



## A potent larvicidal agent against *Aedes aegypti* mosquito from cardanol

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*Manuscript received on September 13, 2016; accepted for publication on October 24, 2016*

### ABSTRACT

Cardanol is a constituent of Cashew Nut Shell Liquid that presents larvicidal activity against *Aedes aegypti*. The isolation of cardanol is somewhat troublesome, however, in this work we describe an efficient and inexpensive method to obtain it as a pure material. The compound was used as starting material to make chemical transformation leading to saturated cardanol, epoxides and, halohydrins. These derivatives were tested for toxicity against *Aedes aegypti* larvae. The results showed that iodohydrins are very promising compounds for making commercial products to combat the vector mosquito larvae presenting a  $LC_{50}$  of 0.0023 ppm after 72 h of exposure.

**Key words:** *Aedes aegypti*, insecticide, larvicide, phenolic lipids, CNSL.

### INTRODUCTION

Cashew nut shell liquid (CNSL) is a pericarp dark reddish brown viscous liquid of the cashew nut. The fluid has low added value (Soares 1986,

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\* Contribution to the centenary of the Brazilian Academy of Sciences.

Lomonaco et al. 2009), however, it is well known its abundance in phenolic lipid microcomponents such as: cardanol (**1**), cardol (**2**), anacardic acid (**3**), and traces of 2-methyl cardanol (**4**) (Figure 1). These compounds are obtained by typical solvent extraction. Technical CNSL is obtained by roasting shell at 180-200 °C, and anacardic acid is transformed to cardanol by decarboxylation during

the extraction process. The main constituents of technical CNSL are cardanol (60-65%), cardol (15-20%), and polymeric materials (10%) (Kumar et al. 2002). Unsaturated phenolic components comprise monoenes, dienes, and trienes (Figure 1).

Studies have shown that CNSL present insecticidal activity. Lomanaco (2009), reported that technical CNSL exhibits smaller insecticidal activity than cold solvent extracted CNSL (*in natura*) because the presence of anacardic acid in the latter. Subsequent studies (Guissoni et al. 2013) showed that CNSL when extracted by solvent at 40 °C preserves intense insecticidal activity, which is eightfold greater than that reported by Lomonaco. This methodology allows a more efficient extraction of anacardic acid. Emulsion formulation of CNSL has been used as a natural insecticide applied to ants, termites, and others (Craveiro 2001). Anacardic acid is described as antimicrobial (Kubo et al. 1993, Reddy et al. 2012), antitumor, antioxidant, gastro-protective (Hamad and Mubofu 2015), potential anticarcinogenic such as prostate cancer (Schneider et al. 2016), besides it is used as starting material for building many other derivatives of pronounced biological activity (Jiang et al. 2015). Cardanol has potential to prevent diseases transmitted by bacteria, fungi, and protozoa when is added in feed formulation to birds and pigs (Campmany 2007). Moreover, cardanol has industrial use as a component of paints and varnish (Tyman 1996).

The presence of cardanol, cardol, and anacardic acid are also present in propolis (Silva et al. 2008) has been a motivation to extensive biological activity studies of this resinous mixture as anti-inflammatory, antibacterial, antiprotozoal, antifungal, antiseptic, cytotoxic, antioxidant, spasmolytic and, anesthetic (El-Bassiony et al. 2012).

*Aedes aegypti* mosquito is the main vector for yellow fever, dengue, chikungunya, and zika virus (Rodhain and Rosen 1997). The diseases

have caused millions of complications such as microcephaly, chronic pain and, death in Brazil and, worldwide. The main classes of insecticides used to control of the mosquito are organophosphates and pyrethroids. Nevertheless, besides the fact that these compounds contaminate the environment, there has been occurred vector resistance to them all over the world. Therefore, there is a request for the development of new efficient agents with lower environmental impact.

Many investigations in Brazil have demonstrated the importance of mosquito resistance to synthetic insecticides, (Diniz et al. 2014, Silva et al. 2015, Chediak et al. 2016) and the fact that currently about 50 million people are exposed to this vector (WHO 2016). Several factors are connected to propagation of the mosquito and consequently causing epidemic, for instance: housing precariousness, disoriented occupation of areas without infrastructure, inadequate storage of water, unimproved sanitation and, inefficient programs to control insects (Freitas et al. 2014).

