SYNTHESIS AND BRINE SHRIMP LETHALITY TEST OF SOME BENZOXAZINE AND AMINOMETHYL DERIVATIVES OF EUGENOL

by Juni Ekowati

SYNTHESIS AND BRINE SHRIMP LETHALITY TEST OF SOME BENZOXAZINE AND AMINOMETHYL DERIVATIVES OF EUGENOL

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ABSTRACT

The specific objective of this research is to synthesize novel 1,3-benzoxazine and aminomethyl compounds from eugenol and study their biological activity. Eugenol was reacted with formaldehyde and primary amines following Mannich reactions. The obtained 1,3-benzoxazine compounds were then hydrolyzed to give the aminomethyl derivatives. All the obtained 1,3-benzoxazine and aminomethyl compounds were tested for biological activity using brine shrimp lethality test (BST). It was found that 6-allyl-8-methoxy-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine, 6-allyl-3-benzyl-8-methoxy-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine, 4-allyl-2-methoxy-6-phenylaminomethylphenol, 4-allyl-2-(benzylaminomethyl)-6-methoxyphenol, and 4-allyl-2-{[(furan-2-ylmethyl)-amino]-methyl}-6-methoxyphenol show toxicity on BST, and therefore potential to be further studied for their bioactivity.

Keywords: Eugenol, Benzoxazines, Aminomethyl, Synthesis, Mannich reaction, BST.

INTRODUCTION

Indonesia is the world's largest producer and user of clove. In Indonesia, clove is used mostly in kretek-cigarette industry. Following an increasing public awareness on the bad influence of smoking against health, the demand on clove is consequently decreasing. We are interested in finding new utilizations for clove by using eugenol, the main constituent of clove, as starting material for the synthesis of novel biologically active compounds. Hopefully it will help to increase economic value of clove and support the nation's independence in the field of medicine.

Eugenol has been reported to have biological activities, such as antityrosinase, antibacterial, antifungal, antiacne, inhibition of 5-lipoxygenase [1]. It is also used to cure dentinal hypersensitivity [2]. Eugenol has several functional groups, i.e. hydroxyl group, methoxy group, aromatic ring, and olefinic double bond, giving many possibilities to use it as starting material for the synthesis of more advanced valuable compounds.

Some examples for compounds prepared from eugenol are: ester derivatives of eugenol as soybean 15-lipoxygenase (SLO) inhibitor [3], coumestan and pterocarpan compounds having anticancer, antimalaria, and antileishmania properties [4], alilbendol [5], and ibuprofen eugenol ester, a promising NSAID prodrug [6]. Oliveira (1980) performed aromatic nitration of methyl eugenol, followed by derivatization of amino group [7]. Furthermore, eugenol was reported to be used as starting material for the syntheses of derivatives of 3-alkylmuconic acid, 3-allyladipic acid, and 4,4-dialkylbutenolide [8, 9].

A Japanese group has previously reported the synthesis of 1,3-benzoxazine and alkylaminomethyl derivatives of phenols [10]. The synthesized compounds were studied for antireserpine, analgesic, and antiinflammatory activities. The same group has patented thirteen 1,3-benzoxazine derivatives as antidepressant [11]. It was also reported that some benzoxazine compounds have antimalarial activity [12].

Since eugenol is a phenol derivative, we came to an idea to perform the similar transformations (Figure 1). Thus, eugenol was transformed to its 1,3-benzoxazine derivatives by Mannich reaction [13], and then the benzoxazines were hydrolyzed to give aminomethyl derivatives. In this paper we wish to report the results of our studies in the synthesis of some 1,3-benzoxazine and alkyl- and arylaminomethyl derivatives of eugenol, and brine shrimp lethality test (BST) on the obtained compounds.
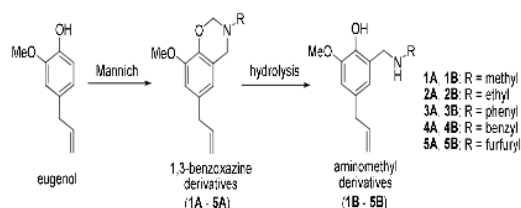

