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Alkylation of Theobromine: Preparation of Isopropyl and *sec*-butyl-theobromines using *N*, *N*-dimethylformamide as Solvent

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Abstract : N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine were synthesized via nucleophilic substitution reaction by reacting theobromine and two kind of alkyl bromide derivatives, i.e. isopropyl bromide and *sec*-butyl bromide using *N*, *N*- dimethylformamide (DMF) as a solvent. Yields (N^1-isopropyltheobromine = 7.70%; N^1-*sec*-butyltheobromine = 5.89%) were slightly less than the previous synthesis which used ethanol-water (10%) as a solvent.

Key words: N^1-isopropyltheobromine, N^1-*sec*-butyltheobromine, dimethylformamide

Abstrak : N^1-isopropyltheobromine dan N^1-*sec*-butyltheobromine telah disintesiskan melalui tindakbalas penggantian nukleofil antara teobromin dengan terbitan alkyl bromide, ialah isopropyl bromide dan *sec*-butyl bromide menggunakan *N*, *N*-dimethylformamid sebagai pelarut. Kedua-dua sebatian diperolehi dalam jisim yang rendah (N^1-isopropyltheobromine = 7.70%; N^1-*sec*-butyltheobromine = 5.9%) berbanding dengan sintesis sebelumnya yang menggunakan pelarut ethanol-air (10%).

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Introduction

Xanthine (3,7-dihydro-purine-2,6-one) is an alkaloid which has a weak base character. There are three main xanthin derivatives, i.e. caffeine, theophyline, and theobromine. Theophylin has been used as a bronchodilator in asthmatic disease treatment, but it has a strong stimulant effect to the central nervous system (CNS). Theobromine (3,7-dimethylxanthine) is one of the xanthine derivatives that has a weak stimulant effect to the CNS but it still has bronchodilatation activity although not as strong as theophylline [1,2].

In 1985, there were disclosed theobromin derivatives wherein theobromine was substituted at the 1 position with substituted piperazino, homopiperazino and piperidino groups, and pharmacologically acceptable acid addition salts thereof. The compounds exhibited vasodilating, psychotropic and analgesic activities [3,4]. Other alkyl-xanthine derivatives were synthesized and examined as bronchodilating agent, i.e. 1-methyl-3-propylxanthine in 1988 [5].

Further study in 2000s showed that the lower alkylation of N^1-theobromine provided its tracheospasmolytic activity on new guinea pig *in vitro* induced by histamine. The synthetic products are N^1-*n*-propyltheobromine, N^1-*n*-butyltheobromine, N^1-*n*-amyltheobromine, N^1-isopropyltheobromine, and N^1-*sec*-butyltheobromine. Among the five of these alkyltheobromine derivatives, N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine showed two of the best tracheospasmolytic activities. The reaction was carried out by refluxing theobromine and alkyl halide derivatives using ethanol-water as a solvent and NaOH as catalyst for 24 hours. Unfortunately, the yields were not satisfactorily obtained yet in both the normal alkyl chain substitution (± 30%) and the branched alkyl one (± 10%) [6,7]. The use of a polar aprotic solvent such as DMF was well-known in alkylation of *N*-benzylphtalimide that presented a higher yield (60%) than the such analogues synthesis method using ethanol-water mentioned above [8] .

In this present study, N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine were synthesized by reacting theobromine with isopropyl bromide for the first compound and used *sec*-butyl bromide for the second one. The method was similar with the previous synthesis but the solvent used was DMF which is a polar aprotic solvent and often used as a medium during S_N2 reaction. It has been known that secondary alkyl halides such as isopropyl

bromide and *sec*-butyl bromide can be substituted via both of S_N2 and S_N1 reactions depending on the medium. When the reaction was in a polar aprotic solvent such as DMF, DMSO, acetonitrile, etc., a S_N2 reaction occurred while the use of a polar protic solvent such as water and ethanol will make it S_N1 reaction [9]. The aim of this study was to synthesize N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine using DMF as the solvent. It was predicted that the use of DMF as a solvent might enhance the yields and that secondary alkyl halide substituted by theobromine would occur (S_N2 reaction).

