

Synthesis of Phenobarbital, An anticonvulsant Drug

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ABSTRACT

This project studied the synthesis of phenobarbital which has a potential in the treatment of convulsion. There are eight methods for the synthesis of phenobarbital. In this research work, only two methods were investigated. The first method was based on the reaction of diethyl ethylphenylmalonate and urea in the presence of sodium ethoxide (by adding 1/2, 1/4, 1/8 and 1/8 portion of sodium ethoxide solution for first, second, third and fourth hour, respectively). The second method was based on the reaction of diethyl ethylphenylmalonate and urea in the presence of sodium methoxide. This method was divided into two categories. The first category; diethyl ethylphenylmalonate was added into sodium methoxide and then urea was added. For the second category; urea was added into sodium methoxide and finally diethyl ethylphenylmalonate was added. The synthesis of phenobarbital, using the second category, gave the highest percentage yield (17.45%). The synthesized phenobarbital was identified by using 3 techniques, thin layer chromatography, infrared spectrophotometer and melting point determination.

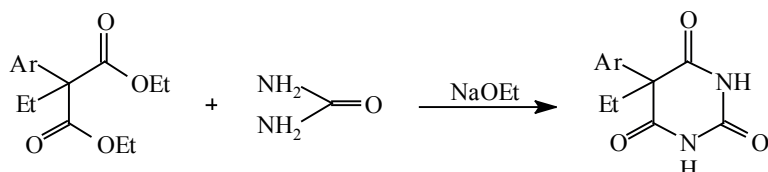
Key words: Phenobarbital, Synthesis

INTRODUCTION

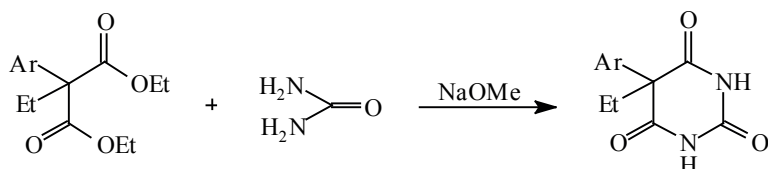
Conventional antiepileptic drugs have been used for a long time. Their therapeutic uses and effectiveness are satisfactory. Their adverse effects are more well-known than the new antiepileptic drugs. Conventional antiepileptic drugs which are used currently are phenytoin, ethosuximide, carbamazepine, valproic acid and phenobarbital. (Andrejus, 1988 ; Nantachit, 2002) The objective of this project is to synthesize phenobarbital.

There are eight methods of synthesis of phenobarbital. (Daniel and Lester, 1977 ; Roth and Kleeman, 1988)

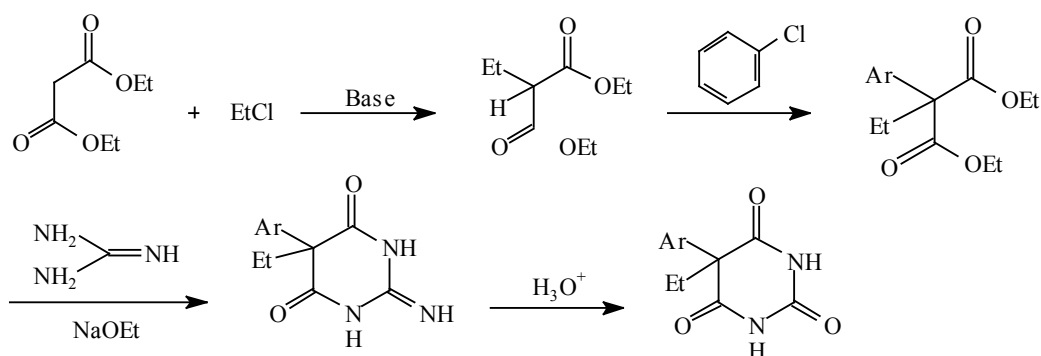
In the first method, phenylethylmalonic diethyl ester was reacted with urea in the medium of sodium ethoxide.