Fig. 1: Transformation of eugenol to 1,3-benzoxazine and aminomethyl derivatives

MATERIALS AND METHODS

General Commercially available materials were used as received. Eugenol, methylamine solution, ethylamine solution, aniline and benzylamine were purchased from Merck. Furfurylamine was purchased from Aldrich. Reactions were monitored with TLC using *p*-anisaldehyde stain. Purification of products was carried out by column chromatography on silica gel using hexane-ethyl acetate or chloroform-methanol as eluent. IR spectra were obtained using a Perkin Elmer Spectrum One spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL JNM-ECS 400 (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 100 MHz) instrument for solutions in CDCl$_3$. Mass spectra were measured with a JEOL JMS 600 spectrometer.

Preparation of 1,3-benzoxazine derivatives

Preparation of compound **1A** is described for general procedure. Eugenol (2.0 g, 12.2 mmol) was dissolved in methanol (24 mL). The mixture was cooled in ice bath. To the mixture were added 37% formaldehyde solution (2.7 mL, 36.5 mmol) and 40% methylamine solution (1.84 mL, 24.3 mmol). The resulting mixture was stirred at room temperature for 36 h and at 65 °C for 4 h. The mixture was concentrated by evaporation of the solvent under reduced pressure. The crude product was purified using column chromatography to give compound **1A**. Compounds **2A**, **3A**, **4A** and **5A** were prepared by substituting methylamine solution with ethylamine solution, aniline, benzylamine, and furfurylamine, respectively.

Preparation of aminomethyl derivatives

Preparation of compound **1B** is described for general procedure. Compound **1A** (142.5 mg, 0.65 mmol) was dissolved in *n*-propanol (24 mL). To the solution were added concentrated hydrochloric acid (2.0 mL) and distilled water (1.0 mL), and the resulting mixture was refluxed for 4 h. After cooling to 0 °C, to the mixture was added 25%

ammonia solution in water (5 mL). The resulting mixture was stirred at room temperature for 1 h, and extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified by column chromatography to give compound **1B**.

Brine shrimp lethality (BST) test

The BST assay was carried out according to Meyer [14] with minor modifications. Eggs of *Artemia salina* (about 30 mg) were placed into hatching chamber and kept under constant aerator for 24 h. After hatching, active nauplii were collected with Pasteur pipette to be used for assay. Test samples were prepared as follows. Twenty milligrams of each synthesized compounds were weighed, dissolved, and diluted following dilution procedure described by McLa 17 in [15] to give a variety of sample amounts corresponding to 1.000 ppm, 100 ppm, 10 ppm, 1 ppm, and 0.1 ppm, each in triplicate. For the control, three vials were stained with 0.5 mL of solvent. The solvent was evaporated by staying overnight in fume hood. The residues were redissolved by adding 50 ⊡L of dimethyl sulfoxide and 4 mL of sea water. After ten nauplii were introduced into each test vials, sea water was added to make volume of 5 mL. After being incubated for 24 h, the numbers of survivors were counted, and percentages of deaths were calculated. The resulting data were converted to probit analysis method for determination of LC_{50}.

RESULTS AND DISCUSSION

1, 3-Benzoxazine derivatives

Mannich reaction on eugenol using formaldehyde and five primary amines mentioned above provided the desired compounds **1A** to **5A**. Detailed physicochemical and spectral data of the obtained compounds are as follows.

6-Allyl-8-methoxy-3-methyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (1A)

Obtained in 94% yield as a yellow oil. ^{1}H-NMR (CDCl$_3$, δ, ppm): 6.56 (2H, d, *J*=1.6 Hz), 6.41 (1H, d, *J*=1.6 Hz), 2.99-5.89 (1H, m), 5.11-5.04 (2H, m), 4.85 (2H, s), 3.92 (2H, s), 3.86 (3H, s), 3.29 (2H, d, *J*=6.8 Hz), 2.61 (3H, s). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.5, 141.2, 137.5, 131.7, 120.0, 119.0, 115.7, 109.7, 84.1, 55.7, 51.8, 39.9, 39.8. HRMS calculated for C$_{13}$H$_{17}$NO$_2$ 219.1259; found 219.1275. All the spectral data are in agreement with the structure of compound **1A**.

