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Synthesis and Antibacterial Activity of 1,3,5,7-Tetrahydroxy-9,10-Anthraquinone and Anthrone Derivatives

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Abstract

In this research, the synthesis of 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**) and two anthrone derivatives, 1,3,5,7-tetrahydroxy-10*H*-anthracene-9-one (**2**) and 1-hydroxy-3,5,7,9-tetramethoxyanthracene (**3**) has been done. Compound **1** was synthesized by a symmetrical condensation reaction of 3,5-dihydroxybenzoic acid in concentrated sulfuric acid. Reduction of the carbonyl group in compound **1** with $SnCl_2$/HCl-HOAc affords compound **2**. Compound **3** was prepared by modifying the hydroxy groups of compound **2** by a methylation reaction. The synthesized compounds were identified using nuclear magnetic resonance spectroscopy (NMR) and a high-resolution mass spectrometry (HR-ESI-MS). The antibacterial activity test of the synthesized compounds against four pathogenic bacteria, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*, was carried out using the microdilution method. Compound **3** showed moderate activity against *B. subtilis*, *E. coli* and *S. typhi* with a MIC value of 37.5 µg/mL. Moderate activity was also shown by compound **2** against *S. aureus*, while compound **1** showed weak activity with a MIC value of 75 µg/mL against the four test bacteria.

Keywords: anthraquinone, anthrone, antibacterial, methylation, reduction.

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1. INTRODUCTION

Anthraquinone is a polycyclic aromatic compound consisting of an anthracene ring with two ketone groups at positions C-9 and C-10. The reduction of one of the ketone groups in anthraquinone produces anthrone compound. Different types of anthraquinone have been successfully isolated from plants (Dave & Ledwani, 2012; Xu *et al.*, 2014), fungi (Masi & Evidente, 2020), lichen (Manojlovic *et al.*, 2010), and insects (Shamim et al., 2014). The variety and position of functional groups on the aromatic rings of anthraquinone and anthrone affect their biological activity. The results of research on anthraquinone and anthrone derivative compounds (**Figure 1**) show various biological activities, including anticancer (Ali *et al.*, 2000; Li *et al.*, 2020), antiviral (Barnard *et al.*, 1992; Feilcke *et al.*, 2019), antioxidant (Malterud *et al.*, 1993; Zengin *et al.*, 2016; Al-Tamimi *et al.*, 2020) and antibacterial (Park *et al.*, 2006; Hamed *et al.*, 2015; Bunbamrung *et al.*, 2018). As antibacterials, some anthraquinone-derived compounds (**Figure 2**) show a MIC (minimum inhibitory concentration) value of less than 10 µg/mL (Chukwujekwu *et al.*, 2006; Kuete *et al.*, 2007). Therefore this group of compounds has the potential to be developed as antibiotic raw materials.

The development of anthraquinone and anthrone as antibacterial compounds must be followed by anticipation of their provision, one of which is a provision by synthesis. The synthesis of anthraquinone derivatives is mainly carried out through the Friedel-Crafts reaction between phthalate anhydride and substituted benzene using catalysts such as $AlCl_3/H_2SO_4$ (Naeimi & Namdari, 2008) and $KAl(SO_4)_2.12H_2O$ (Madje *et al.*, 2010).

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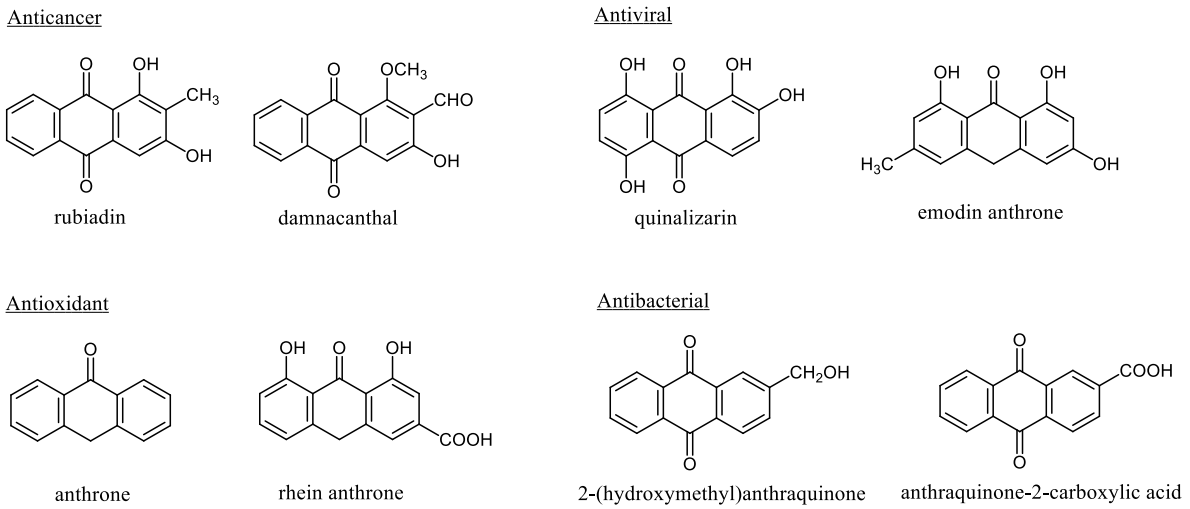

Figure 1. Biological activity of anthraquinone and anthrone-derived compounds (Barnard *et al.,* 1992; Malterud *et al.,* 1993; Ali *et al.,* 2000; Park *et al.,* 2006)

