

# One-Pot Isolation of 4 Novel Compounds Resulting from the Mythically Therapeutic Mixture of *Cocos nucifera* and *Citrus aurantifolia* Juices Used for Curing the "Bellyache"

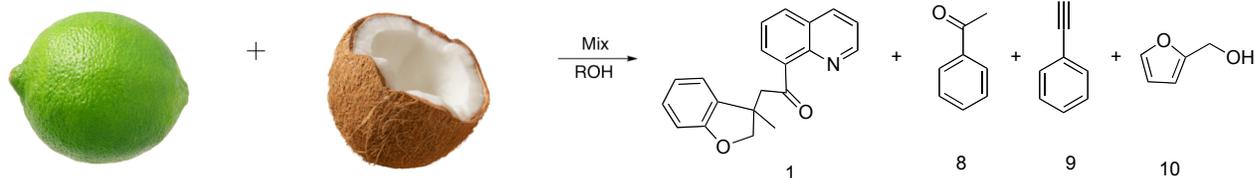
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## ABSTRACT



Motivated by the fabled cure for bellyache<sup>a</sup>, **1** and three other molecules (**8**, **9** and **10**) were isolated from a reaction of *Citrus aurantifolia* and *Cocos nucifera* juices. **1** appears to be the major product and features an interesting quinoline substructure. The structures of **1** and the three other molecules were determined by 1D and 2D spectroscopic analysis.

Folk cures for common ills are present in all cultures. A popular legend of Jamaica, which asserts that mixing a lime and a coconut can cure a bellyache, was made famous by Harry Nilsson and Kermit the Frog (for Flipperache).<sup>F</sup> The biological mechanism responsible for the therapeutic response is not yet understood as the molecule responsible for the phenomenon has not been isolated to date. The molecule, **1**, was obtained by

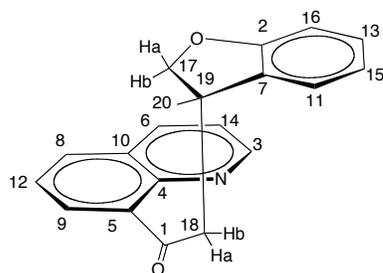
mixing the juices of *Citrus aurantifolia* (key lime) and *Cocos nucifera* (coconut) in a blender with methanol to facilitate the reaction followed by distillation. It should be noted that the reaction will also work with uninhibited ethanol. The structure of **1** was determined along with three other molecules, **8**, **9**, **10**, isolated from the lime and coconut reactions. Further biological studies will

<sup>a</sup> Based on a calypso song written by Harry Nilsson, 1969. The Calypso style is Afro-caribbean and has origins in Trinidad and Tobago. This style of music is also present in Jamaica. For example, the popular banana boat song "Day-O" is Jamaican calypso.

hopefully determine the therapeutic potential for this novel **1**.

**1** was obtained after distillation as a green oil with a molecular formula of  $C_{20}H_{17}NO_2$  as determined from an ESI ion at  $m/z$  304.1337 [ $M+H^+$ ] (calcd 304.3648) resulting in an estimated molecular weight of 303.1258 [ $M^+$ ] and 13 degrees of unsaturation. The IR absorptions indicated the molecule contained an unsaturated ketone ( $1682\text{ cm}^{-1}$ ) and aromatic protons (overtone from  $1800$  to  $2000\text{ cm}^{-1}$  and olefinic protons at  $3046\text{ cm}^{-1}$ ). The  $^1H$  NMR confirmed the presence of 17 protons and the  $^{13}C$  NMR confirmed the presence of 20 carbons.

