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Synthesis 4-Piperoilmorpholine from Piperine

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Abstract. Piperine was isolated from black pepper by soxhletation method using technical grade ethanol as a solvent. This compound was used as precursor for the synthesis of 4-piperoilmorpholine. The synthesis was carried out via a pre-target piperoilchloride, where the piperine was initially hydrolyzed using KOH ethanolate for 24 hours, added SOCl₂ and then mixed with morpholine at 0-5° C. The result of synthesis was obtained 4-piperoilmorpholine with yield of 40,80%.

1. Introduction

Pepper plant (*Piper nigrum*, Linn), is one of the natural sources of several alkaloid substances such as piperine, chavicine, and piperittine, as well as non-alkaloid substances such as dienamide, trienamide, volatile oil, and cytosterol. The compound contained in the fruit with the highest content is piperine [1]. Considering the enormous potential of compounds found in pepper fruit, in this study, piperoil morpholine, which is belongs to amide compounds, was synthesized from piperine isolated from black pepper fruit. The synthesis of piperoil morpholine was proposed since amide compounds have been known to exhibit bioactivity [2-6].

So far, pepper is only used as a spice and traditional medicine, and research on the use of bioactive compounds contained in pepper fruit as insecticides is still very limited. The use of natural ingredients contained in pepper fruit is a diversification from the use of pepper fruit, so that it will further increase the economic value of pepper fruit, of course this will improve the welfare of pepper farmers. The use of natural ingredients in agriculture, especially as pesticides will be very helpful in increasing the productivity of Indonesian people whose livelihoods are mostly farming.

Insecticide bioactivity tests was carried out on cabbage pests that attack many vegetables such as cabbage, mustard greens, spinach, and kale. If the activity data is known and obtained, it will be very useful and plays an important role not only in the fields of chemistry and biology, but also will play an important role in agriculture, pharmacy and medicine. This research was proposed as an alternative to look for new compounds from piperine derivatives. The use of piperine compounds in Indonesia in biological tests has not been widely developed, so this is a separate and interesting challenge to find out the results.

In a previous study that had been carried out in our study group, it was found that alkaloid compounds, especially piperine isolated from black pepper fruit, had activeness as insecticides against warehouse pests and pests that attacked spinach and cabbage [2-3]. While amide compounds synthesized from piperine have never been tested for biological activity, so this research will be very



interesting and important especially for the development of chemistry in particular and become the basis for the use of the development of agricultural, biological, pharmaceutical and medical sciences. Formulations and combinations of several isolation compounds and synthesis results that lead to hybrid synthesis are a new breakthrough in the search for medicinal raw materials and vegetable insecticides [7-9].

2. Materials and Methods

The sample used in this study was black pepper fruit (*Piper nigrum*, Linn) obtained from pepper plantations in Baradatu district, Way Kanan Regency. Before use, black pepper fruit is first dried and mashed using porcelain. The black pepper fine powder that has been prepared is wrapped in filter paper, formed in a cylinder whose size is adjusted to the size of the soxhlet extraction used. After everything settles then filtered in the normal way and the filtrate is left overnight for a shiny yellow crystal needle. The crystal is filtered with a Buchner funnel and washed with a little technical ethanol until pure, so that it is obtained by pure piperine crystals [7, 10]. The crystals were then tested for their melting point and treated with TLC. Hydrolysis piperine to obtain piperic acid carried out by piperine refluxed for 95 minutes using KOH ethanolate 10% as much as 100 ml. The reflux solution is concentrated with an evaporative rotary device and the residue obtained is cooled in ice. The residue obtained was suspended with hot water in a water bath, then acidified with 6 N HCl to pH 3. Then recrystallized with technical ethanol and left overnight. Piperic acid as much as 0.0046 mol (1 g) in a round flask was suspended in dry chloroform (10 ml), then spiked with thionylchloride (0.4 ml) and dimethylformamide (5 drops), then heated with hot water in a water bath temperature of 50 °C and occasionally rocked. At the beginning of the reaction bubbles will arise, after being reduced then the reaction mixture is refluxed at boiling point (60 °C). After the SO₂ and HCl gases run out (tested with litmus paper) the reaction results are cooled down [11].

