SYNTHESIS OF <u>dl</u>-Septicine

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Cycloaddition reaction of l-pyrroline l-oxide with 2,3-bis(3,4dimethoxyphenyl)butadiene proceeded regioselectively to give two stereoisomeric isoxazolidine derivatives, one of which was converted into septicine by three-step reactions.

Septicine is an indolizidine alkaloid isolated from Ficus septica, and the structure(I) was assigned from chemical and spectral properties.¹⁾ This alkaloid is the first instance of an unfused indolizidine alkaloid occurring in nature, and was postulated to be a biosynthetic intermediate of phenanthroindolizidine alkaloids.²⁾ Septicine was found to be changed by UV irradiation into an another alkaloid, tylophorine(II),³⁾ which is a congener of septicine in the plant. Synthesis of septicine was reported by four groups.⁴⁾



Previously we have reported that the 1,3-dipolar cycloaddition reactions of nitrones accomodate an efficient method for synthesis of pyrrolizidine alkaloids.⁵⁾ Herein, we wish to report the synthesis of <u>dl</u>-septicine using this cycloaddition reaction. Retrosynthetic analysis of septicine(I) indicated that one of the efficient means of assembling the molecular framework would involve 1,3-dipolar addition of readily available l-pyrroline l-oxide(III) to diphenylbutadiene. Regioselectivity of the 1,3-dipolar cycloaddition of nitrones to conjugated dienes was not thoroughly

studied, but a few instances⁶⁾ suggested that a reaction of 1-pyrroline 1-oxide(III) with a substituted butadiene(IV) affords 5-vinylisoxazolidine(V) rather than 4-vinyl-isoxazolidine(VI). The adduct (V) has a secoindolizidine alkaloid skeleton and is



expected to be convertible into the indolizidine alkaloid.

A dipolarophile, 2,3-bis(3,4-dimethoxyphenyl)butadiene(IV),⁷⁾ was prepared from veratraldehyde by four-step reactions including pinacol type condensation and dehydration with phosphoryl chloride.



When the diene (IV) was refluxed in toluene with 1-pyrroline 1-oxide(III) for 2 h, two adducts, (VII) and (VIII),⁷⁾ were obtained in 42% and 21% yields, respectively. These two products were separated by column chromatography on silicic acid. The structures of the adducts were determined from chemical and spectral properties. The PMR spectra of both adducts showed the presence of terminal methylene group, (VII):5.38(d,J=2Hz) and 5.73(d,J=2Hz); (VIII): 5.17(d,J=1.5Hz) and 5.27(d,J=1.5Hz), but the absence of the signal due to $-OCH_2$ - group assignable to structure (VI). Any other regioisomer was not detected from the mixture of cycloaddition product. The stereochemistry of the adducts was tentatively assigned from a chemical property described later. The formation of the two stereoisomers, (VII) and (VIII), was explained in terms of exo- and endo-addition reactions, respectively.

The N-O bond in the isoxazolidine (VII) was reduced easily with zinc in aqueous acetic acid(54°C, 2 h) to give an amino alcohol (IX)⁷⁾ in 98% yield. However, several attempts on direct cyclization of the amino alcohol (IX) to a piperidine ring or replacing the allylic hydroxyl group by halogen were unsuccessful. So, another



approach to construct the septicine skeleton from the initial adduct (VII) was tried. Bromine treatment of (VII) in chloroform at room temperature afforded a bromoammonium bromide (X)⁷⁾ in 88% yield by concomitant bromine addition and cyclization. The bromide (X) was reduced with lithium aluminium hydride in tetrahydrofuran to afford the original adduct (VII), a diphenylethylene (XI),⁷⁾ and an epoxide (XII) [δ 2.58(1H, d,J=12Hz), 3.12(1H,d,J=12Hz); m/e 411]⁷⁾ in 43, 4.1, and 24% yield, respectively. These products were separated by column chromatography on silicic acid. Although many methods were known for converting epoxy group into ethylene group, we devised a following method. The epoxide (XII) was allowed to react with trimethylsilyl iodide in chloroform at room temperature to produce a trimethylsilyl iodohydrin (XIII). Without isolation of the product, the reaction mixture was directly treated with zinc powder in acetic acid/ethanol(1:10) on refluxing for 1.5 h under an atmosphere of argon to afford a deoxygenated compound (I) in 74% yield: mp 135-136°C; $ir(CH_2Cl_2)$, 1601, 1581, 1509, 1461, 1235, 1138, 1026 cm⁻¹; PMR(CDCl_3), δ 3.58(3H,s), 3.60(3H,s), 3.80(6H,s), 6.56(2H,s), 6.70(4H,s); m/e 395(M⁺), 295(base). The spectral properties of the synthetic compound completely agreed with those of authentic dl-septicine.

