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Reactions of Protoberberine-Type Alkaloids. IX. The Structure of a $KMnO_4$ Oxidation Product of Acetoneberberine.[1] (1)

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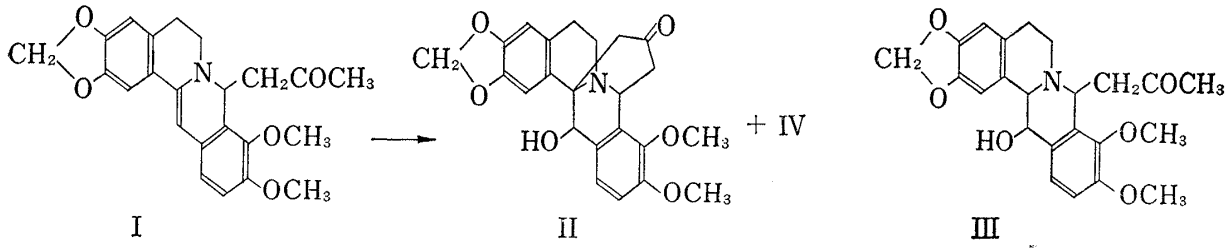
Potassium permanganate oxidation of acetoneberberine gave rise to so called neoxyberberine acetone and 2-(2,3-dimethoxy-6-carboxy-α-acetonyl-benzyl)-1-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (IV). The structure of IV was established by chemical and spectral data.

In the course of work on the synthesis of *dl*-ophiocarpine, we have studied potassium permanganate oxidation of acetoneberberine (I).[3] Although the oxidation product, so called neoxyberberine acetone has been previously described as the structure III, Iwasa, *et al.*[4] recently revised to an alternative bridged structure II by means of the nuclear magnetic resonance analysis.



I II III

Chart 1

We now wish to report a second oxidation product. I was treated with potassium permanganate as previous procedure.[3] After separation of the main product, neoxyberberine acetone, an acidic substance IV, mp 235° (decomp.) was obtained by silica gel column chromatography. Combustion analysis and a mass measurement of IV methyl ester established the composition, $C_{23}H_{23}O_8N$. The infrared spectrum of IV had principal absorption bands at 3410 (hydroxyl), 1712 (ketone and carboxyl) 1692 (infl) and 1650 cm^{-1} (cyclic tertiary amido) (Fig. 1), and the ultraviolet absorption spcetrum showed maxima at 262 nm (log ε 4.03) and 301 nm (log ε 3.70) from which IV was anticipated to be a derivative of the noroxyhydrastinine type.

Under a more drastic oxidation procedure using excess potassium permanganate, in an acidic solution IV gave noroxyhydrastinine (VI).

The nuclear magnetic resonance (NMR) spectrum established the structure IV, *i.e.*, 2-(2,3-dimethoxy-6-carboxy-α-acetonyl-benzyl)-1-oxo-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, for the permanganate oxidation product. It displayed the signals of the acetyl group, the two methoxyls, the methylenedioxy, the two isolated ring protons and

1) This work was presented at the Meeting of the Tohoku Branch, the Pharmaceutical Society of Japan, Sendai, December, 1965. Part VIII: Y. Kondo, *Yakugaku Zasshi*, **84**, 146 (1964).
2) Location: *Aobayama, Sendai.*
3) T. Takemoto and Y. Kondo, *Yakugaku Zasshi*, **82**, 1413 (1962).
4) J. Iwasa and S. Naruto, *Yakugaku Zasshi*, **86**, 534 (1966).

the two ring protons having an AB type splitting (see Experimental). One-proton triplets (J=5.7 Hz) centered at 5.07 ppm which couple with the methylene at 3.03 ppm favor the partial structure, >CH–CH_2COCH_3.

IV was methylated with diazomethane to monomethyl ester V, mp 135—135.5°. V showed no hydroxyl absorption in the IR spectrum (Fig. 2) and displayed a new carboxymethyl signal at 3.89 ppm in the NMR spectrum.