Synthesis of 4-piperoilmorpholine

A solution containing 0.0092 mol (0.79 ml) morpholine in chloroform is cooled at 0-5° C in a container containing ice water. Then the piperoilchloride-containing solution that has been made before is dripped slowly through a separating funnel while stirring. The reaction temperature was maintained between 0-5° C for 30 minutes after the addition of all piperoilchloride and stirring continued. The precipitate formed is separated from the filtrate, then boiled with water for several minutes and the insoluble solid is filtered with a Buchner funnel, then recrystallized with methanol solvent. The filtrate was extracted using 2 ml of 10% HCl and then washed several times with water until the pH approached [11]. The precipitate formed was filtered, recrystallized with methanol solvent, and tested by TLC. Against crystals obtained are examined for the determination of their structure.

3. Results and discussion

3.1 Isolation of Piperine

The extraction of piperine compounds from black pepper fruit was carried out using soxhlet and technical ethanol solvents. The residue obtained is cooled at room temperature. To separate the glycosides which were extracted, the evaporator residue was cooled and then 10% KOH ethanolate was added. The obtained filtrate is left overnight for a shiny yellow needle crystal. The yellow crystals washed with technical ethanol and recrystallized with ethanol. The melting point of the crystals isolated from 128.0-129.0 °C. The structure was traced to crystals by mass (figure 1), ultraviolet, and infrared spectroscopy. Piperine gave the mass spectrum with the peak of the M + = 285 (73.9%) molecular ion, and the base peak appeared in m / e = 201 (100%) which corresponded to piperine. The peaks of the fragment ions which appear at m / e = 256 (2.1%), m / e = 173 (38.95%), m / e = 143 (23,

16%), $m/e = 115$ (60.53%), $m/e = 89$ (8.42%), $m/e = 84$ (20.53%), $m/e = 637.37$), and $m/e = 41$ (8.42 %).

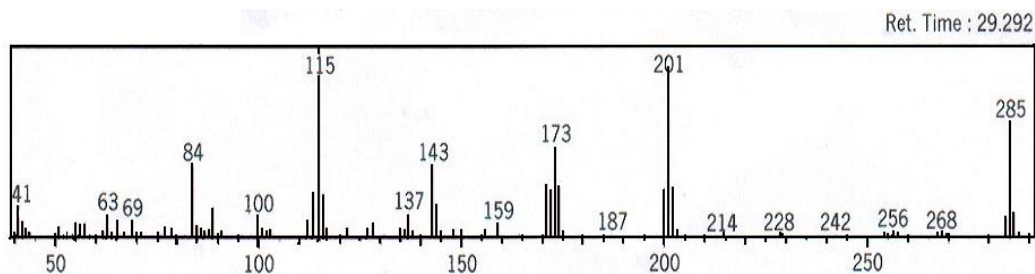


Figure 1. mass spectrum of piperine

The uv spectrum obtained (figure 2) shows peaks at maximum wavelengths of 208.0 nm, 254.0 nm, 308.0 nm, and 342.0 nm. The peak at 208.0 and 254.0 nm wavelengths is referred to as benzenoid uptake, while the bands at wavelengths 308.0 and 342.0 nm are conjugated carbonyl uptake by diene bound to benzene and the methylenedioxy substituents in the meta and para positions (effect resonance).

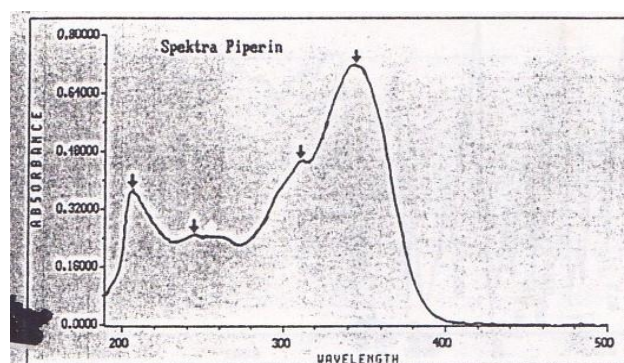


Figure 2. Uv spectrum of piperine

Tracing with the infrared spectrometer shows the spectrum (figure 3) detailed as follows: the strong absorption peak in the area of 1638.6 cm^{-1} is the characteristic absorption for stretch vibration of C = O carbonyl, the vibration of CO-N amide stretch occurs in the area of 1490.9 cm^{-1} (s). Weak uptake in the area of 3008.7 cm^{-1} is a characteristic absorption for the aromatic CH strain, this assumption is reinforced by the presence of strong absorption in the area of $846.7\text{-}785.0 \text{ cm}^{-1}$ which is a characteristic absorption for CH strain of the conjugated aromatic system. Medium uptake in the area $2939.3\text{-}2802.4 \text{ cm}^{-1}$ is characteristic for aliphatic C-H strain.

