Lakshminine, a New Rare Oxoisoaporphine Alkaloid from *Sciadotenia toxifera*, and Structural Revisions of Telazoline and Teladiazoline, Two Related Oxoaporphines from *Telitoxicum peruvianum* and *T. glaziovii*

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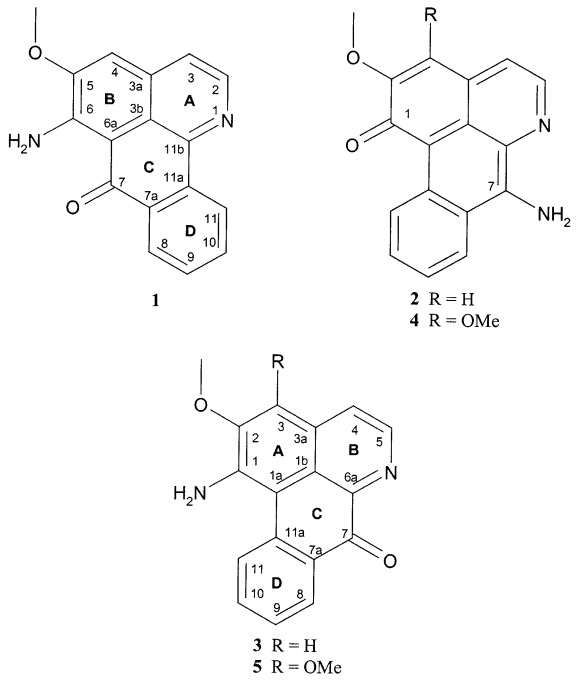
Lakshminine (**1**), a novel oxoisoaporphine alkaloid possessing a C-6 amine substituent, was isolated from a basic fraction from the woody vines (collected from two bush-ropes) of *Sciadotenia toxifera*. This compound represents the first documented occurrence of an oxoisoaporphine from any Menispermaceae species other than *Menispermum dauricum*. The structures of two related aporphine alkaloids, telazoline (**3**) and teladiazoline (**5**), were revised on the basis of a comparison of their spectral data with that of lakshminine (**1**).

Although several aporphine alkaloids from a variety of natural sources have been described in the literature, the number of oxoaporphine alkaloids reported is rather limited. Among the oxoaporphines there exists an even smaller subset of compounds known as oxoisoaporphines,[1] in which the aromatic isoquinoline ring incorporating the nitrogen atom is part of a biphenyl system. To date, *Menispermum dauricum* (Menispermaceae) represents the sole reported natural source for oxoisoaporphines in the literature.[1−10]

A recent investigation of the active components among the total bases of *Sciadotenia toxifera* (Krukoff and A. C. Smith) (Menispermaceae) led to the isolation and structural elucidation of a novel oxoisoaporphine alkaloid, lakshminine (**1**), the structure of which was entirely determined by spectroscopic means. Lakshminine represents the first documented occurrence of an oxoisoaporphine from a Menispermaceae other than *Menispermum dauricum*, and it is one of the few reported oxoisoaporphine alkaloids to possess an amine substituent. Other alkaloids isolated from the basic fraction of *Sciadotenia toxifera* included the azafluoroanthene telitoxine,[11] the oxoaporphine atherospermidine,[12] the α-hydroxybisbenzylisoquinoline cavanine,[13] and seven bisbenzylisoquinoline alkaloids, (+)-sciadenine, (+)-sciadoline, (+)-sciadoferine, (+)- and (−)-isochondodendrines, (+)-*O*,*O*-dimethylcurine, and *epi*-norcycleanine.[14] South American Menispermaceae, such as *S. toxifera*, have previously been shown to possess curare activity, and on the basis of this activity *S. toxifera* was selected for investigation.[14]

The spectral results obtained for lakshminine (**1**) prompted a more thorough investigation of the structure previously reported for the aporphine telazoline (**2**), which was previously isolated from *Telitoxicum peruvianum*,[11] and led to a revised structure **3** in which the positions of the oxo and amine substituents were reversed. The revision of the structure of telazoline (**3**) prompted additional investigation into the structure of teladiazoline (**4**), the 3-methoxyl analogue of telazoline that was previously isolated from *Telitoxicum glaziovii*.[15] Consequently the structure of teladiazoline was also revised to that of the analogous 1-amino-7-oxoaporphine, **5**.



