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Confirmation of the Revised Structure of Samoquasine A and a Proposed Structural Revision of Cherimoline

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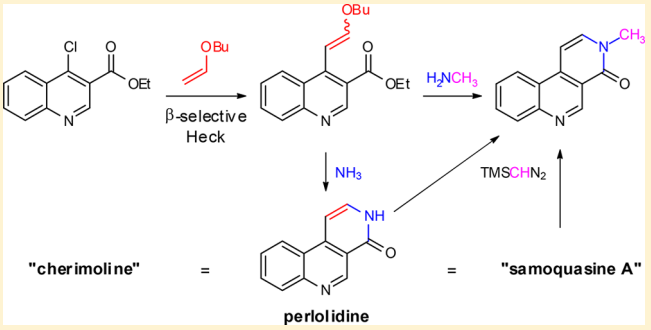
Supporting Information

ABSTRACT: The identity of the natural product samoquasine A has remained obscure since its isolation from custard apple seeds in 2000. One of the proposed structures, benzo[*f*]phthalazin-4(3*H*)-one, was prepared in two steps by regioselective *ortho*-lithiation/formylation of *N*,*N*-diisopropyl-2-naphthylamide, followed by cyclization with hydrazine, but was shown to be different from the natural product. Perlolidine, another candidate structure, was synthesized by a novel route involving a *β*-selective Heck reaction of butyl vinyl ether. Both perlolidine and samoquasine A are converted by trimethylsilyldiazomethane into the same *N*-methyl derivative. In addition, the ^{13}C NMR spectra of perlolidine and another structurally mis-assigned natural product, cherimoline, are almost identical. Thus, both samoquasine A and cherimoline are actually perlolidine.



The cytotoxin samoquasine A was isolated in 2000 from the seeds of the custard apple, *Annona squamosa* and, based on spectroscopic and chemical evidence, assigned structure **1** (Figure 1).[1] The authors later retracted their structural assignment, reporting samoquasine A to be identical with perlolidine (**2**).[2] However, they did not specify what led them to this conclusion. 3,4-Dihydrobenzo[*h*]quinazolin-4-one (**1**) was subsequently synthesized and, indeed, is different from samoquasine A.[3] In addition, perlolidine has since been isolated from *A. squamosa* stems.[3a] Nevertheless, enough uncertainty around the identity of samoquasine remained for it to continue to attract research interest.[4] One outstanding discrepancy is that the NMR spectra for samoquasine A were reportedly acquired in $CDCl_3$ solution,[1] but perlolidine is practically insoluble in this solvent.[3a]

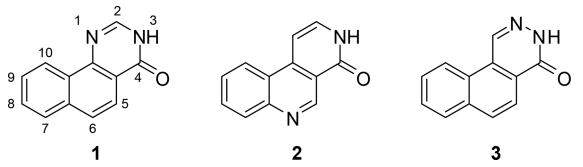


Figure 1. Proposed structures for samoquasine A.

Based on the 2D NMR data for samoquasine A, Wu and co-workers suggested that it may actually be benzo[*f*]phthalizin-4(3*H*)-one (**3**, Figure 1).[3a] Mátyus, Maes, and co-workers later synthesized **3** and, again, showed it to be different from samoquasine A.[5] Until now, the last word on samoquasine A came from Timmons and Wipf, whose DFT predictions of the ^{13}C NMR chemical shifts of 48 isomeric compounds supported the co-identity of perlolidine and samoquasine A.[6] However, the question still remained: if samoquasine A really is perlolidine, how was a ^{13}C NMR spectrum in $CDCl_3$ obtained? Furthermore, the reported ^{13}C NMR spectrum of samoquasine A in $CDCl_3$ contains a resonance at 101.6 ppm,[1] whereas the compound isolated by Wu and co-workers and identified as perlolidine, exhibits no signals in this region in pyridine-d_5 solution.[3a] Building on our interest in natural product mis-identification/characterization,[7] herein these questions and anomalies are addressed, and through total synthesis, the structure of "samoquasine A" is proven unequivocally. These investigations have also allowed us to recommend a structural revision for the natural product cherimoline.

RESULTS AND DISCUSSION

We began working on samoquasine A shortly after it was proposed that it may be benzo[*f*]phthalizin-4(3*H*)-one (**3**, Figure 1).[3a] Thus, our first endeavors involved the preparation of this compound. Lithiation of *N*,*N*-diethyl-2-naphthylamide (**4a**, Scheme 1) with *t*-BuLi was attempted first, as the 6-methoxy derivative has been regioselectively lithiated with this reagent and alkylated in 68% yield.[8] Despite this precedent, the reaction with **4a** was complicated by significant addition of *t*-BuLi to the naphthalene core, as has been noted previously in related systems.[9] *N*,*N*-Diisopropyl-2-naphthylamide (**4b**) has been *o*-lithiated with *s*-BuLi, followed by formylation with DMF to give the required naphthaldehyde **5** along with 3-formyl isomer in 22% and 10% yields, respectively.[10] We found

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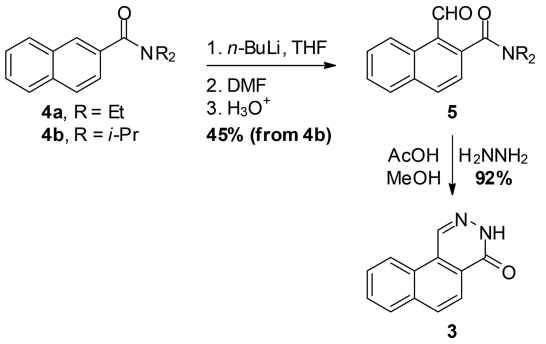
Scheme 1. Synthesis of Benzo[*f*]phthalizin-4(3*H*)-one, One of the Structures Proposed for Samoquasine A

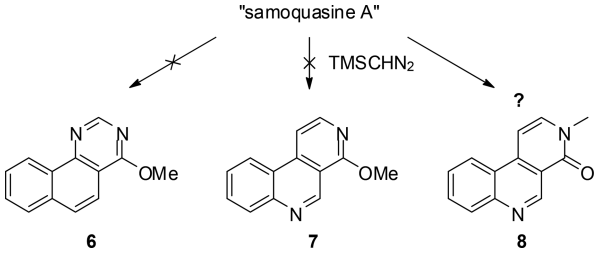


that with *n*-BuLi the yield and regioselectivity of the lithiation were improved, and quenching with DMF afforded **5** in 45% yield after crystallization.