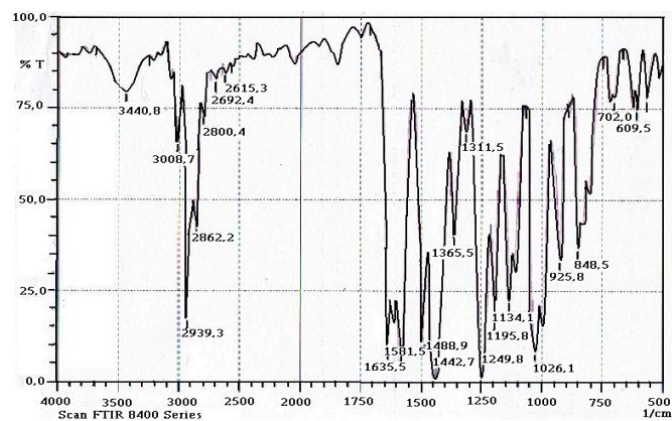


Figure 3. FT IR spectrum of piperine

3.2 Hydrolysis of piperine

The piper obtained from pepper fruit was hydrolyzed with 10% KOH ethanolate for 24 hours. After acidification, the precipitate obtained was filtered and recrystallized with ethanol (p.a.). In the recrystallization process, the filtrate was examined by TLC. The crystalline melting point obtained was measured by the Fisher-John Melting Point, that was 217.2-218°C. Ultraviolet spectra of piperic acid (figure 4) show absorption bands at maximum wavelengths of 204.0 nm, 230.0 nm, 304.0 nm, and 332.0 nm. This spectrum is not much different from what has been reported by previous researchers. The band at a wavelength of 204.0 nm and 230.0 nm is referred to as benzenoid uptake. In the ultraviolet spectrum the piperine benzenoid bands appear at wavelengths 206.0 nm and 224.0 nm.

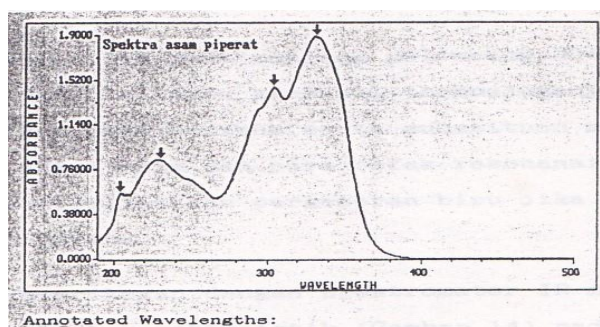


Figure 4. Uv spectrum of piperic acid

Analysis with an IR spectrometer (figure 5) gives characteristic peaks. The presence of hydroxyl groups of carboxylic acids is seen in weak absorption (w) which spreads in the area of $3600\text{--}3200\text{ cm}^{-1}$. This absorption band is not strong because it forms a hydrogen bond (dimer) between two carboxylic acid molecules. This assumption is strengthened by the presence of wide absorption in the $2700\text{--}2300\text{ cm}^{-1}$ medium (m) area which is related to the aliphatic C-H strain, this absorption is typical for carboxylic acid dimers. Furthermore, the strong band at 1674.1 cm^{-1} is characteristic of the strain $\text{C}=\text{O}$ of the conjugated acid. Medium bands in the area of 3000 cm^{-1} and 2922.0 cm^{-1} are characteristic absorption for aromatic CH, this assumption is reinforced by the absorption at 1598.9 cm^{-1} (strain $\text{C}=\text{C}$ aromatic) and strong bands (s) in the area of $850\text{--}500\text{ cm}^{-1}$ the characteristics for external bending of CH midwives from substituted benzene. Furthermore, the stretching vibration of the C-O-Ar methylenedioxy group appears in the area of 1255.6 cm^{-1} (s) (symmetric) and 1035.7 cm^{-1} (s) (asymmetric).