1

2 R = H
4 R = OMe

3 R = H
5 R = OMe

Chromatographic separation of the basic fraction from the woody vines (bush-ropes) of *S. toxifera* yielded a new alkaloid (**1**) isolated as an orange-yellow amorphous powder. Using DCI-MS (methane) **1** was shown to possess a molecular weight of 276, and high-resolution FTMS indicated that the molecular formula was $C_{17}H_{12}N_2O_2$. The ^{1}H NMR spectrum of **1** dissolved in $CDCl_3$ is summarized in Table 1. It revealed the presence of seven aromatic hydrogen atoms, two broad NH signals at δ 10.71 and 6.46 that shared a mutual COSY correlation (primary amine), and a methoxyl singlet at δ 4.13, reminiscent of the aporphine telazoline (**2**) previously isolated from *T. peruvianum*, which also possessed an amine substituent.[11] Paucity of material resulted in a weak ^{13}C NMR GASPE spectrum, revealing all but one of the 17 carbon signals (see Table 1). The IR spectrum of **1** showed absorbances at 3278, 3136, and 1635 cm^{-1}, confirming the presence of an amine and a carbonyl functionality.

COSY NMR data for **1** indicated that the seven aromatic signals were incorporated into three separate spin systems,

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Table 1. ^{1}H and ^{13}C NMR Assignments for Lakshminine (**1**) in $CDCl_3$

position	δ_C (mult.)	δ_H (mult., *J*, integral)	HMBC
2	142.0 (d)	8.70 (d, 5.2 Hz, 1H)	3, 3a, 11b
3	120.2 (d)	7.61 (d, 5.2 Hz, 1H)	3b,4
3a	129.6 (s)		
3b	119.5 (s)		
4	108.5 (d)	7.19 (s, 1H)	3, 3b, 5, 6
5	150.4 (s)		
6	148.1 (s)		
6a	not observed		
7	184.0 (s)		
7a	132.9 (s)		
8	126.4 (d)	8.57 (dm, 7.9 Hz, 1H)	7, 10, 11a
9	129.0 (d)	7.69 (m, 1H)	7a, 11
10	132.3 (d)	7.83 (m, 1H)	8, 11a
11	124.8 (d)	9.06 (dm, 8.1 Hz, 1H)	7a, 9, 11b
11a	136.4 (s)		
11b	143.4 (s)		
OMe-5	56.1 (q)	4.13 (s, 3H)	5
NH_2-6		10.71 (b, 1H)	
		6.46 (b, 1H)	

Table 2. ^{1}H and ^{13}C NMR Assignments for Telazoline (**3**) in $CDCl_3$

position	δ_C (mult.)	δ_H (mult., *J*, integral)	HMBC
1	139.8 (s)		
1a	107.0 (s)		
1b	122.8 (s)		
2	152.4 (s)		
3	104.1 (d)	7.06 (s, 1H)	1, 1b, 2, 4
3a	133.0 (s)		
4	123.4 (d)	7.70 (d, 5.0 Hz, 1H)	1b, 3, 5
5	143.4 (d)	8.80 (d, 5.0 Hz, 1H)	3a, 4, 6a
6a	143.8 (s)		
7	182.5 (s)		
7a	132.4 (s)		
8	129.5 (d)	8.62 (dd, 1.3, 7.9 Hz, 1H)	7, 10, 11a
9	126.8 (d)	7.49 (m, 1H)	7a, 11
10	133.5 (d)	7.73 (m, 1H)	8, 11a
11	124.8 (d)	8.56 (dm, 7.9 Hz, 1H)	1a, 7a, 9
11a	136.0 (s)		
OMe-2	56.3 (q)	4.12 (s, 3H)	2
NH_2-1		5.51 (s, 2H)	1a, 2