The target phthalazinone **3** was formed in excellent yield upon heating a mixture of **5** and hydrazine hydrate in AcOH/MeOH. During the course of this work, Mátyus, Maes, and co-workers published an 8-step synthesis of **3**.[5] In agreement with these authors, the physical and spectroscopic data clearly indicate that **3** is not samoquasine A.

Unsatisfied with this conclusion, the original samoquasine A isolation paper was revisited for clues about its true identity. Methylation of samoquasine A with trimethylsilyldiazomethane was reported to give an *O*-methyl derivative, originally formulated as **6** (Scheme 2), and giving rise to the ^{1}H NMR data in Table 1.[1] The *O*-methyl derivative of perlolidine, 4-methoxybenzo[*c*]-2,7-napthyridine (**7**), has been prepared several times but its ^{1}H NMR data[11] are clearly different from those of "methylated samoquasine A"[1] (Table 1). However, adding to the confusion, the ^{1}H NMR data for **7** from two literature sources are also at variance. The chemical shift of the methyl group in the samoquasine A derivative (3.72 ppm)[1] suggests that it is attached to N not O. Thus, if perlolidine (**2**) is converted by $TMSCHN_2$ into the *N*-methyl derivative **8**, and the NMR data for this derivative match "methylated samoquasine A", then samoquasine A is, unequivocally, perlolidine.

Scheme 2. Methylation of Samoquasine A Does Not Give 6 or 7; If Samoquasine Is Perlolidine, It Would Give 8



Thus, a synthesis that provided perlolidine (**2**) and *N*-methylperlolidine (**8**), ideally from a common precursor, was required. For the latter target, it was deemed beneficial to unambiguously install the *N*-methyl substituent, i.e., not by derivatization of perlolidine. In addition, we saw an opportunity to improve on the eight existing syntheses of perlolidine.[11b,12] Hence, the route shown in Scheme 3 was devised.

The quinolone **9**, which is commercially available or readily prepared from aniline in two steps,[13] was converted into the chloride **10a**, as described previously.[14] As we were not certain the chloride would be reactive enough for the subsequent Heck reaction, the novel bromide **10b** was similarly prepared. Heck reactions of vinyl ethers usually result in predominant coupling α to the oxygen,[15] but this natural tendency can be reversed in poly(ethylene glycol).[16] Pleasingly, using this solvent, exclusive β-coupling of butyl vinyl ether was achieved with both the bromide **10b** and, in better yield, with the chloride **10a**. In both cases the product **11** comprised a 13:10 mixture of *E* and *Z* isomers. Interestingly, upon standing, the mixture became enriched in the *Z* isomer, presumably due to photoisomerization of the *E* isomer. In any case, *E*/*Z* isomerism was of little consequence as both isomers converged to the same product in the next step. The superiority of the chloride **10a** in the Heck coupling was somewhat surprising, and given our recent experience with nucleophilic additions of vinyl ethers to activated quinones,[17] we considered whether nucleophilic aromatic substitution might actually be at play. Thus, the reaction was repeated in the absence of the $Pd(OAc)_2$. The chloride **10a** was also heated in a sealed vessel in neat butyl vinyl ether at 150 °C. Under both sets of conditions, no reaction of the chloride was observed.

Table 1. ^{1}H NMR Data for "Methylated Samoquasine A", 7, and 8, in $CDCl_3$

	δ_H (*J*, Hz)				
	7			"methylated samoquasine A"	8
	Gronowitz et al.[11a]	Godard et al.[11c]	current	Kobayashi et al.[1]	current
position	–[b]	300 MHz	500 MHz	600 MHz	600 MHz
1	7.93, d	7.88, d (5.8)	7.93 d (5.9)	7.20 d (7.4)	7.15 d (7.3)
2	8.43, d	8.31, d (5.8)	8.43 d (5.9)	7.54 d (7.4)	7.51 d (7.4)
5	9.67, s	9.70, s	9.68 s	9.78 s	9.76 s
7	8.23, dd	8.20, d (8.2)	8.23 d (8.1)	8.22 d (8.0)	8.19 dd (0.8, 8.1)
8	7.85, m	7.80, dd (7.6, 8.2)	7.85 ddd (1.4, 7.1, 8.3)	7.86 t[a] (8.0)	7.84 ddd (1.2, 7.7, 8.2)
9	7.72, m	7.64, dd (7.6, 8.2)	7.72 ddd (1.2, 7.1, 8.2)	7.69 t[a] (8.0)	7.67 ddd (1.2, 7.7, 8.2)
10	8.49, dd	8.39, d (8.2)	8.50 d (7.4)	8.33 d (8.0)	8.31 dd (0.8, 8.1)
CH_3	not reported	4.01, s	4.22 s	3.72 s	3.69 s

[a]Sic[1] — a dd with $J_1 = J_2$. [b]Neither spectrometer frequency nor coupling constants were reported. Assignments not proven by 2D NMR spectroscopy. Literature signals in this table have been aligned to our data (which were assigned with the assistance of 2D NMR spectra) based on chemical shift.

