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Synthesis and Insecticidal Activity of *O*-alkylated Oxirane Eugenol Derivatives †

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Abstract: The synthesis of three *O*-alkylated eugenol derivatives, bearing a hydroxypropyl chain and propyl esters were synthesised and further converted into the corresponding oxiranes. Oxirane derivatives were then evaluated against their effect upon the viability of the insect cell line *Sf9* (*Spodoptera frugiperda*), in comparison with the starting *O*-alkylates. The results pointing to their potential as bioinsecticides, with structural changes eliciting significant effects in terms of potency.

Keywords: essential oils; eugenol derivatives; eugenol epoxide; bioinsecticides; natural products

1. Introduction

In the last decades, the need to prevent diseases and damage caused by the attack of various pests on plants, has led to the application of high amounts of synthetic pesticides, including insecticides, which has resulted in the development of resistance to them by several harmful organisms [1]. As an alternative, natural products with insecticide activity have been shown promise for insect control in agriculture [2,3]. The use of bioactive compounds of plants presents many advantages as insecticide: they are less hazardous to human and animal health, more cheap, non-toxic to non-target species, and less resistance in the target organism besides being environmentally friendly [4]. Essential oils (EOs) exhibit antimicrobial activities with particular potential as insecticides [5]. Structural modifications in the constituents of EOs can further enhance their biocidal effect [2,4,6,7], being the best alternatives of synthetic chemicals and can be utilized as biopesticides or green pesticides [8–10].

Eugenol, the major component of clove oil, presents numerous applications including in pharmaceutical, food and agricultural industries. It is an important insecticide with large efficiency on a wide variety of domestic arthropod pests [6,11].

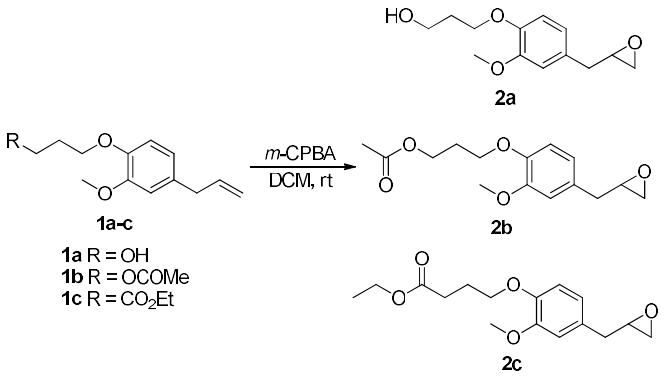
Considering all these facts, the synthesis of three *O*-alkylated eugenol derivatives and the respective oxiranes was carried out and then evaluated against their effect upon the viability of the insect cell line *Sf9* (*Spodoptera frugiperda*), in comparison with the starting eugenol *O*-alkylates.

2. Results and Discussion

2.1. Synthesis of Eugenol Derivatives

4-Allyl-2-methoxyphenol, eugenol, was extracted from clove, and used in the synthesis of three O-alkylated derivatives **1a–c**, which were then converted in the respective oxiranes **2a–c** as shown in Scheme 1. Alkylation of the hydroxyl group of 4-allyl-2-methoxyphenol with 3-bromopropan-1-ol using cesium carbonate as a base, by heating at 65 °C in acetonitrile, gave methoxyphenoxy)propan-1-ol **1a**. This compound was further reacted with acetic anhydride by heating at 65 °C to obtain 3-(4-allyl-2-methoxyphenoxy)propyl acetate **1b**. 4-Allyl-2-methoxyphenol was also alkylated with ethyl 4-bromobutanoate by following the same method mentioned above to yield ethyl 4-(4-allyl-2-methoxyphenoxy)butanoate **1c**. Compounds **1a–c** were obtained as oils in 53 to 84% yields. Their ^{1}H NMR spectra showed the different characteristic signals for the aliphatic protons of methylene and methyl groups (δ 1.21–4.27 ppm), as well as the expected protons for the eugenol's double bond as multiplets, CH_2 (δ 5.01–5.14 ppm) and CH (δ 5.91–6.01 ppm). ^{13}C NMR spectra of all compounds showed signals of the aliphatic carbons from the methylene (δ 24.57–68.69 ppm) and methyl groups (δ 14.14–20.66 ppm), in addition to signals of the ester carbonyl groups (δ 170.76 and 173.20 ppm, respectively) for compounds **1b** and **1c**.

To perform epoxidation of the double bond of eugenol derivatives **1a–c**, they were allowed to react with m-chloroperbenzoic acid in dichloromethane at room temperature, and the respective derivatives, namely 3-(2-methoxy-4-(oxiran-2-ylmethyl)phenoxy)propan-1-ol **2a**, 3-(2-methoxy-4-(oxiran-2-ylmethyl)phenoxy)propyl acetate **2b**, and ethyl 4-(2-methoxy-4-(oxiran-2-ylmethyl)phenoxy)butanoate **2c** were obtained. Compounds **2a–c** were isolated as yellow oils in yields of 13 to 57%, and were fully characterized by the usual analytical techniques. It stands out that epoxidation of compounds **2a–c** was verified by the presence of the protons signals related the oxirane ring (δ 2.52–3.17 ppm) and the absence of the signals of protons for the double bond of eugenol skeleton. The presence of carbon signals relative to oxirane ring, CH_2 (δ 46.77–46.78 ppm), and CH (δ 52.55–52.56 ppm) also confirmed the structure of expected eugenol derivatives **2a–c**.