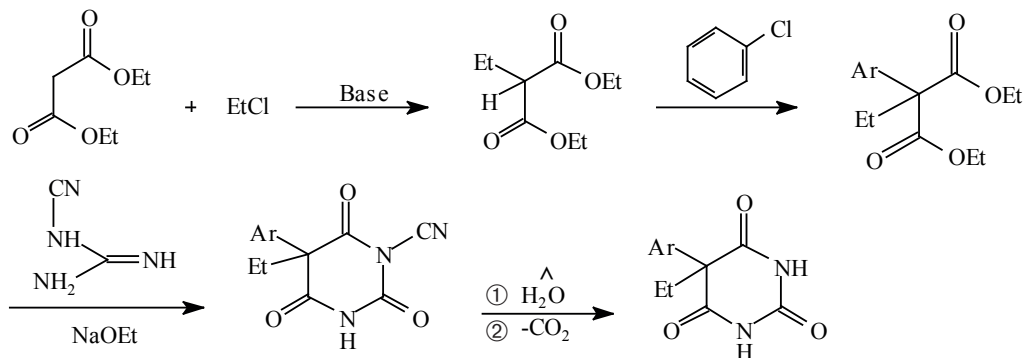
In the second method, the reaction was the same as the first method but sodium methoxide was used instead of sodium ethoxide.



In the third method, we alkylated the malonate twice in the basic medium. In the first time, malonate was alkylated with ethyl chloride, and in the second time it was alkylated with phenyl chloride. The product was ethylphenylmalonate reacting with guanidine and cyclization occurred, after that imino group was hydrolysed to become oxygen and phenobarbital was yielded.

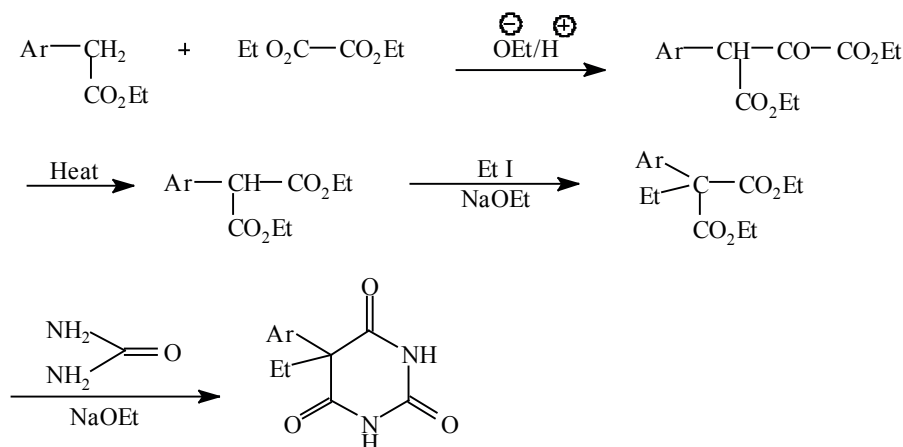


In the fourth method, ethylphenylmalonate was synthesized as in the third method. It was reacted with cyanoguanidine and was hydrolysed and decarboxylated to yield phenobarbital.

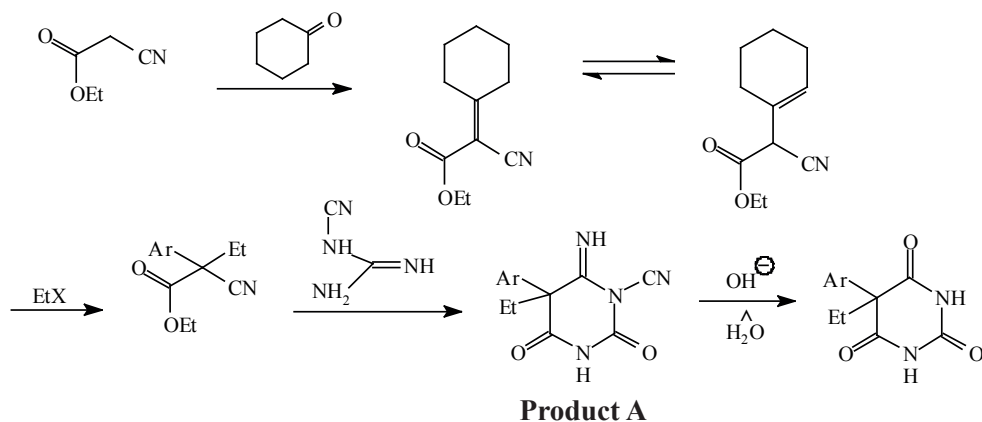


In the fifth method, ethylphenylmalonate was reacted with diethyloxalate in the medium of sodium ethoxide and sulfuric acid. The product was ethylphenylacetate