The ester V was treated with sodium borohydride to afford a monool derivative VII. Although the monool VII had sharp melting point and a homogeneous crystal form, a methyl signal of the hydroxyisopropyl group in VII showed a pair of overlapping doublets owing to a mixture of diastereoisomers. Acetylation of VII with pyridine–acetic anhydride afforded a crystalline monoacetate VIII, mp 130—133°.

On the other hand, lithium alanate reduction of V followed immediately by extraction with methylene chloride gave a tetrahydroisoquinoline derivative IX as a crystalline picrate.

A reasonable mechanism for the formation of IV would start with hydroxylation to give the diol, which cleave between C 13 and C 14 to IV.

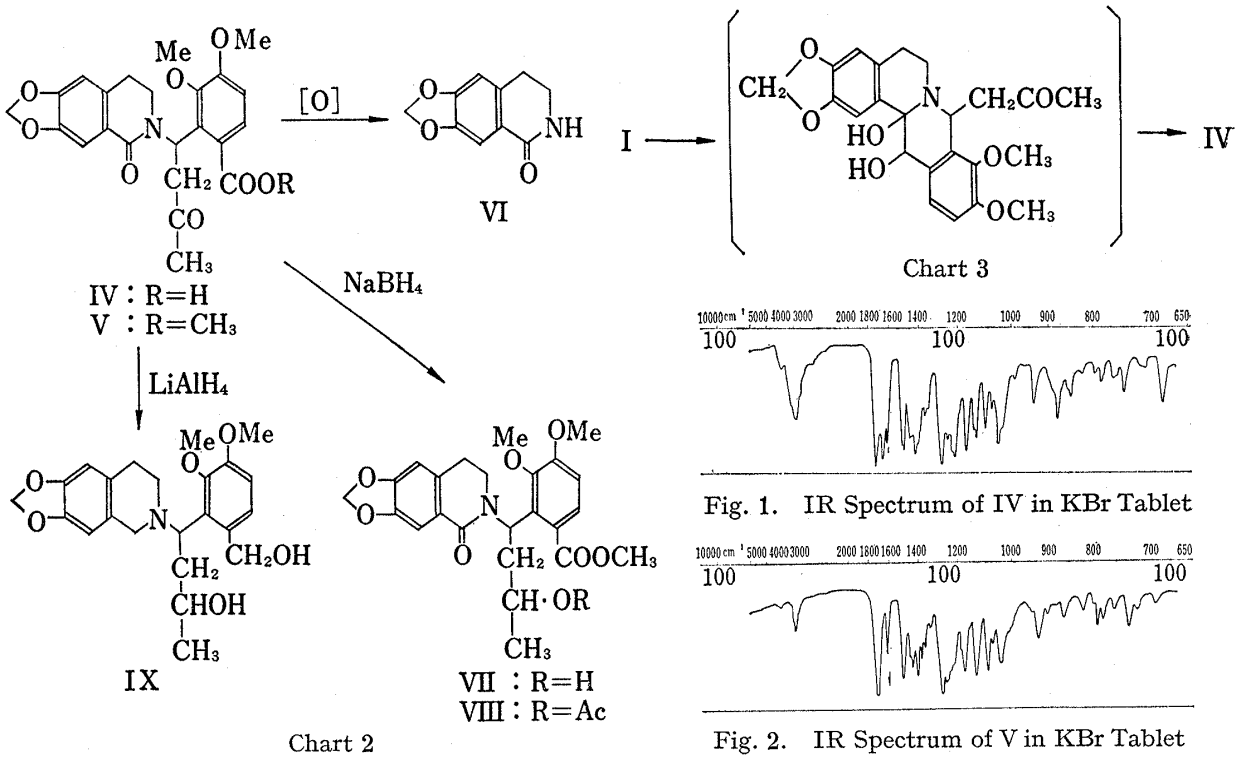


Chart 2

Fig. 1. IR Spectrum of IV in KBr Tablet

Fig. 2. IR Spectrum of V in KBr Tablet

Experimental[5]