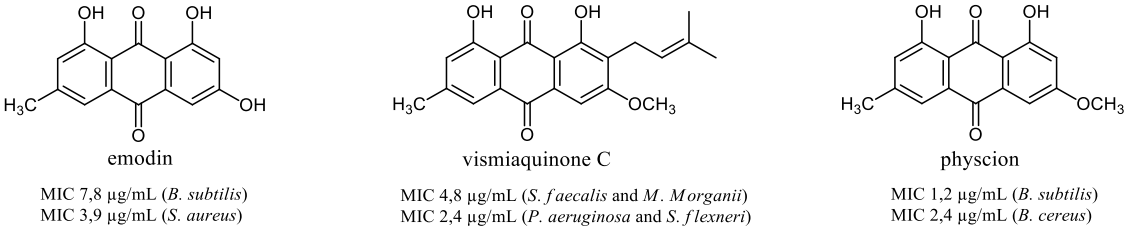

Figure 2. Antibacterial activity of anthraquinone-derived compounds (Chukwujekwu *et al.,* 2006; Kuete *et al.,* 2007)

Another method was carried out by Murschell & Sutherland (2010), who succeeded in synthesizing anthraquinone derivatives, rufigallol (1,2,3,5,6,7-hexahydroxy-9,10-anthraquinone) through the self-condensation reaction of gallic acid (3,4,5-trihydroxybenzoic acid) in concentrated sulfuric acid. The synthesis of this method relies on the presence of a free hydroxy (–OH) group in benzoic acid and is very suitable for manufacturing anthraquinones with a symmetrical hydroxy (–OH) group in both aromatic rings.

Therefore, this study synthesized anthraquinone derivatives, 1,3,5,7-tetrahydroxy-9,10-anthraquinone, through the self-condensation reaction of 3,5-dihydroxybenzoic acid in concentrated sulfuric acid. Anthrone-derived compounds are synthesized by reducing anthraquinone compound, followed by modification of functional groups through methylation reactions. All pure synthesized compounds are tested for antibacterial activity *in vitro* using the microdilution method to obtain MIC values.

2. MATERIALS AND METHODS

Tools and Materials

The tools and instruments used in this study include ^{1}H-NMR and ^{13}C-NMR (1D and 2D) with Agilent DD2 and JEOL ECA 500 spectrometers working at 500 MHz (^{1}H) and 125 MHz (^{13}C), high-resolution mass spectrometry (HR-ESI-MS) with Waters LCT XE ESI-TOF (Electrospray Ionization-Time of Flight), melting point measurement using Fisher-Johns tools, thin-layer chromatography (TLC) using silica gel 60 GF_{254} silica coated aluminium plates, radial chromatography (stationary phase of silica gel Merck 60 GF_{254}), and glassware commonly used in laboratories.

The chemicals used in synthesis reactions include 3,5-dihydroxybenzoic acid (Aldrich), $SnCl_2$ (Aldrich), $(CH_3O)_2SO_2$ (Merck), K_2CO_3 (Merck), $NaHCO_3$ (Merck), NaCl (technical grade), Na_2SO_4 anhydrous (Merck), concentrated H_2SO_4 (Merck), HCl (Merck), acetic acid glacial (Merck), dichloromethane (Merck), hexane (technical grade), ethyl acetate (technical grade), and acetone (technical grade). The solvents and reagents used for the reactions

are pro-analytical (p.a), while pre-distilled technical solvents are used for separation and purification. The staining reagent on TLC uses a solution of 1.5% (w/v) $Ce(SO_4)_2$ in H_2SO_4 2N. The chemicals used for antibacterial tests include DMSO (Merck), NaCl (Merck), MHB (Mueller Hinton Broth) and MHA (Mueller Hinton Agar).

3,5-dihydroxybenzoic Acid Condensation Reaction

3,5-dihydroxybenzoic acid (0.45 g; 2.80 mmol) was put in a round flask, and then concentrated sulfuric acid (5 mL) was added. The mixture was reacted at 120 °C (reflux). During the reaction, monitoring was carried out using TLC analysis by comparing the retention factor (R_f) value of the reagent spot to the reaction results after spraying the staining reagent. After heating for 2 hours, the reaction was completed, where no more reactant spots were observed with TLC. Next, the mixture was poured into cold distilled water and filtered. The residue was dissolved in acetone and filtered, and the obtained filtrate was concentrated. The obtained compound **1** was tested for melting point and identified with NMR and HR-ESI-MS.

Reduction Reaction with $SnCl_2$/HCl-HOAc

Compound **1** (0.10 g; 0.37 mmol) was added with acetic acid glacial (10.6 mL) and heated (reflux) at 118 °C. Then, a solution of $SnCl_2$ (1.32 g; 5.85 mmol) in 37% HCl (2.75 mL) was slowly dripped into the mixture. The mixture is reheated for up to 18 hours, then removed and cooled. The mixture was poured into the distilled water, and added NaOH solution until the pH of neutral. The mixture was extracted with ethyl acetate. The organic phase was washed with distilled water, and a saturated $NaHCO_3$ was added. Furthermore, the organic phase was separated and concentrated. The resulting solid (compound **2**) was tested for melting point and identified with NMR and HR-ESI-MS.

Methylation Reaction with Dimethyl Sulfate

Compound **2** (0.10 g; 0.39 mmol) was dissolved in acetone (5 mL), added K_2CO_3 (0.32 g; 2.34 mmol) and heated (reflux) for 2 hours, then dimethyl sulfate $(CH_3O)_2SO_2$ (0.15 mL; 1.56 mmol) was added. The reaction was carried out for 18 hours. Next, the mixture was added distilled water and extracted with dichloromethane. The organic phase was washed with a saturated NaCl solution and evaporated. The residue was purified by radial chromatography using the hexane-ethyl acetate 8:2. The obtained pure compound **3** was tested for melting point and identified with NMR and HR-ESI-MS.

Antibacterial Activity Test

Antibacterial activity test of synthetic compounds was carried out *in vitro* against four pathogenic bacteria, including two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and two Gram-negative bacteria (*Escherichia coli* and *Salmonella typhi*). The bacteria test used was local isolates of the Bandung Health Polytechnic Microbiology Laboratory. Antibacterial activity test by microdilution method, referring to the CLSI standard method (CLSI, 2012). This test was carried out to determine the value of minimum inhibitory concentration (MIC).