6-Allyl-3-ethyl-8-methoxy-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (2A)

Obtained in 88% yield a yellow oil. ^{1}H-NMR (CDCl$_3$, δ, ppm): 6.54 (2H, d, *J*=1.6 Hz), 6.39 (1H, d, *J*=1.6 Hz), 5.98-5.87 (1H, m), 5.10-5.02 (2H, m), 4.93 (2H, s), 3.96 (2H, s), 3.84 (3H, s), 3.27 (2H, d, *J*=6.8 Hz), 2.80 (2H, q, *J*=7.2 Hz), 1.15 (3H, t, *J*=7.2 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.4, 141.6, 137.5, 131.5, 120.3, 118.8, 115.6, 109.6, 81.0, 55.6, 49.6, 45.3, 39.8, 13.3 HRMS calculated for C$_{14}$H$_{20}$NO$_2$ 234.1494; found 234.1470. All the spectral data are in agreement with the structure of compound **2A**.

6-Allyl-8-methoxy-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (3A)

Obtained in 59% yield as a yellow oil. ^{1}H-NMR (CDCl$_3$, δ, ppm): 7.25-7.21 (2H, m), 7.12-7.08 (2H, m), 6.92-6.87 (1H, m), 6.54 (1H, d, *J*=1.6 Hz), 6.44 (1H, d, *J*=1.6 Hz), 5.97-5.87 (1H, m), 5.40 (1H, m), 5.11-5.04 (2H, m), 4.59 (2H, s), 3.82 (3H, s), 3.28 (2H, d, *J*=6.8 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 148.3, 147.9, 141.9, 137.4, 131.9, 129.1 (2C), 121.3, 121.1, 118.2, 118.0 (2C), 115.7, 109.9, 79.6, 55.7, 50.2, 39.8. HRMS calculated for C$_{18}$H$_{20}$NO$_2$ 282.1494; found 282.1513. All the spectral data are in agreement with the structure of compound **3A**.

6-Allyl-3-benzyl-8-methoxy-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (4A)

Obtained in 98% yield as a yellow oil. ^{1}H-NMR (CDCl$_3$, δ, ppm): 7.37-7.26 (5H, m), 6.59 (1H, d, *J*=1.6 Hz), 6.37 (1H, d, *J*=1.6 Hz), 5.99-5.89 (1H, m), 5.11-5.04 (2H, m), 4.97 (2H, s), 3.95 (2H, s), 3.93 (2H, s), 3.89 (3H, s), 3.29 (2H, d, *J*=6.8 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.5, 141.5, 138.2, 137.4, 131.7, 128.8 (2C), 128.3 (2C), 127.2, 120.1,

118.9, 115.6, 109.7, 82.5, 55.7, 55.5, 49.0, 39.8. HRMS calculated for C$_{19}$H$_{21}$NO$_2$ 295.1572; found 295.1585. All the spectral data are in agreement with the structure of compound **4A**.

6-Allyl-3-furan-2-ylmethyl-8-methoxy-3,4-dihydro-2*H*-benzo[*e*][1,3]oxazine (5A)

Obtained in 90% yield as a white solid, mp. 86 °C. ^{1}H-NMR (CDCl$_3$, δ, ppm): 7.39 (1H, d, *J*=1.6 Hz), 6.58 (1H, d, *J*=1.6 Hz), 6.39 (1H, d, *J*=1.6 Hz), 6.31 (1H, d, *J*=3.2, 1.6 Hz), 6.24 (1H, d, *J*=3.2 Hz), 5.88 (1H, m), 5.11-5.04 (2H, m), 4.94 (2H, s), 3.98 (2H, s), 3.93 (2H, s), 3.86 (3H, s), 3.28 (2H, d, *J*=6.8 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 151.5, 147.4, 142.4, 141.3, 137.4, 131.8, 119.7, 118.8, 115.6, 110.0, 109.8, 108.8, 82.2, 55.6, 49.0, 48.1, 39.8. HRMS calculated for C$_{17}$H$_{19}$NO$_3$ 285.1365; found 285.1384. All the spectral data are in agreement with the structure of compound **5A**.