Material and Method

Reagents and apparatus

All reagents used were analytical grade. Theobromine, isopropyl bromide, *sec*-butyl bromide (Aldrich Sigma); DMF, NaOH, ethanol, chloroform, ethyl acetate, silica gel F_{254} plate and powder (Merck); distilled water (Bratachem Indonesia); N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine (product synthesized by Hariono, *et al*., 2007 was used as referrence); glassware (Pyrex); rotary evaporator (Heidolph VB 2000, German); melting point apparatus (MELT-TEMP pyrometer digital 1202D); UV-Visible spectrophotometer (Spectronic UV-Vis Shimadzu 1240); IR spectrophotometer (Shimadzu FTIR- 820 IPC); ^{1}H-NMR spectrometer (JNM – PMX 5O High Resolution NMR, Instrument JEOL Ltd.); GC-MS (Shimadzu OP 5000)

Synthesis of N^1-isopropyl and N^1-*sec*-butyltheobromines

The synthesis of N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine from the corresponding alkyl halide compounds were carried out according to the general procedure described below.

In the three necks rounded bottom flask, theobromine (11 mmol) was suspended by DMF (25 ml) and NaOH 1N in the DMF (15 ml). The mixture was refluxed at 100^{o}C and then the alkyl halide (18 mmol) was dropped gradually over about 1 hour and heating was continued while checking the completed reaction using Thin Layer Chromatography (TLC) prepared using silica F_{254} and chloroform-ethyl acetate (1.5: 3.5). The reflux was stopped after 24 hours. The product was isolated using liquid-liquid extraction since the theobromine spot was still presented.

Isolation and Purification

The mixture was poured into a separating funnel and then extracted using 3x @30 ml of chloroform-ethanol (3:1). The chloroform phase was collected and evaporated by rotary evaporator until the concentrated extract to be obtained. The purity of theobromine was checked by TLC as mentioned above and found still contain theobromine, therefore needed further purification using preparative TLC. The spot band of the product was scrapped and dissolved into chloroform. After that, the solution was filtered and the filtrate was evaporated to be obtain the synthetic product. The crude products were 190 mg for N^1-isopropyltheobromine and 153 mg for N^1-*sec*-butyltheobromine.

Analysis

The product was analyzed by TLC (silica gel F_{254} and $CHCl_3$-ethyl acetate (1.5: 3.5)), melting point apparatus, UV, IR (KBr pellets), ^{1}H-NMR ($CDCl_3$; TMS) and GC (ODS ;150^{o}C) -MS (EI-MS) spectroscopy.

Results and Discussion

N^1-isopropyltheobromine

White powder, odorless, bitter; Yield 7.7%; R_f 0.28; R_t 7.098 min; m.p. 154-155^{o}C (literature value: 154-155^{o}C) ; λ_{max} 274 nm; IR spectrum (3109 cm^{-1}, 2939 cm^{-1}, 1662 cm^{-1}, 1380 cm^{-1}, 1238.2 cm^{-1}); ^{1}H-NMR spectrum (δ 1.5 ppm, *d*, 6H, *J* = 6.75 Hz; δ 2.1 ppm, s, 1H; δ 3.5 ppm, *s*, 3H, N^7-CH_3; δ 4.0 ppm, *s*, 3H, N^3-CH_3; δ 7.5 ppm, *s*, 1H, =CH); EI-MS (m/z 222; 180 (100%) ; 151; 137; 109; 42).

