SYNTHESIS OF SESQUITERPENE ALKALOIDS, GUAIPYRIDINE, EPIGUAIPYRIDINE AND RELATED COMPOUNDS

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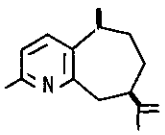
Abstract —— Synthesis of sesquiterpene alkaloids, guaipyridine, epiguaipyridine and related compounds, was accomplished by application of Diels-Alder reaction of 1,2,3-triazine with enamines.

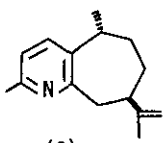
Guaipyridine (1)[1,2] was isolated from patchouli oil (leaf oil of Pogostemon patchouli Pellet.), and synthesis of guaipyridine (1) and epiguaipyridine (2) have been completed by Gen and his co-workers[1].

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[3].

3-Isopropenyl-6-methylcycloheptanone (3) was synthesized according to the method of Heathcock and his co-workers[4]. Pyrrolidine enamines (4), which were synthesized from ketone (3) by standard procedure, were immediately treated with 4-methyl-1,2,3-triazine in dry $CHCl_3$ in a sealed glass tube at 100 °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[5]. The less-polar one was the mixture of diastereoisomers (1) and (2) (guaipyridine and epiguaipyridine) in a ratio of 1:2 [11.6%; $\nu_{max}^{CHCl_3}$: 3075, 1640, 1590, 1570, 1375$_{cm}^{-1}$; MS m/z : 215.1666 (M^+, calcd for $C_{15}H_{21}N$, 215.1672)], and then we could separate them by HPLC[6].



(1)



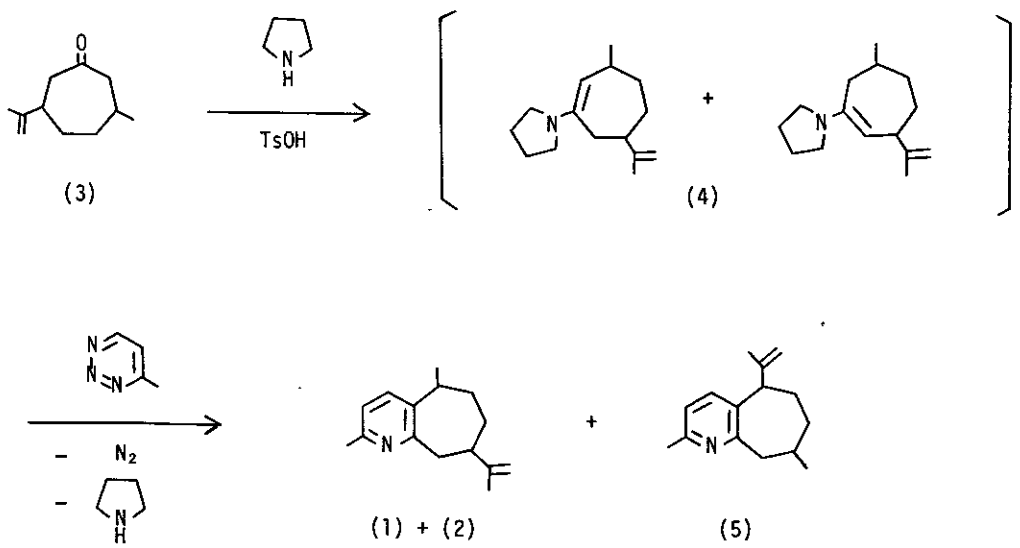
(2)

Guaipyridine(1) ; NMR($CDCl_3$) δ : 1.31 (3H, d, J=7Hz, 5-Me), 1.79 (3H, s, Me-C(=)-), 2.49 (3H, s, 2-Me), 4.71 (2H, d like, >C=CH_2), 6.92 (1H, d, J=8Hz, 3-H), 7.31 (1H, d, J=8Hz, 4-H). Epiguaipyridine(2) ; NMR($CDCl_3$) δ : 1.34 (3H, d, J=7Hz, 5-Me), 1.78 (3H, s, Me-C(=)-), 2.50 (3H, s, 2-Me), 4.73 (2H, d like, >C=CH_2), 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-isopropenylcyclohepta[b]pyridine (5) [22.8% ; $\nu_{max}^{CHCl_3}$: 3100, 1650, 1595, 1575, 1380cm^{-1} ; NMR($CDCl_3$) 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(=)-), 2.49 and 2.50 (3H, s each, 2-Me), 4.40 - 5.10 (2H, m, >C=CH_2), 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^+, calcd for $C_{15}H_{21}N$, 215.1672)].

Spectroscopic properties of (1) and (2) showed a good agreement with those described in the literature.[1] 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.



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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 Δ^{1}- and Δ^{7}- isomers.

6 HPLC was preformed with a Shimazu LC-3A chromatograph system under the following conditions ; column, Cosmosil $5C_{18}$ (8mm × 250mm) ; solvent, CH_3OH/H_2O (85:15 v/v) ; flow rate, 1.8ml/min ; detection, uv ; retention time, (1)=17.8 min, (2)= 20.0 min.

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