Except for the reaction with aniline which gave moderate yield (59%), Mannich reaction of eugenol with primary amines provided the desired 1,3-benzoxazines in high yield (88-98%). The difference between aniline and the other primary amines is that aniline is an arylamine while the others are alkylamines. In arylamines, the lone pair of nitrogen atom is in conjugation with the aromatic ⊡ electrons, making arylamines more stable and less reactive as nucleophiles [16].

Infrared spectra of the obtained 1,3-benzoxazines show no peak above 3000 cm^{-1}, means there are no OH or NH groups in the structures. Ratios of protons as seen from integrations in ^{1}H-NMR spectra, the splitting patterns of the peaks in ^{1}H-NMR spectra, number of peaks in ^{13}C-NMR spectra, as well as the exact mass of molecular ion as measured by high resolution mass spectroscopy confirmed the structures of compounds **1A** to **5A**.

Aminomethyl derivatives

Hydrolysis on the obtained **1A** to **5A** following the procedure mentioned above provided the desired aminomethyl compounds. Detailed physicochemical and spectral data of the obtained compounds are as follows.

4-Allyl-2-methoxy-6-methylaminomethylphenol (1B)

Obtained in 71% yield as yellow solid, mp. 73 °C. IR (cm^{-1}): 3332. ^{1}H-NMR (CDCl$_3$, δ, ppm): 6.53 (1H, d, *J*=1.6 Hz), 6.44 (1H, d, *J*=1.6 Hz), 5.99-5.89 (1H, m), 5.09-5.02 (2H, m), 3.93 (2H, s), 3.86 (3H, s), 3.28 (2H, d, *J*=6.8 Hz), 2.46 (3H, s). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.8, 145.3, 137.9, 130.1, 122.2, 120.2, 115.4, 111.2, 55.8, 54.3, 39.8, 35.2. HRMS calculated for C$_{12}$H$_{18}$NO$_2$ 208.1337, found 208.1347. All these spectral data are in agreement with the structure of compound **1B**.

4-Allyl-2-ethylaminomethyl-6-methoxyphenol (2B)

Obtained as a pink solid in 90% yield, mp. 52 °C. IR (cm^{-1}): 3399. ^{1}H-NMR (CDCl$_3$, δ, ppm): 6.61 (1H, d, *J*=1.6 Hz), 6.42 (1H, d, *J*=1.6 Hz), 5.98-5.88 (1H, m), 5.09-5.01 (2H, m), 3.96 (2H, s), 3.85 (3H, s), 3.27 (2H, d, *J*=6.8 Hz), 2.70 (2H, q, *J*=7.2 Hz), 1.14 (3H, t, *J*=7.2 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.9, 145.6, 137.9, 130.0, 122.5, 120.0, 115.3, 111.0, 55.8, 52.2, 42.9, 39.8, 14.8. HRMS calculated for C$_{13}$H$_{19}$NO$_2$ 221.1416, found 221.1417. All these spectral data are in agreement with the structure of compound **2B**.

4-Allyl-2-methoxy-6-phenylaminomethylphenol (3B)

Obtained as yellow oil in 15% yield. IR (cm^{-1}): 3509, 341. ^{1}H-NMR (CDCl$_3$, δ, ppm): 7.19-7.13 (2H, m), 6.70-6.67 (4H, m), 6.61 (1H, d, *J*=1.6 Hz), 6.36 (1H, br s), 5.96-5.86 (1H, m), 5.07-5.01 (2H, m), 4.31 (2H, s), 4.09 (1H, br s), 3.83 (3H, s), 3.28 (2H, d, *J*=6.4 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 148.0, 146.6, 142.3, 137.7, 131.2, 129.1 (2C), 124.2, 120.9, 118.1, 115.5, 113.7 (2C), 110.3, 55.9, 44.3, 39.8. HRMS calculated for C$_{17}$H$_{19}$NO$_2$ 269.1416, found 269.1422. All these spectral data are in agreement with the structure of compound **3B**.

