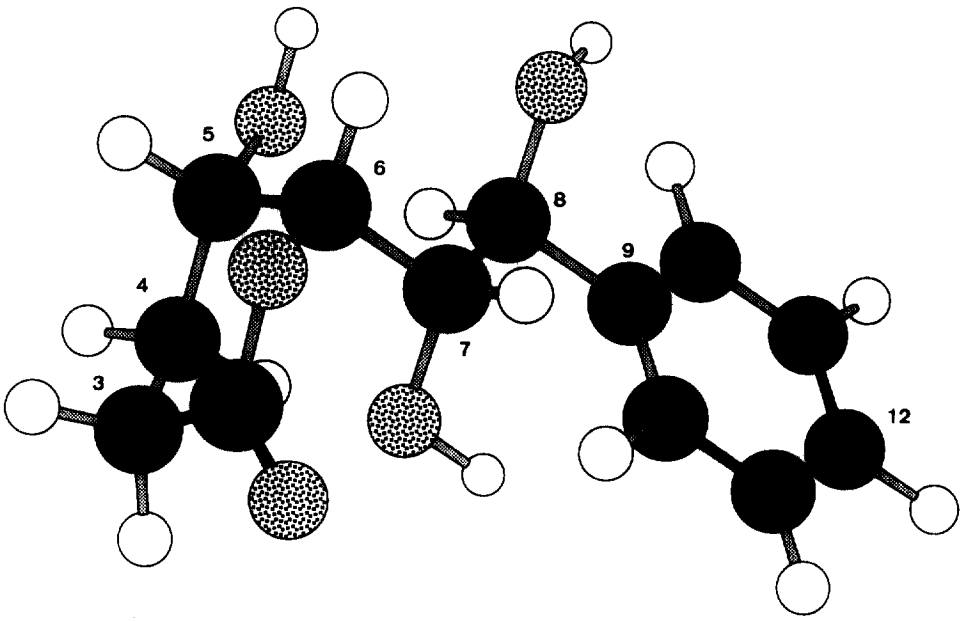
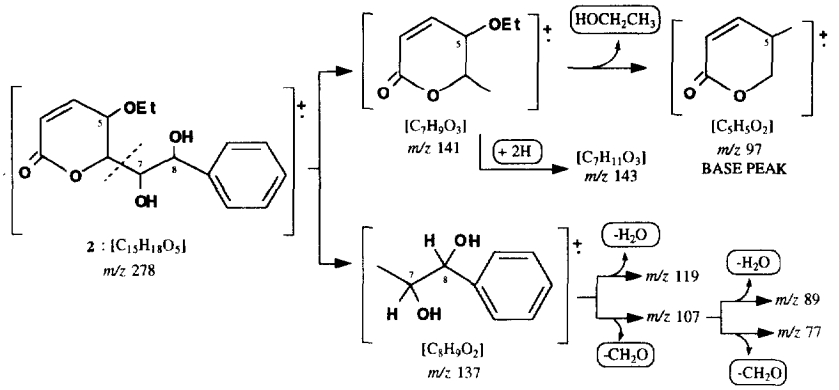


Fig. 3. Perspective 3D representation of the fully energy-minimized structure of (+)-garvensintriol (**1**) using MM2 calculations.

bited IR absorption bands for 2-pyrone, aromatic and hydroxyl groups. Furthermore, the presence of a monosubstituted phenyl moiety, a δ-lactone ring and a vicinal diol was confirmed by mass spectral and NMR data (Tables 1 and 2). However, comparison between **2** and **1** NMR spectrum, suggested the same plain skeleton for both compounds but a different configuration and degree of saturation concerning their δ-lactone system (Figs. 1 and 2).

The presence of an ethoxyl group in **2** was suggested in the CI mass spectrum by a fragment ion at *m/z* 233 due to the direct loss of 46 m. u. from the $[M+H]^+$, $[M+H-HOCH_2CH_3]^+$, confirmed in the ^1H NMR by resonances at δ 4.20 (*q*, 2H, CH_2) and δ 1.31 (*t*, 3H, CH_3) and, in the ^{13}C NMR, at δ 60.9 (CH_2) and δ 14.2 (CH_3) (Table 1). The existence of two hydroxyl moieties in **2** was indicated by successive losses of water in the CI mass spectrum, at *m/z* 261 $[M+H-H_2O]^+$ and *m/z* 243 $[M+H-2H_2O]^+$, and by a broad IR absorption band at 3404 cm^{-1}. An α,β-unsaturated δ-lactone subunit is justified by an IR absorption band at 1711 cm^{-1}, a carbon resonance at δ 167.1 (C-2) and two olefinic resonances at δ 6.0 and δ 6.46, and at δ 120.8 and δ 148.3 in the ^1H and ^{13}C NMR, respectively (Table 1).

Four resonances due to oxygen-linked methines



Scheme 1. EI mass spectral fragmentations of (+)-etharvendiol (**2**).

were observed in the ^1H and ^{13}C NMR spectra of **2**. The ^1H-^1H COSY spectrum showed a correlation between an olefinic proton (H-4 at δ 6.46) and a vicinal oxygenated methine (H-5 at δ 5.65), and consecutive proton correlations between the remaining oxygen-bearing methines (H-5 to H-8) (Table 1 and Fig. 2). The location of the ethoxyl group at C-5 was supported by the EI mass spectral fragments at *m/z* 141 and *m/z* 143, corresponding to the ethoxylated α,β-unsaturated δ-lactone moiety, and, at *m/z* 97, due to the direct loss of an ethoxyl group. The placement of the two hydroxyl groups at C-7 and C-8 was confirmed by a fragment ion at *m/z* 137 in the EI mass spectrum (Scheme 1).

