A Modified Method of Preparing 1-methyl 4-phenyl piperidine 4-carboxylic acid Derivatives and Pharmacological Studies of its Derivatives

Keyung Ho Kim

Dept. of Pharmacology, College of Medicine, Seoul National University, Seoul, Korea.

=**Abstract**=

1-methyl 4-phenyl piperidine 4-carboxylic acid 誘導體의 改良合成과 藥理實驗

서울大學校 醫科大學 藥理學敎室

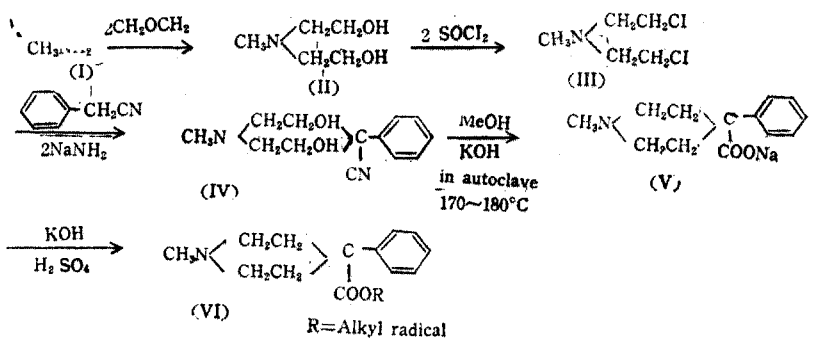
金 京 鎬

Otto Eisleb는 methyl amine과 Ethylene oxide를 反應하여 얻은것을 Thionyl chloride와 sodium amide를 作用시켜 1-methyl 4-phenyl piperidine 4-cyanide를 얻고 이것을 autoclave에서 methanol性 KOH와 反應시켜 1-methyl 4-phenyl piperidine 4-carboxylic acid를 合成하였다.

著者는 Otto Eisleb의 合成法 途中 Yperite와 類似한 化學的性質을 갖는 物質이 生成되여 이것을 大端히 取扱하기 困難하므로 合成法을 改良하여 好收得量으로 上記物質을 合成하게되였다.

Benzyl cyanide에 sodium amide를 作用시켜 얻은 物質을 Ethylene chlorhydrine, methyl amine과의 反應으로 1-methyl 4-phenyl piperidine 4-cyanide를 얻어 methanol性 KOH로 加水分解 하여 1-methyl 4-phenyl piperidine 4-carboxylic acid을 얻었다. 이것을 methyl,ethyl, n-butyl의 各己 ester로 誘導하여 鎭痛作用 實驗 한 結果, ethyl, methyl, n-butyl의 ester 順位로 鎭痛作用이 强함을 認知하였다.

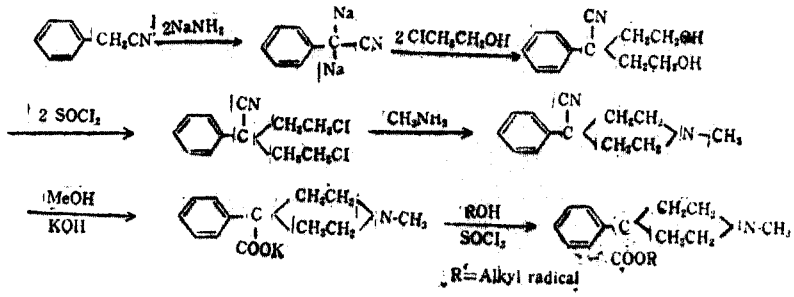
Otto Eisleb's method[1,2] of preparing the piperidine derivatives using arylacetnitril was to substitute the hydrogen atom of (CH_2) methylen radical of benzylcyanide by means of the reagents such as metalic sodium or sodium amide, and the compound thus obtained was condensed with methyl N-di(chlor ethyl) amine to synthesize 1-methyl 4-phenyl piperidine 4-carboxylic acid. The reaction processes are shown below;



The presence of methyl N-di(chlor ethyl) amine which has the similar chemical behavior with Yperite in these synthesis processes, however, made the separation and purification rather difficult. This study

is to present a new modified method of preparing such derivatives. The hydrogen atom of methylen radical was substituted with liberation of ammonia gas by addition of 2 Mol of sodium amide to benzylcyanide. If 2 Mol of ethylene chlorhydrine was then added to this, di($\alpha\alpha'$-hydroxy ethyl) benzylcyanide was produced. 1-methyl 4-phenyl piperidine nitrile yielded, if this compound was halogenated using thionyl chloride and heated in the autoclave at 110-120°C.

Saponification occurred and corresponding esters were prepared by heating the compound in the auto-



clave at 170-180°C with methyl alcoholic KOH.