HMQC correlations confirmed 1 methyl, 2 methylenes, 10 methines (all olefinic), and 7 quaternary carbons (Table 1). HMQC allowed us to place the protons with the corresponding carbon. Aromatic protons H-3, H-6, H-8, H-9, H-12, and H-14 were placed on C-3 ( $\delta$  150.7), C-6 ( $\delta$  136.2), C-8 ( $\delta$  131.0), C-9 ( $\delta$  129.0), C-12 ( $\delta$  126.1), and C-14 ( $\delta$  121.5) respectively. The two overlapping aromatic protons found at  $\delta$  7.10 were placed on C-11 ( $\delta$  128.2) and C-13 ( $\delta$  123.0). The overlapping protons at  $\delta$  6.8 were placed on C-15 ( $\delta$  120.5) and C-16 ( $\delta$  109.8). Methylene hydrogens found at  $\delta$  4.71 (17a) and  $\delta$  4.58 (17b) were assigned to C-17 ( $\delta$  83.0). Similarly, methylene protons at  $\delta$  3.94 (18a) and  $\delta$  3.79 (18b) were placed on C-18 ( $\delta$  54.1). The only group of methyl protons were assigned to C-20 ( $\delta$  26.0).



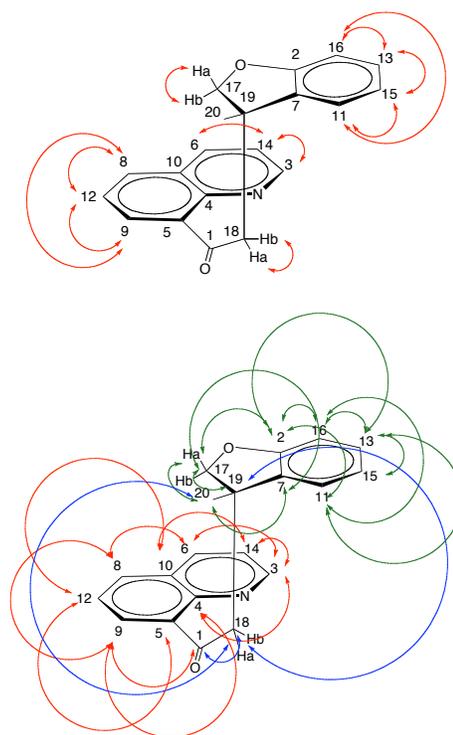
**Figure 1.** Hypothesized structure of **1**.

Analysis of  $^1H$  NMR determined that one methylene was adjacent to an oxygen ( $\delta_H$  4.7 and 4.57,  $J = 9.20$ , diastereotopic geminal protons) and one was in the presence of a deshielding aromatic ring current ( $\delta_H$  3.74 and 3.94,  $J = 17.6$ , diastereotopic geminal protons). It was determined that the  $^1H$  NMR resonance at 8.95 ppm was associated with the olefinic carbon 3 from HMQC correlation and therefore could not be a proton of an aldehyde or an amide. It was hypothesized that this proton belonged to a carbon which was double bonded to a nitrogen based on chemical shift. The  $^{13}C$  NMR shift for the associated carbon 3 (Figure 1) also support this hypothesis with a shift of about 150 ppm which is similar to previously studied carbons double bonded to

nitrogen.<sup>1</sup> This number correlated extremely well with heteroaromatic,  $C=N$ ,  $^{13}C$  shift of 151 ppm occurring in a quinoline bicyclic ring structure.<sup>1</sup>

Based on the total of 8 olefinic carbons, 1 carbonyl carbon and 1  $C=N$ , it was deduced that there were 4 remaining degrees of unsaturation and could only exist as rings.

Careful analysis of COSY and HMBC correlations allowed determination of the relative positions of carbons and protons in the structure. The positions of carbons 3, 14 and 6 in Figure 1 were determined from both COSY and  $J$  values from coupling in 1D  $^1H$  NMR. Carbon 14 was positioned in between 3 and 6 based on the dd splitting of the proton associated with carbon 14 ( $\delta_H$  7.44,  $J = 8.3, 4.2$ ). HMBC correlations supported this arrangement. The associated  $J$  values also support the previously stated hypothesis of a quinolinic substructure assuming these three protons (on C-3, C-6 and C-14) are part of the heteroaromatic ring.<sup>2</sup>



**Figure 2.** Top: Important COSY couplings; Bottom: key HMBC correlations (bottom rings shown in red, top rings in green and connection between rings in blue)

HMBC correlations positioned quaternary carbon 10 two carbons away from 14 and carbon 4 two carbons

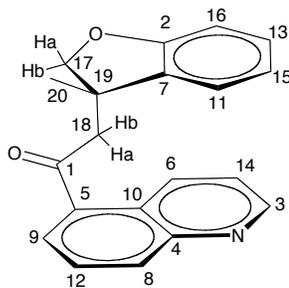
<sup>1</sup> Pretsch, E. Buhlman, P; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*. New York, 2000. p. 110.

