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Structure of Pyrindicin

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Pyrindicin isolated from *Streptomyces griseofluvus* var. *pyrindicus* is determined to be 5-(*trans*-1′-butenyl)-3-methyl-3,4,6,7-tetrahydro-2*H*-1-pyrindine by its chemical reactions and the physico-chemical methods.

Recently, an alkaloid, which was named pyrindicin, has been isolated from the fermentation broth of *Streptomyces griseofluvus* var. *pyrindicus*.[2] We now wish to report the elucidation of the structure of pyrindicin.

Pyrindicin (I) is an unstable *tert*-amine, whose molecular formula, $C_{13}H_{19}N$, is determined by the microanalyses and the mass spectra of the I hydrochloride and the I picrate. The nuclear magnetic resonance (NMR) spectrum of the I picrate shows the signals due to two methyl groups at δ 1.13 (t, J=7.25) and 1.17 (d, J=5.75). Irradiation of the former signal results in conversion of the octet at δ 2.38 (J=7.25 and 5, 2H) into a doublet (J=5). The signal corresponding to two protons is observed as an overlapping multiplet in a vinyl proton region (δ 6.61). Irradiation of this signal results in change of the octet at δ 2.38 into a quartet (J=7.25). These data reveal the presence of a CH_3CH_2CH=C fragment in I. Further, double resonance experiments exhibit that the prons at δ 2.12 (d, J=11.25, 1H) and 3.275 (q, J=14.2 and 7.5, 1H) couple with the protons at δ 2.73 (t, J=11.25, 1H) and 3.925 (d, J=14.2, 1H), respectively. From the coupling constants[3a,c] these coupled protons are deduced to be the

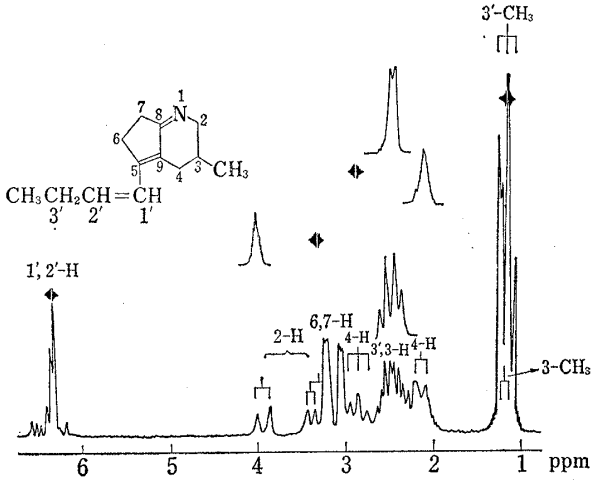


Fig. 1. NMR Spectrum of I Picrate

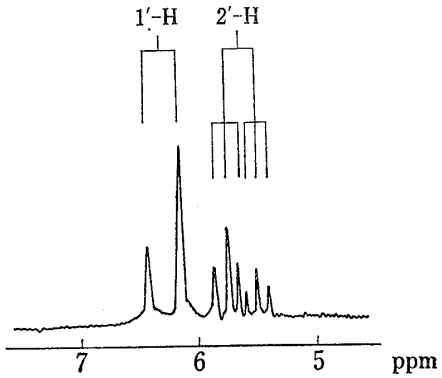


Fig. 2. NMR Spectrum of II

1) Location: *Minato-ku, Tokyo, 108, Japan.*
2) T. Hata, Y. Narimatsu, H. Tanaka, Y. Konda, J. Awaya, and S. Ōmura, *Agr. Biol. Chem.* (*Tokyo*), submitted.
3) *a*) J.W. Emsley, J. Feeney, and L.H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press Inc., New York, **1966**, pp. 677—681; *b*) *Ibid.*, pp. 712—716; *c*) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press Inc.," New York, **1969**, pp. 270—276 and pp. 280—289; *d*) *Ibid.*, pp. 301—302.

protons in two methylene groups. These proton coupling patterns indicate the presence of two systems containing a methine group adjacent to the methylene group, *i.e.*, two $-CH_2CH<$ groups, in which a vicinal coupling constant is apparently zero.

The sodium borohydride reduction of the I methiodide gave a *tert*-amine (II), $C_{14}H_{23}N$, indicating the presence of a $>C=N-$ group. The signals due to two vinyl protons are observed at δ 5.60 (sext, J=14.6 and 6) and 6.33 (d, J=14.6) in the NMR spectrum of II. From the coupling constant[3b,d] these protons can be assigned to be *trans*. Taking account of the NMR data of I, these protons are the vinyl protons in the *trans*-1-butenyl group. The observed λ_{max}^{EtOH} at 225 (6400) and 239 mμ (6800) in the ultraviolet (UV) spectrum of the II methiodide support the presence of a conjugated diene group.

