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**Shoshichiro Kimoto, Masao Okamoto, and Hiroshi Kondo :** Studies on the Alkaloids of *Amsonia elliptica* ROEM ET SCHULT. IV.[1] 17-Ketoyohimbine.

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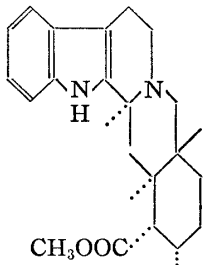
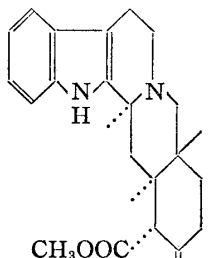
In 1943, Witkop[2] proposed the exact structure of yohimbone, which can be regarded as the most important substance in the field of structural research of yohimbine-type alkaloids.

When yohimbine was refluxed with aluminum phenoxide and cyclohexanone in xylene, yohimbone was obtained with a good yield and it was assumed that the hydroxyl group at C-17 in yohimbine (I) should be oxidized to a β-ketoester (II), followed by saponification of the methoxycarbonyl group at C-16 and decarboxylation to yohimbone.




(I)




(II)

Accordingly, it was expected that if milder reaction conditions were used in the above-mentioned Oppenauer oxidation, the unknown intermediate substance, the β-ketoester (II), would be obtained. In order to clarify this assumption, yohimbine was refluxed with aluminum phenoxide and cyclohexanone by the use of benzene as a solvent, instead of xylene, and the β-ketoester (II) was obtained as expected, which was named 17-ketoyohimbine.

This new compound formed faint yellow needles of m.p. 254~255°, $[\alpha]_D^{20}$ +15.8° (pyridine); UV $\lambda_{max}^{EtOH}$ mμ (log ε) 232(4.05), 283(3.96), and exhibited two absorption peaks at 5.78 μ and 5.88 μ in its infrared spectrum (Nujol), associated with the ester group and the carbonyl group, respectively, and the band at 2.82 μ ($\nu_{OH}$) recognized in yohimbine had disappeared.

In addition, yohimbone, m.p. 302~303°(decomp.), was obtained from 17-ketoyohimbine by heating the latter with potassium hydroxide in ethanol and it may be concluded that the preceding assumption was correct.

In an earlier paper[3] it was shown that a new base had been isolated from *Amsonia elliptica* ROEM ET SCHULT and was named amsonine. It was later found that amsonine was identical with β-yohimbine,[1] while Janot and co-workers[4] pointed out that β-yohimbine might be the C-17-epimer of yohimbine; therefore, the former might carry an equatorial hydroxyl group at C-17. However, there is no positive evidence as to this point. As a rule, compounds carrying equatorial hydroxyl groups are oxidized more slowly than their epimers carrying axial hydroxyl groups, and it might be anticipated that β-yohimbine would hardly be oxidized under foregoing mild condition. Although experiments were repeated by an improved method, 17-ketoyohimbine was not obtained from β-yohimbine and the starting material was recovered unchanged.

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The authors wish to express their indebtedness to the Research Laboratory of Tanabe Seiyaku Co., Ltd. for the measurement of infrared spectra.

## Experimental

**Oppenauer Oxidation of Yohimbine**—To a mixture of yohimbine (2.0 g.) and $Al(OPh)_3$ (12.0 g.), 50 cc. of purified cyclohexanone (b.p. 156°) and 50 cc. of dehyd. benzene were added, and the mixture was heated at 115~125° in an oil bath for 48 hr. After cool, the resulting reddish brown solution was treated with 10% NaOH solution and the organic layer was shaken with successive portions of 30% $H_2SO_4$ solution until the aqueous layer no longer produced a precipitate with Mayer reagent. After the combined aq. acid solution was allowed to stand overnight, the resulting white precipitate was collected and washed successively with 10% $Na_2CO_3$ solution and water.

The same precipitate was also obtained from the mother liquor by addition of 20% $Na_2CO_3$ solution. This crystalline base was collected and recrystallized from MeOH to faint yellow needles, m.p. 254~255°(decomp.); $[\alpha]_D^{20}$ +15.8°(c=1, pyridine). *Anal.* Calcd. for $C_{21}H_{24}O_3N_2 \cdot CH_3OH$ : C, 68.72; H, 7.34; N, 7.29. Found : C, 69.20; H, 6.91; N, 7.67.

**Hydrolysis of 17-Ketoyohimbine**—A solution of 17-ketoyohimbine (0.03 g.) and KOH (0.01 g.) in EtOH (5 cc.) was refluxed on a water bath for 4 hr. The reaction mixture was evaporated under a reduced pressure, the residue was washed with water, and recrystallized from MeOH. The white crystalline needles melted at 302~303°, undepressed on admixture with an authentic sample of yohimbone.

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# Hisao Tsukamoto, Satoshi Toki, and Kyokuritsu Kaneda : Metabolism of Drugs. XX.[1] Metabolic Fate of Methylhexabital (5-Cyclohexenyl-3,5-dimethylbarbituric Acid). (9).[2] Interconversion of 3-Keto-MHB (5-(3-Oxo-1-cyclohexenyl)-3,5-dimethylbarbituric Acid) and 3-OH-MHB (5-(3-Hydroxy-1-cyclohexenyl)-3,5-dimethylbarbituric Acid) in the Rabbit.

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In an earlier investigation on the metabolic fate of methylhexabital (MHB, 5-cyclohexenyl-3,5-dimethylbarbituric acid) in the dog, Bush *et al.*[3] have shown that keto-MHB-I and -II, and other metabolites were excreted in the urine. Cooper and Brodie[4] also reported that the same oxidation products were obtained by enzymic biotransformation of MHB. On the other hand, Tochino isolated hydroxy-MHB from the urine of rabbits administered MHB,[5] and confirmed its formation by *in vitro* study using a rabbit liver.[6]

Previous work[7,8] from this laboratory showed that two diastereoisomeric $\alpha$- and $\beta$-3-OH-MHB ($\alpha$- and $\beta$-5-(3-hydroxy-1-cyclohexenyl)-3,5-dimethylbarbituric acid), 3-keto-MHB (5-(3-oxo-1-cyclohexenyl)-3,5-dimethylbarbituric acid), 3-keto-nor-MHB (5-(3-oxo-1-

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