Seeking for new insecticides using biomass and/or industrial by-products in order to give alternatives to the conventional ones has been stimulating researches to investigate oils, extracts, or isolated constituents of plants. This pursuit has been intensively focused on insecticidal activity associated to extracts or isolated molecules that are biodegradable, renewable and, of low toxicity. Additionally, it is expected to give opportunity to add value to productive chain of the product characterized by inexpensive eco-friendly commercial exploration resulting in income generation and employment.

Aiming to develop green insecticides, herein we report the larvicidal activity against *A. aegypti* of cardanol and cardanol derivatives. Cardanol has known larvicidal activity against *A. aegypti* through the inhibition of acetylcholinesterase enzyme similar to synthetic insecticides (Oliveira et al. 2011, Barbosa-Filho et al. 2007). The use of this

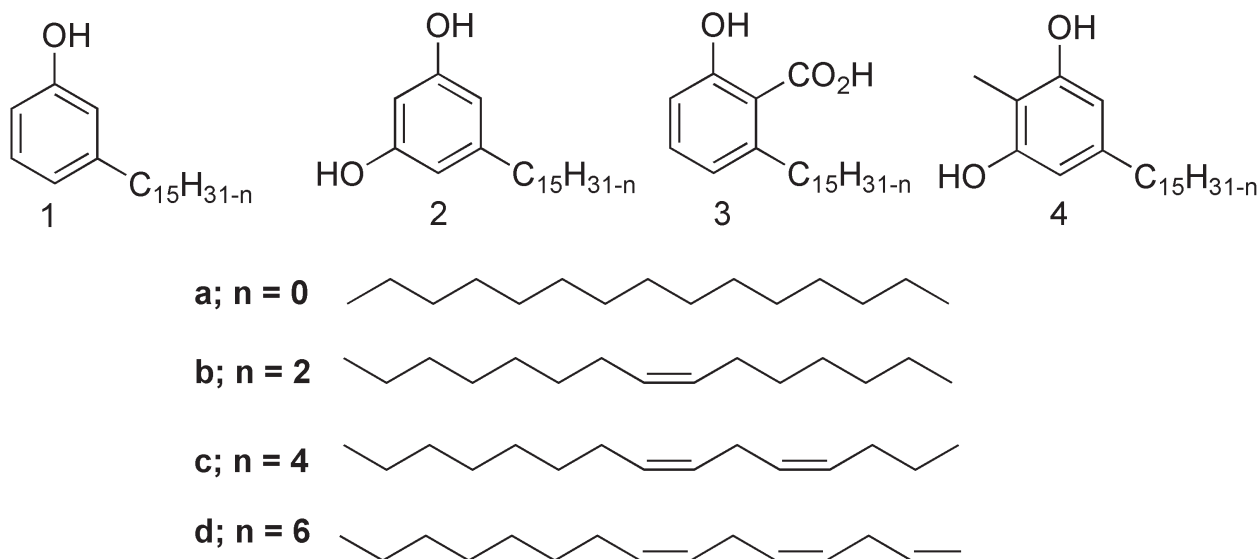


Figure 1 - CNSL constituents.

inexpensive compound to prepare biodegradable derivatives increases the possibilities to design strategies for alternative functionalization approaches in case of vector resistance.

#### MATERIALS AND METHODS

The  $^1H$ -NMR spectra were registered using the following spectrometers: 1-Varian, DPX-300 and Gemini 2002 Varian. The analyses made use of  $CDCl_3$  as a solvent and, shifts were related to internal reference standard tetramethylsilane (TMS).  $^{13}C$ -NMR spectra were registered at 75 MHz, using a Varian DPX-300 spectrometer and at 50 MHz using Gemini 200 Varian equipment. High-resolution mass spectra were registered by using a Bruker Daltonics, modelo micrOTOF - Q II - ESI - TOF equipment. The reactions were monitored by TLC using silica gel Merck 60 F254 supported on aluminum plate. Developed plates were visualized under UV light or sprayed with vanillin in presence of concentrated sulfuric acid followed by heating. Michelson Bomem MB100FT-IR spectrometer was used to register infrared spectra. Solvents and reagents were treated following data of literature (Perrin 1980). Microwave-assisted reactions were

carried out with CEM Discover S series microwave reactor.