4-Allyl-2-(benzylaminomethyl)-6-methoxyphenol (4B)

Obtained in 65% as a yellow oil. IR (cm^{-1}): 3300. ^{1}H-NMR (CDCl$_3$, δ, ppm): 7.34-7.25 (5H, m), 6.63 (1H, d, *J*=1.6 Hz), 6.43 (1H, d, *J*=1.6 Hz), 5.99-5.88 (1H, m), 5.09-5.02 (2H, m), 3.96 (2H, s), 3.86 (3H, s), 3.79

(2H, s), 3.28 (2H, d, *J*=6.8 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 147.8, 145.3, 138.3, 137.8, 130.2, 128.5 (2C), 128.3 (2C), 127.4, 122.2, 120.3, 115.3, 111.2, 55.8, 52.5, 51.5, 39.7. HRMS calculated for C$_{18}$H$_{21}$NO$_2$ 283.1572, found 283.1588. All these spectral data are in agreement with the structure of compound **4B**.

4-Allyl-2-{[(furan-2-ylmethyl)-amino]-methyl}-6-methoxyphenol (5B)

Obtained in 5% as a yellow solid, mp. 44 °C. IR 27): 3303. ^{1}H-NMR (CD 7 δ, ppm): 7.35 (1H, d, *J*=2.0 Hz), 6.63 (1H, d, *J*=1.6 Hz), 6.42 (1H, d, *J*=1.6 Hz), 6.30 (1H, d 2 =3.2, 2.0 Hz), 6.18 (1H, d, *J*=3.2 Hz), 5.98-5.88 (1H, m), 5.09-5.01 (2H, m), 3.90 (2H, s), 3.85 (3H, s), 3.78 (2H, s), 3.28 (2H, d, *J*=6.4 Hz). ^{13}C-NMR (CDCl$_3$, δ, ppm): 151.9, 147.7, 145.1, 142.0, 137.7, 130.2, 122.1, 120.4, 115.3, 111.2, 110.0, 107.7, 55.7, 50.6, 44.1, 39.6. HRMS calculated for C$_{16}$H$_{19}$NO$_3$ 273.1365; Found 273.1348. All the spectral data are in agreement with the structure of compound **5B**.

Hydrolysis of the obtained 1,3-benzoxazines provided the desired aminomethyl compounds in 34-90% yield. Although the reaction conditions were not optimized, the yield of compound **3B** (34%) is relatively low compared to the others (65-90%). The low yield of compound **3B** is probably because this arylaminomethyl compound is less stable and more susceptible to degradation compared to the alkylaminomethyl compounds. The opening of oxazine ring was proved by IR spectra which show absorption band of OH and/or NH at around 3300 cm^{-1}. Except for compound **3B**, peaks of NH and OH protons were not appearing on ^{1}H-NMR spectra. However, chemical shifts, integrations and splitting patterns of all the C-H protons are in agreement with structures of the desired products. Analysis by ^{13}C-NMR and high resolution mass spectroscopies provided further confirmation on the structures.

Brine shrimp lethality test (BST)

The results of toxicity test of all the obtained 1,3-benzoxazine and aminometyl derivatives of eugenol against *Artemia sp.* are shown in Table 1.

Table 1: Results of Brine Shrimp Lethality Test

1,3-Benzoxazine derivatives		Aminomethyl derivatives	
Compound	LC$_{50}$ (ppm)	Compound	LC$_{50}$ (ppm)
1A	>100	1B	>100
2A	>100	2B	>100
3A	12.9	3B	6.4
4A	10.2	4B	11.2
5A	73.5	5B	10.2

Based on Meyer's criterium that a pure substance considered toxic if the LC$_{50}$ value is less than 30 ppm, compounds **3A**, **3B**, **4A**, **4B** and **5B** are toxic and potential to be studied further (Table 1). Since compounds **1A**, **1B**, **2A** and **2B** did not show toxicity, it can be concluded that aromatic group in amino moiety is necessary for the toxicity. Compound **3B** having aromatic group directly attached to nitrogen showed the highest toxicity.

CONCLUSION

Five 1,3-benzoxazine derivatives have been obtained from eugenol by Mannich reaction with formaldehyde and five different primary amines. Five aminomethyl derivatives of eugenol were obtained from acid hydrolysis of 1,3-benzoxazines derivatives. Some of the obtained products show toxicity on *Artemia salina*.

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