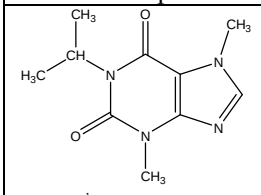
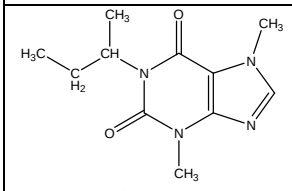
N^1-sec-butyltheobromine

White powder, odorless, bitter; Yield 5.9%: m.p. 112-113^{o}C (literature value: 112-113^{o}C); R_f 0.35); R_t (2.300 min; λ_{max} 274 nm; IR spectrum (3109 cm^{-1}, 2939 cm^{-1}, 1662 cm^{-1}, 1423 cm^{-1}, 1238 cm^{-1}); ^{1}H-NMR (δ 1.0 ppm, *t*, 3H, *J* = 7.35 Hz; δ 1.3 ppm, *d*, 3H, *J* = 7.35 Hz; δ 1.6 ppm, *d*, 2H, *J* = 7.35 Hz; δ 2.2 ppm, *m*, 2H, *J* = 6.75 Hz and 7.35 Hz; δ 3.7 ppm, *s*, 3H, N^7-CH_3; δ 4.1 ppm, *s*, 3H, N^3-CH3; δ 7.5 ppm, *s*, 1H, =CH); EI-MS (m/z 236; 207; 180 (100%) ; 165; 136; 109; 42)

The alkylation of theobromine using secondary alkyl halide in the DMF was slightly lower in yield compared to that using ethanol-water-NaOH as solvent. It can be assumed that S_N2 reaction occurred during the reaction. Sodium hydroxide was used as a catalyst to remove the proton from N^1 to enhance the nucleophilic character of imide of theobromine in view of its resonance character [10].

The lower yield of the products may be caused by the presence of sodium hydroxide. Besides the E_2 reaction, this alkaline solution is a strong base so it is nucleophilic in character and competes with the desired reaction. The results of the synthesis were summarized in Table 1.

Table 1 : The comparison of melting point and yield of N^1-isopropyl and N^1-*sec*-butyltheobromines obtained in DMF and in ethanol-water system respectively.

Compound	Solvent	Melting point (°C)	Yield (%)
 N^1-isopropyltheobromine	DMF Ethanol-water	154-155°C 154-155°C	7.7 9.4
 N^1-*sec*-butyltheobromine	DMF Ethanol-water	112-113°C 112-113°C	5.9 9.2

It is proposed that perhaps sodium theobromine be used instead of theobromine to avoid competitive reaction. Sodium theobromine can be prepared from the reaction of theobromine and Na_2CO_3. Non-reactive strong base likes lithium diisopropylamine (LDA), sodium hydride or triethylamine have also been suggested either to overcome this [11]. .

The UV spectrum of N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine showed that both N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine have the same chromophore system because the maximum wave length of those two alkyltheobromine derivatives are quite similar.

The IR spectrum of N^1-isopropyltheobromine and N^1-*sec*-butyltheobromine are similar too except in their finger print regions. Two or more substances that posses differences in the finger print region are indicative of the presence of different molecule structure. The broad band at 3400 cm^{-1} in both the products shows the present of OH group. It may be caused by absorbed water from the air by a hygroscopic KBr pellets.

The ^{1}H-NMR spectra of the products show a similar hydrocarbon environment in the xanthine ring. The difference of signals can be seen at δ 1.3 ppm and δ 1.6 ppm from the ^{1}H-NMR spectrum of N^1-*sec*-butyltheobromine which were absent in the ^{1}H-NMR spectrum for N^1-isopropyltheobromine. The δ 1.3 ppm signal is derived from methyl group of substituted alkyl at C_1 position while the δ 1.6 ppm signal is derived from methylene group at the C_3 of *sec*-butyl group. Theoretically, the signal at δ 1.6 ppm of N^1-*sec*-butyltheobromine and δ 2.1 ppm of N^1-isopropyltheobromine should be splitted as multiplet. However our low frequency NMR instrstrument (60 MHz), was unable to resolve this and remained a singlet signal [12].

The molecule structure of the products was confirmed by their mass spectrum with N^1-isopropyltheobromine present at m/z 222 while N^1-*sec*-buthyltheobromine present at m/z 236 corresponding to their molecule weights.

Conclusion

The alkylation of theobromine using secondary alkyl halide can be carried o ' in DMF as a medium via the S_N2 reaction mechanism. The lower yields can be caused by the competition reaction between secondary alkyl halide and theobromine against NaOH.

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