#### CHEMISTRY

**Isolation and purification of cardanol (1a-d):** A solution of CNSL (100 mL, 86 g) in ethyl acetate and hexane 1:1 (200 mL) was filtered through a Büchner funnel loaded with celite (200 g). The solvent mixture was fully removed by rotary evaporation. Then, the filtrate was placed into a round-bottomed flask coupled to an apparatus similar to a short path and submitted to vacuum drying (40-60 mmHg) at temperature of 169-210 °C. It was obtained an oily material (40.6 g, 80% yield). Spectroscopy data are in accordance with those reported in the literature (Shibata et al. 2013).

$^1H$ -NMR (300 MHz,  $CDCl_3$ );  $\delta$  (ppm): 7.10 (t,  $J=7.7$  Hz); 6.73 (d,  $J=7.6$  Hz); 6.64 (d,  $J=7.5$  Hz); 5.94 (s); 5.39 (m); 5.00 (ddd,  $J=13.6$  Hz,  $J=11.4$  Hz,  $J=1.4$  Hz); 2.81 (dd,  $J=10.2$  Hz,  $J=4.6$  Hz); 2.51 (t,  $J=7.7$  Hz); 2.04 (dd,  $J=15.4$  Hz,  $J=8.9$  Hz); 1.55 (d,  $J=6.3$  Hz); 1.36 (m); 0.89 (q, 3H,  $J=7.1$  Hz).  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ ),  $\delta$  (ppm) 155.2; 144.8; 136.7; 130.3; 130.0; 129.9; 129.8; 129.7; 129.3; 128.1; 127.8; 127.9; 127.5; 126.7; 120.8; 115.3;

114.6; 112.5; 107.8; 35.7; 31.8; 31.7; 31.4; 31.2; 29.7; 29.5; 29.35; 29.2; 29.1; 27.1; 25.6; 25.5; 22.7; 22.6; 14.0; 13.7

**Hydrogenated cardanol (1a):** Into a 500 mL flask was added cardanol (11.174 g, 37 mmol) solubilized in ethyl acetate (300 mL) and 10% Pd-C catalyst (1.13 g, 1.04 mmol). The reaction mixture was reduced for 30-60 minutes in a Paar hydrogenation shaker under a pressure of 60 psi. After decantation, the catalyst Pd-C residue can be reused. The supernatant was removed and filtered under reduced pressure using Büchner funnel loaded with celite. Followed, the solvent was removed by rotary evaporation to give viscous liquid that transformed to a solid when treated with cold hexane. After removing the solvent, it was obtained a white solid (10.9 g, 98% yield of saturated cardanol – **1a**). The product was employed in the next reaction without further purification.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.12 (t, 1H, *J*=7.6 Hz); 6.73 (d, 1H, *J*=7.6 Hz); 6.62 (m, 2H); 4.70 (s, 1H); 2.53 (t, 2H, *J*=7.8 Hz); 1.55 (m, 2H); 1.26 (m, 24H); 0.86 (t, 3H, *J*=6.6 Hz), RMN <sup>13</sup>C (75 MHz, CDCl<sub>3</sub>) δ (ppm): 155.43; 144.9; 129.3; 120.9

#### *Synthesis of epoxide and halohydrin derivatives of cardanol*

**Reaction of cardanol with epichlorohydrin:** Into a 25 mL rounded-bottom flask were added cardanol (0.302 g, 1 mmol), epichlorohydrin (0.78 mL, 10 mmol) and, DMAP (12 mg, 9.8x10<sup>-7</sup> mmol). The mixture was heated at 90 °C under water bath for 1 hour. By TLC analysis using as eluent hexane: ethyl acetate (9:1) it was observed 100% of conversion of the starting material. After recovering the excess of epichlorohydrin by rotary evaporation, the residue was dissolved in dichloromethane (3 mL) and placed into a separatory funnel. The solution was washed with distilled water (1 mL) and, to the formed emulsion it was added ammonium chloride (0.5 g).