<sup>2</sup> Pretsch, E. Buhlman, P; Affolter, C. *Structure Determination of Organic Compounds: Tables of Spectral Data*. New York, 2000. p. 195.

away 3 and  $^{13}\text{C}$  shifts help confirm their position.<sup>1</sup> Two subgroups of carbons were then identified to piece together two halves of the molecule. Group 1, which includes carbons 3, 4, 5, 6, 8, 9, 10, 12, and 14, was relatively isolated from group two, which includes carbons 2, 7, 11, 13, 15 and 16, based on COSY and HMBC correlations. Since only 5 degrees of unsaturation had been accounted for carbonyl and pyridine ring, the remaining 8 degrees of unsaturation along with the relatively few number of carbons left, implied that multiple aromatic rings or rings with double bonds at least were likely remaining pieces of the puzzle. The dd coupling between carbon 12's proton and protons of carbons 8 and 9 also supported a benzene ring structure including olefinic carbons from group 1 (carbons 4, 10, 5, 8, 9, 12) where carbon 12 was situated with C-8 and C-9 at both ortho positions (dd,  $J = 8, 7$ ). It appeared that 2 bond HMBC correlations were often suppressed. Because of this, it is likely that the evident C-H coupling between the proton on C-12 and C-5 is 3 bonds away, not 2, since this is the only coupling observed for C-5. This coupling confirms the location of C-5 meta, and not ortho, to C-12.

The ketone associated with C-1 was positioned at C-5 with the aid of the HMBC correlation between C-1 and the proton on C-9 (3 bond coupling).

There were two possible ways to place carbon 5 in the ring system: either adjacent to carbon 4 (**Figure 1**). Or adjacent to carbon 10 (**Figure 3**). Placing carbon 5 adjacent to 10 (**Figure 3**) would support the HMBC correlation between C-12 and C-5. This placement would require the coupling observed between C-10 and C-12 to be 4 bond coupling which is a bit of a stretch.



**Figure 3.** Alternative positioning of C-5, C-8, C-9 and C-12.

The placement of C-5 (**Figure 1**) would still allow 3 bond coupling between C-12 proton and C-5 but would also 3 bond coupling between C-12 proton and C-10. This placement is also supported by the 3 bond coupling observed for: C-8 proton to C-4, C-6, C-9; C-9 proton coupling to C-1, C-4 and C-8; C-6 proton couples to C-3, C-4 and C-8 (not possible in **Figure 3**). These 3 bond couplings seem to fit better with the structure proposed in **Figure 1** than the structure proposed in **Figure 3**. Comparison of 1D  $^{13}\text{C}$  NMR data to previously studied quinoline substructures indicates that either structure

could result in the  $^{13}\text{C}$  NMR resonances observed for C-5, C-8, C-9 and C-12 (**Table 1**).<sup>1</sup>

C-18 was difficult to assign. It was the only protonated carbon coupled to C-1 in HMBC but the high chemical shift of 18a and 18b ( $\delta_{\text{H}}$  3.94, 3.79,  $J = 17.6$ ) indicated that C-18 was connected to an electronegative substituent such as oxygen. One could argue that strong deshielding from the outer ring current of the quinoline could effectively deshield nearby C-18 protons enough to raise their chemical shift to  $\sim 3.8$  or 3.9. The minimal to non-existent coupling observed in 1D  $^1\text{H}$  NMR between C-18 protons and other protons supported both the positioning of C-18 between two quaternary carbons (C-1 and C-19) and the HMBC correlation between C-18 protons and C-1. Furthermore, only geminal coupling was observed C-18 protons ( $J = 17.6$  Hz).

Based on the calculated degrees of unsaturation, the remaining portion of the molecule had to contain 5 degrees of unsaturation. With 6 olefinic carbons still unassigned, this implied that the remaining portion of the molecule contained 3 double bonds and 2 rings.