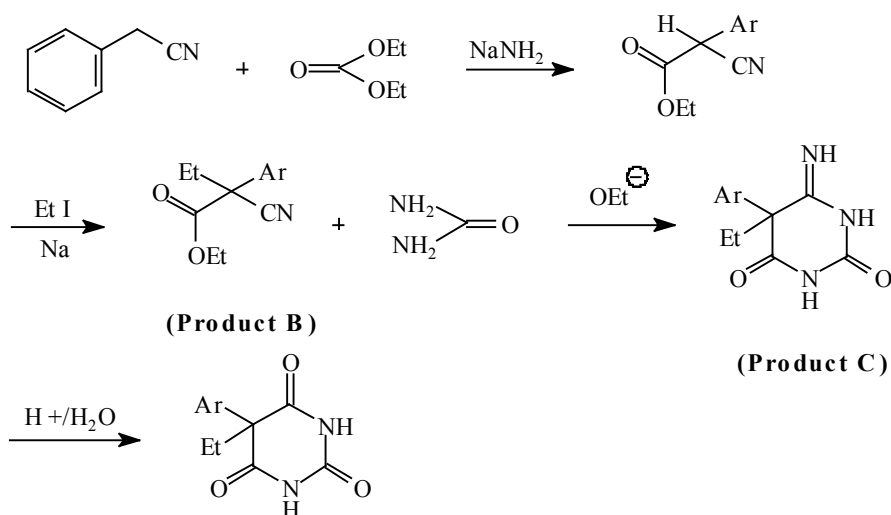
which was heated to 175°C and kept at this condition until carbon monoxide was completely released and the product was diethylphenylmalonate which was alkylated with ethyl iodide in the medium of sodium ethoxide. The reaction product was diethyl ethylphenylmalonate reacting with urea in the medium of sodium ethoxide. Condensation and cyclization reaction took place which yielded phenobarbital.



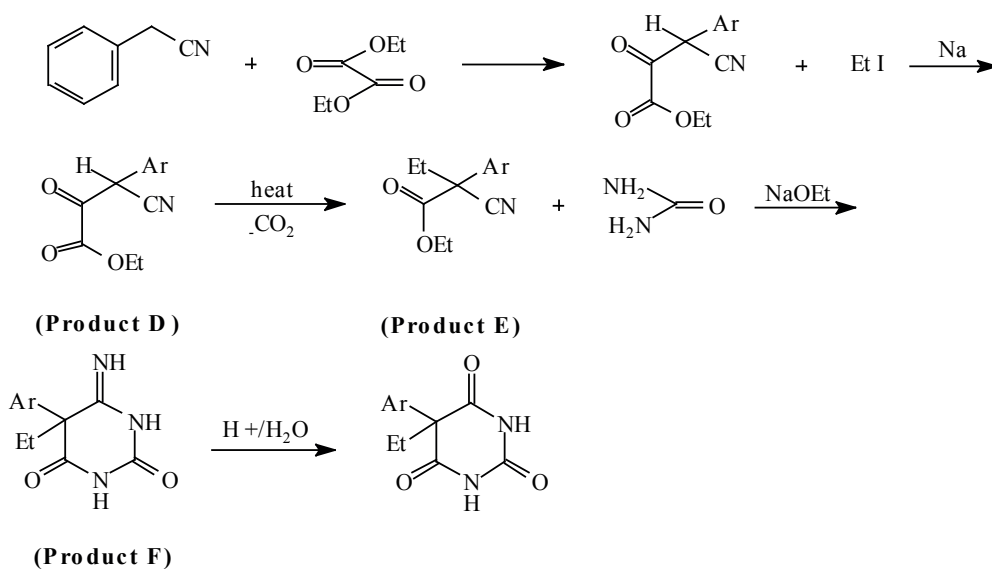
In the sixth method, Knoevenagel reaction was used by condensing cyclohexanone with cyanoacetate and olefinic intermediate was yielded. It was alkylated with ethyl halide and was condensed with urea or cyanoguanidine. The product A was hydrolysed and decarboxylated. Phenobarbital was the final product.



In the seventh method, phenylacetone nitrile was reacted with diethyl carbonate in the medium of sodium amide and then iodoethane and sodium metal was added into the reaction mixture. The product B was yielded. It was reacted with urea in the medium of sodium ethoxide and cyclization reaction took place. The product C was yielded and it was hydrolyzed by hydrochloric acid. Phenobarbital was the final product.