The antibacterial test begins with the preparation of a bacterial suspension. Bacteria in the MHA medium were incubated for 24 hours at 37 °C (aerobic conditions). Furthermore, the bacteria were suspended in a 0.9% (w/v) NaCl solution and equalized to a 0.5 Mc Farland standard (approximately $1\text{-}2x10^5$ bacterial cells/mL). The sample was dissolved in dimethylsulfoxide (DMSO) to a concentration of 300 µg/mL. A total of 200 µL of MHB liquid medium was put into the microplate wells (96 wells). Into the first well was added 200 µL of test solution. Preparation of the solution concentration series was created by transferring 200 µL of solution from the first well to the second well. From the second well, another 200 µL was taken and put into the third well. The same was done until the eighth well. The amount of solution in each well is 200 µL. Then into each well was inserted 10 µL of microbial suspension. Furthermore, the microplates were incubated at 37 °C for 24 hours. Microbial growth was determined using a microplate spectrometer at 600 nm. The MIC is the lowest concentration that can inhibit microbial growth. The antibiotic chloramphenicol was used as a positive control.

3. RESULTS AND DISCUSSION

Compound 1

Compound **1** was obtained as a dark green solid with a melting point above 300 °C. The results of the HR-ESI-MS measurement of

compound **1** showed the $[M-H]^-$ ion at m/z 271.0245 according to the molecular formula $C_{14}H_8O_6$ (calculation $[M-H]^-$ 271.0243). The ^{1}H-NMR spectrum of compound **1** (**Figure 3**) shows the presence of a singlet signal from OH-chelates (δ_H 12.81) and a pair of doublet signals from *meta*-oriented aromatic protons (J = 2.3 Hz) at δ_H 6.65 and 7.30 ppm. Since there are no other proton signals, compound **1** is suggested to have a symmetry structure corresponding to the structure of 1,3,5,7-tetrahydroxy-9,10-anthraquinone.

Self-condensation or cyclodehydration reaction of 3,5-dihydroxybenzoic acid in concentrated sulfuric acid produced 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**) of 0.35 g with a yield of 92% (**Figure 4**). This result was better than Murschell & Sutherland (2010) when performing the self-condensation reaction of gallic acid in concentrated sulfuric acid to synthesize ruffigalol with a yield of 78%. The difference in amendments is due to the Murschell & Sutherland (2010) method with a microwave, while this study used heating with reflux. Another example of a cyclodehydration reaction that produces anthraquinone is the reaction of *o*-benzoyl benzoic acid in concentrated sulfuric acid. The cyclodehydration mechanism of *o*-benzoyl benzoic acid involves intramolecular electrophilic substitution, wherein an acylium ion (oxocarbonium) acts as an electrophile (Liler, 1971).