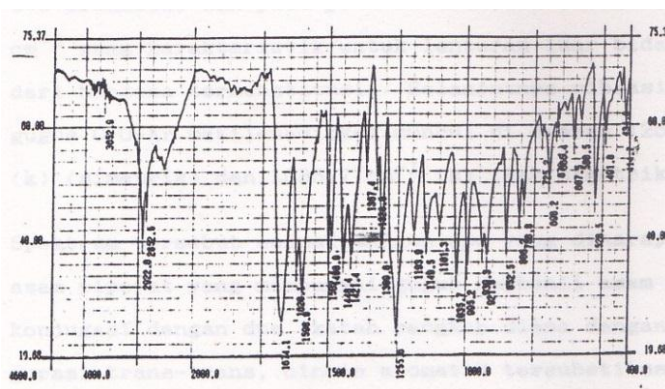


Figure 5. FT-IR spektrum of piperic acid

3.3. Synthesis of 4-piperoilmorpholine through pre-target Piperoilchloride

Synthesis of 4-piperoilmorpholine compounds is carried out through pre-target piperoilchloride. Piperoilchloride compounds are reactive compounds, can react with water to form piperic acid. To prevent the hydrolysis reaction from occurring, the synthesis is carried out in a water-free state. This

reaction of 4-piperoilmorpholine formation follows the nucleophilic chloride addition elimination reaction mechanism (figure 6). Synthesis through piperoilchloride pre-targets takes place easily without the need for a catalyst, even at 0-5°C. Besides that hydrogen chloride gas produced during the reaction can be separated easily. The precipitate obtained from the reaction was recrystallized by methanol p.a.

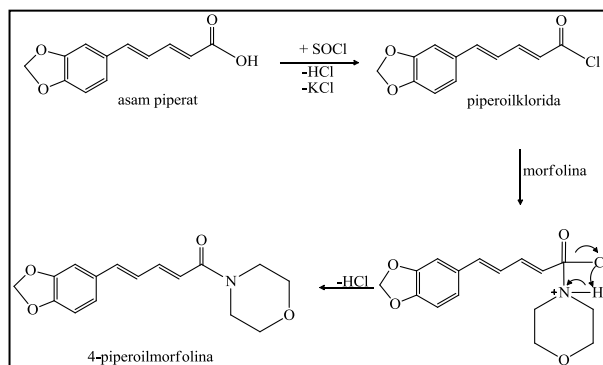


Figure 6. Mechanism of 4-piperoil morpholine synthesis [11, 12]

The crystal obtained in the form of needle is smooth reddish brown with a melting point of 147.3-148°C, greater than piperina (128-129°C). Measurement by GC-MS obtained the peak of the molecular ion (figure 7) at $m/e = 287$ (38.39%) and the base peak at $m/e = 201$ (100%), besides that the peaks of the fragment ion in $m/e = 173$ (35.8%), $m/e = 143$ (20.8%), $m/e = 115$ (40.1%), $m/e = 55$ (17.5%), and $m/e = 40$ (47.2%). This spectrum supports the estimation that the synthesized compound is 4-piperoilmorpholine.

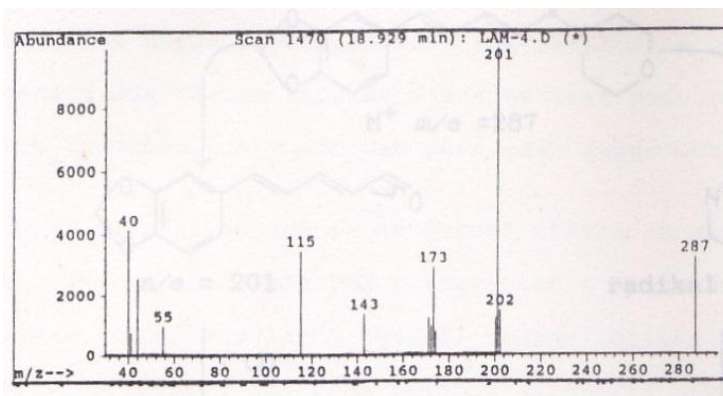


Figure 7. GC-MS of 4-piperoil morpholine

The molecular ion peak at $m/e = 287$ is the molecular weight of the 4-piperoilmorfolina compound. The base peak in $m/e = 201$ is the target compound minus 86, namely the release of radical morfolina. The ion at $m/e = 173$ is suitable for the release of the radical $C = O$ from the fragment ion $m/e = 201$, the ion at $m/e = 143$ is suitable for the release of formaldehyde from the ion at $m/e = 173$. Ion at $m/e = 115$ according to the radical removal: $C = O$ from the fragment ion at $m/e = 143$. Then the ion at $m/e = 55$ is suitable for the release of formaldehyde from the morpholine radical and the ion at $m/e = 40$ according to the release of the CH_3 group of ions in $m/e = 55$.