one of which consisted of an isolated singlet on an otherwise fully substituted aromatic ring. Two other aromatic proton signals appeared as doublets sharing a unique 5.2 Hz coupling, and the remaining aromatic proton multiplets were identified as four contiguous hydrogen atoms about a third aromatic ring. The isolation of additional isoquinoline alkaloids from this basic fraction and the observation of the two unique aromatic doublets sharing a characteristic 5.2 Hz coupling constant in the ^{1}H NMR spectrum indicated that compound **1** is also probably an aporphine alkaloid similar to telazoline possessing a methoxyl and an amine substituent. Upon NOE saturation of the aromatic singlet at δ 7.19, enhancement of the adjacent methoxyl singlet on one side and the 5.2 Hz doublet at δ 7.61 on the other side confirmed that the isoquinoline rings were fully aromatic. Positioning the four contiguous hydrogen atoms in their traditional positions on the bottom aromatic ring, it only remained to place the amine and the oxo groups in the appropriate positions about the aporphine skeleton of **1**. The number of ^{1}H NMR signals observed for **1**, their multiplicities, and their relationship to one another were nearly identical to those reported for the aporphine alkaloid, telazoline (**2**), possessing a C-1 oxo and a C-7 amine substituent. However, clear-cut differences in their ^{1}H NMR chemical shifts and the color of the isolated material (telazoline is reddish brown rather than orange-yellow) indicated that **1** was not telazoline, but rather it was probably an isomer of telazoline, possibly having C-1 amine and C-7 oxo substituents.

The HMQC and the HMBC heteronuclear NMR correlation data allowed for the identification of the proton-bearing carbons as well as the quaternary carbon atoms. The quaternary carbons comprising the top two isoquinoline rings were readily assigned, and the results are summarized in Table 1. From the HMBC data it became clear that the oxo carbon was not part of the top two rings as was the case for telazoline, since none of those protons correlated with the characteristic oxo carbon at δ 184.0. Instead, a carbon possessing a δ 148.1 chemical shift was situated in that position based on HMBC correlations, consistent with an amine substituent.

Additionally, the H-8 terminal proton multiplet (δ 8.57) in the bottom ring shared a three-bond correlation with the oxo carbon resonating at δ 184.0, thereby fixing the position of the oxo carbon at C-7 in ring C. H-11, the other terminal proton multiplet in the bottom ring (δ 9.06), shared a three-bond correlation with the quaternary C-11b carbon at δ 143.4 in the top isoquinoline ring. This correlation in particular established that the bottom ring D shared a biphenyl relationship with the nitrogen-containing aromatic ring. Collectively, the spectral data confirmed that compound **1**, which was named lakshminine, is a rare oxoisoaporphine with a C-7 oxo substituent and a C-6 primary amine.

The proximity of the oxo group at C-7 to the amine group at C-6 in lakshminine (**1**) readily accounted for the diverse NMR chemical shifts exhibited by the geminal primary amine hydrogen atoms at δ 10.71 and 6.46. The δ 10.71 downfield chemical shift of one of the amine hydrogens was indicative of a significant degree of hydrogen bonding between it and the neighboring C-7 oxo substituent.

In the literature description of menisporphine,[1] the original oxoisoaporphine, the authors proposed a biogenetic pathway that began with a papaverinol precursor and went through an isoquinoline intermediate containing a spiro cyclobutane ring. Lakshminine (**1**), tyraminoporphine,[2] and daurioxoisoporphines A−C[3] are all oxoisoaporphine alkaloids known to possess C-6 amine functionalities, and they probably share a common heritage.

A useful comparison of the ^{13}C NMR chemical shifts of lakshminine (**1**) with those of the isomeric aporphine telazoline (**2**) was not possible because there were no carbon NMR data available for **2** in the literature.[11] Therefore, a determination of the ^{13}C NMR spectral assignments for telazoline (**2**) was undertaken. To avoid confusion it is important to note that the traditional numbering system and ring designations for the oxoaporphines differ from those of the oxoisoaporphines.