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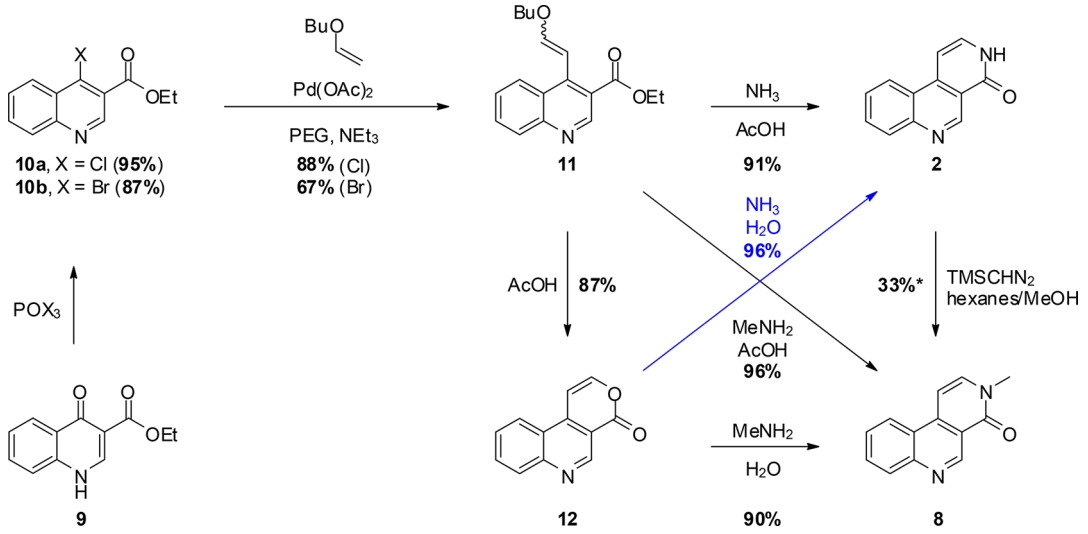
Scheme 3. Novel Synthesis of Perlolidine (2) and *N*-Methylperlolidine (8)[a]



[a]Plus 9% of the *O*-methyl derivative **7** (Scheme 2).

Unsurprisingly, **11** was unstable in $CDCl_3$, or on silica gel that had not been pretreated with base, giving rise to traces of the desired lactone **12**. A brief survey of acidic conditions aimed at deliberate unmasking of the aldehyde functionality and facilitating cyclization/dehydration showed gentle heating with AcOH to give a good yield of **12** (Scheme 3). 4*H*-Pyrano[3,4-*c*]quinolin-4-one (**12**) is the structure originally assigned to cherimoline, another mis-identified natural product isolated from an *Annona* species (*A. cherimola*).[18] Soon after the reported isolation, Alvarez, Joule, and co-workers synthesized **12** and showed it to be different from cherimoline.[19] Their synthesis involved the Sonogashira coupling of trimethylsilylacetylene with the triflate analogue of **10a/b**, followed by desilylation and base-induced saponification/cyclization. The present synthesis of **12** compares well in terms of number of steps and overall yield. We will return to the structure of cherimoline below.

As expected based on related precedents,[20] the conversion of the pyranone **12** to perlolidine (**2**) upon stirring with concentrated ammonia, proceeded cleanly and in excellent yield. It was subsequently found that vinyl ether **11** could be directly converted into perlolidine (**2**) by treatment with warm aqueous NH_3 in AcOH. The brevity of this route and overall yield of perlolidine (**2**) make it the most efficient of the existing nine syntheses.[11b,12] The other advantage of this synthesis for the purpose at hand is that treatment of **12** with aqueous $MeNH_2$,[21] or **11** with $MeNH_2$/AcOH, provided the required *N*-methyl derivative **8**. Although the synthesis of **8** is unambiguous, its structure was confirmed by X-ray crystallography (Figure 2). Critically, the ^{1}H NMR data for **8** are similar to those reported for "methylated samoquasine A" [1] (Table 1). ^{13}C NMR data for "methylated samoquasine A" were not published, preventing a comparison of these spectra.

The key derivatization experiment undertaken during the original isolation of samoquasine A was then replicated; that is, perlolidine (**2**) was treated with trimethylsilyldiazomethane (Scheme 3). The major product was identical with *N*-methylperlolidine (**8**) synthesized directly from **11** or **12**. In addition, a small quantity of the *O*-methyl derivative **7** was isolated. The ^{1}H NMR data for **7**, in particular the chemical shift of the methoxy protons, differ somewhat from those

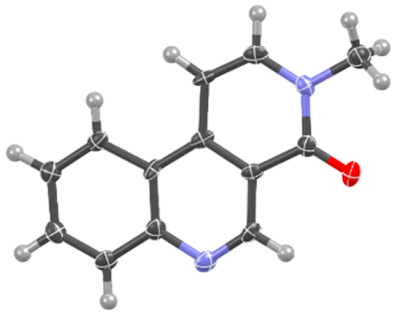


Figure 2. Representation of one of the molecules in the asymmetric unit of the X-ray crystal structure of *N*-methylperlolidine (**8**). The conformation of the other molecule is not substantially different. Thermal ellipsoids are shown at 50% probability amplitude and hydrogen atoms have arbitrary radii.

reported by Godard et al.,[11c] but are a good match (despite the missing methoxy signal) for the data from Gronowitz and co-workers.[11a] Thus, the evidence presented here proves conclusively that samoquasine A is perlolidine, confirming Timmons and Wipf's prediction.[6] However, it was still unclear how a ^{13}C NMR spectrum of samoquasine A (perlolidine, **2**) had been obtained in $CDCl_3$ solution.