Isolation of IV——To a solution of 16 g of acetoneberberine in 800 ml of acetone was quickly added with rapid stirring 800 ml of a 1.0% $KMnO_4$ aq. solution. The reaction mixture was worked up as the reported procedure.[3] 10 g of neoxyberberine acetone which deposited on standing was filtered off. The aqueous mother liguors were evaporated to one fifth volumes under reduced pressure and was added conc. HCl to deposit a brown resinous substance. The resinous substance was triturated with MeOH to give yellow crystals. Purification by chromatography over a silica gel column and crystallization from a mixture of $CHCl_3$ and MeOH afforded colorless prisms, mp 235° (decomp.). Yield: 570 mg. *Anal.* Calcd. for $C_{23}H_{23}O_8N$: C, 62.58; H, 5.25; N, 3.17. Found: C, 62.68; H, 5.38; N, 3.12. IR ν_{max}^{KBr} cm^{-1}: 3420, 1712, 1692 (infl.),

5) All melting points are uncorrected. IR spectra were obtained with a Hitachi EPI-2 spectrometer and UV spectra were measured on a Hitachi EPS-3 spectrophotometer. NMR spectra were recorded on a Hitachi H-60 spectrometer. Chemical shifts of $CDCl_3$ are reported as ppm with TMS as an internal standard.

1650, 1622. UV λ_{max}^{EtOH} nm(log ε): 262 (4.03), 301 (sh) (3.70). NMR ($CDCl_3$) ppm: 2.16 (-COC$\underline{H}_3$), 3.03 (d, J=5.7 Hz, -C$\dot{H}$-C$\underline{H}_2$-CO-), 3.83 (-OC$\underline{H}_3$), 3.94 (-OC$\underline{H}_3$), 5.07 (t, J=5.7 Hz, -C$\underline{H}$-CH_2-), 5.98 (-O-C$\underline{H}_2$-O-), 6.80 (C 8 proton of benzene ring), 7.03 (d, J=9.7 Hz, C 5′ proton of benzene ring), 7.46 (C 5 proton of benzene ring), 7.52 (d, J=9.7 Hz, C 4′ proton of benzene ring).

IV Methyl Ester (V)——To a solution of 550 mg of IV in $CHCl_3$ was added a ethereal solution of diazomethane (prepared from 3 g of N-methyl-N-nitroso-*p*-toluenesulfonamide). The reaction mixture was allowed to stand over-night at room temp. The solvent was removed and the residue was recrystallized from aq. MeOH to yield colorless plates, mp 135—135.5°. Yield: 520 mg. *Anal.* Calcd. for $C_{24}H_{25}O_8N$: C, 63.29; H, 5.52; N, 3.03. Found: C, 63.02; H, 5.65; N, 3.02. M^+ 455 (mass spectrum). IR ν_{max}^{KBr} cm^{-1}: 1706, 1692, 1656 (infl.), 1621, 1271, 1250. UV λ_{max}^{EtOH} nm(log ε): 263 (4.40), 296 (sh) (3.83). NMR ($CDCl_3$) ppm: 2.12 (-COC$\underline{H}_3$), 3.83 (-OC$\underline{H}_3$), 3.80 (-OC$\underline{H}_3$), 3.89 (-COOC$\underline{H}_3$), 5.05 (t, J=5.4 Hz, -C$\underline{H}$-CH_2), 5.94 (-O-C$\underline{H}_2$-O-), 6.78 (C 8 proton of benzene ring), 6.95 (d, J=8.5 Hz, C 5′ proton of benzene ring), 7.36 (C 5 proton of benzene ring), 7.52 (d, J=8.5 Hz, C 4′ proton of benzene ring).

Oxidation of IV——To a solution of 170 mg of IV in 18 ml of AcOH was added dropwise 31 ml of a 1% $KMnO_4$ solution during 1 hr. After stirring for 1 hr the reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 2.5% NaOH aq. and then with water and dried. The solvent was removed to yield crystalline residue. Recrystallization from benzene gave colorless plates, mp 185°. This material was identical with an authentic specimen of noroxyhydrastinine (VI) in direct comparison.