The water phase was treated with dichloromethane (2 x 3 mL). The organic extracts were combined and dried over anhydrous sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>). It was obtained the products (0.350 g) that proved to be NMR, a mixture of epoxypropyl ether (70%) and halohydrin (30%) when the starting material was cardanol. The halohydrin mixture was totally converted to the corresponding epoxides by using the following procedure.

#### **Conversion of halohydrin 6 to epoxides 5:**

A mixture of cardanol epoxides and halohydrins in methanol (6 mL) was treated with a methanol solution of LiOH (3 mL, 0.5 M). The mixture was kept under vigorous stirring for 1 hour. The solvent was removed by rotary evaporation and the residue was redissolved in dichloromethane and transferred to a separatory funnel. The mixture was washed (3 x H<sub>2</sub>O). The organic phase was dried over anhydrous sodium sulfate and it was obtained only cardanol epoxides without the necessity of further purification.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.18 (t, 1H, *J*=7.7 Hz); 6.78 (d, 1H, *J*=7.5 Hz); 6.71(m, 2H); 5.86 (m, 1H); 5.35 (m, 3H); 5.00 (m, 2H), 4.21(d, 2H, *J*=3.0 Hz); 3.82 (dd, 2H, *J*=11.0 Hz, *J*=5.2 Hz); 3.77 (d, 1H, *J*=5.7 Hz); 3.35 (m, 1H); 2.91(m, 1H) 2.75 (t, 1H, *J*=6 Hz); 2.57 (t, 2H, *J*=8.1 Hz); 2.03 (m, 2H); 1.63 (m, 2H); 1.32 (m, 8H); 0.86 (t, 3H, *J*=6.7 Hz). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 158.1; 144.6; 136.7; 130.3; 129.9; 129.1; 126.7; 121.3; 114.8; 114.8; 111.4; 68.5; 50.1; 44.7; 35.9; 31.7; 31.3; 28.9; 27.17; 25.6; 22.6; 14.1; 13.8.

#### **Conversion de cardanol epoxide 5 to halohydrins 6:**

An ice bath solution of cardanol epoxide **5** solubilized in chloroform (20 mL) was treated with concentrated HCl (30 drops) and mixture was stirred for 30 minutes. The reaction mixture was then placed into a separatory funnel and washed with distilled water (2 x 50 mL). The organic phase was washed with sodium bicarbonate solution (25 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced

pressure to give the product that was submitted to purification by flash chromatography using as eluent a mixture of hexane:ethyl acetate (9:1). It was obtained a pale yellow oil (0.65 g, 85% yield).

<sup>1</sup>H-NMR (300 MHz) 7.10 (t, *J*=7,7 Hz); 6.73 (d, *J*=7.6 Hz); 6.64 (d, *J*=7.5 Hz); 6.73 (s); 5.39 (m); 5.00 (ddd, *J*=13.6 Hz, *J*=11.4 Hz, *J*=1.4 Hz); 4.21(q, 1H, *J*=12 Hz, *J*=6 Hz); 4.07 (ddd, 1H, *J*=6 Hz, *J*=3 Hz); 2.81 (dd, *J*=10.2 Hz, *J*=4.6 Hz); 2.51 (t, *J*=7.7 Hz); 2.00 (dd, *J*=15.4 Hz, *J*=8.9 Hz); 1.54 (d, *J*=6.3 Hz); 1.29 (m); 0.88 (q, 3H, *J*=7.1 Hz). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 158.2; 144.8; 129.9; 129.8; 129.3; 121.6; 114.7; 111.5; 111.4; 69.9; 68.3; 53.4; 45.9; 35.9; 35.8; 31.7; 31.3; 31.1; 31.1; 29.7; 29.6; 29.63; 29.6; 29.5; 29.3; 29.3; 29.2; 29.1; 29.1; 29.0; 29.0; 29.0; 28.9; 28.8; 28.8; 28.8; 28.7; 28.7; 28.7; 28.6; 28.6; 27.1; 25.5; 22.6; 14.0. Spectroscopy data are in accordance with those reported in the literature (T.M. Cossa, unpublished data).