Attempts at solving this conundrum began by acquiring NMR spectra of our synthetic perlolidine (**2**) in $CDCl_3$. Although it was possible to obtain a noisy ^{1}H NMR spectrum of a saturated solution of **2** (see Supporting Information, p 15), the solution was too dilute for ^{13}C NMR spectroscopy, even with 72 h of acquisition time. A comparison of the ^{1}H NMR spectrum in $CDCl_3$ with the reported spectroscopic data for samoquasine A (Table 2) was informative. While similar, the differences are significant enough to suggest that the spectra may have been acquired in different solvents. The ^{1}H NMR spectrum in pyridine-d_5 closely matched the data reported by Wu and co-workers for isolated perlolidine in the same solvent,[3a] but not those for samoquasine A. There were some differences in the ^{1}H NMR data reported by Quéguiner et al.[12e] for synthetic perlolidine compared with our spectrum in DMSO-d_6, but these are probably attributable to the different spectrometer frequencies, and once again, the data are different

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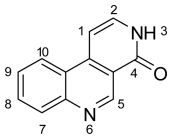
Table 2. ^{1}H NMR Data for Perlolidine (2)



	δ_H (J, Hz)						
	$CDCl_3$	"samoquasine A"[a]	CD_3OD	pyridine-d_5		DMSO-d_6	
position	current 600 MHz	Kobayashi et al.[1] 600 MHz	current 600 MHz	Wu et al.[3a] 400 MHz	current 500 MHz	Quéguiner et al.[12e] 200 MHz	current 600 MHz
1	7.28, d[e]	7.30, d (7.3)	7.51, d (7.2)	7.32, d (7.2)	7.33, d (7.1)	7.58, d (7.0)	7.43, d (7.1)
2	7.52, m	7.55, d (7.3)	7.71, d (7.1)	7.84, d (7.2)	7.90–7.81, m[d]	7.90–8.15, m[d]	7.72, d (7.1)[d]
5	9.75, s	9.60, s	9.54, s	10.21, s	10.24, s	9.52, s	9.47, s
7	8.24, d (8.3)	8.12, dd (1.0, 8.3)	8.14, d (7.7)	8.40, d (8.4)	8.42, dd (1.0, 8.3)	8.33, d (8.2)	8.11, d (8.2)
8	7.89, ddd (1.3, 7.0, 8.3)	7.87, dt[b] (1.0, 8.3)	7.94, ddd (1.3, 7.0, 8.3)	7.85, dd (1.6, 7.2)	7.90–7.81, m[d]	7.90–8.15, m[d]	7.92, dd [app. t] (7.3)
9	7.72, ddd (1.2, 7.0, 8.2)	7.71, dt[b] (1.0, 8.3)	7.79, ddd (1.2, 7.0, 8.2)	7.65, dd (1.6, 7.2)	7.66, ddd (1.2, 7, 8.4)[d]	7.90–8.15, m[d]	7.76, dd [app. t] (7.5)
10	8.36, dd (0.7, 8.2)	8.40, dd (1.0, 8.3)	8.59, dd (0.7, 8.3)	8.48, dd (1.6, 7.2)	8.50, d (8.3)	8.82, d (8.2)	8.63, d (8.2)
NH	9.60, br s	not reported	–	13.05, br s	*c*	12.73, s	12.00, br s

[a]Reportedly in $CDCl_3$, but the current work raises some uncertainty about the NMR spectroscopy solvent. [b]Sic[1] — a ddd with two approximately equivalent, large coupling constants. [c]Too broad to be observed. [d]Signals overlap. [e]Partially obscured by the $CHCl_3$ signal.

from those reported for samoquasine A.[1] The spectrum of perlolidine in CD_3OD was a closer match to the samoquasine A data. If the original spectrum of samoquasine A had been acquired in CD_3OD, this would also explain the lack of a reported NH signal. However, there were still enough differences in the data to cause doubt. Thus, we turned to ^{13}C NMR spectra, which are more definitive than ^{1}H NMR data for comparing compounds.

The ^{13}C NMR spectrum of perlolidine in CD_3OD is in close agreement with the reported data for samoquasine A[1] (blue bars in Figure 3, Table 3), with an average absolute variation of

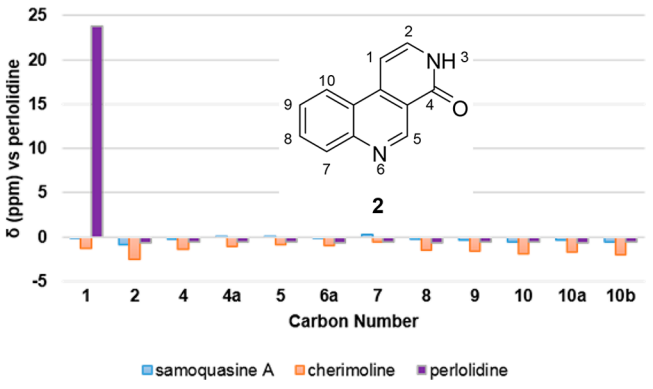


Figure 3. Difference plot of reported ^{13}C NMR data for samoquasine A,[1] cherimoline,[18] and perlolidine isolated from *A. squamosa*,[3a] versus synthetic perlolidine (current work) in the matched solvent.

0.3 ppm and a maximum difference of 0.8 ppm. Thus, a solution to the mystery of how a ^{13}C NMR spectrum of samoquasine A (= perlolidine) was obtained in $CDCl_3$ can be proffered: It was not—the solvent was actually CD_3OD.

Timmons and Wipf[6] suggested that the natural product isolated by Wu and co-workers from *A. squamosa*, and identified as perlolidine, is actually a different compound, because of the large difference in chemical shift for C-1 acquired in pyridine-d_5 (purple bars in Figure 3). However, if this signal is ignored, the remaining signals closely match the ^{13}C NMR spectrum obtained for synthetic perlolidine in the same solvent, with an average absolute difference of just 0.5 ppm (Table 3). Thus, it seems likely that Wu and co-workers[3a] did indeed isolate perlolidine, and the spurious signal attributed to C-1 was actually due to an impurity in the sample.