Having a sample of telazoline available, it was important to initially verify that the spectral data generated from it matched well with that previously reported in the literature[11] to ensure that they were one and the same compound. DCI-MS (methane) indicated that **3** possesses a molecular weight of 276 ($C_{17}H_{12}N_2O_2$), which was consistent with the data previously published for telazoline. By ^{1}H NMR, the seven aromatic hydrogen multiplets, two equivalent NH protons at δ 5.51, and the methoxyl singlet at δ 4.12 (see Table 2) were in good agreement with published values. Once again, the COSY data allowed for the subdivision of the seven aromatic signals into three separate spin systems as before. NOE saturation of the H-3 aromatic singlet in ring A caused enhancement of the adjacent methoxyl singlet on one side and the H-4 doublet (J = 5.0 Hz) in ring B on the other side as expected. Saturation of

the solitary amine resonance caused an enhancement of the terminal ring D doublets of doublets at δ 8.56 as anticipated. The mass spectral and proton NMR data for **3** were identical to the data presented for telazoline in the literature.[11]

Fortunately there was a sufficient quantity of telazoline (**3**) available to detect all 17 carbon atoms in a ^{13}C GASPE NMR experiment, and the resulting carbon chemical shifts are summarized in Table 2. The HMQC and the HMBC heteronuclear correlation data, while supporting the presence of an oxoaporphine skeleton for telazoline, provided definitive evidence that the structure originally proposed, **2**, was incorrect. In the revised structure for telazoline (**3**) the primary amine was repositioned at C-1 and the oxo carbon was shown to be C-7, resulting in a structure identical to lakshminine (**1**) except for having the C and D rings reversed.

The key NMR evidence leading to the structural revision of telazoline (**3**) emanated from the amine protons at δ 5.51, which correlated to C-1a at δ 107.0 and C-2 at δ 152.4 in ring A. The identity of the C-2 position was firmly established by mutual NOEs shared between the methoxyl protons at δ 4.12 and the H-3 singlet at δ 7.06 in conjunction with an HMBC correlation between the methoxyl protons and C-2 at δ 152.4. Therefore, the amine group must be attached at C-1 in ring A. The H-8 proton multiplet at δ 8.62 correlated with the C-7 oxo carbon at δ 182.5 in ring C, and likewise the H-11 proton multiplet at δ 8.56 correlated with C-1a in ring A as well as shared a mutual NOE enhancement with the primary amine protons at C-1. Since the oxo group at C-7 exerts little influence on the amine group at C-1 on the opposite side of the molecule, it was reasonable for the two amine protons to have identical chemical shifts, reflecting the absence of hydrogen bonding. The revised ^1H and ^{13}C NMR assignments for the oxoaporphine telazoline (**3**) are summarized in Table 2.

A comparison of the body of mass spectral data obtained for the structural isomers lakshminine (**1**) and telazoline (**3**) revealed some interesting spectral analogies between the oxoisoaporphine and oxoaporphine compound classes. Lakshminine (**1**) and telazoline (**3**) produced virtually identical positive CI mass spectra using methane as the reagent gas. For both compounds the base peak was the protonated molecular ion (*m*/*z* 277), with no significant fragment ions observed. In the negative methane CI ion mode, the mass spectra of both **1** and **3** were also essentially identical with base peaks of *m*/*z* 261 $(M - CH_3)^-$. A molecular anion (*m*/*z* 276) was also observed for compounds **1** and **3** (25% and 45%, respectively).

Using an ion trap mass spectrometer to perform an MS/MS experiment, the *m*/*z* 277 $[M + H]^+$ ion was selected in the ion trap for both compounds **1** and **3** and then allowed to undergo collision-induced dissociation (CID) with helium. The subsequent reaction product ions were swept from the ion trap and analyzed, and the resulting MS/MS methane DCI mass spectral data proved useful in differentiating between the structurally similar oxoisoaporphine and oxoaporphine alkaloids. The MS/MS fragments generated from the *m*/*z* 277 $[M + H]^+$ ion of lakshminine and telazoline are summarized in Table 3. These data clearly indicated that both compounds are unique and isomeric.

An MS/MS/MS experiment was performed on the ion at *m*/*z* 262 $(m/z\ 277 - CH_3)^{+\bullet}$. In this experiment the *m*/*z* 277 protonated molecular ion was trapped and then fragmented via CID, producing a *m*/*z* 262 product ion, which was again isolated, fragmented, and analyzed. The MS^3 results for the fragment ions arising from *m*/*z* 262 in both **1** and **3** are presented in Table 4.