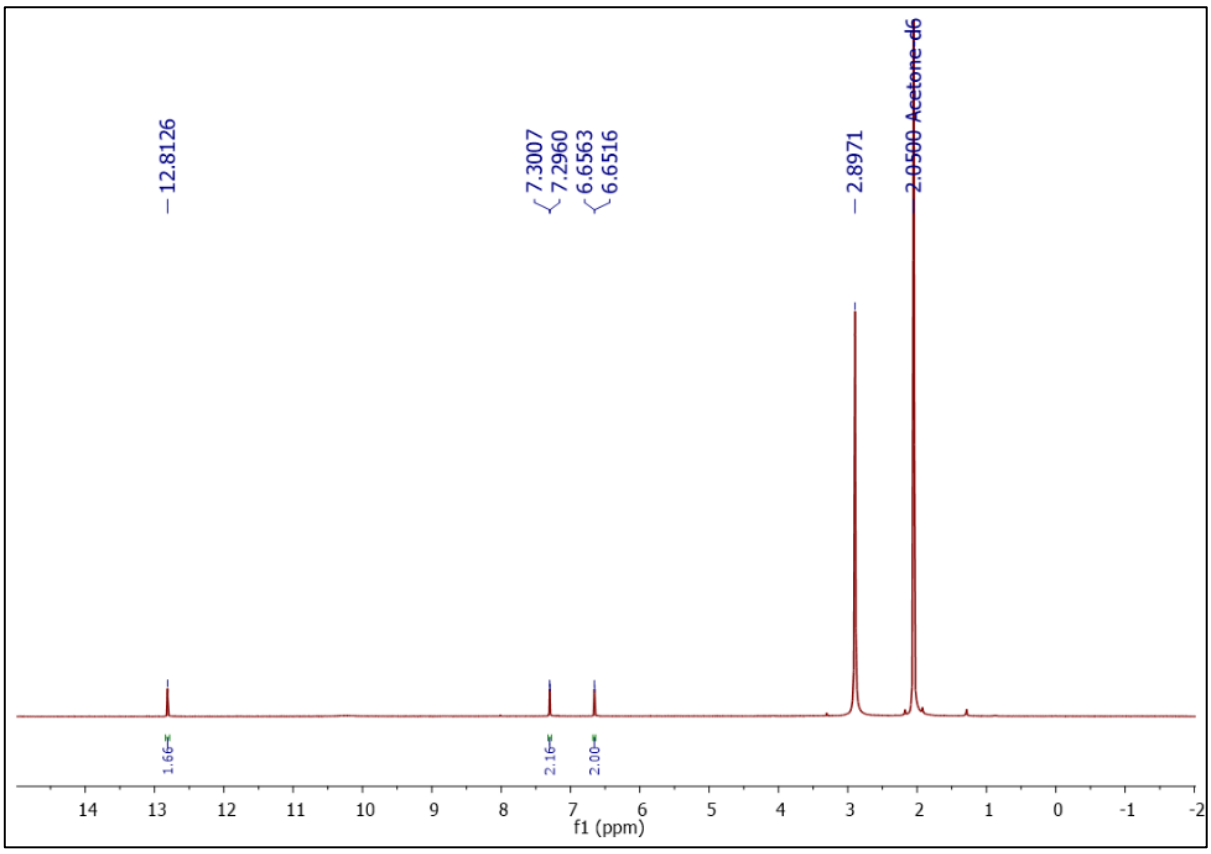

Figure 3. ^{1}H-NMR spectrum (500 MHz, acetone-d_6) of compound **1**

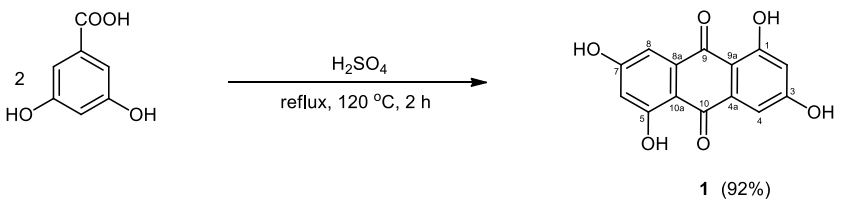

Figure 4. Synthesis of 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**)

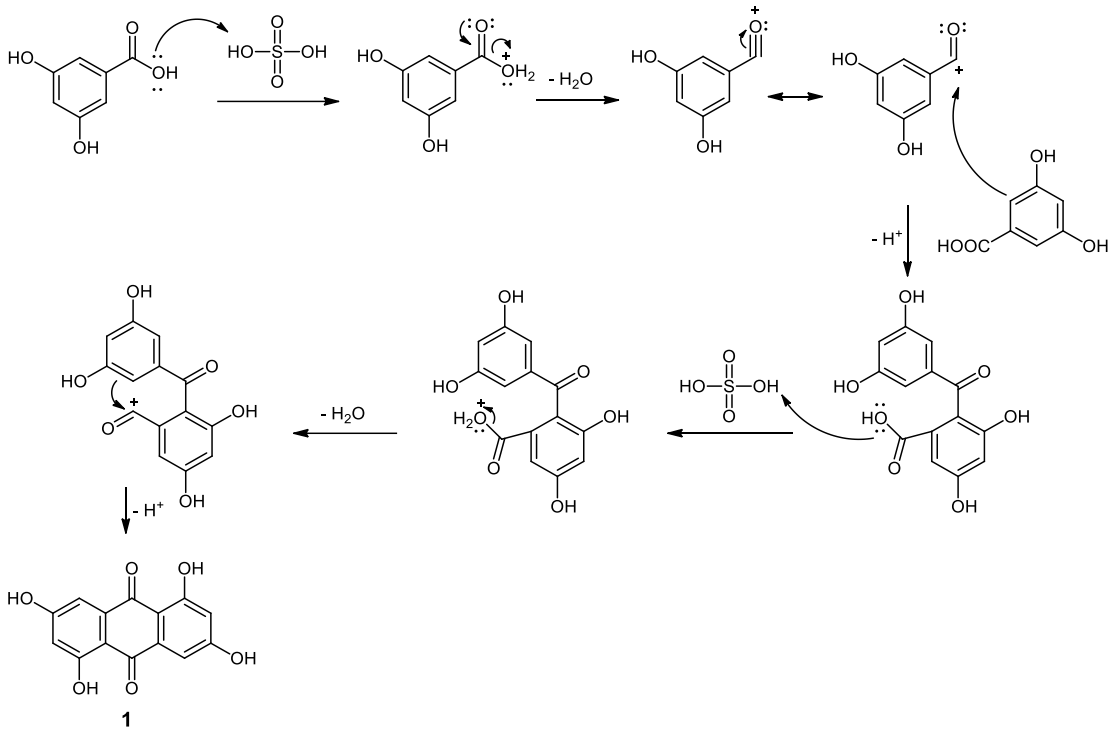

Figure 5. Proposed mechanism of 3,5-dihydroxybenzoic acid condensation reaction

The mechanism of the 3,5-dihydroxybenzoic acid condensation reaction is estimated to occur as in **Figure 5**. First, the concentrated sulfuric acid protonates oxygen-hydroxy from carboxylic acids, forming hydronium ions. Furthermore, the release of water molecules (dehydration) occurs so that oxonium ions are produced. The resonance of oxonium ions produces acylium ions, a stable carbocation. The acylium ions act as electrophiles against other 3,5-dihydroxybenzoic acid molecules. Electrophilic substitution takes place at C-2, which is the *ortho*- and *para*- positions of the two hydroxy groups of the 3,5-dihydroxybenzoic acid. Furthermore, protonation, dehydration and cyclization occur again to form 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**).

Compound 2

Compound **2** is a brown solid with a melting point above 300 °C. Based on the results of mass spectrum measurements of HR-ESI-MS, this compound shows $[M+H]^+$ ion at m/z 259.0612, which corresponds to the molecular formula $C_{14}H_{10}O_5$ (calculation $[M+H]^+$ 259.0606). The ^{13}C-NMR spectrum of compound **2** (**Figure 6**) shows one ketone signal (δ_C 188.8 ppm) and methylene carbon (δ_C 27.8 ppm), indicating that one of the two ketone groups of compound **1** has been reduced. It was confirmed by the presence of one OH-chelate signal (δ_H 13.43 ppm), three OH-phenol signals (δ_H 8.62; 9.04 and 9.53 ppm) and one methylene proton singlet signal (δ_H 4.06 ppm) on the ^{1}H-NMR spectrum (**Figure 7**).

Further evidence regarding the structure of compound **2** was obtained from a long-distance correlation of ^{1}H-^{13}C on the HMBC spectrum. Based on the spectroscopic analysis data (**Table 1**), it suggested that compound **2** is 1,3,5,7-tetrahydroxy-10*H*-anthracene-9-one.