As our attention had been drawn to cherimoline, which as mentioned earlier, was incorrectly assigned structure **12**[18] (Scheme 3), the evidence presented for its structural elucidation was reexamined. The carbonyl stretch absorption in the IR spectrum of cherimoline was originally reported at 1760 cm^{-1}, consistent with a lactone.[18] However, after synthesizing **12** and showing it to be different from cherimoline, Alvarez, Joule, and co-workers obtained a sample of the natural product and reacquired the IR spectrum.[19] They observed a carbonyl absorption at 1670 cm^{-1} (film), consistent with a lactam, and concluded that an accidental transposition of "6' and '7" had occurred in the original report. The reported C=O absorption for synthetic perlolidine is 1645 cm^{-1} (KBr),[12b] while our material absorbed at 1658 cm^{-1} (neat, ATR). We also noted a broad NH stretch band at ~2100–3100 cm^{-1}, indicative of strong hydrogen bonding. It is likely that subtle variations in solid state structure and accompanying differences in hydrogen bonding arrays account for the small differences in the carbonyl absorption frequency among the three samples.

The ^{1}H NMR data for cherimoline (not shown) and perlolidine are similar, but perhaps vary enough to suggest they may be different compounds. However, the ^{13}C NMR data in CD_3OD are very similar (orange bars in Figure 3), with an average absolute difference of just 1.4 ppm, and a maximum difference of 2.5 ppm (Table 3). In addition, all signals for "cherimoline" are slightly upfield of those for perlolidine, suggesting that different calibration could account for at least part of the small discrepancies in the data. The HRMS data reported for cherimoline match the lactone **12**, not perlolidine

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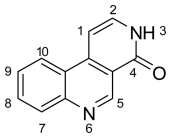
Table 3. ^{13}C NMR Data (δ ppm) for Perlolidine, "Samoquasine A", and "Cherimoline" [a]



	perlolidine	"samoquasine A" [b]	"cherimoline"	perlolidine		
			CD_3OD	benzene	pyridine-d_5	
carbon [c]	CD_3OD current	Kobayashi et al.[1]	Wu et al.[18] 100 MHz	Timmons and Wipf[6] predicted	Wu et al.[3a,f] 100 MHz	current
1	101.7	101.6	100.4	98.2	123.7	99.9
2	136.8	136.0	134.3	133.0	135.9	136.5
4	164.2	164.0	162.8	161.0	162.8	163.3
4a	118.6	118.7	117.5	118.2	118.6	119.1
5	150.4	150.5	149.5	152.2	150.4	150.9
6a	148.6	148.5	147.6	152.1	148.8	149.4
7	130.1	130.4	129.6	133.2	130.6	131.1
8	133.0	132.8	131.5	130.5	131.2	131.8
9	129.0	128.7	127.4	126.2	127.3	127.8
10	125.5	125.0	123.6	123.1	124.6	125.1
10a	123.9	123.6	122.2	122.7	123.0	123.6
10b	144.8	144.3	142.8	142.9	142.8	143.3
avg |difference|[d]	–	0.3	1.4[e]	2.7	[g]2.5 (0.5[e])[h]	–
max |difference|[d]	–	0.8	2.5	3.8	23.8 (0.6)	–

[a]Spectra were acquired at 125 MHz unless otherwise indicated. [b]Reportedly in $CDCl_3$, but the NMR spectroscopy solvent was shown to be CD_3OD in the current work. [c]Perlolidine numbering. [d]Compared to the data for perlolidine in CD_3OD obtained in the current work. [e]All signals are upfield of those we recorded for perlolidine. [f]The atom numbering used in this paper is incorrect and has been corrected here. [g]Compared to the data for perlolidine in pyridine-d_5 obtained in the current work. [h]The values in parentheses ignore the outlier for carbon 1.

(**2**); however, it is worth noting that the exact mass of monodeuterioperlolidine ($C_{12}{}^1H_7{}^2HN_2O$, 197.0689 amu), which would be derived by exchange of the NH in CD_3OD, is quite close to that reported for cherimoline ($C_{12}H_7NO_2$, 197.0477 amu). This evidence, especially the similarity in the ^{13}C NMR data, coupled with the fact that cherimoline and perlolidine have both been isolated from *Annona* species, indicate that cherimoline is actually perlolidine. At the very least, an attempt to re-isolate cherimoline (perlolidine?) from *Annona cherimola* is warranted.

In conjunction with the isolation of "samoquasine A", the natural product was shown to be cytotoxic to the murine lymphoma cell line L1210, with an IC_{50} value of 0.38 μg/mL (1.9 μM).[1] Perlolidine is also modestly toxic to NUGC and HONE-1 cancer cell lines (growth inhibition of 63 and 62% at 50 μg/mL in vitro, respectively).[3a] Accordingly, synthetic perlolidine (**2**), the *N*-methyl derivative (**8**) and the precursor **12** were submitted to the US National Cancer Institute to be screened against their panel of 60 cell lines (Supporting Information, pp 20–23). None of these compounds exhibited sufficient cytotoxicity at 10 μM to warrant a determination of IC_{50}.

CONCLUSION

Controversy has surrounded the structure of the natural product samoquasine A since its isolation from custard apple seeds in 2000.[1] A two-step synthesis of benzo[*f*]phthalizin-4(3*H*)-one (**3**), one of the structures proposed for samoquasine A, involving regioselective directed *ortho*-lithiation/formylation and ring-closure by condensation with hydrazine, was developed; however, in agreement with others,[5] the spectroscopic data for **3** do not match those for samoquasine A.

The isomeric alkaloid perlolidine (**2**) has also been proposed as the true identity of samoquasine A,[2,6] but without conclusive evidence to support this claim. Hence, a new three-step synthesis was devised that involves a key β-selective Heck coupling of butyl vinyl ether in polyethylene glycol, and provides perlolidine in 76% overall yield. The *N*-methyl derivative of perlolidine was also prepared, and shown to be identical with the major product of methylation of "samoquasine A" with trimethylsilyldiazomethane. Thus, through a combination of total synthesis, derivatization and spectroscopic analysis, it was proven definitively that samoquasine A is in fact perlolidine.