Table 3. MS^2 Data at *m*/*z* 277 $[M + H]^+$ for Lakshminine (**1**) and Telazoline (**3**)

m/*z*	ion description	lakshminine (%)	telazoline (%)
277	$[M + H]^+$	95.5	42.3
262	$[M + H - CH_3]^{+\bullet}$	48.9	100.0
261	$[M + H - NH_2]^{+\bullet}$	60.5	3.1
245	$[M + H - CH_3OH]^+$	34.2	2.1
234	$[M + H - CH_3 - CO]^{+\bullet}$	100.0	26.4

Table 4. MS^3 Data at *m*/*z* 262 $[M + H - CH_3]^+$ for Lakshminine (**1**) and Telazoline (**3**)

m/*z*	ion description	lakshminine (%)	telazoline (%)
262	$[M + H - CH_3]^{+\bullet}$	13.8	7.6
247	$[M + H - CH_3 - O + H]^+$	0	87.8
246	$[M + H - CH_3 - NH_2]^+$	19.6	8.2
234	$[M + H - CH_3 - CO]^{+\bullet}$	100.0	8.7
219	$[M + H - CH_3 - O - CO + H]^+$	2.3	100.0

The MS^3 data in Table 4 clearly emphasized the structural difference between the oxoisoaporphine and oxoaporphine alkaloids. With this information at hand and keying on the MS^3 product ions *m*/*z* 247, 234, and 219 for lakshminine (**1**), it was clear that compound **1** possesses an oxoisoaporphine alkaloid skeleton rather than an oxoaporphine alkaloid skeleton. Since MS^2 type experiments are widely used for determining subtle structural differences between isomeric compounds, it is thought that such experiments might prove useful in the future, particularly in cases where two-dimensional NMR was impractical.

The revision of the telazoline structure from **2** to **3** prompted further investigation into the published structure of teladiazoline (**4**), the 3-methoxy analogue of telazoline isolated from *Telitoxicum glaziovii*.[15] DCI-MS (methane) indicated that teladiazoline (**4**) possesses a molecular weight of 306 ($C_{18}H_{14}N_2O_3$), which was consistent with the data previously published. By ^1H NMR the six aromatic hydrogen multiplets, two equivalent NH protons at δ 5.53, and two methoxyl singlets at δ 4.15 and 4.11 were also in good agreement with published values. The COSY data allowed for the subdivision of the six aromatic signals into two separate spin systems. NOE saturation of the 1-amine singlet caused enhancements of the adjacent 2-methoxyl singlet on one side and the H-11 terminal ring D doublets of multiplets at δ 8.51 on the other side, while saturation of the 3-methoxyl singlet enhanced the H-4 doublet at δ 8.10. The previous structure for teladiazoline (**4**) was therefore revised to the oxoaporphine structure **5**, accommodating the primary amine repositioned at C-1 and the oxo carbon at C-7. The ^{13}C NMR data further reinforced **5** as the correct structure for teladiazoline.

The intensities of the MS^2 and MS^3 fragments observed for teladiazoline (**5**) were not totally analogous to those in telazoline (**3**). Presumably, the additional methoxyl group present in teladiazoline altered the fragmentation pattern sufficiently that the MS^2 and MS^3 fragmentation intensities were not conserved from telazoline to teladiazoline. This fragmentation data apparently can only be used to reliably discriminate between isomers, such as lakshminine (**1**) and telazoline (**3**).

Experimental Section

General Experimental Procedures. UV spectra were collected on a Hewlett-Packard 5842 diode array UV/vis spectrophotometer. IR spectra were collected via FT-IR trans-

mission microscopy using a Magna IR-760/NICPLAN instrument with no sample preparation. The NMR data were acquired on either a Bruker AMX-400 spectrometer equipped with a 5 mm inverse-broadband probe or a Bruker Avance-700 spectrometer equipped with a 2.5 mm inverse-broadband gradient probe. All of the one- and two-dimensional NMR data sets were collected and processed using standard pulse sequences and processing techniques. All samples were dissolved in $CDCl_3$, and all of the NMR chemical shifts were referenced to TMS via a secondary solvent signal. DCI mass spectra (methane) were collected on a Finnigan Polaris Q Ion Trap mass spectrometer scanned from 70 to 770 Da at a rate of 700 Da/s. The mass spectral data were acquired and processed using Xcaliber software. A 0.1 μg/μL methanolic solution was prepared for each compound, and then one microliter of each solution was applied to the DCI probe tip and allowed to evaporate to dryness. The DCI probe was heated to 1000 mA at a rate of 50 mA/s. Analytical and preparative TLC were carried out on precoated silica gel G (Kieselgel G254) plates, and reagent grade chemicals (VWR) were used throughout.