Method of Preparation

Eleven and seven tenth grams of benzylcyanide was dissolved in 100g of toluene in three necked flask fitted with a mechanical stirrer. Four grams of sodium amide was added and after complete removal of ammonia gas, 8g of ethylene chlorhydrine diluted with 30cc of tolune was dropped. This was heated at 60-70°C for about 1-1.5 hours and 4g of sodium amide was again slowly dropped. When the gas was completely removed 8g of ethylene chlorhydrine was added and heated at 100-110°C. for about 2 hours. The substance thus obtained was filtered with suction and toluene layer was separated. Toluene was distilled and the residue was redistilled under the reduced pressure,and di($\alpha\alpha'$-hydroxy ethyl) benzylcyanide was obtained at 130-135°C(5mmHg). The redistillation was at 132-135°C(5mmHg). The yield was about 7g, colorless solution with the b. p. at 257-260°C(dec)

Theoretical value: $C_{12}H_{15}O_2N$(MW=205)

C:70.2 H:7.31 N:6.83

Experimental value: C:69.56 H:7.62 N:6.60

10.3g of the compound was dissolved in 100cc of benzene and the mixture was put into the three necked flask fitted with a mechanical stirrer. 20g of thionyl chioride was slowly added and heated at 60-70°C for about an hour. The excess thionyl chloride was distilled under the reduced pressure, and the residue was washed two to threetimes with ether. 33cc(3Mol) of 30% methyl amine solution was then added and heated in the autoclave at 100-110°C for 6 hours. The benzene solution of this reaction substance was filtered and the methyl amine hydrochloric acid salt crystals which simultaneously produced as side products was eliminated. when benzene was distilled the oily compound remained. The yellowish filuid compound was distilled at 150-157°C(5mmHg). Purification was carried out at 155-157°C(5mmHg). This was the colorless fluid which was gradually solidified in the air and changed to the white crystal. The m. p. was 52-54°C, hydrochloric acid salt, 220-222°C. The complete saponification occured when about 7g of this crystal was dissolved in 200cc of methanol and about 3g of KOH was added and heated in the autoclave at 170-180°C for about 3 hours. After coolng, methanol was removed by distillation and the proper amount of water was added. Hydrochloric acid was dropped untill phenolphthalein reaction disappeared, and 1-methyl 4-phenyl piperidine 4-carboxylic acid crystalled out. As the crystal was an amphoteric compound, it formed the sodium salt or hydrochloric acid salt. The m.p. was 298-300°C(dec), and no changed were observed in the mixed sample test with the compound obtained by the Eislebs method.

Theoretical value: $C_{13}H_{17}O_2N$(MW=219)

C:71.2 H:7.76 N:6:39

Experimental value: C:70.70 H:8.00 N:6.36

6g of 1-methyl 4-phenyl piperidine 4-carboxylic acid was then chlorinated with 15cc of thionyl chloride and the latter was eliminated under reduced pressure, washed two to three times with dehydrous ether, and divided into three groups, which were treated with methanol, ethanol and n-butanol respectively to prepare corresponding esters. recrystallization was done with acetone.

1-methyl 4-phenyl piperidine 4-carboxylic methyl ester hydrochloride: m.p., 200-202°C, colorless crystal

Theoretical value: $C_{14}H_{19}O_2N$(MW=233)

C:72.1 H:8.15 N:6.01

Experimental value: C:71.7 H:8.2 N:6.10

1-methyl 4-phenyl piperidine 4-caboxylic ethyl ester hydrochloride: m.p., 186-188°C, colorless crystal.

Theoretical value: $C_{15}H_{21}O_2N$(MW=247)

C:72.8 H:8.50 N:5.66

Experimental value: C:72.2 H:8.60 N:5.80

1-methyl 4-phenyl piperidine 4-carboxylic n-butyl ester hydrochloride: m.p., 160-162°C, colorless crystal.

Theoretical ualue: $C_{17}H_{25}O_2N$(MW=275)

C:74.1 H:9.09 N:5.09

Expermiatal value: C:73.5 H:9.21 N:5.20

Analgesic and antispasmodic activity of 1-methyl 4-phenyl piperidine 4-carboxylic ethyl ester and its analog were comparatively exemined in man. Antispasmodic activity against spasm induced by cholinecarbonate. $BaCl_2$ and histamine showed the tendency of gradual increase of according to the order of methyl ester, ethyl ester and n-butyl ester of 1-methyl 4-phenyl piperidine 4-carboxylic acid.

Analgesic potency of n-butyl ester is less active than ethyl ester of 1-methyl 4-phenyl piperidine 4-carboxylic acid, but activity of ethyl ester and methylester are relatively same.

Table 1. Pharmacodynamic Activity of Analogs of 1-mehyl 4-phenyl piperidine 4-carboxylic ethyl ester.

	Analgesia	Antispasmodic Acitivity against spasms induced by		
		Choline Carbonate	$BaCl_2$	Histamine
1-methyl 4-phenyl piperidine 4-carboxylic ethyl ester.	1	1	1	1
1-methyl 4-phenyl piperidine 4-carboxylic methyl ester	0.75-1.0	1	0.5	1
1-methyl 4-phenyl piperidine 4-carboxylic n-butyl ester	0.16	1	1.5	1.5

REFERENCES

1) Eileb: *Ber. 74, 1433*

2) *Japan Patent schrift 136894*