On hydrogenation over Adams' platinum, I absorbed three moles of hydrogen to afford a *sec*-amine (III), $C_{13}H_{25}N$, indicating the presence of three double bonds (-CH=CH-, $>C=C<$, $>C=N-$) which were deduced to conjugate mutually by the UV spectroscopy.

Dehydrogenation of III over palladium carbon gave a *tert*-amine (IV), $C_{13}H_{19}N$, whose picrate showed λ_{max}^{EtOH} at 273 mμ (9500) in the UV spectrum and the signals at δ 7.90 (bs, 1H) and 8.30 (bs, 1H) in the NMR spectrum. These spectral data coincide with that of a trisubstituted pyridine. The NMR spectrum of the IV picrate, also, shows the presence of a methyl group (δ 2.52, s) on the pyridine ring. This methyl group corresponds to the *sec*-methyl group in the original compound (I). From the chemical shifts and the coupling constants of the aromatic protons in IV and the existence of the $>C=N-$ group in I, three partial structures (A, B, and C) are considered for IV. The remaining moiety, C_7H_{14}, contains a *n*-butyl group originated in the *trans*-1-butenyl group in I and no vinyl proton from the NMR data. Accordingly, the remaining moiety, C_3H_5, in the C_7H_{14} fragment must be a part of a ring, excluding the partial structures (B and C) (Chart 1). The presence of the conjugated triene (-CH=CH-, $>C=C<$, $>C=N-$) leads to 5-(*trans*-1′-butenyl)-3-methyl-3,4,6,7-tetrahydro-2*H*-1-pyrindine and 5-*n*-butyl-3-methyl-6,7-dihydro-5*H*-1-pyrindine for I and IV, respectively. The mass spectrum of IV shows the base peak at *m/e* 132 which is considered to be formed by the expected fragmentation at the β position to the pyridine ring (Chart 2).

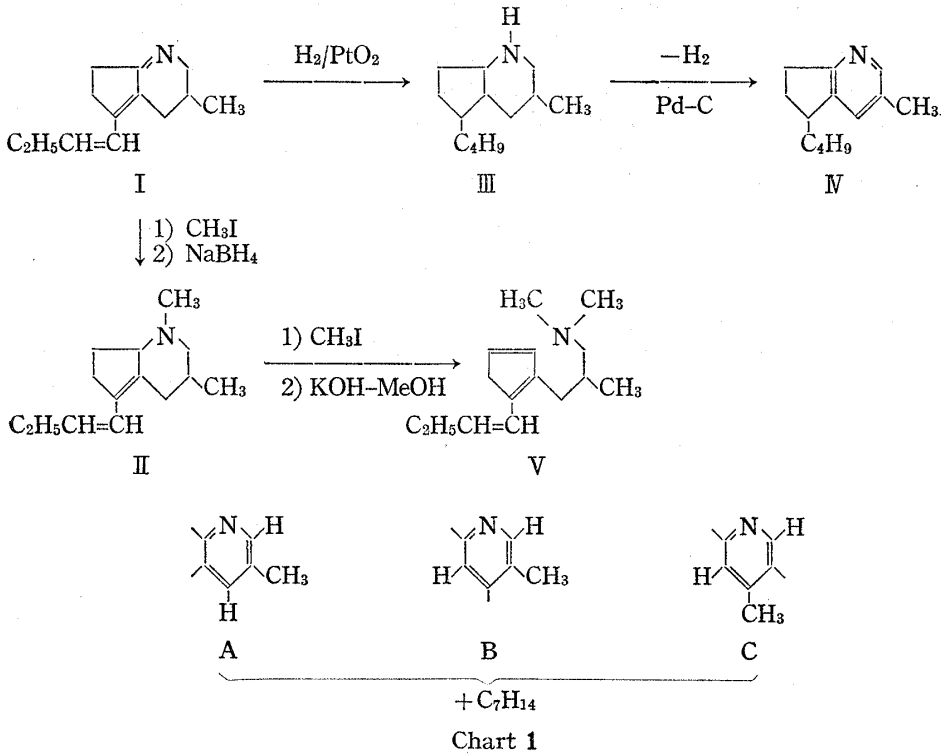
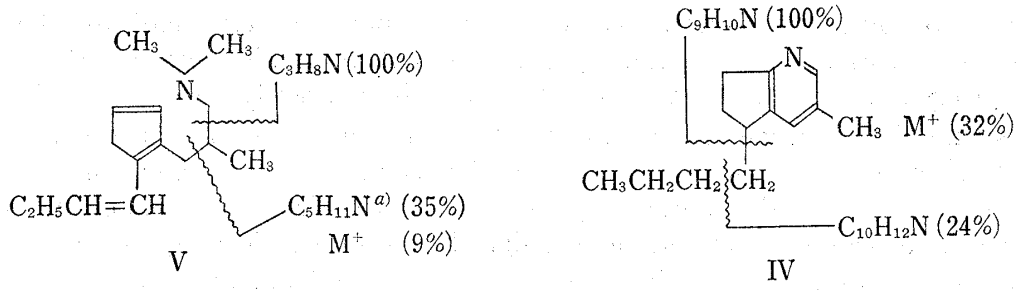