Plant Material. The woody vines (collected from two bushropes) of *Sciadotenia toxifera* were collected in San Martin, Peru, in 1977 by Jose Schunke V. A voucher specimen number 9835, identified by Dr. B. A. Krukoff, was placed in the New York Botanical Garden Herbarium, Bronx, NY.

Extraction and Isolation. The ground plant material (4.2 kg) was moistened with 1:1 NH_4OH-H_2O and extracted exhaustively with 9:1 EtOAc−EtOH. The extract was concentrated and then partitioned between CH_2Cl_2 and 2% H_2SO_4 to obtain the CH_2Cl_2-soluble neutral fraction (19.5 g) and the total bases. Gradient pH extractions were conducted over a pH range of 6.0−12.0 to separate the total bases. The extracts from pH range 6.0−8.5 (38.57 g) were combined and further subjected to column chromatography on silica gel. Fractions eluted with 0.25% CH_3OH in CH_2Cl_2 gave an orange-yellow amorphous powder, lakshminine (**1**, 2 mg). Fractions eluted with 1.5% CH_3OH in CH_2Cl_2 (0.93 g) yielded telitoxine[11] (3 mg) and atherospermidine[12] (1 mg) in pure form only after two additional chromatographic separations followed by a recrystallization.

Lakshminine (1): orange-yellow amorphous powder; IR (KBr) ν_{max} 3278, 3136, 1635, 1581, 1535 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 250 (3.46), 264 sh (3.13), 350 (1.96), 400 sh (2.05), 424 (2.81), 450 (2.96) nm; for ^1H and ^{13}C NMR data, see Table 1; DCI-MS (CH_4) *m/z* 317 $[M + C_3H_5]^+$, *m/z* 305 $[M + C_2H_5]^+$, *m/z* 277 $[M + H]^+$; HRFTMS *m/z* 276.0899 $(M)^+$, calcd for $C_{17}H_{12}N_2O_2$, 276.0897; for MS^2 data, see Table 3; for MS^3 data, see Table 4.

Revised Data for Telazoline (3) and Teladiazoline (5). **Telazoline (3):** previously isolated from *Telitoxicum peruvianum*;[11] for ^1H and ^{13}C NMR data, see Table 2; DCI-MS (CH_4) *m/z* 317 $[M + C_3H_5]^+$, *m/z* 305 $[M + C_2H_5]^+$, *m/z* 277 $[M + H]^+$; for MS^2 data, see Table 3; for MS^3 data, see Table 4.

Teladiazoline (5): previously isolated from *Telitoxicum glaziovii*;[15] ^1H NMR ($CDCl_3$, 400 MHz) δ 8.87 (1H, d, J = 5.1 Hz, H-5), 8.61 (1H, dd, J = 1.6 and 7.9 Hz, H-8), 8.51 (1H, dm, J = 7.9 Hz, H-11), 8.10 (1H, d, J = 5.1 Hz, H-4), 7.73 (1H, ddd, J = 1.6, 7.9, and 7.9 Hz, H-10), 7.47 (1H, ddd, J = 1.0, 7.9, and 7.9 Hz, H-9), 5.53 (2H, b, NH_2-1), 4.15 (3H, s, OCH_3-2), 4.11 (3H, s, OCH_3-3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 182.4 (s, C-7), 146.3 (s, C-3), 144.0 (s, C-6a), 143.3 (s, C-1), 143.2 (s, C-2), 143.1 (d, C-5), 136.1 (s, C-11a), 133.6 (d, C-10), 131.9 (s, C-7a), 129.5 (d, C-8), 129.0 (s, C-3a), 126.4 (d, C-9), 124.3 (d, C-11), 123.6 (s, C-1b), 118.6 (d, C-4), 104.1 (s, C-1a), 61.4 (q, OCH_3-3), 60.8 (q, OCH_3-2); DCI-MS (CH_4) *m/z* 347 $[M + C_3H_5]^+$, *m/z* 335 $[M + C_2H_5]^+$, *m/z* 307 (100%) $[M + H]^+$.

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