**Microwave assisted reaction of cardanol with epichlorohydrin to prepare 5:** A 25 mL round-bottomed flask containing a mixture of cardanol (**1a-d**) (0.302 g, 1 mmol), epichlorohydrin (0.78 mL, 10 mmol) and DMAP (12mg, 9.8x10<sup>-7</sup>) was inserted into a microwave reactor (potency of 60 W), with temperature average of 80 °C. By using TLC, the reaction was monitored over 10 minutes when it was observed the complete consumption of the starting materials. After recovering the excess of epichlorohydrin by rotary evaporation, it was obtained a yellow oil (0.350 g) containing a mixture of epoxides (70%) and halohydrins (30%) (87% yield).

**Synthesis of 7 - Reaction of cardanol epoxides with resublimed iodine:** Into a 50 mL rounded-bottomed flask it was added cardanol epoxides **2** (1.80 g, 5 mmol) and resublimed iodine (0.634 g, 5 mmol) dissolved in chloroform (25 mL). The mixture was heated to 80 °C for 2 hours. The reaction progress was monitored by TLC. The resulting solution was washed with brine (500

mL) and extracted with ethyl ether. The organic phases were combined and carefully washed with a saturated solution of NaHCO<sub>3</sub> followed by brine. The solution was dried over Na<sub>2</sub>SO<sub>4</sub> and, after filtration; the solvent was removed under reduced pressure. The iodohydrins **7** obtained had no need for further purification. (85%). <sup>1</sup>H-NMR (300 MHz) ppm 7.20 (m, 1H *J*=2.5 Hz); 6.82 (d, 1H, *J*=6.0 Hz); 6.75 (t, 2H, *J*=6.0 Hz); 5.37 (m, 1H); 4.97 (m, 1H); 4.45 (s, 1H); 4.22 (d, 1H, *J*=3.0 Hz); 4.18 (d, 1H *J*=3.0 Hz); 4.08-3.98 (m, 3H); 3.47 (dd, 1H, *J*=10.2 Hz, *J*=5.3 Hz); 3.38 (dd, 1H, *J*=10.2 Hz, *J*=5.6); 2.58 (t, 2H *J*=8.1 Hz); 2.00 (m, 3H); 1.62 (m, 2H); 1.29 (m, 13H); 0.89 (t, 1H, *J*=6.6 Hz). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 158.4; 158.1; 144.8; 130.4; 129.9; 129.2; 121.6; 114.8; 111.5; 70.2; 69.9; 68.6; 44.8; 35.9; 32.6; 31.9; 31.7; 29.3; 27.2; 22.7; 14.1; 9.2. ESI (+) – FT – ICR MS [M + H]<sup>+</sup> m/z; Anal. Calcd for **7c** (diene) C<sub>24</sub>H<sub>38</sub>IO<sub>2</sub><sup>+</sup>: 486.1950, found: 486.1927; Anal. Calcd for **7d** (triene) C<sub>24</sub>H<sub>36</sub>IO<sub>2</sub><sup>+</sup>: 483.1760. Found: 483.1762.

#### LARVICIDAL ASSAY AGAINST *Aedes aegypti*

Bioassays were performed in accordance with WHO guidelines (2005) to determine median lethal concentration (LC<sub>50</sub>) and 90% (LC<sub>90</sub>) by means of baseline of susceptibility. It was used the concentrations ranging from 0.0002 ppm to 50 ppm. Each compound was treated with five concentrations; each test was repeated four times employing groups of 25 larvae of 3rd-stage and 4th-stage of *A. aegypti* (Rockefeller). As a positive control, we used the solvent DMSO (0.4%), used to prepared the concentrations of the compounds evaluated here and also diagnostic concentration of 0.012 ppm temephos determined by WHO (1992), this being an organophosphate insecticide used commercially. As a negative control was used only bottled water. Observation of mortality was made every 24 hours until 72 hours after application.