Reduction of 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**) with $SnCl_2$ in HCl-HOAc obtained 74 mg of anthrone derivative, 1,3,5,7-tetrahydroxy-10*H*-anthracene-9-one (**2**) with a yield of 77% (**Figure 8**). The reagent $SnCl_2$ reduces only one of the two ketone groups in compound **1** to a hydrocarbon. Prinz *et al.* (1996) also used this reagent to selectively reduce other anthraquinone derivatives to anthrone with a yield range of 34-71%. Although several other reduction agents like $NaBH_4$ and $LiAlH_4$ reduce anthraquinone, they do not produce an anthrone but dihydroanthracene-9,10-diol and 9,10-dihydroanthracene (Criswell & Klanderman, 1974; Shyamasundar & Caluwe, 1981).

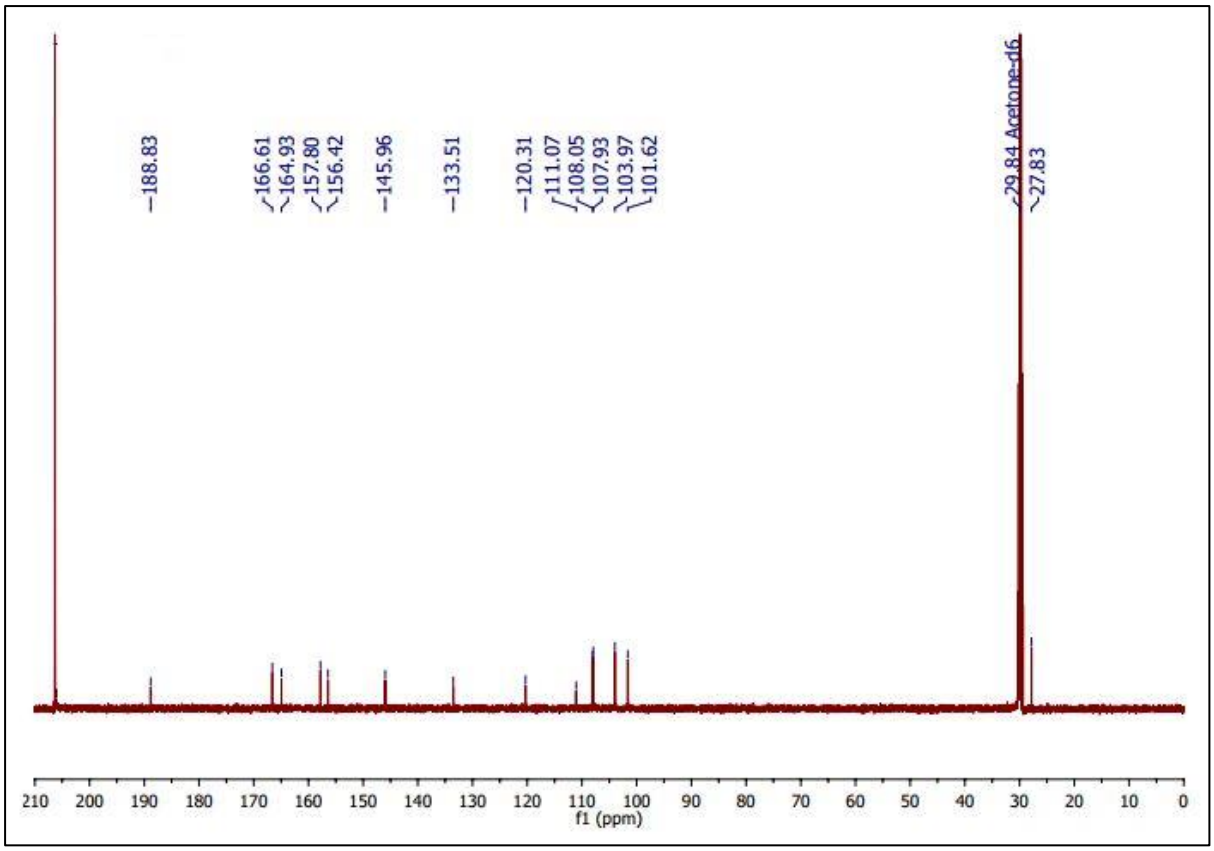

Figure 6. ^{13}C-NMR spectrum (125 MHz, acetone-d_6) of compound **2**

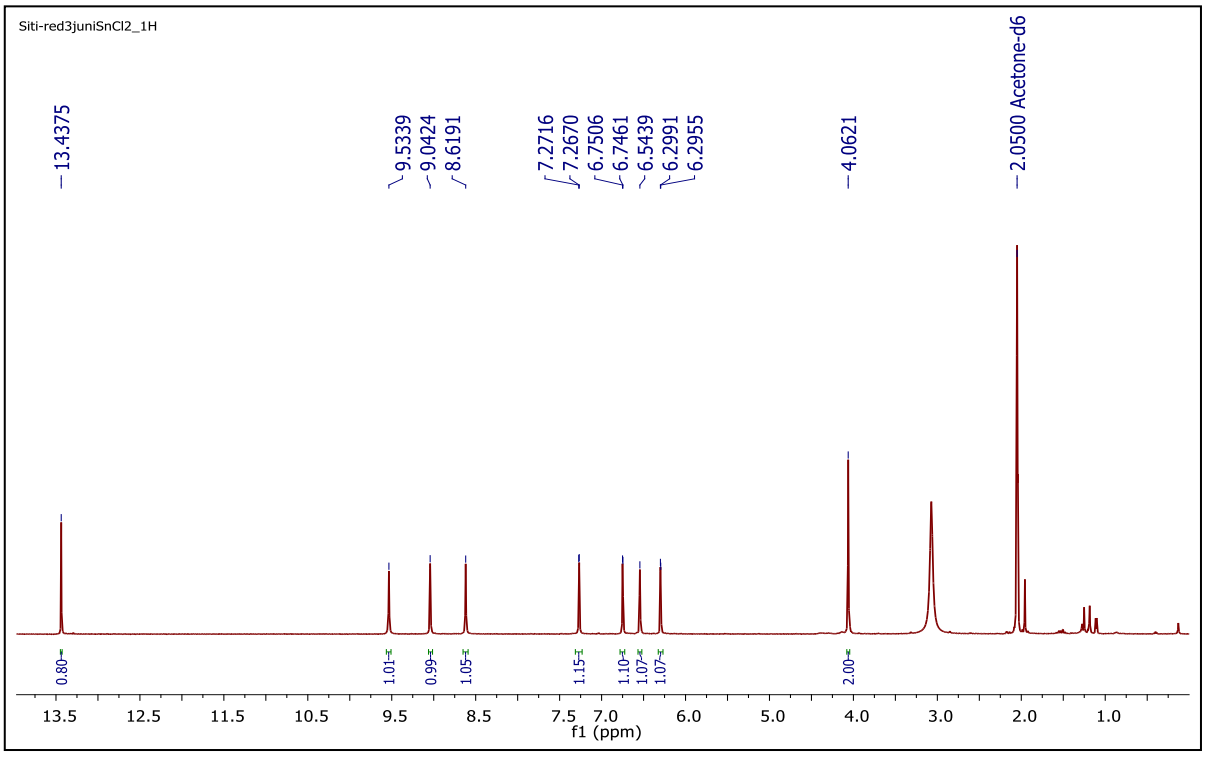

Figure 7. ^{1}H-NMR spectrum (500 MHz, acetone-d_6) of compound **2**

Table 1. NMR spectrum data of compound **2** in acetone-d_6

No. C	δ_H ppm (multiplicity, *J* Hz)	δ_C ppm	HMBC ($^1H \leftrightarrow {}^{13}C$)
1-OH	13.43 (*s*)	166.6	C-1, C-2, C-9a
2	6.30 (*d*, 1.8)	101.6	C-1, C-3, C-4, C-9a
3-OH	9.53 (*s*)	164.9	C-2, C-3, C-4
4	6.54 (*d*, 1.8)	107.9	C-2, C-3, C-9a, C-10
4a	-	146.0	-
5-OH	9.04 (*s*)	156.4	C-5, C-6, C-10a
6	6.74 (*d*, 2.3)	108.1	C-5, C-7, C-8, C-10a
7-OH	8.62 (*s*)	157.8	C-6, C-7, C-8
8	7.27 (*d*, 2.3)	104.0	C-6, C-7, C-9, C-10a
8a	-	133.5	-
9	-	188.8	-
9a	-	111.1	-
10	4.06 (*s*)	27.8	C-4, C-4a, C-5, C-8a, C-9a, C-10a
10a	-	120.3	-

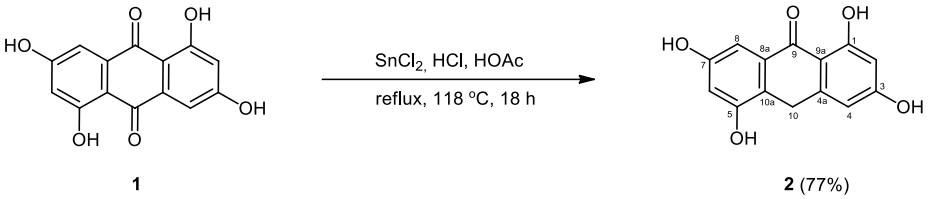

Figure 8. Synthesis of 1,3,5,7-tetrahydroxy-10*H*- anthracene-9-one (**2**)

Compound 3