Examination of a Dreiding molecular model, ^1H-^1H COSY correlations and the magnitude of the coupling constants $J_{3,4}$ (11.7 Hz), $J_{4,5}$ (6.2 Hz), $J_{5,6}$ (2.2 Hz), $J_{6,7}$ (5.2 Hz) and $J_{7,8}$ (5.4 Hz), revealed that (+)-etharvendiol (**2**) has a relative configuration identical to that of (+)-goniotriol (**4**). Thus, the absolute configuration of **2** should be [5*S*, 6*R*, 7*R*, 8*R*].

EXPERIMENTAL

Plant material

Goniothalamus arvensis Scheff. was collected in the National Park of Varirata, in the Central Province of Papua New Guinea. A voucher specimen is deposited in the herbarium of the University of Papua New Guinea.

Extraction and isolation

Dried and powdered stem bark (368 g) were macerated with MeOH at room temp. The concd MeOH extract was partitioned between hexane (extract A) and 50% aq. MeOH. The aq. extract was fractionated successively with CH_2Cl_2 and EtOAc (extracts B and C, respectively). Extract B (7 g) was applied to a 60H silica gel column (Merck 7736) and eluted with CH_2Cl_2–EtOAc (3:2). Repeated CC afforded **2** (8 mg) and **3** (40 mg). Extract C (1.2 g) was fractionated on a 60H silica gel column with CH_2Cl_2–EtOAc (1:4) and purified by prep. TLC using $CHCl_3$–Me_2CO (9:1) to give **1** (15 mg).

(+)-*Garvensintriol* (**1**). $C_{13}H_{16}O_5$. $[\alpha]_D$ +7.8° (EtOH; c 3.3). UV λ_{max} EtOH nm (log ε): 220 (2.22), 250 (2.07) 256 (2.08). IR ν_{max} (film) cm^{-1}: 3380, 2914, 2846, 2353, 2343, 2331, 1755, 1601, 1490, 1450, 1413, 1192, 1154, 1104, 1043, 925, 808, 768, 700. LSIMS *m/z*: 253 $[M+H]^+$. CIMS *m/z*: 235 $[M+H-H_2O]^+$, 217 $[M+H-2H_2O]^+$, 199 $[M+H-3H_2O]^+$, 175, 145, 128, 115, 121, 107, 91. EIMS *m/z* (rel. int.): 234 $[M-H_2O]^+$ (7), 216 $[M-2H_2O]^+$ (3), 120 (10), 115 (4), 107 (100), 97 $[C_5H_5O_2]^+$ (6), 77 (36). ^1H and ^{13}C NMR (400 and 62.5 MHz, $CDCl_3$): Tables 1 and 2.

(+)-*Garvensintriol* 5,7,8-*triacetate* (**1a**). **1** (1.2 mg) was treated with pyridine (0.5 ml) and Ac_2O (1 ml) to give triacetate **1a** (1.7 mg; 94%). $C_{19}H_{22}O_8$. CIMS *m/z*: 379 $[M+H]^+$, 320 $[M+H-OCOCH_3]^+$, 277 $[M+H-OCOCH_3-COCH_3]^+$, 259 $[M+H-2HOCOCH_3]^+$, 217 $[M-2OCOCH_3-COCH_3]^+$, 201 $[M-3OCOCH_3]^+$. ^1H NMR ($CDCl_3$, 250 MHz): δ 7.34–7.32 (*m*, 5H, H-10 to H-14), δ 5.71 (*d*, H-8), δ 5.51 (*m*, H-5), δ 5.45 (*dd*, H-7), δ 3.61 (*brd*, H-6), δ 2.52 (*m*, 2H, H-3a,b), δ 2.30 (*m*, 2H, H-4a,b), δ 2.17, δ 2.04 and δ 1.88 (3*s*, 9H, $OCOCH_3$).

(+)-*Etharvendiol* (**2**). $C_{15}H_{18}O_5$. $[\alpha]_D$ +25.4° (EtOH; c 1.3). UV λ_{max} EtOH nm (log ε): 230 (2.64), 268 (2.61). IR ν_{max} (film) cm^{-1}: 3404, 3057, 3028, 2928, 2353, 2345, 2332, 1711, 1647, 1491, 1449, 1412, 1385, 1299, 1194, 1129, 1080, 1040, 1023, 968, 919, 890, 859, 827, 758, 698. CIMS *m/z*: 279 $[M+H]^+$, 261 $[M+H-H_2O]^+$, 243 $[M+H-2H_2O]^+$, 233 $[M+H-HOCH_2CH_3]^+$, 215 $[M+H-HOCH_2CH_3-H_2O]^+$, 197 $[M+H-HOCH_2CH_3-2H_2O]^+$, 137, 97. EIMS *m/z* (rel. int.): 278 $[M]^+$ (3), 201 (1), 185 (2), 143 (32), 141 $[C_7H_9O_3]^+$ (3), 137 $[C_8H_9O_2]^+$ (12), 120 (16), 119 (61), 107 (60), 97 $[C_5H_5O_2]^+$ (100), 91 (56), 89 (9), 77 (48) (see Scheme 1). ^1H and ^{13}C NMR ($CDCl_3$, 300 and 75 MHz): Tables 1 and 2.

(+)-*Goniofufurone* (**3**). $C_{13}H_{14}O_5$. Mp: 154–155° (EtOAc–hexane) {lit. mp 152–154 [14]}. $[\alpha]_D$ +12° (EtOH; c 1.1), {lit. $[\alpha]_D$ +9° (EtOH; c 0.5 [14]}. EIMS

m/z (rel. int.): 250 $[M]^+$, 107 $[C_7H_7O]^+$ (100). ^1H and ^{13}C NMR: see refs [11, 14, 15].

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