Chart 1



a) with a rearrangement of a hydrogen atom

Chart 2

The methine base (V) derived from the II methiodide *via* the Hofmann degradation has the signals due to two vinyl protons in addition to the two vinyl protons in the *trans*-1-butenyl group in the NMR spectrum and λ_{max}^{EtOH} at 282 mμ in the UV spectrum. The mass spectrum of V shows a simple fragmentation pattern which is reasonably explained as shown in Chart 2. These spectral data support the cyclopentadiene structure for V and conclusively, the structure (I) for pyrindicin.

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Ultraviolet spectra were measured with a Hitach EPS-2U. Nuclear magnetic resonance spectra were taken on a JEOL's JNM-4H-100 (100 MHz) in a deuteriochloroform. Mass spectra were measured with a JEOL's JMS-OlS.

Pyrindicin (I)——Hydrochloride: colorless scales, mp 145°. $[\alpha]_D^{20} = +22.9$ ($c=0.7$, H_2O). UV λ_{max}^{MeOH}: 311 mμ (41500). *Anal.* Calcd. for $C_{13}H_{19}N \cdot HCl$: C, 69.16; H, 8.92; N, 6.20. Found: C, 68.94; H, 8.82; N, 5.98. Mass Spectrum Calcd. for $C_{13}H_{19}N$: mol. wt., 189.151. Found: M+, 189.151. Picrate: yellow needles, mp 174—176° (decomp.). UV λ_{max}^{MeOH}: 310 mμ (57250). *Anal.* Calcd. for $C_{19}H_{22}O_7N_4 \cdot 2H_2O$: C, 50.21; H, 5.77; N, 12.33. Found: C, 50.02; H, 5.81; N, 12.66. Methiodide: light yellow crystals, mp 187—188°. *Anal.* Calcd. for $C_{14}H_{22}NI$: C, 50.76; H, 6.69; N, 4.22. Found: C, 50.77; H, 6.71; N, 4.40.

1-Methyl-1,8-dihydropyrindicin (II)——To a solution of I methiodide (60 mg) in ethanol (10 ml) was added a solution of $NaBH_4$ (20 mg) in ethanol (10 ml) and the reaction mixture was stirred for 5 min at room temperature. After work-up, there was obtained a syrup (60 mg). Mass Spectrum Calcd. for $C_{14}H_{23}N$: mol. wt., 205.193. Found: M+, 205.191. Methiodide: colorless needles, mp 202—204°. *Anal.* Calcd. for $C_{15}H_{26}NI$: C, 51.87; H, 7.54; N, 4.03. Found: C, 51.97; H, 7.61; N, 3.97.

Hexahydropyrindicin (III)——A solution of I hydrochloride (100 mg) in ethanol (15 ml) was hydrogenated over platinum black obtained from PtO_2 (20 mg) at room temperature. H_2 (31 ml) was absorbed during 10 min. After filtration, the residue was recrystallized from ethyl acetate to give colorless plates (42 mg) of mp 209—210°. Mass Spectrum Calcd. for $C_{13}H_{25}N$: mol. wt., 195.198. Found: M+, 195.194. Acetate: syrup. Mass Spectrum Calcd. for $C_{15}H_{27}ON$: mol. wt., 237.209. Found: M+, 237.211.

5-*n*-Butyl-3-methyl-6,7-dihydro-5*H*-1-pyrindine (IV)——A mixture of III (50 mg) and Pd-C (30 mg) was heated at 200° for 2 hr in a sealed tube. The reaction mixture was extracted with carbon tetrachloride to afford a syrup (40 mg). Mass Spectrum Calcd. for $C_{13}H_{19}N$: mol. wt., 189.151. Found: M+, 189.154. Picrate: yellow needles, mp 109—110°. *Anal.* Calcd. for $C_{19}H_{22}O_7N_4$: C, 54.54; H, 5.30; N, 13.39. Found: C, 54.52; H, 5.38; N, 13.42.

Methine Base (V)——A solution of II methiodide (40 mg) in 30% KOH–MeOH (3 ml) was refluxed for 10 hr. After work-up, there was obtained a syrup (25 mg), whose thin-layer chromatography howed one spot. NMR: δ 6.225 (d, $J=17$), 5.44 (sext, $J=17$ and 7) (vinyl protons in 1-butenyl group), 6.15 (d, $J=5$), 5.875 (m) (vinyl protons in cyclopentadiene ring), 2.22 (s, NMe_2), 1.25 (t, $J=7.5$, Me), 0.88 (d, $J=5$, Me). Mass Spectrum Calcd. for $C_{15}H_{25}N$: mol. wt., 219.198. Found: M+, 219.190.