Compound **3** is a black solid with a melting point of 105-106 °C. The ^{13}C-NMR spectrum (**Figure 9**) shows that there are 18 carbon signals, including five carbon oxyaryl signals (δ_C 150.1; 154.1; 156.8; 157.3 and 157.7 ppm) and four methoxy carbon signals (δ_C 55.4; 55.6; 55.9 and 63.0 ppm). The presence of four methoxy groups is confirmed by the appearance of four singlet signals (δ_H 3.91, 3.97, 4.03 and 4.11 ppm) in the ^{1}H-NMR spectrum (**Figure 10**). The ^{1}H-NMR spectrum also showed the presence of a singlet signal from the OH-phenol group at δ_H 9.76 ppm and a singlet signal from methine protons at δ_H 8.36 ppm.

The positions of the methoxy and hydroxy groups were determined based on a correlation of ^{1}H-^{13}C on the HMBC, HSQC and NOESY spectra. Based on the analysis of these spectroscopic data (**Table 2**), compound **3** is suggested to have a structure of 1-hydroxy-3,5,7,9-tetramethoxyantrachene.

Alkylation of functional groups is carried out in order to create a derivative of a compound and protection of functional groups. The alkylation of 1,3,5,7-tetrahydroxy-10*H*-anthracene-9-one (**2**) with dimethyl sulfate and K_2CO_3 obtained a tetramethylated product 1-hydroxy-3,5,7,9-tetramethoxyanthracene (**3**) of 20 mg with a yield of 16%. The yield obtained is relatively small, this could be due to side reactions so that the synthesis of compound **3** did not run perfectly. The synthesis reaction of compound **3** is shown in **Figure 11**. It explains compound **2** (enone) tautomer equilibrium with **2a** (enol). The enone form (**2**) is preferred over its enol form (**2a**) because the hydrogen chelate bond with the carbonyl group is stronger than the hydroxy group. However, the solvent also influences the ratio of enone to enol. Solvents that can be acceptors of hydrogen bonds raise the amount of enol in equilibrium (Korth & Mulder, 2013). In this study, an acetone solvent was used, an acceptor of hydrogen bonds, so that compound **2** is possible in its enol form (**2a**).