Part of the cause of original confusion about the identity of samoquasine A was the mis-reporting of the solvent used for acquisition of its NMR spectra. We established that the original ^{13}C NMR spectrum must not have been acquired in $CDCl_3$ as reported, but rather in CD_3OD. Intriguingly, the ^{13}C NMR data for perlolidine in this solvent are almost identical with those reported for another structurally mis-assigned natural product, cherimoline. Thus, cherimoline is almost certainly also perlolidine.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined using a Reichert hot stage melting point apparatus. IR spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer with Attenuated Total Reflectance (ATR) using neat samples. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired using Bruker Avance IIIHD (600 MHz for ^{1}H and 150 MHz for ^{13}C), Bruker Avance IIIHD (500 MHz for ^{1}H and 125 MHz for ^{13}C), and Varian (400 MHz for ^{1}H and 100 MHz for ^{13}C)

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spectrometers, as indicated. ^{1}H and ^{13}C NMR spectroscopic assignments were made based upon 2D NMR spectroscopy experiments for each assigned compound. $CDCl_3$ was used as the solvent for NMR spectroscopy samples unless otherwise indicated. Spectra were calibrated as shown in Table 4.[22]

Table 4. Calibration Information for NMR Spectroscopy Solvents

solvent	^{1}H	δ	^{13}C	δ
$CDCl_3$	$CHCl_3$	7.26	$CDCl_3$	77.16
CD_3OD	CD_2HOD	3.31	CD_3OD	49.00
DMSO-d_6	CD_3SOCD_2H	2.50	$(CD_3)_2SO$	39.52
pyridine-d_5	CHD_4N	7.22	CD_5N	123.90

HRMS data were acquired on a Waters Liquid Chromatograph Premier mass spectrometer using atmospheric pressure chemical ionization (APCI) in positive mode.

Reaction progress was monitored by TLC using Merck aluminum-backed TLC silica gel 60 F_{254} plates, which were also used for preparative TLC. Spots were visualized using ultraviolet light. Flash column chromatography was performed using Davisil chromatographic silica media LC60A 40−63 μm. All solvents were distilled prior to use. Anhydrous THF was obtained from a Pure Solv 5-Mid Solvent Purification System (Innovative Technology Inc.). Anhydrous DMF was obtained by drying over activated 3 Å molecular sieves for 24 h, followed by distillation under reduced pressure onto activated 3 Å sieves. All other reagents and materials were purchased from commercial suppliers and used as received. Temperatures reported for reactions refer to bath temperatures unless the reaction mixtures were heated under reflux. Organic extracts were dried over anhydrous $MgSO_4$. Solvents were evaporated under reduced pressure at approximately 45 °C, and then traces of solvent were removed under a flow of nitrogen.

Synthesis. *1-Formyl-N,N-diisopropyl-2-naphthamide (**5**).* A 2.0 M solution of *n*-BuLi in cyclohexane (1.2 mL, 2.4 mmol) was added dropwise to a stirred solution of **4b**[23] (0.50 g, 2.0 mmol) in anhydrous THF (40 mL) at −78 °C. After 1 h the reaction was quenched with DMF (0.29 g, 4.0 mmol). The resulting yellow solution was allowed to gradually warm to room temperature, then water (2 mL) was added cautiously. The reaction mixture was diluted with 1 M HCl (100 mL) and extracted with ether (2 × 50 mL). The extract was washed with water (2 × 50 mL) and brine (50 mL), then dried and evaporated to give a viscous yellow oil, which crystallized from hexanes/EtOAc to afford **5** as an off-white solid (0.28 g, 45%), mp 129−130 °C (lit.[10] 127−128 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 10.60 (s, 1H, CHO), 9.17−9.26 (m, 1H, Ar), 8.11 (d, J = 8.1 Hz, 1H, Ar), 7.88−7.94 (m, 1H, Ar), 7.55−7.77 (m, 2H, 2 × Ar), 7.37 (d, J = 8.3 Hz, 1H, Ar) 3.49−3.74 (m, 2H, NCH), 1.64 (d, 6 H, J = 6.8 Hz, 2 × CH_3), 1.12 (d, 6 H, J = 6.7 Hz, 2 × CH_3). The spectrum was similar to the data reported.[10]

*Benzo[f]phthalazin-4(3H)-one (**3**).* Hydrazine hydrate (62 mg, 1.1 mmol) was added to a solution of **5** (100 mg, 0.353 mmol) and AcOH (85 mg, 1.4 mmol) in MeOH (2 mL). The mixture, which immediately turned yellow, was stirred at room temperature for 10 min, then under reflux overnight. The resulting solution was cooled and the solvent was evaporated. The residue was dissolved in DCM (30 mL) and the solution was washed with saturated $NaHCO_3$ solution (20 mL), water (2 × 20 mL), brine (20 mL), then dried and evaporated to afford **3** as an off white crystalline solid (64 mg, 92%). IR ν_{max} 1651 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.87 (br s, 1H, NH), 9.02 (s, 1H, H1), 8.54−8.60 (m, 1H, H10), 8.40 (d, J = 8.8 Hz, 1H, H5), 8.17 (d, J = 8.7 Hz, 1H, H6), 8.01−8.07 (m, 1H, H7), 7.75−7.83 (m, 2H, H8/H9). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.8 (CO), 135.2, 134.7, 132.6, 129.24, 129.16, 128.4, 127.8, 127.7, 127.1, 123.2, 121.6. The NMR spectra matched the reported data.[5]