$^1\text{H}$  NMR resonances indicated that protons on C-11, C-13, C-15 and C-16 were part of an aromatic benzene ring substructure. Coupling between protons on these carbons also supported this assignment (**Table 1**). Quaternary carbons C-2 and C-7 provided the link between this benzene substructure and the quinoline-ketone pieces. The high shift of C-2 (159.0 ppm) indicated that this olefin was adjacent to a deshielding electronegative substituent, the remaining unassigned oxygen.

C-17 was positioned on the other side of the oxygen based on the highly deshielded  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR resonances which support the assignment of C-17 positioned adjacent to an oxygen (**Table 1**). The quaternary C-19 was then positioned between C-17 and C-7 to close the final ring and obtain the desired 13 degrees of unsaturation. This connection also supported the observation that only geminal coupling was observed for C-17 protons indicating that there were no protons alpha to C-17. The stereochemistry of C-17 protons is difficult to assign based on the spectroscopic data given since COSY and HMBC coupling from other protons to C-17 protons is not specific as to whether the coupling is to 17a or 17b.

The C-20 methyl group was finally connected to C-19. This connection supported the observation that C-20 was adjacent to a quaternary carbon due to the lack of coupling observed in the  $^1\text{H}$  NMR (singlet,  $\delta_{\text{H}}$  1.56).

Three other compounds (8, 9 and 10) were isolated from the mixture of the lime and the coconut. Although more work is needed to confirm, it is our hypothesis that these compounds are side products which formed during the reaction between the lime and the coconut. Our retrosynthetic hypothesis of how the reaction between the lime and the coconut produces compound **1** (**Scheme 1**) involves retrosynthetic synthons which, upon various reactions and cyclizations could

altogether produce compound **1**. Compounds **8**, **9** and **10** are likely side products as they resemble early synthons for our hypothetical reaction pathway. Similar

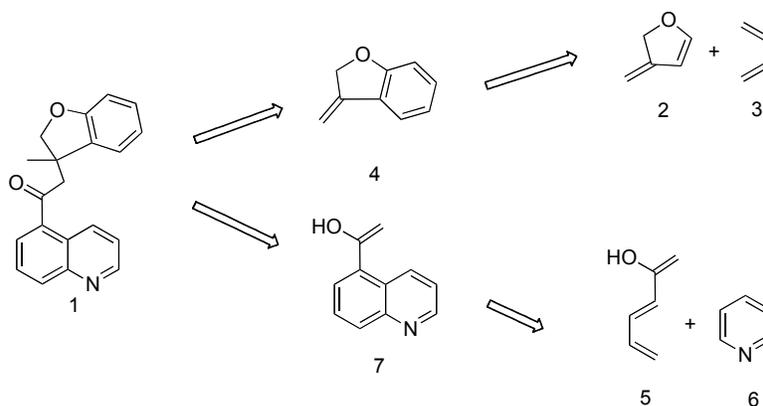
biosynthetic pathways have been observed for reactions between pineapple and coconut juices in the 'pina colada' drink.

**Table 1.**  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and 2D NMR data for **1** (in  $\text{CDCl}_3$ )<sup>a</sup>

no.	$\delta_{\text{C}}$	$\delta_{\text{H}}$ (multi, $J$ in Hz)	COSY	HMBC
1	204.5			
2	159.0			
3	150.7	8.95 (dd, 4.2, 1.8)	6, 14	4, 6, 14
4	145.2			
5	140.0			
6	136.2	8.18 (dd, 8.3, 1.7)	3, 14	3, 14, 8
7	135.0			
8	131.0	7.92 (dd, 8.1, 1.3)	12, 9	4, 6, 9,
9	129.0	7.81 (dd, 7.1, 1.4)	12, 8	1, 4, 8
10	128.2			
11	128.2	7.10 (m)	15, 16	2, 11, 13, 15
12	126.1	7.56 (dd, 8.03, 7.25)	8, 9	5, 10
13	123.0	7.10 (m)	15, 16	2, 11, 15
14	121.5	7.44 (dd, 8.3, 4.2)	6, 3	10
15	120.5	6.80 (m)	11, 13	2, 7, 11, 16
16	109.8	6.80 (m)	11, 13	2, 7, 11, 15
17a	83.0	4.71 (d, 9.20)	17b	2, 7, 18, 19, 20
17b		4.58 (d, 9.20)	17a	2, 7, 18, 19, 20
18a	54.1	3.94 (d, 17.6)	18b	1, 7, 17, 19, 20
18b		3.79 (d, 17.6)	18a, 20	1, 7, 17, 19, 20
19	44.1			
20	26.0	1.56 (s)	18b	7, 17, 18, 19