## STATISTICAL ANALYSIS

The Probit analysis method was applied to obtain the  $LC_{50}$  and the respective confidence intervals by using the software Statplus, v. 5. The data were submitted to analysis of variance by F test, and the means compared by Tukey Test ( $p < 0.05$ ).

## RESULTS AND DISCUSSION

## CHEMISTRY

The cardanol molecule is amphipathic since it bears hydrophilic and lipophilic regions. Taking advantage of this feature, we decide to perform chemical transformations at its phenolic portion so as to increase the polarity to generate more water-soluble non-ionic surfactants. Therefore, we idealized to couple cardanol with epichloridrin to achieve epoxides **5**, which in turn would suffer nucleophilic attack by halides to lead to the corresponding halohydrins **6** and **7** (Figure 2).

Cardanol had to be previously distilled at reduced pressure. In general, this process has been cumbersome and difficult since there is a contamination of distillate material due to foaming and liquid ejection, leading to low yields. Such a problem could be circumvented by distilling cardanol after its filtration from a mixture of hexane:ethyl acetate (1:1) followed by solvent removal. This procedure yields 80% of cardanol (**1**).

In order to synthesize epoxides **5** we apply a protocol developed in our research group (Figure 3), without using solvent and base and, the excess of reagent is recovered. The target products in this step are prepared in a quantitative yield without the need of extra purification. The obtained mixture is composed of epoxides and chlorohydrins (7:3), respectively, and can be totally converted to the pure epoxides **5** in basic condition or, to the pure chlorohydrins **6** in acidic media (Figure 3).

The reaction of epoxides **5** with resublimed iodine provided the corresponding iodohydrins **7**

with 85% yield (Figure 3). Usually, it is necessary to use a catalyst to perform this reaction (Sharghi et al. 2002, Wu et al. 2006, Torabi et al. 2012), however, our procedure worked fine by only carrying on the reaction in toluene under reflux.  $^1H$  NMR spectrum showed two doublet of doublets at 3.47 ppm ( $J_{gem} = 10.2$  Hz,  $J_{H1/H'1-H2} = 5.3$  Hz) and 3.38 ppm ( $J_{gem} = 10.2$  Hz,  $J_{H1/H'1-H2} = 5.6$  Hz) assigned to the diastereotopic hydrogens of methylene group (H1/H1') attached to iodine atom.  $^{13}C$  NMR spectrum showed a signal at 9.2 ppm attributed to the same methylene carbon.

LARVICIDAL ASSAY AGAINST *Aedes aegypti*

The larvicidal activities of the cardanol, hydrogenated cardanol (**1a**) and the halogenated derivative **7** in different period of exposure to *A. aegypti* larvae are presented in Table I. Cardanol (**1a-d**) had a medium lethal concentration  $LC_{50} = 18.355$  (14.611 - 26.334) at 24 h of exposure, which is different to the values found by Oliveira et al. (2011) ( $LC_{50} = 8.20 \pm 0.15$ ). Cardanol (**1a-d**) was more effective in causing larval death at 48 h and 72 h of exposure, reaching an average mortality of 93.3% (sd 4.61) at a concentration of 25 ppm. After 72 hours, there was 96% mortality (sd 5.67) at the concentration of 19.25 ppm. Hydrogenated cardanol (**1a**) caused maximum mortality within 24 h of 1.5% (sd 0.57) and 48 h 10.5% (sd 0.57) at a concentration of 50 ppm. These results are in accordance with Lomonaco et al. (2009), and suggest that toxicity has a direct relationship with unsaturation when compared to cardanol (**1a-d**) (mainly composed of monoene, diene and triene) since hydrogenated cardanol **1a** showed  $LC_{50} > 100$  ppm.