*Ethyl 4-Bromoquinoline-3-carboxylate (**10b**).* Phosphoryl bromide (1.26 g, 4.38 mmol) was added to ethyl 4-oxo-1,4-dihydroquinolone-3-carboxylate (**9**)[13] (309 mg, 1.42 mmol) and the mixture was stirred at 120 °C under Ar for 8 h. The reaction mixture was allowed to cool to room temperature then diluted with $NaHCO_3$ (20 mL) and stirred until the evolution of CO_2 had ceased. The aqueous mixture was extracted with DCM (3 × 20 mL). The extract was washed with $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL), then dried and evaporated. The residue was subjected to flash chromatography. Elution with 10% EtOAc/hexanes gave **10b** as a white solid (0.348 g, 87%). R_f = 0.3 (10% EtOAc:hexanes). IR ν_{max} 1694 cm^{-1} (CO). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.08 (s, 1H, H2), 8.40 (dd, J = 8.5, 1.0 Hz, 1H, H5), 8.11 (dd, J = 8.4, 1.0 Hz, 1H, H8), 7.83 (ddd, J = 8.3, 7.0, 1.4, Hz, 1H, H7), 7.70 (ddd, J = 8.4, 7.1, 1.2 Hz, 1H, H6), 4.50 (q, J = 7.2 Hz, 2H, H9), 1.46 (t, J = 7.2 Hz, 3H, H10). ^{13}C NMR ($CDCl_3$, 125 MHz): 165.4 (C11), 149.7 (C2), 149.3 (C4), 135.1 (C8a), 131.9 (C7), 130.0 (C8), 128.8 (C6), 128.5 (C5), 127.8 (C4a), 126.4 (C3), 62.4 (C9), 14.4 (C10). HRMS: observed, 279.9973; $C_{12}H_{11}N_2O_2{}^{79}Br^+$ requires 279.9968.

*Ethyl 4-(2-Butoxyvinyl)quinoline-3-carboxylate (**11**).* A mixture of ethyl 4-chloroquinolone-3-carboxylate (**10a**)[14] (0.590 g, 2.51 mmol), butyl vinyl ether (2.60 g, 26.0 mmol), $Pd(OAc)_2$ (0.058 g, 0.26 mmol), NEt_3 (3.5 mL, 25 mmol) and poly(ethylene glycol) (avg M_w = 400) (7 mL) was purged with N_2, then stirred at 80 °C in a sealed flask for 18 h. The cooled reaction mixture was diluted with water (70 mL) and extracted with EtOAc (3 × 25 mL). The extract was washed with water (3 × 25 mL) and brine (25 mL), then dried and evaporated. The residue was subjected to flash column chromatography. Elution with 0.1%: 20% NEt_3/EtOAc/hexanes gave **11**, a 13:10 ratio of *E* and *Z* isomers, as a yellow oil (0.658 g, 88%). R_f = 0.3 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.21 (s, 1H, H2, *Z*), 9.18 (s, 1H, H2, *E*), 8.31 (dd, J = 8.5, 0.8 Hz, 1H, H5, *E*), 8.11 (dd, J = 8.5, 0.8 Hz, 1H, H5, *Z*), 8.07 (dd, J = 8.5, 0.8 Hz, 2H, H8, *E* and *Z*), 7.71−7.76 (m, 2H, H7, *E* and *Z*), 7.50−7.56 (m, 2H, H6, *E* and *Z*), 6.80 (d, J = 13.1 Hz, 1H, H12, *E*), 6.60 (d, J = 13.1 Hz, 1H, H11, *E*), 6.48 (d, J = 7.1 Hz, 1H, H12, *Z*), 5.99 (d, J = 7.1 Hz, 1H, H11, *Z*), 4.41 (q, J = 7.1 Hz, 2H, H9, *E*), 4.39 (q, J = 7.1 Hz, 2H, H9, *Z*), 3.99 (t, J = 6.5 Hz, 2H, H13, *E*), 3.80 (t, J = 6.5 Hz, 2H, H13, *Z*), 1.71−1.79 (m, 2H, H14, *E*), 1.44−1.52 (m, 4H, H18 and 14, *E* and *Z*) 1.41 (t, J = 7.1 Hz, 3H, H10, *E*), 1.40 (t, J = 7.1 Hz, 1H, H10, *Z*), 1.17−1.26 (m, 2H, H15, *Z*), 0.98 (t, J = 7.4 Hz, 3H, H16, *E*), 0.81 (t, J = 7.4 Hz, 3H, H16, *Z*). ^{13}C NMR ($CDCl_3$, 125 MHz): 167.2 (*E*, C17), 167.1 (*Z*, C17), 154.6 (*E*, C12), 150.37 (*E*,C2), 150.35 (*E*, C2), 149.5 (*E*, C8a), 149.1 (*Z*, C8a), 148.8 (*Z*, C12), 145.6 (*E*, C4), 143.7 (*Z*, C4), 130.9 (*E*, C7), 130.8 (*Z*, C7), 129.9 (*E*, C8), 129.7 (*Z*, C8), 127.5 (*Z*, C5), 127.1 (*E*, C5), 126.8 (*Z*, C4a), 126.7 (*E*, C6), 126.5 (*Z*, C6), 126.2 (*E*, C4a), 122.9 (*Z*, C3), 121.6 (*E*, C3), 99.3 (*E*, C11), 99.2 (*Z*, C12), 73.4 (*Z*, C13), 69.9 (*E*, C13), 61.4 (*E*, C9), 61.3 (*Z*, C9), 31.8 (*Z*, C14), 31.3 (*E*, C14), 19.3 (*E*, C15), 18.9 (*Z*, C15), 14.4 (*E*, C10), 14.3 (*Z*, C10), 14.0 (*E*, C16), 13.8 (*Z*, C16).