Scheme 1. Synthesis of eugenol derivatives **2a–c**.

2.2. Toxicity of Eugenol Derivatives

In a general way, all molecules of the **1** and **2** series presented the same activity profile, namely a mild toxic effect around 30–35% of viability reduction. The exception was **2c**, which elicited a loss of around 50% of viability. Considering that **2b** and **2c** present a rather similar structure, the only difference being the ester type, this feature seems to be of importance, given that the latter was more toxic than the former.

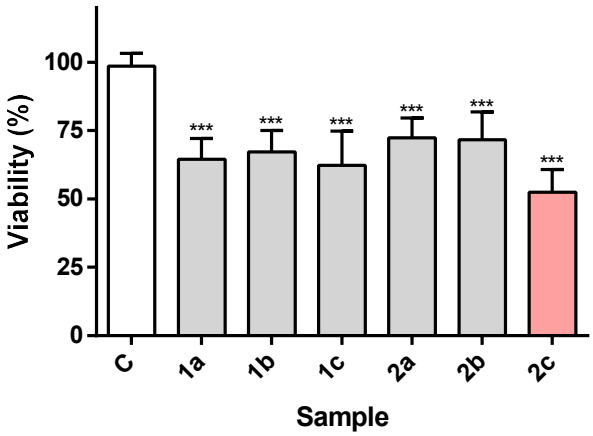


Figure 1. Viability of *Sf9* cells after exposure to the designated molecules for 24 h at 100 μg/mL. *** $p < 0.001$. C: control.

3. Experimental

3.1. Typical Procedure for the Preparation of Compounds 2a–c (Illustrated for 2a)

3-(4-Allyl-2-methoxyphenoxy)propan-1-ol (0.156 g, 7.03×10^{-4} mol, 1 eq.) (4 mL) dissolved in dichloromethane was added dropwise to a solution of *m*-chloroperbenzoic acid (0.346 g, 2.0×10^{-3} mol, 1 eq.) in dichloromethane (6 mL) at 0 °C. After stirring for 1 h, *m*-chloroperbenzoic acid was again added (1 eq.), and the reaction mixture was stirred for more 12 h. A 10% aqueous solution of sodium sulfate (10 mL) was added and the resulting solution was washed with 5% aqueous solution of sodium hydrogen carbonate (2 × 10 mL). The organic phase was dried with anhydrous magnesium sulfate and solvent was evaporated giving 3-(2-methoxy-4-(oxiran-2-ylmethyl)phenoxy)propan-1-ol **2a** as a yellow oil (0.096 g, 57% yield). R_f = 0.58 (silica; ethyl acetate). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.08 (2H, quint, *J* 6.0 Hz, $OCH_2CH_2CH_2OH$), 2.55 (1H, q, CH_2 oxirane), 2.80–2.85 (3H, m, CH_2Ph and CH_2 oxirane), 3.13–3.17 (1H, m, CH oxirane), 3.86 (3H, s, OCH_3), 3.89 (2H, t, *J* 5.6 Hz, $OCH_2CH_2CH_2OH$), 4.19 (2H, t, *J* 5.6 Hz, $OCH_2CH_2CH_2OH$), 6.71–6.73 (2H, m, H-3 and H-5), 6.84 (1H, d, *J* 8.4, H-6) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 31.75 ($OCH_2CH_2CH_2OH$), 38.34 (CH_2Ph), 46.78 (CH_2 oxirane), 52.56 (CH oxirane) 55.83 (OCH_3), 61.57 ($OCH_2CH_2CH_2OH$), 68.64 ($OCH_2CH_2CH_2OH$), 112.50 (C-3), 113.45 (C-6), 120.96 (C-5), 130.52 (C-4), 146.95 (C-1), 149.41 (C-2) ppm. HRMS: *m*/*z* (ESI): Calcd. for $C_{13}H_{18}NaO_4$ $[M+Na]^+$ 261.1097; found 261.1098.

3.2. Procedure for Insecticidal Activity

3.2.1. Cell Culture

Sf9 (*Spodoptera frugiperda*) cells were cultivated in Grace's medium with 10% FBS and 1% penicillin/streptomycin, at 28 °C.

3.2.2. Viability Assessment

For the assessment of viability, a resazurin assay was used. *Sf9* cells were plated at a density of 3.0×10^4 cells/well andincubated for 24 h with each molecule. After this period, a commercial solution of resazurin was added (1:10) and the kinetic reaction of fluorescence increase monitored at 560/590 nm. It was used 60 min of incubation.