However, the iodine derivative **7** showed a dramatic increase of toxicity against *A. aegypti* larvae showing  $LC_{50} = 3.725$  (2.651 - 5.148) and 0.0023 (0.0015 - 0.0034) after 48 and 72 h of exposure, respectively. At a concentration of 1.56

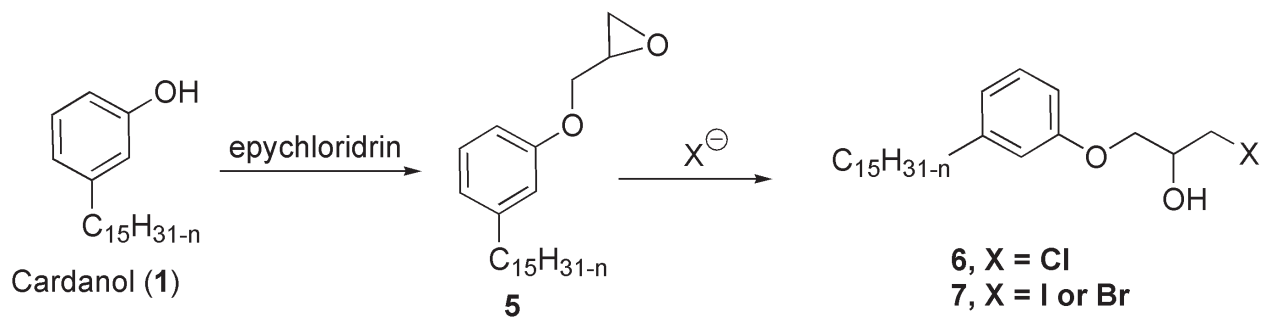


Figure 2 - Synthetic route to new derivatives of cardanol.

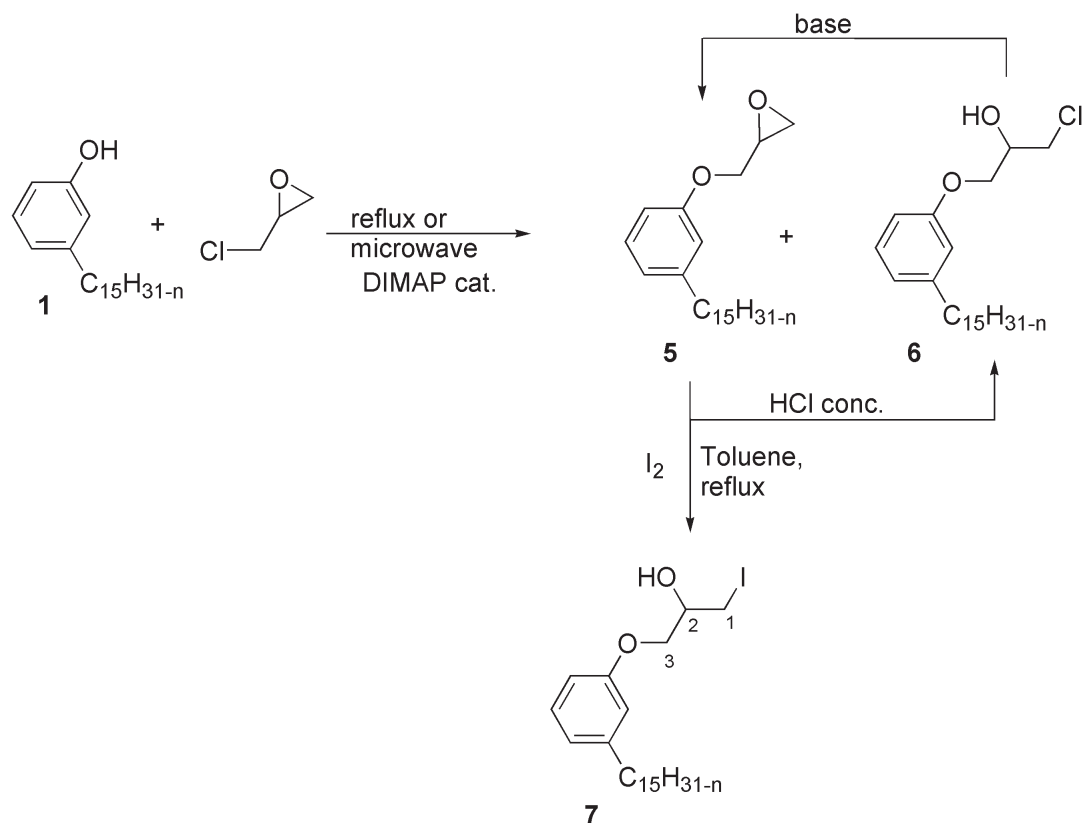


Figure 3 - Synthetic routes to the epoxides and halohydrins.

ppm, the mortality was 96.48% (SD 3.06) after a period of 72 h. The commercial insecticide themephos at a diagnosis concentration of 0.012 ppm killed 100% of the larvae within 24 h.