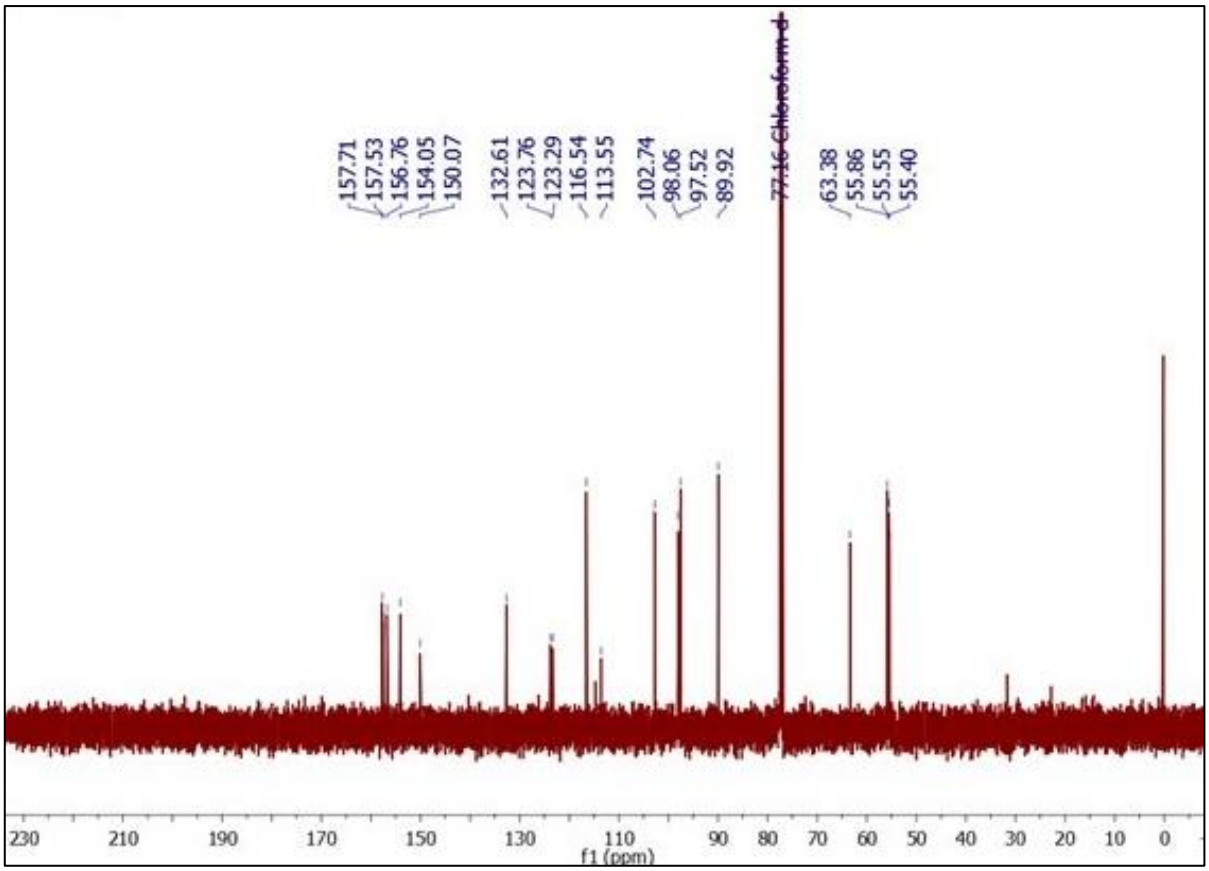

Figure 9. ^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of compound **3**