4. Conclusions

Three new three *O*-alkylated eugenol derivatives, bearing a propyl chain with hydroxyl, methyl and ethyl esters as terminals and further converted into the corresponding oxiranes were successfully synthetised.

It was made the evaluation of all derivatives against their effect upon the viability of insect cell line Sf9 (Spodoptera frugiperda) and all molecules of the **1** and **2** series presented a mild toxic effect around 30–35% of viability reduction. When compared all the compounds, **2c** exhibited a loss of around 50% of viability, presenting promising insecticidal activity.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Vargas-Méndez, L.Y.; Sanabria-Flórez, P.L.; Saavedra-Reyes, L.M.; Merchan-Arenas, D.R.; Kouznetsov, V.V. Bioactivity of semisynthetic eugenol derivatives against *Spodoptera frugiperda* (Lepidoptera: Noctuidae) larvae infesting maize in Colombia. *Saudi J. Biol. Sci.* **2019**, *26*, 1613–1620, doi:10.1016/j.sjbs.2018.09.010.
2. Filomeno, C.A.; Barbosa, L.C.A.; Teixeira, R.R.; Pinheiro, A.L.; Farias, E.S.; Ferreira, J.S.; Picanço, M.C. Chemical diversity of essential oils of Myrtaceae species and their insecticidal activity against *Rhyzopertha dominica*. *Crop Prot.* **2020**, *137*, 105309, doi:10.1016/j.cropro.2020.105309.
3. Pavela, R.; Benelli, G.; Canale, A.; Maggi, F.; Mártonfi, P. Exploring essential oils of Slovak medicinal plants for insecticidal activity: The case of *Thymus alternans* and *Teucrium montanum* subsp. *jailae*. *Food Chem. Toxicol.* **2020**, *138*, 111203, doi:10.1016/j.fct.2020.111203.
4. Mwanauta, R.W.; Mtei, K.A.; Ndakidemi, P.A. Prospective Bioactive Compounds from *Vernonia amygdalina*, *Lippia javanica*, *Dysphania ambrosioides* and *Tithonia diversifolia* in Controlling Legume Insect Pests. *Agric. Sci.* **2014**, *5*, 1129–1139, doi:10.4236/as.2014.512123.
5. Ainane, A.; Khammour, F.; Charaf, S.; Elabboubi, M.; Elkouali, M.; Talbi, M.; Benhima, R.; Cherroud, S.; Ainane, T. Chemical composition and insecticidal activity of five essential oils: Cedrus atlantica, Citrus limonum, Rosmarinus officinalis, Syzygium aromaticum and Eucalyptus globules. In Proceedings of the International Conference on Materials and Environmental Science, ICMES 2018 ICMES2018, Mohammed Premier University, Oujda, Morocco, 26–28 April 2018.
6. Silva, F.F.M.; Monte, F.J.Q.; Lemos, T.L.G.; Nascimento, P.G.G.; Costa, A.K.M.; Paiva, L.M.M. Eugenol derivatives: Synthesis, characterization, and evaluation of antibacterial and antioxidant activities. *Chem. Cent. J.* **2018**, 12, 34, doi:10.1186/s13065-018-0407-4.
7. Xie, Y.; Huang, Q.; Wang, Z.; Cao, H.; Zhang, D. Structure-activity relationships of cinnamaldehyde and eugenol derivatives against plant pathogenic fungi. *Ind. Crops Prod.* **2017**, *97*, 388–394, doi:10.1016/j.indcrop.2016.12.043.
8. Saroj, A.; Oriyomi, O.V.; Nayak, A.K.; Haider, S.Z. Phytochemicals of plant-derived essential oils: A novel green approach against pests. In *Natural Remedies for Pest, Disease and Weed Control*; Egbuna, C., Sawicka, B., Eds.; Elsevier Science: Amsterdam, The Netherlands, 2020; pp. 65–79, doi:10.1016/B978-0-12-819304-4.00006-3.
9. Novato, T.; Gomes, G.A.; Zeringóta, V.; Franco, C.T.; Oliveira, D.R.; Melo, D.; Carvalho, M.G.; Daemon, E.; Monteiro, C.M.O. In vitro assessment of the acaricidal activity of carvacrol, thymol, eugenol and their acetylated derivatives on *Rhipicephalus microplus* (Acari: Ixodidae). *Vet. Parasitol.* **2018**, *260*, 1–4, doi:10.1016/j.vetpar.2018.07.009.
10. Chen, C.-H.; Tung, S.-H.; Jeng, R.-J.; Abu-Omar, M.M.; Lin, C.-H. A facile strategy to achieve fully bio-based epoxy thermosets from eugenol. *Green Chem.* **2019**, *21*, 4475–4488, doi:10.1039/C9GC01184F.

11. Maurya, A.K.; Agarwal, K.; Gupta, A.C.; Saxena, A.; Nooreen, Z.; Tandon, S.; Ahmad, A.; Bawankule, D.U. Synthesis of eugenol derivatives and its antiinflammatory activity against skin inflammation. *Nat. Prod. Res.* **2020**, *34*, 251–260, doi:10.1080/14786419.2018.1528585.