*4H-Pyrano[3,4-c]quinolin-4-one (**12**).* A solution of **12** (380 mg, 1.27 mmol) in AcOH (12 mL) was heated at 80 °C under N_2 for 12 h, then poured onto ice/water (50 mL), and basified with $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ (3 × 25 mL). The extract was evaporated and the residue was subjected to flash chromatography. Elution with 2% MeOH/DCM yielded **12** as a white solid (218 mg, 87%), mp = 154−156 °C [lit.[19] 144−146 °C]. R_f = 0.3 (2% MeOH/DCM). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 9.36 (s, 1H, H5), 8.60 (d, J = 8.3 Hz, 1H, H10), 8.14 (d, J = 8.3 Hz, 1H, H7), 8.06 (d, J = 5.7 Hz, 1H, H2), 8.00 (ddd, J = 8.3, 7.0, 1.2, Hz, 1H, H9), 7.81 (dd, J = 8.3, 7.0, 1.2 Hz, 1H, H8), 7.70 (d, J = 5.7 Hz, 1H, H1). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 160.7 (C4), 152.1 (C2), 149.2 (C5), 148.8 (C6a), 142.4 (C10b), 132.9 (C9), 129.7 (C7), 128.1 (C8), 125.2 (C10), 121.0 (C10a), 112.5 (C4a), 101.9 (C1). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.60 (s, 1H, H5), 8.27 (dd [app. t], J_1 = J_2 = 7.8 Hz, 2H, H10, H7), 7.93 (dd [app. t], J_1 = J_2 = 7.3 Hz, 1H, H8), 7.74 (dd [app. t], J_1 = J_2 = 7.8 Hz, 1H, H9), 7.70 (d, J = 5.6 Hz, 1H, H2), 7.23 (d, J = 5.6 Hz, 1H, H1). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.1 (C4), 150.8 (C2), 150.2 (C5), 149.7 (C6a), 142.4 (10b), 132.8 (C8), 130.8 (C7), 128.2 (C9), 123.9 (C10), 121.3 (C10a), 113.2 (C4a), 101.8 (C1). The ^{1}H NMR spectrum in $CDCl_3$ matched the reported data.[19]

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*Benzo[c][2,7]naphthyridin-4(3H)-one (Perlolidine) (**2**).* Method A: A mixture of **12** (100 mg, 0.507 mmol) and conc. NH_3 (12 mL) was stirred for 5 h. Within 1 h the product precipitated as a white solid, which was isolated by vacuum filtration, affording **2** as a white solid (80 mg). The filtrate was evaporated to yield a further 16 mg (total yield 96 mg, 96%), mp >300 °C (lit.[12b] 337−341 °C). R_f = 0.1 (1:20 MeOH/$CHCl_3$). See Tables 2 and 3 for NMR data.

Method B: A mixture of vinyl ether **11** (50 mg, 0.17 mmol), AcOH (5 mL) and 25% NH_3 (4 mL) was heated at 80 °C for 12 h. Upon cooling the product precipitated. Filtration yielded **2** as a white solid (32 mg, 91%), identical with the material described above.

*3-Methylbenzo[c][2,7]naphthyridin-4(3H)-one (N-Methylperlolidine) (**8**).* Method A: A mixture of **12** (100 mg, 0.507 mmol) and 40% $MeNH_2$ in water (10 mL) was stirred for 5 h. The reaction mixture was evaporated to yield **8** as a white solid (96 mg, 90%), mp = 190−192 °C. R_f = 0.3 (5% MeOH/$CHCl_2$). IR ν_{max} 1651 cm^{-1} (CO). ^1H NMR ($CDCl_3$, 600 MHz): δ 9.75 (s, 1H, H5), 8.31 (dd, J = 8.1, 0.8 Hz, 1H, H10), 8.19 (dd, J = 8.1, 0.8 Hz, 1H, H7), 7.84 (ddd, J = 8.2, 7.7, 1.2 Hz, 1H, H8), 7.67 (ddd, J = 8.2, 7.7, 1.2 Hz, 1H, H9), 7.51 (d, J = 7.4 Hz, 1H, H2), 7.15 (d, J = 7.3 Hz, 1H, H1), 3.69 (s, 1H, H11). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 162.2 (C4), 150.4 (C5), 148.1 (C6a), 141.4 (C10b), 138.6 (C2), 131.3 (C8), 130.5 (C7), 127.3 (C9), 123.5 (C10), 122.3(C10a), 117.4 (C4a), 100.0 (C1), 37.5 (C11). HRMS: (m/z) observed 211.0865, $C_{13}H_{11}N_2O^+$ requires 211.0866.

Method B: A mixture of butyl vinyl ether **11** (50 mg, 0.17 mmol), AcOH (5 mL) and 40% $MeNH_2$ in water (4 mL) was heated at 80 °C for 12 h. The reaction mixture was poured onto ice/water and the mixture was extracted with $CHCl_3$ (3 × 20 mL). The extract was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried and evaporated to give **8** as a white solid (34 mg, 96%), identical with the material described above.

Method C: A 2 M solution of trimethylsilyldiazomethane (0.5 mL) in hexanes was added to a stirred solution of (**2**) (20 mg, 0.10 mmol) in MeOH (1.5 mL). After 1 h, the volatiles were evaporated under a stream of N_2 and the residue was subjected to purification by preparative TLC, affording **8** as a pale white solid (15 mg, 70%), identical with the material described above.

Isolation of the compound in the higher R_f band gave **7** as a white solid (2 mg, 9%). R_f = 0.6 (5% MeOH/DCM). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.68 (s, 1H, H5), 8.50 (d, J = 7.4, 1H, H10), 8.43 (d, J = 5.9, 1H, H2), 8.23 (d, J = 8.1, 1H, H7), 7.93 (d, J = 5.9 Hz, 1H, H1), 7.85 (ddd, J = 1.4, 7.1, 8.3, 1H, H8), 7.73 (ddd, J = 1.2, 7.1, 8.2, 1H, H9), 4.22 (s, 3H, H11). ^{13}CNMR ($CDCl_3$, 125 MHz): 162.4 (C4), 148.9 (C5), 146.5 (C2), 146.3 (C6a), 140.3 (C10b), 130.8 (C8), 130.4 (C7), 127.5 (C9), 123.3 (C10), 122.3 (C10a), 111.5 (C4a), 109.5 (C2), 54.3 (C11). HRMS: (m/z) observed 211.0864, $C_{13}H_{11}N_2O^+$ requires 211.0866.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.8b00319.

X-ray crystallographic data for **8** [CCDC 1560369] (CIF)

^1H, ^{13}C, and 2D NMR spectra, and NCI-60 results (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Bob Stick, who advised: "I think you'd better work out what the structure is before you publish".

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