<sup>a</sup>Recorded at 500 MHz ( $^1\text{H}$  NMR) and 125 MHz ( $^{13}\text{C}$  NMR). <sup>b</sup>Assignments from HMQC correlations.

**Scheme 1.** Retrosynthetic Scheme for Synthetic Pathway for the Belly-Aching Drug (Cmpd **1**).<sup>a</sup>



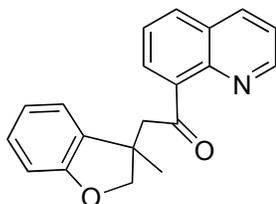
<sup>a</sup>Based on previously discovered synthons for pina colada: Light Rum + Coco Lopez + crushed ice + pineapple juice.

**Acknowledgment** This work was done with the support of the International Healthy Muppets Society. Work was based on previous studies on Lime and Coconuts by Harry Nilsson and Kermit D. Frog. Formatting was completed in *Organic Letters* journal format, and modelled after one specific paper: Zhang, Chuan-Rui; Fan, C-Q; Zhang, L. Yang, S.-P.; Wu, Y.; Lu, Y.; Yue, J.-M.; Chuktabrins A and B, Two

Novel Limonoids from the Twigs and Leaves of *Chukrasia tabularis*. *Organic Letters*, **2008**, *10*, 15, 3183-3186.

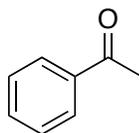
# Supporting Information

## Compound 1



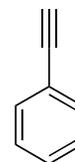
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.95 (dd,  $J = 4.2, 1.8$ , 1H), 8.18 (dd,  $J = 8.3, 1.7$ , 1H), 7.92 (dd,  $J = 8.1, 1.3$ , 1H), 7.81 (dd,  $J = 7.1, 1.4$ , 1H), 7.56 (m, 1H), 7.44 (dd,  $J = 8.3, 4.2$ , 1H), 7.10 (m, 2H), 6.80 (m, 2H), 4.65 (dd,  $J = 9.20, 66.8$ , 2H), 3.94 (d,  $J = 17.6$ , 1H), 3.79 (d,  $J = 17.6$ , 1H), 1.56 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  204.5, 159.0, 150.7, 145.2, 140.0, 136.2, 135.0, 131.0, 129.0, 128.2, 128.2, 126.1, 123.0, 121.5, 120.5, 109.8, 83.0, 54.1, 44.1, 26.0; IR 3046, 2961, 2881, 1682, 1595, 1568, 1479, 1458, 1346, 1247, 1216, 1187, 1093, 1054, 971, 831, 793, 751, 653  $\text{cm}^{-1}$ ; mass spectrum, calcd for  $\text{C}_{20}\text{H}_{17}\text{NO}_2$  326.1153 ( $\text{M}+\text{Na}^+$ ); observed, 326.1208  $m/z$  ( $\text{M}+\text{Na}^+$ ); ESI  $m/z$  (% relative intensity): 337 (1), 328 (1), 327 (3), 326 (79), 304 (2), 172 (10), 132 (6).

## Compound 8



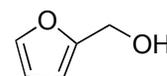
$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (dddd,  $J = 6, 1, 1, 0.6$  Hz, 2H), 7.55 (dddd,  $J = 6, 6, 1, 1$  Hz 1 H), 7.45 (dddd,  $J = 6, 6, 1, 0.6$  Hz 2 H), 2.60 (s, 3H);  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ , DEPT)  $\delta$  C 198.3, CH 137.2, 133.2, 128.7, 128.4; CH3 26.7; IR 3604, 3352, 3087, 3063, 3040, 3029, 3006, 2967, 2925, 2867, 1686, 1646, 1599, 1583, 1545, 1492, 1450, 1430, 1360, 1313, 1303, 1267, 1181, 1160, 1103, 1079, 1025, 1001, 966, 928, 761, 731, 691, 618, 588  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (% relative intensity): 120 (26), 101 (8), 100 (100), 78 (8), 77 (73), 51 (22), 50 (8), 43 (12), 39 (4).