In the eighth method, phenylacetonitrile was reacted with ethyloxalate ester and then iodoethane was added in the medium of metal. Product D was yielded and it was heated to form decarboxylation reaction and the product E was yielded. It was condensed with urea in the medium of sodium ethoxide. Condensation and cyclization reactions took place and the product F which was yielded was hydrolysed by hydrochloric acid. Phenobarbital was yielded at last.



MATERIALS AND METHODS

Two methods were used to synthesize phenobarbital. The first method was the method from Pharmaceutical Manufacturing Encyclopedia 1979. (Marshall, 1979). This method was based on the reaction of diethyl ethylphenylmalonate and urea in

the presence of sodium ethoxide (by adding 1/2, 1/4, 1/8 and 1/8 portion of sodium ethoxide solution for first, second, third and fourth hour, respectively). The second method was the method from Vogel's Textbook of Practical Organic Chemistry 1989. (Brain et al., 1978 ; 1989). This method was based on the reaction of diethyl ethylphenylmalonate and urea in the presence of sodium methoxide. It was divided into two categories. The first category; diethyl ethylphenylmalonate was added into sodium methoxide and then urea was added. For the second category; urea was added into sodium methoxide and finally diethyl ethylphenyl malonate was added. Synthesized phenobarbital was identified by using thin layer chromatography, infrared spectrophotometer and melting point determination by comparing with standard phenobarbital. (Hamed and Ann, 1990 ; Windholz, 1983).

RESULTS

The synthetic method of phenobarbital that gave the highest % yield was the second method category 2 (the method from Vogel's Textbook of Practical Organic Chemistry 1989). The percent yield of this method was 17.45%. The first method (the method from Pharmaceutical Manufacturing Encyclopedia 1979) gave low percent yield. Rf-value, IR peak of functional groups and melting point value are shown in Tables 2, 3 and 4.

Table 1. % Yield of Synthesized Phenobarbital.

Descriptions	Experimental method	Crude % yield	% Yield of 1 st recrystallization	% Yield of 2 nd recrystallization	Total % yield
1	1 st method	15.84	-	-	-
1 st time	2 nd method, 1 st category	1.66	0.54	-	0.54
2 nd time	2 nd method, 1 st category	1.36	1.02	-	1.02
1 st time	2 nd method, 2 nd category	13.02	6.90	2.81	9.71
2 nd time	2 nd method, 2 nd category	22.48	14.52	2.93	17.45

Table 2. Rf-Value of Standard and Synthesized Phenobarbital (from 2nd method, 2nd category)

Description	Rf-value	
	St ^d Phenobarbital	Synthesized Phenobarbital
*1 st Time	0.56, 0.55	0.53, 0.57
*2 nd Time	0.54, 0.56	0.55, 0.56

*Developing solvent = CHCl₃ : MeOH (9.5 : 0.5)

Adsorbent of thin layer chromatogram used was silicagel GF 254

Table 3. IR Peak of Standard Phenobarbital.

Functional groups	Wave number (cm ⁻¹)
C = C (stretching)	1475, 1650
C - H (bending)	3100
CH ₃ (deformation)	1450, 1375
C = O (stretching)	1725
C - H (stretching)	2850
N - H (stretching)	3500-3100

IR Peak of Synthesized Phenobarbital (from 2nd method, 2nd category)

Functional groups	Wave number (cm ⁻¹)
C = C (stretching)	1480, 1650
C - H (bending)	3100
CH ₃ (deformation)	1450, 1375
C = O (stretching)	1725
C - H (stretching)	2850
N - H (stretching)	3500-3100

Table 4. Melting Point of Std Phenobarbital and Synthesized Phenobarbital (from 2nd method, 2nd category).

No.	Std Phenobarbital	Synthesized Phenobarbital
1 st time	172.3-174.3	172.0-172.9
2 nd time	171.2-173.5	171.3-172.5
3 rd time	171.4-173.5	170.3-171.7

DISCUSSION AND CONCLUSION

The first method gave low percent yield (see Table 1) because the quantity of base (sodium ethoxide) was not enough, so the reaction was not complete. The first category of the second method also showed low percent yield (see Table 1) because diethyl ethylphenylmalonate was hydrolyzed by sodium methoxide and the reaction product was ethylphenylmalonic acid instead of phenobarbital. In our investigation, the second method category 2 gave the highest percent yield (see Table 1).

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