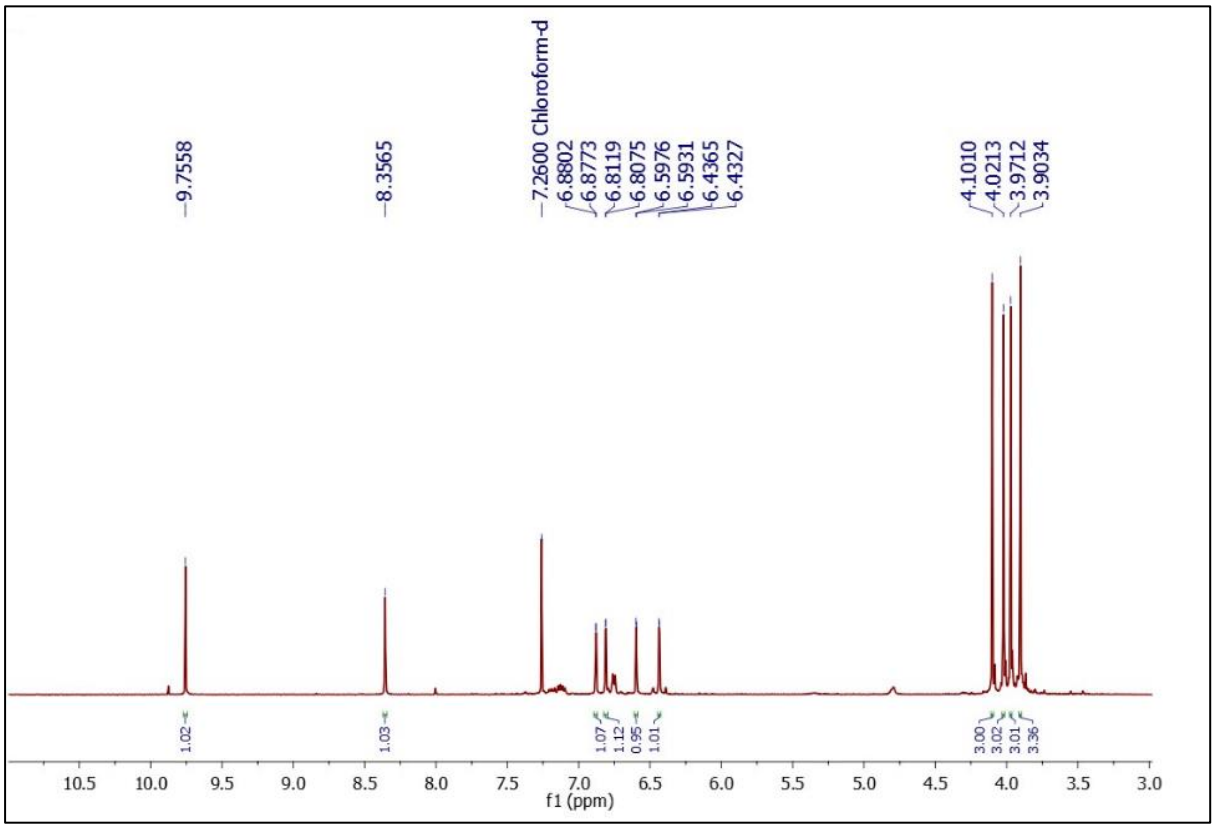

Figure 10. ^{1}H-NMR spectrum (500 MHz, $CDCl_3$) of compound **3**

Table 2. NMR spectrum data of compound **3** in $CDCl_3$

No. C	δ_H ppm (multiplicity, *J* Hz)	δ_C ppm	HMBC ($^1H \leftrightarrow {}^{13}C$)
1-OH	9.76 (*s*)	154.1	C-1, C-2, C-9a
2	6.60 (*d*, 2,2)	102.7	C-1, C-3, C-4, C-9a
3	-	157.7	-
4	6.82 (*d*, 2,2)	97.5	C-2, C-3, C-9a, C-10
4a	-	132.6	-
5	-	156.8	-
6	6.44 (*d*, 1.9)	98.1	C-5, C-7, C-8, C-10a
7	-	157.3	-
8	6.89 (*d*, 1.5)	89.9	C-6, C-7, C-9, C-10a
8a	-	123.3	-
9	-	150.1	-
9a	-	113.5	-
10	8.36 (*s*)	116.5	C-4, C-5, C-8a, C-9a
10a	-	123.8	-
11	3.91 (*s*)	55.6	C-3
12	4.03 (*s*)	55.9	C-5
13	3.97 (*s*)	55.4	C-7
14	4.11 (*s*)	63.0	C-9

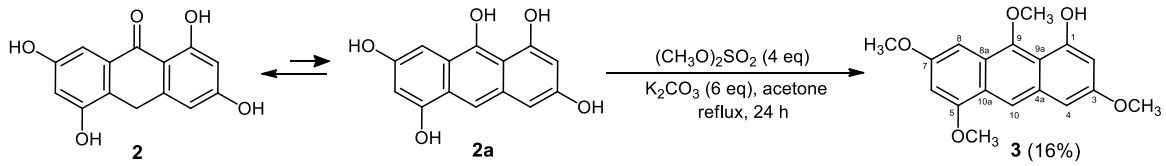

Figure 11. Synthesis of 1-hydroxy-3,5,7,9-tetramethoxyanthracene (**3**)

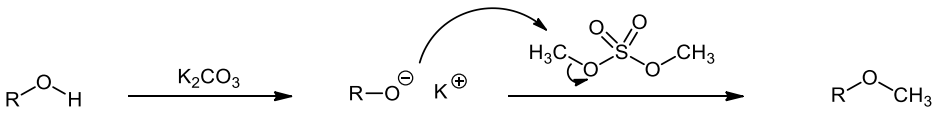

Figure 12. Methylation reaction mechanism of alcohol

The mechanism of alkylation with dimethyl sulfate (**Figure 12**) is the Williamson ether formation reaction through the S_N2 reaction (Solomon & Fryhle, 2011). The alcohol compound reacts with K_2CO_3 to form alkoxide ions. Then, alkoxide ions attack the carbon atom on dimethyl sulfate, simultaneously releasing methyl sulfate ions as a leaving group to obtain methyl ether products.

Antibacterial Activity

The three synthesized compounds were tested for the bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi* using the microdilution method. Their MIC values show the synthesized compounds' ability to inhibit bacterial growth. The smaller the MIC value means the higher its antibacterial activity. The results of antibacterial tests of synthesized compounds are shown in **Table 3**.

The antibacterial activity of the three synthesized compounds was lower than the positive control of chloramphenicol. The activity of compound **2** against *S. aureus*, with a MIC value of 37.5 µg/mL, is higher than compound **1**. The compound **2** structure exhibited the ketone group in C-10 has been reduced to methylene. It is suspected that a methylene group in C-10 can increase activity against *S. aureus*. Next, when compound **3** and compound **2** are compared to their activity against the four bacteria, the activity of compound **3** is higher except for *S. aureus*. It indicates that the presence of four methoxy groups in anthrone compounds increases activity against *B. subtilis*, *E. coli* and *S. typhi* but decreases activity against *S. aureus*.

Table 3. MIC value of the synthesized compounds

Compound	MIC value (µg/mL)			
	B. subtilis	***S. aureus***	***E. coli***	***S. typhi***
1,3,5,7-Tetrahydroxy-9,10-anthraquinone (**1**)	75	75	75	75
1,3,5,7-Tetrahydroxy-10*H*-anthracene-9-one (**2**)	75	37.5	75	75
1-Hydroxy-3,5,7,9-tetramethoxyanthracene (**3**)	37.5	75	37.5	37.5
Chloramphenicol	**9.38**	**9.38**	**9.38**	**4.69**

4. CONCLUSIONS

Synthesis of 1,3,5,7-tetrahydroxy-9,10-anthraquinone (**1**) and two anthrone derivatives 1,3,5,7-tetrahydroxy-10*H*-anthracene-9-on (**2**) and 1-hydroxy-3,5,7,9-tetramethoxyanthracene (**3**) has been successfully carried out. Compound **3** exhibits moderate activity against *B. subtilis*, *E. coli* and *S. typhi*, while compound **2** shows moderate activity against *S. aureus*. Compound **1** has weak activity against the four test bacteria.

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