## Compound 9



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53(dddd,  $J=6.7,1.7,1.2,0.5$  Hz, 2H), 87.35(dddd,  $J=7.1, 6.7, 1.3,0.5$  Hz, 2H),87.30(dd,  $J=7.1, 1.7$  Hz, 1H), 83.09(s,1H);  $^{13}\text{C}$  (300MHz,  $\text{CDCl}_3$ , DEPT) C 122.2, 83.7; CH 132.2, 128.9, 128.4, 77.3; IR (Thin film NaCl) 3306, 3291, 3081, 3058, 3034, 3022, 2110, 1245, 757, 692  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (% relative intensity): 102(100), 76(20), 63(6), 50(9).

## Compound 10



$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40(dd,  $J=1.8,0.8$  Hz, 1H), 86.34(dd,  $J=3.2, 1.8$  Hz, H),86.29(dd,  $J=3.2, 0.6$  Hz, 1H), 84.60(s, 2H), 82.08 (s, 1H);  $^{13}\text{C}$ (300MHz,  $\text{CDCl}_3$ , DEPT) C 153.9; CH 142.5, 110.31, 107.73; CH<sub>2</sub> 57.37; IR (Thin film NaCl) 3339, 3329, 3123, 2929, 2873, 1504, 1010  $\text{cm}^{-1}$ ; GC-MS  $m/z$  (% relative intensity): 98(100), 81(58), 69(37), 53(58), 41(69).

## Lyrics to **Put the Lime in the Coconut**

by Harry Nilsson

Brother bought a coconut  
He bought it for a dime.  
His sister had another  
She paid it for the lime.

She put the lime in the coconut  
she drank them both up.

she put the lime in the coconut  
she called the doctor, woke him up, and said  
"Doctor, ain't there nothing I can take"  
I said, "Doctor, to relieve this belly ache?"  
I said, "Doctor ain't there nothing I can take"  
I said, "Doctor, to relieve this belly ache?"

Now let me get this straight;  
You put the lime in the coconut  
You drank them both up  
You put the lime in the coconut,  
You drank them both up  
put the lime in the coconut,  
you drank them both up  
put the lime in the coconut,  
called your doctor, woke him up, and said,

"Doctor, ain't there nothing I can take"  
I said, Doctor, to relieve this belly ache?"  
I said, Doctor, ain't there nothin' I can take"  
I said, Doctor, to relieve this belly ache?"

You put the lime in the coconut, you drink them both together,  
put the lime in the coconut, then you'll feel better.  
Put the lime in the coconut, and drink them both up,  
Put the lime in the coconut, and call me in the morning."

Brother bought a coconut  
He bought it for a dime.  
His sister had another  
She paid it for the lime.

She put the lime in the coconut  
she drank them both up.  
she put the lime in the coconut  
Called the doctor, woke him up, and said  
"Doctor, ain't there nothing I can take"  
I said, "Doctor, to relieve this belly ache?"  
I said, "Doctor ain't there nothing I can take"  
I said, "Doctor"

Now let me get this straight;  
You put the lime in the coconut  
You drank them both up  
put the lime in the coconut,  
You drink them both up  
the lime in the coconut,  
you drink them both up  
you put the lime in the coconut,  
you're such a silly woman,  
put a lime in the coconut,  
and drink them both together,  
put the lime in the coconut,  
then you'll feel better.  
put the lime in the coconut,  
drink them both down,  
put the lime in the coconut,  
and call me in the morning

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<sup>F</sup> Harry Nilsson's Cure for Bellyache:  
<http://www.youtube.com/watch?v=Tbgv8PkO9eo>

Kermit D. Frog's Cure for Flipperache:  
[http://www.youtube.com/watch?v=1wg\\_L0wGTyA](http://www.youtube.com/watch?v=1wg_L0wGTyA)