Reduction of V with Sodium Borohydride to VII——To a stirred solution of 200 mg of V in 20 ml of MeOH was added 80 mg of $NaBH_4$. Stirring was continued for 30 min. Then 20 ml of water was added and the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried. The solvent was removed *in vacuo*. The residue was recrystallized from ether or EtOAc to give colorless prisms, mp 156—157°. Yield: 140 mg. *Anal.* Calcd. for $C_{24}H_{27}O_8N$: C, 63.01; H, 5.95; N, 3.06. Found: C, 63.10; H, 6.21; N, 3.17. IR ν_{max}^{KBr} cm^{-1}: 3413, 1715, 1675, 1621. UV λ_{max}^{EtOH} nm(log ε): 263.5 (4.36), 300 (3.76). NMR ($CDCl_3$) ppm: 1.03 and 1.26 (pair of overlapping doublets, J=6.9 Hz, diastereoisomers of HO-C$\dot{H}$-C$\underline{H}_3$), 3.91 (-OC$\underline{H}_3$), 3.97 (-OC$\underline{H}_3$), 3.97 (-COOC$\underline{H}_3$), 4.85 (t, J=4.3 Hz, -C$\underline{H}$-CH_2), 6.02 (-O-C$\underline{H}_2$-O-), 6.87 (C 8 proton of benzene ring), 7.07 (d, J=8.5 Hz, C 5′ proton of benzene ring), 7.44 (C 5 proton of benzene ring), 7.58 (d, J=8.5 Hz, C 4′ proton of benzene ring).

VII Acetate (VIII)——A solution of 100 ml of VII was allowed to react with 1 ml of acetic anhydride in dry pyridine at 100° for 20 hr. The reaction mixture was worked up in the usual fashion. The residue was chromatographed over an Al_2O_3 column (10×30 mm) and the column was eluted with benzene. Recrystallization from ether gave colorless prisms, mp 130—133°. *Anal.* Calcd. for $C_{26}H_{29}O_9N$: C, 62.51; H, 5.85; N, 2.80. Found: C, 62.18; H, 6.00; N, 2.87. IR ν_{max}^{KBr} cm^{-1}: 1736, 1715, 1687, 1672 (infl.), 1622. NMR ($CDCl_3$) ppm: 1.06 (d, J=6.8 Hz, -C$\dot{H}$-C$\underline{H}_3$), 1.90 (Ac), 3.89 (-OC$\underline{H}_3$), 3.94 (-OC$\underline{H}_3$), 3.94 (-COOC$\underline{H}_3$), 4.71 (t, J=4 Hz, -C$\underline{H}$-CH_2-), 5.99 (-O-C$\underline{H}_2$-O-), 6.83 (C 8 proton of benzene ring), 7.02 (d, J=8.5 Hz, C 5′ proton of benzene ring), 7.42 (C 5 proton of benzene ring), 7.54 (d, J=8.5 Hz, C 4′ proton of benzene ring).

Reduction of V with Lithium Alanate to IX——To a solution of 290 mg of IV in 15 ml of dry THF was portionwise added with rapid stirring 200 mg of $LiAlH_4$. After stirring for 2 hr the excess $LiAlH_4$ was decomposed by wet ether and inorganic materials were removed by filtration. The solution was evaporated *in vacuo* to yield a brown oil. The oily substance was dissolved in MeOH and was added a MeOH solution of picric acid. The deposited picrate was recrystallized from MeOH to afford greenish-yellow needles, mp 138—139° (decomp.). *Anal.* Calcd. for $C_{29}H_{32}O_{13}N_4 \cdot 1/2\ H_2O$: C, 53.28; H, 5.08; N, 8.57. Found: C, 53.01; H, 5.31; N, 8.47. IR ν_{max}^{KBr} cm^{-1}: 3413—3257 (br.), 1629, 1613, 1550, 1342.

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