

SYNTHESIS OF SESQUITERPENE ALKALOIDS, GUAIPYRIDINE, EPIGUAIPYRIDINE AND RELATED COMPOUNDS

Teruyo Okatani (née, Sugita)\*, Junko Koyama, Kiyoshi Tagahara, and Yukio Suzuta

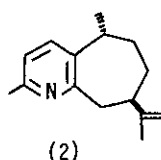
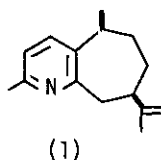
Kobe Women's College of Pharmacy, Kobe 658, Japan

**Abstract** — Synthesis of sesquiterpene alkaloids, guaipyridine, epiguaipyridine and related compounds, was accomplished by application of Diels-Alder reaction of 1,2,3-triazine with enamines.

Guaipyridine (1)<sup>1,2</sup> was isolated from patchouli oil ( leaf oil of *Pogostemon patchouli* Pellet. ), and synthesis of guaipyridine (1) and epiguaipyridine (2) have been completed by Gen and his co-workers.<sup>1</sup>

In this paper we report the synthesis of these alkaloids by application of our recent work concerning Diels-Alder reaction of 1,2,3-triazine with enamines.<sup>3</sup>

3-Isopropenyl-6-methylcycloheptanone (3) was synthesized according to the method of Heathcock and his co-workers.<sup>4</sup> Pyrrolidine enamines (4), which were synthesized from ketone (3) by standard procedure, were immediately treated with 4-methyl-1,2,3-triazine in dry  $\text{CHCl}_3$  in a sealed glass tube at  $100^\circ\text{C}$  ( bath temperature ) for 2 h. The crude products obtained were separated by preparative thin layer chromatography on silica gel to give two parts of pyridines arising from the corresponding enamine isomers.<sup>5</sup> The less-polar one was the mixture of diastereoisomers (1) and (2) ( guaipyridine and epiguaipyridine ) in a ratio of 1:2 [ 11.6%:  $\nu_{\text{max}}^{\text{CHCl}_3}$ : 3075, 1640, 1590, 1570,  $1375\text{cm}^{-1}$  ; MS  $m/z$  : 215.1666 (  $M^+$ , calcd for  $\text{C}_{15}\text{H}_{21}\text{N}$ , 215.1672 )], and then we could separate them by HPLC.<sup>6</sup>

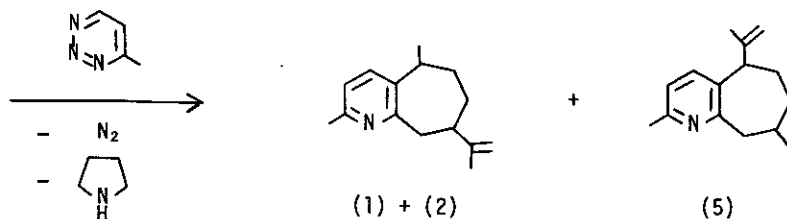
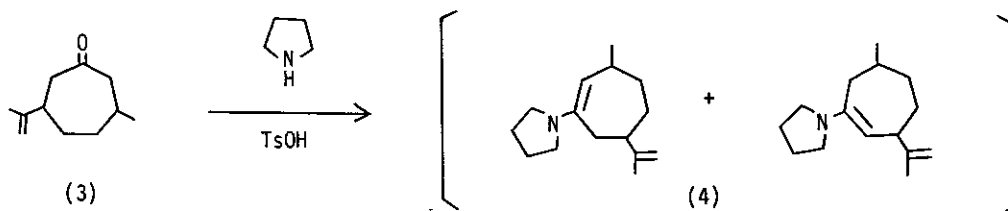


Guaipyridine(1) ; NMR(CDCl<sub>3</sub>) δ : 1.31 ( 3H, d, J=7Hz, 5-Me ), 1.79 ( 3H, s, Me-C<sup>H</sup>- ), 2.49 ( 3H, s, 2-Me ), 4.71 ( 2H, d like, >C=CH<sub>2</sub> ), 6.92 ( 1H, d, J=8Hz, 3-H ), 7.31 ( 1H, d, J=8Hz, 4-H ). Epiguaipyridine(2) ; NMR(CDCl<sub>3</sub>) δ : 1.34 ( 3H, d, J=7Hz, 5-Me ), 1.78 ( 3H, s, Me-C<sup>H</sup>- ), 2.50 ( 3H, s, 2-Me ), 4.73 ( 2H, d like, >C=CH<sub>2</sub> ), 6.96 ( 1H, d, J=8Hz, 3-H ), 7.38 ( 1H, d, J=8Hz, 4-H ).

The other one was the mixture of diastereoisomers of 2,8-dimethyl-5-isopropenyl-cyclohepta[b]pyridine (5) [ 22.8% ; ν<sub>max</sub><sup>CHCl<sub>3</sub></sup>: 3100, 1650, 1595, 1575, 1380<sub>cm</sub><sup>-1</sup> ; NMR(CDCl<sub>3</sub>) δ : 0.95 and 1.04 ( 2:3 ) ( 3H, d each, J=6.5Hz, 8-Me ), 1.77 and 1.79 ( 3H, s each, Me-C<sup>H</sup>- ), 2.49 and 2.50 ( 3H, s each, 2-Me ), 4.40 - 5.10 ( 2H, m, >C=CH<sub>2</sub> ), 6.90 ( 1H, d, J=8Hz, 3-H ), 7.23 and 7.25 ( 1H, d each, J=8Hz, 4-H ) ; MS m/z : 215.1665 ( M<sup>+</sup>, calcd for C<sub>15</sub>H<sub>21</sub>N, 215.1672 ) ].

Spectroscopic properties of (1) and (2) showed a good agreement with those described in the literature<sup>1</sup>. In addition, we obtained 3-isopropenyl-6-methylcycloheptanone (3) ( 23% ) which was generated by hydrolysis of enamines (4), and unreacted 4-methyl-1,2,3-triazine ( 12.6% ).

The cycloaddition selectively occurs at N-3 / C-6 of the 1,2,3-triazine nucleus, and the nucleophilic carbon of the enamine attaches to C-6 of the 1,2,3-triazine.



## REFERENCES AND NOTES

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- 2 G. Büchi, I. M. Goldman, and D. V. Mayo, J. Am. Chem. Soc., 1966, 88, 3109.
- 3 T. Sugita, J. Koyama, K. Tagahara, and Y. Suzuta, Heterocycles, 1985, 23, 2789.
- 4 C. H. Heathcock, T. C. Germroth, and S. L. Graham, J. Org. Chem., 1979, 44, 4481
- 5 The used enamine was a mixture of  $\Delta^1$ - and  $\Delta^7$ - isomers.
- 6 HPLC was performed with a Shimazu LC-3A chromatograph system under the following conditions : column, Cosmosil 5C<sub>18</sub> ( 8mm X 250mm ) ; solvent, CH<sub>3</sub>OH/H<sub>2</sub>O ( 85:15 v/v ) ; flow rate, 1.8ml/min ; detection, uv ; retention time, (1)=17.8 min, (2)=20.0 min.

Received, 8th October, 1986