

SYNTHESIS OF GUAIPYRIDINE, EPIGUAIPYRIDINE, AND RELATED COMPOUNDS

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Abstract — Synthesis of sesquiterpene alkaloids, guaipyridine, epiguaipyridine, and related compounds, was accomplished by application of a method for constructing cycloalkenopyridines by thermal rearrangement of oxime O-allyl ethers.

Previously we reported the synthesis¹ of guaipyridine (1)², epiguaipyridine (2)², and related compounds using Diels-Alder reaction of 1,2,3-triazine with enamines. In this paper, we report the synthesis of these sesquiterpene alkaloids and related compounds by application of a new synthetic method³ for constructing cycloalkenopyridine ring system.

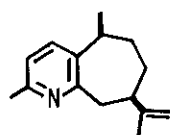
3-Isopropenyl-6-methylcycloheptanone (3)⁴ was treated with O-(α -methylallyl)-hydroxylamine (4)³ in ethanol in the presence of sodium acetate to give oxime O-allyl ether (5) as an oil in 75% yield (mixture of anti and syn form)⁵.

Thermolysis of oxime O-allyl ether (5) in a sealed glass tube under air at 180°C (bath temperature) for 40 h yielded the pyridine compounds, which were separated by preparative thin layer chromatography on silica gel (40% recovery of the starting material).

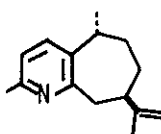
The least-polar one was the mixture of diastereoisomers, guaipyridine (1) and epiguaipyridine (2) (10%)^{6,7}. The middle one was the diastereoisomeric mixture of 2,8-dimethyl-5-isopropenylcyclohepta[b]pyridine (6) (14%)⁶. The other one was the mixture of 4,5-dimethyl-8-isopropenylcyclohepta[b]pyridine (7) and 4,8-dimethyl-5-isopropenylcyclohepta[b]pyridine (8) (10%)^{6,8}. The mixture of (7) and

(8) was separated into three peaks by HPLC⁹. The first and second peaks were diastereoisomers of (7) and the third peak was the mixture of diastereoisomers of (8)¹⁰. The structure of (7) and (8) were elucidated by NMR spectrum. 5-Methyl and 4-methyl protons of (7) showed the signals at δ [1.25 and 1.31] and [2.35 and 2.36], while 8-methyl and 4-methyl protons of (8) showed at δ [1.00 and 1.04] and 2.37^{3,11}.

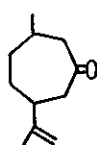
Spectroscopic properties of (1), (2), and (6) showed good agreement with those described in the literature^{1,2}.



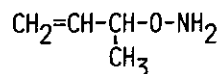
(1)



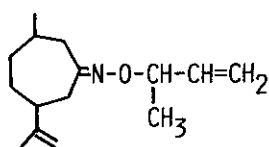
(2)



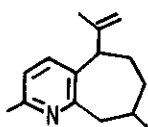
(3)



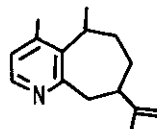
(4)



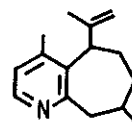
(5)



(6)



(7)



(8)

REFERENCE AND NOTES

1. T. Okatani, J. Koyama, K. Tagahara, and Y. Suzuta, Heterocycles, in press.
2. A. van der Gen, L. M. van der Linde, and J. G. Witteveen, Rec. Trav. Chim. Pays-Bas., 91, 1433(1972); G. Büchi, I. M. Goldman, and D. V. Mayo, J. Am. Chem. Soc., 88, 3109(1966).
3. J. Koyama, T. Sugita, Y. Suzuta, and H. Irie, Chem. Pharm. Bull., 31, 2601(1983).
4. C. H. Heathcock, T. C. Germroth, and S. L. Graham, J. Org. Chem., 44, 4481(1979).
5. $\nu_{\text{max}}^{\text{CHCl}_3}$: 1640 cm^{-1} (C=N); MS m/z : 235.1907 (M^+ , calcd for $\text{C}_{15}\text{H}_{25}\text{NO}$, 235.1934).
6. Pure products were obtained by gas chromatography (not preparative) from the mixtures.

7. Guaipyridine (1) and epiguaipyridine (2) could separate by preparative HPLC¹.
8. $\nu_{\text{max}}^{\text{CHCl}_3}$: 3080, 3060, 1640, 1590, 1560, 1380 cm^{-1} ; MS m/z : 215.1674 (M^+ , calcd for $\text{C}_{15}\text{H}_{21}\text{N}$, 215.1673).
9. HPLC was performed on a Shimadzu LC-3A liquid chromatograph system: Cosmosil 5C₁₈ (8mm X 250mm): solvent, CH₃OH-H₂O (3 : 1 v/v): flow rate, 1.7 ml/min.: uv-detector: retention time, peak 1=28.4 min., 2=32.0 min., 3=35.0 min. (7:3:6)
10. NMR (CDCl₃) δ : (7) peak 1: 1.31 (3H, d, J=7Hz, CH₃), 1.82 (3H, s, CH₃), 2.35 (3H, s, 4-CH₃), 4.72-4.80 (2H, m, >C=CH₂), 6.97 (1H, d, J=5Hz, 3-H), 8.20 (1H, d, J=5Hz, 2-H). peak 2: 1.25 (3H, d, J=7Hz, CH₃), 1.76 (3H, s, CH₃), 2.36 (3H, s, 4-CH₃), 4.64-4.78 (2H, m, >C=CH₂), 6.98 (1H, d, J=5Hz, 3-H), 8.24 (1H, d, J=5Hz, 2-H).
- (8): 1.00 and 1.04 (1:3) (3H, d, J=6.5Hz, CH₃), 1.84 (3H, s, CH₃), 2.37 (3H, s, 4-CH₃), 4.72-4.84 (2H, m, >C=CH₂), 6.96 (1H, d, J=5Hz, 3-H), 8.20 and 8.24 (1H, d, J=5Hz, 2-H).
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