The statistical analysis using ANOVA showed a difference in mean for cardanol (1a-d) in comparison with hydrogenated cardanol ( $F = 21.209$   $p < 0.01$ ) and between hydrogenated cardanol (1a) and compound 7 ( $F = 19.122$   $p < 0.01$ ). With respect

to cardanol (1a-d) and compound 7 there was no significant difference ( $F = 0.924$ ,  $p > 0.05$ ).

The verified increasing of activity for compounds 7 may be ascribed to the introduction of iodine in a specific region of the molecules, incorporating greater electrophilicity and, consequently sensitivity to  $S_N2$  reaction at a primary carbon. Additionally, the possible wetting effect of these compounds could, even in low concentrations, leads to rupture of protective membrane of larvae

**TABLE I**  
Median lethal concentration ( $LC_{50}$ ) ( $mg L^{-1}$ , ppm) of cardanol, saturated cardanol (1a) and 7 in different period of exposure to *A. aegypti* larvae.

Compound	Time (h)	$LC_{50}$ (CI <sub>0.05</sub> )	b±SD	$\chi^2$	df
Cardanol (Fig. 1, 1a-d)	24	18.355 (14.611 - 26.334)	-0.540±0.040	10.416	3
	48	14.781 (12.030 - 18.164)	-8.982±0.028	5.871	3
	72	11.649 (8.154 - 16.641)	-7.028±0.036	4.351	2
Hydrogenated Cardanol (1a)	48	>100			
	72	>100			
7	48	3.725 (2.651 - 5.148)	2.546±0.073	1.635	4
	72	0.0023 (0.0015 - 0.0034)	3.890±0.084	1.184	4

CI – confidence interval; b – slope; SD – standard deviation; df - degrees of freedom.

facilitating the penetration of 7 into the organism to trigger its death (Moreira et al. 1998). Moreover, the toxicity could be related to the interactions of substrate to active sites serine hydroxyl S 200 and cysteine thiol group C 286 (Pang et al. 2012).

In order to detect the susceptibility of *A. aegypti* to the temephos, Luna et al. (2004) found a  $LC_{50} = 0.0046$  for insect population in the state of Curitiba (PR-Brazil). Lima et al. (2000) described  $LC_{50}$  average of 0.021-0.037 ppm for temephos resistant insect population in the state of Ceará (Brazil) (2000). In addition, it was found  $LC_{50}$  ranging from 0.073 to 1.627 in the state of Paraíba (Brazil) (Beserra et al. 2007). Accordingly,  $LC_{50}$  of compound 7 is similar to temephos, but with the difference that the organophosphorus insecticides have toxic effects on the insect nervous system and thus the mortality of larvae occurs quickly, usually in a shorter interval than 24 h in a non-resistant population. The toxic action of the cardanol-based compounds occurs in the digestive system (Dourado et al. 2015), which results in longer time to cause mortality in larvae. In the case of compound 7 low  $LC_{50}$  occurred after 72 h of exposure.

Temephos until recently was the Brazilian governmental choice of insecticide to control *A. aegypti*. Our work shows that 7 possesses toxic effect against the larvae as organophosphorus

insecticide. Therefore, our synthetic derivatives embrace great opportunities for the development of commercial products to control the diseases vector *A. aegypti*.

#### ACKNOWLEDGMENTS

We are grateful to the Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul (FUNDECT) (PRONEM – Termo de Outorga no. 054/12), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Kardol Ind. Química Ltda. for supporting our studies in this field of research.

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