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 synthesis[1] 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 method[3] for constructing cycloalkenopyridine ring system.

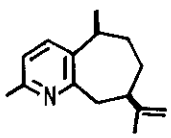
3-Isopropenyl-6-methylcycloheptanone (3)[4] was treated with O-(α-methylallyl)-hydroxylamine (4)[3] in ethanol in the presence of sodium acetate to give oxime O-allyl ether (5) as an oil in 75% yield (mixture of anti and syn form)[5].

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 HPLC[9]. 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].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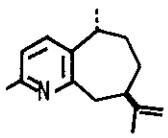
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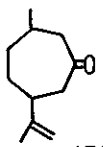
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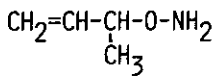
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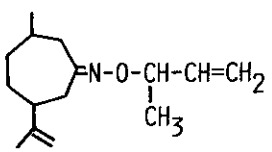
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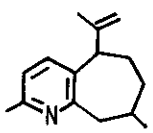
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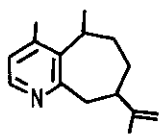
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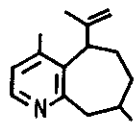
(8)

REFERENCE AND NOTES

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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. $\nu_{max}^{CHCl_3}$: 1640 cm^{-1} (C=N): MS m/z: 235.1907 (M^+, calcd for $C_{15}H_{25}NO$, 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 HPLC[1].
8. $\nu_{max}^{CHCl_3}$: 3080, 3060, 1640, 1590, 1560, 1380 cm^{-1}; MS m/z: 215.1674 (M^+, calcd for $C_{15}H_{21}N$, 215.1673).
9. HPLC was performed on a Shimazu LC-3A liquid chromatograph system: Cosmosil $5C_{18}$ (8mm × 250mm); solvent, CH_3OH-H_2O (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 ($CDCl_3$) δ : (7) peak 1: 1.31 (3H, d, J=7Hz, CH_3), 1.82 (3H, s, CH_3), 2.35 (3H, s, 4-CH_3), 4.72-4.80 (2H, m, >C=CH_2), 6.97 (1H, d, J=5Hz, 3-H), 8.20 (1H, d, J=5Hz, 2-H). peak 2: 1.25 (3H, d, J=7Hz, CH_3), 1.76 (3H, s, CH_3), 2.36 (3H, s, 4-CH_3), 4.64-4.78 (2H, m, >C=CH_2), 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, CH_3), 1.84 (3H, s, CH_3), 2.37 (3H, s, 4-CH_3), 4.72-4.84 (2H, m, >C=CH_2), 6.96 (1H, d, J=5Hz, 3-H), 8.20 and 8.24 (1H, d, J=5Hz, 2-H).
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