The synthesized compound in the methanol solvent showed absorption bands (figure 8) at maximum wavelengths of 202.1 nm, 243.0 nm, 310.3 nm, and 335.9 nm. Bands at wavelengths of 202.1 nm and 243.0 nm are referred to as benzenoid absorption bands, while absorption bands at wavelengths of 310.3 nm and 335.9 nm are absorption of conjugated carbonyl amides by diene which are bound to benzene and substituent methylenedioxy in position. meta and para (resonance effect).

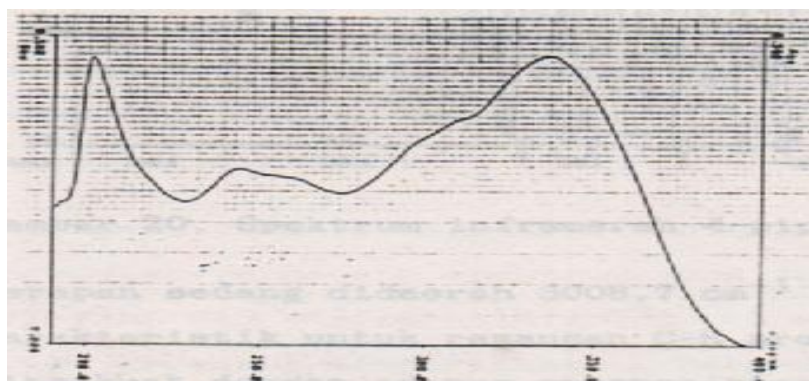


Figure 8. Uv spectrum of 4-piperoil morpholine

Analysis with an IR spectrometer (figure 9) gives characteristic peaks. The strong absorption peak at 1633.6 cm^{-1} is the characteristic absorption for stretch vibration of C = O carbonyl, the CON amide stretch vibration appears in the area of 1490.9 cm^{-1} (s). Medium uptake in the area of 3008.7 cm^{-1} is a characteristic absorption for aromatic C-H strain, this assumption is reinforced by the presence of strong absorption in the area of $846.7\text{-}785.0\text{ cm}^{-1}$ which is a characteristic absorption for C-H flexural from a conjugated aromatic system. Moderate uptake in regions $3000.0\text{-}2700.0\text{ cm}^{-1}$ characteristic for aliphatic C-H strain.

Furthermore, the extension of the CO-Ar methylenedioxy group is shown by absorption in the area of 1251.7 cm^{-1} (not symmetric) and 1031.8 cm^{-1} (symmetric), the band at $1610.5\text{-}1583.4\text{ cm}^{-1}$ (s) characteristic for stretch vibration $\text{-C} = \text{CC} = \text{C-}$ (trans-trans) from the conjugated unsaturated carbonyl system. Furthermore, aliphatic ether C-O-C stretching vibration appears at 1112.9 cm^{-1} (s) (symmetric) and 1070.4 cm^{-1} (s) (asymmetric). The infrared spectrum is as expected from 4-piperoilmorpholine having an unsaturated carbonyl amide group which conjugates with two diene double bonds with a trans-trans configuration, a meta-substituted aromatic ring and para, and a methylenedioxy group. It also has an aliphatic ether group.

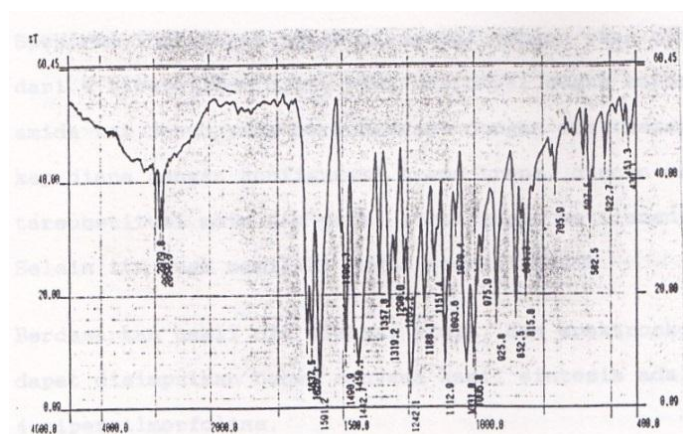


Figure 9. FT-IR spectrum of 4-piperoil morpholine

4. Conclusions

Based on the results of physical, chemical and spectroscopic measurement, it can be concluded that the synthesized compound is an alkaloid, namely 4-piperoilmorpholine.

Acknowledgments

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