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REFERENCES and NOTES

- 1) J.H.Russel, Naturwissenschaften, 50, 443 (1963).
- 2) E.Wenkert, Experientia, <u>15</u>, 165 (1959).
- 3) T.R.Govindachari, M.V.Lakshmikantham, K.Nagarajan, and B.R.Pai, Chem. Ind. (London), 1484 (1957); T.R.Govindachari, M.V.Lakshmikantham, K.Nagarajan, and B.R.Pai, Tetrahedron, <u>4</u>, 311 (1958); T.R.Govindachari, M.V.Lakshmikantham, B.R.Pai, and S.Rajappa, Tetrahedron, <u>9</u>, 53 (1960).
- J.H.Russel and H.Hunziker, Tetrahedron Lett., <u>1969</u>, 4035; T.R.Govindachari and N.Viswanathan, Tetrahedron, <u>26</u>, 715 (1970); R.B.Herbert, F.B.Jackson, and I.Y.Nicolson, J. Chem. Soc., Chem. Commun., <u>1976</u>, 450; R.V.Stevens and Y.Luh, Tetrahedron Lett., <u>1977</u>, 979.
- 5) T.Iwashita, T.Kusumi, and H.Kakisawa, Chem. Lett., <u>1979</u>, 1337.
- 6) R.Huisgen, R.Grashey, H.Seidl, and H.Hauck, Chem. Ber., <u>101</u>, 2559 (1968).
- 7) The physical properties of the intermediates in the synthesis were as follows: (IV); mp 106-108°C; v(KBr) 1600, 1510 cm⁻¹; δ (CDCl₃) 3.76(6H,s), 3.80(6H,s), 5.23 (1H,d,J=2Hz), 5.44(1H,d,J=2Hz), 6.6-7.0(6H,m); Found:C, 73.51;H, 6.81%. Calcd for $C_{20}H_{22}O_4$:C, 73.59;H, 6.79%: (VII); v(CHCl₃) 1600, 1505 cm⁻¹; δ (CDCl₃) 3.68, 3.80, 3.84, 3.86(each 3H,s), 5.38(1H), 5.73(1H), 6.6-7.0(6H,m); Found:m/e 411.2018. Calcd for $C_{24}H_{29}O_5$ N:M, 411.2045: (VIII); v(CHCl₃) 1600, 1505 cm⁻¹; δ (CDCl₃) 3.75, 3.83, 3.84, 3.87(each 3H,s), 5.17(1H), 5.27(1H), 6.6-7.2(6H,m); Found:m/e 411.2045. Calcd for $C_{24}H_{29}O_5$ N:M, 411.2045: (IX); v(CHCl₃) 3250, 1610, 1510 cm⁻¹; δ (CDCl₃) 3.50(3H,s), 3.77(3H,s), 3.82(6H,s), 5.24(1H,d,J=2Hz), 5.75(1H,d,J=2Hz), 6.10-7.10 (6H,m); m/e 395(M⁺-H₂O): (X); v(KBr) 1600, 1515 cm⁻¹; δ (CDCl₃) 3.88(12H,brs), 6.6-7.0(6H,m): (XI); v(CCl₄) 1600, 1510 cm⁻¹; δ (CDCl₃) 3.85(6H,s), 3.90(6H,s), 5.35 (2H,s), 6.90(6H,s); Found:m/e 300.1385. Calcd for $C_{18}H_{20}O_4$:M, 300.1361: (XII); v (CHCl₃) 1605, 1510 cm⁻¹; δ (CDCl₃) 2.58(1H), 3.12(1H), 3.68(3H,s), 3.79(3H.s), 3.80(6H,s), 6.2-7.0(6H,m); Found:m/e 411.2073. Calcd for $C_{24}H_{29}O_5$ N:M, 411.2045.

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